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Sigma Receptors: Biology and Function*

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I. Pharmacology of Sigma-binding Sites

A. Historical Perspective

her research revealed that $(+/-)$ -SKF 10,047 bi
hree types of receptors: $(-)$ -SKF 10,047 binds j
ily to mu and kappa opiate receptors (Mangan et
Abbreviations: PCP, phencyclidine; SAR, structure-active,
octahydro[f]benzoqu **I. Pharmacology of Sigma-binding Sites**

Historical Perspective

Sigma receptors were postulated in 1976 by Martin et

(1976) to account for the actions of $(+/-)$ -SKF 10,047 et
A. Historical Perspective
Sigma receptors were postulated in 1976 by Martin et
al. (1976) to account for the actions of $(+/-)$ -SKF 10,047 cep
(N-allyl-normetazocine) and related racemic benzomor-A. Historical Perspective

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al. (1976) to account for the actions of $(+/-)$ -SKF 10

(N-allyl-normetazocine) and related racemic benzon

phans. These compounds produce a spec Sigma receptors were postulated in 1976 by Martin
al. (1976) to account for the actions of $(+/-)$ -SKF 10,0
(N-allyl-normetazocine) and related racemic benzome
phans. These compounds produce a spectrum of behave
iors in the al. (1976) to account for the actions of $(+/-)$ -SKF 10,047 ceptors, and naloxone-inaccessible sigma receptors

(N-allyl-normetazocine) and related racemic benzomor-

phans. These compounds produce a spectrum of behav-

ior al. (1976) to account for the actions of $(+/-)$ -SKF 10,047 (N-allyl-normetazocine) and related racemic benzomorphans. These compounds produce a spectrum of behaviors in the dog referred to as canine delirium and have psych (N-allyl-normetazocine) and related racemic benzom
phans. These compounds produce a spectrum of beh
iors in the dog referred to as canine delirium and hipsychotomimetic effects in humans (Haertzen, 19
Keats and Telford, 19 phans. These compounds produce a spectrum of behaviors in the dog referred to as canine delirium and have cells, psychotomimetic effects in humans (Haertzen, 1970; methods Keats and Telford, 1964). Great interest in the h psychotomimetic effects in humans (Haertzen, 1970; methyl-4-isothiocyanatophenyl)-3-(2-methyl-phenyl)guanidine; Meta-
Keats and Telford, 1964). Great interest in the hypoth-
esis of Martin et al. concerning sigma receptor psychotomimetic effects in humans (Haertzen, 1970; next states and Telford, 1964). Great interest in the hypoth-
esis of Martin et al. concerning sigma receptors led to $\frac{8}{9}$
intense scrutiny of $(+/-)$ -SKF 10,047. Ten Keats and Telford, 1964). Great interest in the hypothesis of Martin et al. concerning sigma receptors led to intense scrutiny of $(+/-)$ -SKF 10,047. Ten years of further research revealed that $(+/-)$ -SKF 10,047 binds to thr esis of Martin et al. concerning sigma receptors led to intense scrutiny of $(+/-)$ -SKF 10,047. Ten years of further research revealed that $(+/-)$ -SKF 10,047 binds to three types of receptors: $(-)$ -SKF 10,047 binds primarily

OHBQ, octahydro(f]benzoquinoline; DTG, 1,3-di-o-tolylguanidine; R1,

1982); (+)-SKF 10,047 binds to PCP‡ receptors (Zukin
et al., 1986; Zukin, 1982) and to a unique site that retains et al., 1982); (+)-SKF 10,047 binds to PCP‡ receptors (Zukin et al., 1986; Zukin, 1982) and to a unique site that retains the designation sigma receptor (cf. Quirion et al., 1987). 1982); (+)-SKF 10,047 binds to PCP‡ receptors (Zukin et al., 1986; Zukin, 1982) and to a unique site that retains the designation sigma receptor (cf. Quirion et al., 1987).
Sigma receptors have also been called haloperidol 1982); (+)-SKF 10,047 binds to PCP‡ receptors (et al., 1986; Zukin, 1982) and to a unique site that r
the designation sigma receptor (cf. Quirion et al.,
Sigma receptors have also been called haloperido
sitive sigma recept 1982); (+)-SKF 10,047 binds to PCP‡ receptors (Zukin et al., 1986; Zukin, 1982) and to a unique site that retains the designation sigma receptor (cf. Quirion et al., 1987). Sigma receptors have also been called haloperidol et al., 1986; Zukin, 1982) and to a unique site that retains
the designation sigma receptor (cf. Quirion et al., 1987).
Sigma receptors have also been called haloperidol-sen-
sitive sigma receptors, etorphine-inaccessible

ceptors, and naloxone-inaccessible sigma receptors
R_a, R_a, receptor points; UV, ultraviolet; DM, dextromethorphan; PC12
cells, pheochromocytoma cells; Az-DTG, azido-DTG; DIGIT, 1-(2ceptors, and naioxone-inaccessible sigma receptors

R_s, R_s, receptor points; UV, ultraviolet; DM, dextromethorphan; PC12

cells, pheochromocytoma cells; Az-DTG, axido-DTG; DIGIT, 1-(2-

methyl-4-isothiocyanatophenyl)-3 methyl-4-isothormocytoma cells; Az-DTG, azido-DTG; DIGIT, 1-(2-methyl-4-isothiocyanatophenyl)-3-(2-methyl-phenyl)guanidine; Meta-
phit, 1-[1-(3-isothiocyanatophenyl)-3-(2-methyl-phenyl)guanidine; Meta-
phit, 1-[1-(3-isothi **guanine nucleotide-bindingprotein; Gpp(NH)p, nonhydrolyzable guan-** osine **triphosphate** analog-, **PPI, phosphoinositide; NPY, neuropeptide** *Methylerinoxyanatophenyl)-v*-/2-methy-phenyl/guantume, ivectin, phint, 1-[1-(3-isothicoxyanatophenyl)-yclohexyl]piperidine; G protein, guantosine triphosphate analog; PPI, phosphoinositide; NPY, neuropeptide Y; NMDA, N-me PPP, 3-(3-hydroxyphenyl)-N-(1-propyl)piperidine; 5HT, 5-hydroxy-tryptamine; TCP, 1-[1-(2-thienyl)cyclohexyl]piperidine; BD614, (+/-)-
cis-N-methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine; ChTG, N-(o-tolyl)-N'-cyclohexyl guanidine; **AdTG,** N-(o-tolyl)-N-(2-thienyl)cyclohexylipiperidine; BD614, (4
cis-N-methyl-N-(2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)c
hexylamine; ChTG, N-(o-tolyl)-N'-cyclohexyl guanidine; A
N-(o-tolyl)-N'-(edement-1-yl)guanidine; DP *A* symmally a control (3.4-dichlorophenyl)ethyll-2-(1-pyrrolidinyl)cyclo-

AdMs (Cis-N-methyl-N-(2-(3,4-dichlorophenyl)ethyll-2-(1-pyrrolidinyl)cyclo-

hexylamine; ChTG, N-(o-tolyl)-N'-cyclohexyl guanidine; AdTG,

N-(o-to (adamant-1-yl))guanidine.

SIGMA RE
(McLean and Weber, 1988; Su, 1982; Tam, 1983; Walker
et al., 1988) **(McLean and Weber, 1988; Su, 198**
et al., 1988).
B. Properties of Sigma Receptors
1. A non-opiate pharmacology. 8

1. A *non-opiate pharmacology*. Sigma receptors were al., 1983; Walker be pharmacology. Sigma receptors were and is all thought to be a type of opiate receptor, but cine originally thought to be a type of opiate receptors

1. A non-opiate pharmacology. Sigma receptors were

originally thought to be a type of opiate receptor, but

two subsequent findings convincingly demonstrate that B. Properties of Sigma Receptors
1. A non-opiate pharmacology. Sigma receptors were
originally thought to be a type of opiate receptor, but
two subsequent findings convincingly demonstrate that
it is not: (a) whereas opia B. Properties of Sigma Receptors
1. A non-opiate pharmacology. Sigma receptors were
originally thought to be a type of opiate receptor, but
two subsequent findings convincingly demonstrate that
it is not: (a) whereas opia 1. A non-opiate pharmacology. Sigma receptors were
originally thought to be a type of opiate receptor, but
two subsequent findings convincingly demonstrate that
it is not: (a) whereas opiate receptors are enantioselective originally thought to be a type of opiate receptor, but
two subsequent findings convincingly demonstrate that
it is not: (a) whereas opiate receptors are enantioselective
for the $(-)$ -isomers of opium-derived narcotics, n two subsequent findings convincingly demonstrate that
it is not: (a) whereas opiate receptors are enantioselective
for the $(-)$ -isomers of opium-derived narcotics, narcotic
antagonists, and their congeners, sigma receptor it is not: (*a*) whereas opiate receptors are enantioselective
for the $(-)$ -isomers of opium-derived narcotics, narcotic
antagonists, and their congeners, sigma receptors are
enantioselective for the $(+)$ -isomers and (*b* for the $(-)$ -isomers of opium-derived narcotics, narcotic antagonists, and their congeners, sigma receptors are enantioselective for the $(+)$ -isomers and (b) naloxone is Hineffective against both the in vivo and the in v antagonists, and their congeners, sigma receptors are
enantioselective for the $(+)$ -isomers and (b) naloxone is
ineffective against both the in vivo and the in vitro effects
of sigma ligands (Brady et al., 1982; Iwamoto, enantioselective for the $(+)$ -isomers and (b) naloxone is
ineffective against both the in vivo and the in vitro effects
of sigma ligands (Brady et al., 1982; Iwamoto, 1981; Katz
et al., 1985; Slifer and Balster, 1983; V ineffective against both the in vivo and the in vitro effector of sigma ligands (Brady et al., 1982; Iwamoto, 1981; Ka
et al., 1985; Slifer and Balster, 1983; Vaupel, 1983
Therefore, it is clear the sigma receptor is not a

et al., 1985; Slifer and Balster, 1983; Vaupel, 1983). Therefore, it is clear the sigma receptor is not a type of by
opiate receptor.
2. Differences between sigma and phencyclidine receptors. In earlier papers investigator Therefore, it is clear the sigma receptor is not a type of
opiate receptor.
2. Differences between sigma and phencyclidine recep-
tors. In earlier papers investigators asserted that sigma
receptors were identical with PCP opiate receptor.

2. Differences between sigma and phencyclidine receptors. In earlier papers investigators asserted that sigma

receptors were identical with PCP receptors based on the

displacement of $[^{3}H]PCP$ binding 2. Differences between sigma and phencyclidine receptors. In earlier papers investigators asserted that sigma receptors were identical with PCP receptors based on the displacement of $[^3H]PCP$ binding by the prototypic sig tors. In earlier papers investigators asserted that sigma
receptors were identical with PCP receptors based on the
displacement of $[^3H]$ PCP binding by the prototypic
sigma ligand $(+)$ -SKF 10,047 (Mendelsohn et al., 1985; receptors were identical with PCP receptors based on the displacement of $[^3H]$ PCP binding by the prototypic sigma ligand $(+)$ -SKF 10,047 (Mendelsohn et al., 1985; for Zukin et al., 1984). For this reason, sigma receptors displacement of [³H]PCP binding by the prototypic
sigma ligand (+)-SKF 10,047 (Mendelsohn et al., 1985;
Zukin et al., 1984). For this reason, sigma receptors were
sometimes called "sigma opiate/PCP receptors" (Zukin
et a sigma ligand $(+)$ -SKF 10,047 (Mendelsohn et al., 198
Zukin et al., 1984). For this reason, sigma receptors we
sometimes called "sigma opiate/PCP receptors" (Zuk
et al., 1984). However, the drug selectivity pattern
[³H](Zukin et al., 1984). For this reason, sigma receptors were
sometimes called "sigma opiate/PCP receptors" (Zukin cet al., 1984). However, the drug selectivity pattern of e¹H](+)-SKF 10,047 differs from that of $[^{3}H]$ PC sometimes called "sigma opiate/PCP receptors" (Zukin
et al., 1984). However, the drug selectivity pattern of
[³H](+)-SKF 10,047 differs from that of [³H]PCP show-
ing that these substances bind to different receptors. et al., 1984). However, the drug selectivity pattern of example, 1984). However, the drug selectivity pattern defeating that these substances bind to different receptors. For studing, but they are antiply displace $[^3H](+) [^{3}H](+)$ -SKF 10,047 differs from that of $[^{3}H]PCP$ showing that these substances bind to different receptors. For example, antipsychotic drugs (such as haloperidol) potently displace $[^{3}H](+)$ -SKF 10,047 binding, but th ing that these substances bind to different receptors. For
example, antipsychotic drugs (such as haloperidol) po-
tently displace $[^3H](+)$ -SKF 10,047 binding, but they are
weak or inactive against $[^3H]PCP$ binding (Tam 1983 example, antipsychotic drugs (such as haloperidol) potently displace $[^3H]/(+)$ -SKF 10,047 binding, but they are weak or inactive against $[^3H]PCP$ binding (Tam 1983; Tam and Cook, 1984). Conversely, PCP is weak against $[^3H$ tently displace $[^{3}H](+)$ -S
weak or inactive against
Tam and Cook, 1984). C.
 $[^{3}H]$ haloperidol binding (
al., 1986; Itzhak, 1987).
Sigma and PCP recep vak or inactive against [³H]PCP binding (Tam 1983; nm and Cook, 1984). Conversely, PCP is weak against H]haloperidol binding (Tam and Cook, 1984; Downs et , 1986; Itzhak, 1987). Sigma and PCP receptors may also be differ

Tam and Cook, 1984). Conversely, PCP is weak against

[³H]haloperidol binding (Tam and Cook, 1984; Downs et s

al., 1986; Itzhak, 1987).

Sigma and PCP receptors may also be differentiated e

by their distinct anatomica [³H]haloperidol binding (Tam and Cook, 1984; Downs et al., 1986; Itzhak, 1987).

Sigma and PCP receptors may also be differentiated

by their distinct anatomical distributions, because

[³H](+)-SKF 10,047 and [³H]PC al., 1986; Itzhak, 1987).

Sigma and PCP receptors may also be differentiated

by their distinct anatomical distributions, because

[³H](+)-SKF 10,047 and [³H]PCP-binding sites are con-

centrated in different brain ar Sigma and PCP receptors may also be differentiated
by their distinct anatomical distributions, because
[³H](+)-SKF 10,047 and [³H]PCP-binding sites are con-
centrated in different brain areas (Gundlach et al., 1985;
La by their distinct anatomical distributions, because m
[³H](+)-SKF 10,047 and [³H]PCP-binding sites are concentrated in different brain areas (Gundlach et al., 1985; (f
Largent et al., 1984; McLean and Weber 1988; Sirca [³H](+)-SKF 10,047 and [³H]PCP-binding sites are concentrated in different brain areas (Gundlach et al., 1985; (fig Largent et al., 1984; McLean and Weber 1988; Sircar "opet al., 1986; Gundlach et al., 1986). Tam (198 centrated in different brain areas (Gundlach et al., 1985; (fig. 1; table 1). These classes include: (a) the sigma
Largent et al., 1984; McLean and Weber 1988; Sircar "opiates," including benzomorphans, such as pentazocin Largent et al., 1984; McLean and Weber 1988; Sircar
et al., 1986; Gundlach et al., 1986). Tam (1985) pointed
out other differences between [³H]PCP binding and
[³H](+)-SKF 10,047 binding: the sensitivity of [³H]PCP
b et al., 1986; Gundlach et al., 1986). Tam (1985) pointed
out other differences between [³H]PCP binding and
[³H](+)-SKF 10,047 binding: the sensitivity of [³H]PCP
binding to sodium ions and the low affinity and small
 out other differences between [³H]PCP binding and as dext
[³H](+)-SKF 10,047 binding: the sensitivity of [³H]PCP logs of
binding to sodium ions and the low affinity and small nyl)cyc
stereoselectivity shown by PCP r $[^{3}H](+)$ -SKF 10,047 binding: the sensitivity of $[^{3}H]$ PCP logitual binding to sodium ions and the low affinity and small nyl stereoselectivity shown by PCP receptors toward $(+)$ - cis SKF10,047 and $(+)$ -ethylketocyclazo binding to sodium ions and the low affinity and small
stereoselectivity shown by PCP receptors toward $(+)$ -
SKF10,047 and $(+)$ -ethylketocyclazocine. It is clear from
these findings that $[^{3}H](+)$ -SKF 10,047 binds to two
d stereoselectivity shown by PCP receptors toward (+)
SKF10,047 and (+)-ethylketocyclazocine. It is clear from
these findings that $[^{3}H](+)$ -SKF 10,047 binds to two
distinct sites: a haloperidol-sensitive site (subsequentl) SKF10,047 and (+)-ethylketocyclazocine. It is clear from these findings that $[^{3}H](+)$ -SKF 10,047 binds to two distinct sites: a haloperidol-sensitive site (subsequently called the sigma receptor) and a PCP-sensitive site distinct sites: a haloperidol-sensitive site (subsequently called the sigma receptor) and a PCP-sensitive site (subsequently called the PCP receptor; Quirion et al., 1987) 3. Potent binding of antipsychotic drugs to sigma

called the sigma receptor) and a PCP-sensitive site (subsequently called the PCP receptor; Quirion et al., 1987
3. Potent binding of antipsychotic drugs to sigma receptors. Radioligand-binding studies reveal that many ant
 3. Potent binding of antipsychotic drugs to sigma recep-
tors. Radioligand-binding studies reveal that many anti-
psychotic drugs bind to sigma receptors with high affin-
phenoity. Haloperidol is among the most potent inh tors. Radioligand-binding studies reveal that many anti-
psychotic drugs bind to sigma receptors with high affin-
ity. Haloperidol is among the most potent inhibitors of 5
 $[^{3}H](+)-SKF$ 10,047 binding, with a K_{i} of 4 n psychotic drugs bind to sigma receptors with high affin-
ity. Haloperidol is among the most potent inhibitors of 5:
[³H](+)-SKF 10,047 binding, with a K_i of 4 nM (Tam di
and Cook 1984; Itzhak, 1988). Other antipsychot ity. Haloperidol is among the most potent inhibitors $[^{3}H](+)$ -SKF 10,047 binding, with a K_{i} of 4 nM (Tand Cook 1984; Itzhak, 1988). Other antipsychotic druthat possess moderate $(K_{i} < 1000 \text{ nM})$ to high poten includ [³H](+)-SKF 10,047 binding, with a K_i of 4 nM (Tam dic and Cook 1984; Itzhak, 1988). Other antipsychotic drugs cyc that possess moderate $(K_i < 1000 \text{ nM})$ to high potency con include perphenazine, $(-)$ -butaclamol, acet and Cook 1984; Itzhak, 1988). Other antipsychotic drugs
that possess moderate $(K_i < 1000 \text{ nm})$ to high potency
include perphenazine, $(-)$ -butaclamol, acetophenazine,
trifluoperazine, molindone, pimozide, thioridazine, and

BPTORS 357
between sigma receptors and antipsychotic drugs was
further strengthened by the finding that [³H]haloperidol EPTORS
between sigma receptors and antipsychotic drugs was
further strengthened by the finding that [³H]haloperido
binding is strongly reduced by the sigma ligands (+ BEPTORS
between sigma receptors and antipsychotic drugs was
further strengthened by the finding that [³H]haloperidol
binding is strongly reduced by the sigma ligands (+)-
SKF10,047, (+)-pentazocine, and (+)-cyclazocine (between sigma receptors and antipsychotic drugs was
further strengthened by the finding that [³H]haloperidol
binding is strongly reduced by the sigma ligands (+)-
SKF10,047, (+)-pentazocine, and (+)-cyclazocine (Tam
and between sigma receptors and antipsychotic drugs
further strengthened by the finding that [³H]halope
binding is strongly reduced by the sigma ligands
SKF10,047, (+)-pentazocine, and (+)-cyclazocine (
and Cook, 1984). In f further strengthened by the finding that $[^3H]$ haloperidol
binding is strongly reduced by the sigma ligands $(+)$ -
SKF10,047, $(+)$ -pentazocine, and $(+)$ -cyclazocine (Tam
and Cook, 1984). In fact, the sigma ligand $(+)$ -pent binding is strongly reduced by the sigma ligands $(+)$ -SKF10,047, $(+)$ -pentazocine, and $(+)$ -cyclazocine (Tam and Cook, 1984). In fact, the sigma ligand $(+)$ -pentazocine displaces $[^{3}H]$ haloperidol from its binding sites SKF10,047, $(+)$ -pentazocine, and $(+)$ -cyclazocine (Tand Cook, 1984). In fact, the sigma ligand $(+)$ -penticine displaces [³H]haloperidol from its binding site guinea pig brain about 10 times more potently than dopamine l d Cook, 1984). In fact, the sigma ligand $(+)$ -penta:
ne displaces $[^{3}H]$ haloperidol from its binding sites
inea pig brain about 10 times more potently than t
pamine ligand spiperone (Tam and Cook, 1984).
At first glance

cine displaces [³H]haloperidol from its binding sites in guinea pig brain about 10 times more potently than the dopamine ligand spiperone (Tam and Cook, 1984).
At first glance, these findings could lead to the conclusio guinea pig brain about 10 times more potently than the dopamine ligand spiperone (Tam and Cook, 1984).
At first glance, these findings could lead to the conclusion that $[^{3}H](+)-SKF$ 10,047 labels dopamine receptors.
Howeve dopamine ligand spiperone (Tam and Cook, 1984).
At first glance, these findings could lead to the conclu-
sion that $[^{3}H](+)-SKF$ 10,047 labels dopamine receptors.
However, this cannot be the case because the K_i values
o At first glance, these findings could lead to the conclusion that $[^{3}H](+)$ -SKF 10,047 labels dopamine receptors.
However, this cannot be the case because the K_{i} values of dopamine and apomorphine for $[^{3}H](+)$ -SKF sion that $[^{3}H](+)$ -SKF 10,047 labels dopamine receptors.
However, this cannot be the case because the K_i values
of dopamine and apomorphine for $[^{3}H](+)$ -SKF 10,047
are $>10,000$ nM, and $[^{3}H](+)$ -SKF 10,047-binding s However, this cannot be the case because the K_i values
of dopamine and apomorphine for $[^{3}H](+)$ -SKF 10,047
are >10,000 nM, and $[^{3}H](+)$ -SKF 10,047-binding sites
only sparsely populate dopamine-rich areas such as the
b are >10,000 nM, and [³H](+)-SKF 10,047-binding sites
only sparsely populate dopamine-rich areas such as the
basal ganglia (Gundlach et al., 1986; McLean and Weber,
1988; Sircar et al., 1986).
C. Structure-Activity Relat

Binding

88; Sircar et al., 1986).
As shown in table 1, many compounds have been tested
As shown in table 1, many compounds have been tested
their ability to displace sigma radioligands. However, C. Structure-Activity Relationships for Sigma Receptor
Binding
As shown in table 1, many compounds have been tested
for their ability to displace sigma radioligands. However,
until recently, few systematic SAR studies of s C. Structure-Activity Relationships for Sigma Receptor
Binding
As shown in table 1, many compounds have been tested
for their ability to displace sigma radioligands. However,
until recently, few systematic SAR studies of s Binding

As shown in table 1, many compounds have been tested

for their ability to displace sigma radioligands. However,

until recently, few systematic SAR studies of sigma re-

ceptor activity have been conducted. Large As shown in table 1, many compounds have been tested
for their ability to displace sigma radioligands. However,
until recently, few systematic SAR studies of sigma re-
ceptor activity have been conducted. Largent et al. (until recently, few systematic SAR studies of sigma receptor activity have been conducted. Largent et al. (1987) examined a large series of compounds to find structural determinants for sigma receptor affinity. In two SAR ceptor activity have been conducted. Largent et al. (1987)
examined a large series of compounds to find structural
determinants for sigma receptor affinity. In two SAR
studies (Wikstrom et al., 1987; Van de Waterbeemd et
a determinants for sigma receptor affinity. In two SAR
studies (Wikstrom et al., 1987; Van de Waterbeemd et
al., 1987), a series of OHBQ and 3-phenylpiperidines was
analyzed at the sigma site. Manallack and coworkers
(Manall studies (Wikstrom et al., 1987; Van de Waterbeemd et al., 1987), a series of OHBQ and 3-phenylpiperidines was analyzed at the sigma site. Manallack and coworkers (Manallack et al., 1988; Manallack and Beart, 1987) examined al., 1987), a series of OHBQ and 3-phenylpiperidines wanalyzed at the sigma site. Manallack and cowork (Manallack et al., 1988; Manallack and Beart, 198
examined structurally unrelated sigma-ligands and corribed distinct r analyzed at the sigma site. Manallack and coworkers (Manallack et al., 1988; Manallack and Beart, 1987) examined structurally unrelated sigma ligands and described distinct receptor models for both PCP and sigmalike drugs. (Manallack et al., 1988; Manallack and Beart, 1987)
examined structurally unrelated sigma ligands and de-
scribed distinct receptor models for both PCP and sigma-
like drugs. These studies revealed a wide degree of tol-
er examined structurally unrelated scribed distinct receptor model
like drugs. These studies reverance for both stereochemic
mands for the sigma receptor.
Several classes of compound ribed distinct receptor models for both PCP and sigma-
ie drugs. These studies revealed a wide degree of tol-
ance for both stereochemical and topographical de-
ands for the sigma receptor.
Several classes of compounds bin

sequently called the PCP receptor; Quirion et al., 1987). phenyl)piperidine $[(+)-3-PPP]$ (fig. 1, 3: R₁ = n-propyl,
3. Potent binding of antipsychotic drugs to sigma recep-
 $R_2 = 3-OH$;) and OHBQs (fig. 1, 4: R₁ = R₂ = like drugs. These studies revealed a wide degree of tolerance for both stereochemical and topographical demands for the sigma receptor.
Several classes of compounds bind to sigma receptors (fig. 1; table 1). These classes erance for both stereochemical and topographical de-
mands for the sigma receptor.
Several classes of compounds bind to sigma receptors
(fig. 1; table 1). These classes include: (a) the sigma
"opiates," including benzomor mands for the sigma receptor.
Several classes of compounds bind to sigma receptors
(fig. 1, table 1). These classes include: (*a*) the sigma
"opiates," including benzomorphans, such as pentazocine
(fig. 1, *1*: $R = 3,3$ -d Several classes of compounds bind to sigma recepto.
(fig. 1; table 1). These classes include: (*a*) the sigm
"opiates," including benzomorphans, such as pentazocin
(fig. 1, *1*: R = 3,3-dimethylallyl), and morphinans suc
 (fig. 1; table 1). These classes include: "
"opiates," including benzomorphans, such at (fig. 1, 1: R = 3,3-dimethylallyl), and mon
as dextrallorphan (fig. 1, 6: R₁ = H, R₂-a
logs of (+)- and (-)-cis-N-methyl-N-[1
nyl "opiates," including benzomorphans, such as pentazocine
(fig. 1, $l: R = 3,3$ -dimethylallyl), and morphinans such
as dextrallorphan (fig. 1, 6: $R_1 = H$, R_2 -allyl); (*b*) ana-
logs of (+)- and (-)-cis-N-methyl-N-[2-(1-pyr (fig. 1, 1: R = 3,3-dimethylallyl), and morphinans such
as dextrallorphan (fig. 1, 6: R₁ = H, R₂-allyl); *(b)* ana-
logs of (+)- and (-)-cis-N-methyl-N-[2-(1-pyrrolidi-
nyl)cyclohexyl]benzeneacetamide (fig. 1, *8*; su nyl)cyclohexyl]benzeneacetamide (fig. 1, 8; such as the
cis isomers of U50,488, $R_1 = R_2 = Cl$); (c) arylcyclohex-
ylamines, including PCP (fig. 1, 2: $R_1 = H$, R_2 , $R_3 =$
pentamethylene); (d) N,N'-diaryl-substituted guani cis isomers of U50,488, $R_1 = R_2 = Cl$); (c) ary
ylamines, including PCP (fig. 1, 2: $R_1 = H$,
pentamethylene); (d) N,N'-diaryl-substitute
dines such as DTG (fig. 1, 7: $R_1 = R_2 = 2$ -
phenylpiperidines, such as (+)-1-propyl-3ylamines, including PCP (fig. 1, 2: $R_1 = H$, R_2 , R_3 = pentamethylene); (d) N,N'-diaryl-substituted guani-
dines such as DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl); (e)
phenylpiperidines, such as (+)-1-propyl-3-(3-hydroxy-
 pentamethylene); (d) N,N'-diaryl-substituted guani-
dines such as DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl); (e)
phenylpiperidines, such as $(+)-1$ -propyl-3-(3-hydroxy-
phenyl)piperidine $[(+)-3-PPP]$ (fig. 1, 3: $R_1 = n$ -propyl,
 R_2 dines such as DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl);
phenylpiperidines, such as $(+)-1$ -propyl-3-(3-hydro:
phenyl)piperidine [$(+)-3$ -PPP] (fig. 1, 3: $R_1 = n$ -prop
 $R_2 = 3$ -OH;) and OHBQs (fig. 1, 4: $R_1 = R_2 = H$);
steroids, inc phenylpiperidines, such as $(+)-1$ -propyl-3-(3-hydroxy-
phenyl)piperidine $[(+)-3-PPP]$ (fig. 1, 3: $R_1 = n$ -propyl,
 $R_2 = 3-OH$;) and *OHBQs* (fig. 1, 4: $R_1 = R_2 = H$); (*f*)
steroids, including progesterone (fig. 1, *10*); (*g*) $R_2 = 3$ -OH;) and OHBQs (fig. 1, 4: $R_1 = R_2 = H$); (
steroids, including progesterone (fig. 1, 10); (g) butyr
phenones, including the neuroleptic haloperidol (fig.
5: $R_1 = Cl$, $R_2 = F$); and (h) (+)- and (-)-cis-N-[2-(3,
d steroids, including progesterone (fig. 1, *10*); (*g*) butyro-
phenones, including the neuroleptic haloperidol (fig. 1,
5: $R_1 = Cl$, $R_2 = F$); and (*h*) (+)- and (-)-cis-N-[2-(3,4-
dichlorophenyl)ethyl]-N-methyl-2-(1-pyrr congeners. $R_1 = Cl$, $R_2 = F$); and (h) (+)- and (-)-cis-N-[2-(3,4-chlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)
clohexylamine [fig. 1, (+)- and (-)-9, R = Me] and
ngeners.
Initially, we will focus on the SAR relationships that
cur

dichlorophenyl)ethyl]-N-methyl-2-(1-pyrrolidinyl)
cyclohexylamine [fig. 1, $(+)$ - and $(-)$ -9, R = Me] and
congeners.
Initially, we will focus on the SAR relationships that
occur within each class and then examine common fe cyclohexylamine [fig. 1, $(+)$ - and $(-)$ -9, $R = Me$] and
congeners.
Initially, we will focus on the SAR relationships that
occur within each class and then examine common fea-
tures that appear within unrelated classes of si

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⁹¹. Tetrahydrocannabinol
phenycyclidine; DADLE, [D-Ala^s, D-Leu^s]enkephalin; DAGO, [D-Ala^s, MePhe⁴, Gly-ol^s]enkephalin; DTG, N,N'-di(o-tolyl)guanidine; PCP,
phenycyclidine; DADLE, [D-Ala^s, D-Leu^s]enkephali ^{*} Results are *K*_i values expressed in nM, brain. In some cases *K*_i values were derived from IC₂₀ values and *K*₄ of labeling ligand. Abbreviations:
LSD, lysergic acid diethylamide; 8-OH-DPAT, 8-hydroxydipropyla (cyclohexyl)-N'-(adamant-1-yl)guanidine; AdTG, N-(o-tolyl)-N'-(adamant-1-yl)guanidine; DChG, N,N'-(dicyclohexyl)guanidine; BCP, hybergic accid distributions and the of DCH, the Phenycyclidine; DADLE, [D-Ala², D-Leu⁴]en di(2,6-methylphenyl)guanidine; D-Out-Dr Ari, D-diephalin; DAGO, [D-Ala², MePhe⁴, Gly-ol¹⁴]enkephalin; DTG, N,N'-di(phengl)guanidine; AdDG, [D-Ala², D-Leu⁴-Dr Main; DAGO, [D-Ala², MePhe⁴, Gly-ol¹⁴]enkephalin playtychame, DAD, 19-Amino-1,3H-dibenzo[d,f]-[1,3]-diazepine; DAG, N,N'-di(methyl)guanidine; DAG, N,N'-di(phenyl)guanidine; AdChG, N,N'-di(phenyl)guanidine; AdChG, N,N'-di(phenyl)guanidine; AdChG, N,N'-di(phenyl)guanidine; the complete of the main of the main of the state of the complete of the complete of the distribution di(2,6-methylphenyl)guanidine; NH₂-DTG, N-(o-tolyl)-N'-(4-amino-2-methylphenyl)guanidine; DPG, N,N'-di(phenyl)guanidine; Bridge-DPG,
2-amino-1,3H-dibenzo[*d_af*]-[1,3]-diazepine; DMG, N,N'-di(methyl)guanidine; TCM, (1-(

1:Tam (1985). thienyi)cyclohexyl]piperidine; BD614, $(+/-)$ -cis-N-methyl-N-[2-(3,4-dichlorophenyl)ethyl]-2-(1-pyrrolidinyl)cyclohexylamine.
† Tam and Cook (1984).
‡ Tam (1985).
§ Su et al. (1988).
∏ Tam (1988).
† Weber et al. (1986). | **1 Tam (1985).**
| **1 Tam (1985).**
| **1 Tam (1983).**
| **1 Weber et al. (1986).**
| **1 Largent et al. (1984) # Su et al. (1988).
| Tam (1983).
f** Weber et al. (1986).
Largent et al. (1984).
** W. D. Bowen, unpub ***5 W. D. Bowen, unpublished data.** *tt* Contreras **et** al. (19884). **# Largent et al. (1984).**
** W. D. Bowen, unpublish
†† Contreras et al. (1988a).
‡‡ Contreras et al. (1988b).
§§ Ferris et al. (1986). **umpairs of the Secondity of the W. D. Bowen, unput

†† Contreras et al. (1986).

‡†** Contreras et al. (1986).
 §§ Ferris et al. (1986).

┃ Largent et al. (1988). II Largent et al. (1988).
II Campbell et al. (1989). **†† Contreras et al. (1988a).
‡‡ Contreras et al. (1988b).
§§** Ferris et al. (1988).
|∥ Largent et al. (1989).
¶ Campbell et al. (1989).
#∦ Roman et al. (1989). #1/ Roman **et** al. **(1989).**

*** de Costa et al. (1989).

ttt Matsumoto **et** al. (1990). **ttt de Costa et al. (1990).**

*** de Costa et al. (1989).

| † Matsumoto et al. (1990).

| ‡‡‡ de Costa et al. (1990).

| gands. A model for the sigma receptor derived from these

| nobservations will then be reviewed. the Matsumoto et al. (1990).
 tif de Costa et al. (1990).
 gands. A model for the sigma receptions will then be reviewed.
 I. Opiate-related compounds. Example

111 de Costa et al. (1990).
 **nds. A model for the sigma receptor derived from the

servations will then be reviewed.
** *1. Opiate-related compounds.* **Examination of the struces in fig. 1 suggests that the pharmacophore c** gands. A model for the sigma receptor derived from these nobservations will then be reviewed.

1. Opiate-related compounds. Examination of the struc-

tures in fig. 1 suggests that the pharmacophore common st

to most of t gands. A model for the sigma receptor derived from
observations will then be reviewed.
1. Opiate-related compounds. Examination of the
tures in fig. 1 suggests that the pharmacophore con
to most of the compounds is the 3observations will then be reviewed.
1. Opiate-related compounds. Examination of the structures in fig. 1 suggests that the pharmacophore common
to most of the compounds is the 3- and 4-phenylpiperi-
dine moiety. For examp

normetazocine (SKF 10,047; fig. 1, *1*: R = allyl) and other
sigma_opioid_benzomorphans (1)_clearly_reveals_a_4normetazocine (SKF 10,047; fig. 1, *1*: R = allyl) and other
sigma opioid benzomorphans (1) clearly reveals a 4-
phenylpiperidine part structure. A detailed qualitative normetazocine (SKF 10,047; fig. 1, $I: R =$ allyl) and other
sigma opioid benzomorphans (1) clearly reveals a 4-
phenylpiperidine part structure. A detailed qualitative
study of opioid compounds by Largent et al. (1987) normetazocine (SKF 10,047; fig. 1, $l: R =$ allyl) and other
sigma opioid benzomorphans (1) clearly reveals a 4-
phenylpiperidine part structure. A detailed qualitative
study of opioid compounds by Largent et al. (1987)
rev normetazocine (SKF 10,047; fig. 1, $l: R =$ allyl) and other sigma opioid benzomorphans (1) clearly reveals a ophenylpiperidine part structure. A detailed qualitativ study of opioid compounds by Largent et al. (1986) reveal sigma opioid benzomorphans (1) clearly reveals a 4-
phenylpiperidine part structure. A detailed qualitative
study of opioid compounds by Largent et al. (1987)
revealed that the determinants for sigma receptor activ-
ity di

PHARMACOLOGICAL REVIEWS

FIG. **1.** Structures **of** selected **sigma ligands (see** text).

FIG. 1. Structures of selected sigma ligands (see text).
receptors. Intact ringed opiate-related compounds, such
as morphine and naloxone, have negligible affinity for
sigma receptors. The highest affinity among opioids oc receptors. Intact ringed opiate-related compounds, such
as morphine and naloxone, have negligible affinity for
sigma receptors. The highest affinity among opioids oc-
curs with the ring C opened analogs lacking a 4,5-epoxi receptors. Intact ringed opiate-related compounds, such
as morphine and naloxone, have negligible affinity for
sigma receptors. The highest affinity among opioids oc-
curs with the ring C opened analogs lacking a 4,5-epoxi as morphine and naloxone, have negligible affinity for
sigma receptors. The highest affinity among opioids oc-
curs with the ring C opened analogs lacking a $4,5$ -epoxide
ring, or benzomorphans (fig. 1, 1). Also, the morp sigma receptors. The highest affinity among opioids occurs with the ring C opened analogs lacking a 4,5-epoxide
ring, or benzomorphans (fig. 1, 1). Also, the morphinans
(fig. 1, 6), which lack C ring substituents and 4,5curs with the ring C opened analogs lacking a $4,5$ -epoxide
ring, or benzomorphans (fig. 1, 1). Also, the morphinans
(fig. 1, 6), which lack C ring substituents and $4,5$ -epoxide
bridge, show high affinity for sigma recep ring, or benzomorphans (fig. 1, 1). Also, the morphinans

(fig. 1, 6), which lack C ring substituents and 4,5-epoxide

bridge, show high affinity for sigma receptors. With

cos

opiate-related compounds, the sigma recepto bridge, show high affinity for sigma receptors. With opiate-related compounds, the sigma receptor (at least the major subtype) displays reverse stereoselectivity to the classical opiate receptors. The $(+)$ -benzomorphans (bridge, show high affinity for sigma receptors. With opiate-related compounds, the sigma receptor (at least the major subtype) displays reverse stereoselectivity to the classical opiate receptors. The $(+)$ -benzomorphans (f opiate-related compounds, the sigma receptor (at least
the major subtype) displays reverse stereoselectivity to
the classical opiate receptors. The $(+)$ -benzomorphans
(fig. 1, 1) display highest affinity for sigma recepto the maj
the clas
(fig. 1,
followed
1, 6).
Of gre e classical opiate receptors. The $(+)$ -benzomorphang. 1, 1) display highest affinity for sigma receptor
lowed closely by the more bulky $(+)$ -morphinans (fi
6).
Of greater importance than relative bulk of the mole-
le is r (fig. 1, 1) display highest affinity for sigma receptors fieldowed closely by the more bulky (+)-morphinans (fig. U₅ the nole-
1, 6).
Of greater importance than relative bulk of the mole-
cule is relative lipophilicity

followed closely by the more bulky $(+)$ -morphinans (fig. U50
1, 6). Studies of greater importance than relative bulk of the mole-
cule is relative lipophilicity of certain regions of the exh
molecule. Removal of the epoxy 1, 6).
Of greater importance than relative bulk of the
cule is relative lipophilicity of certain regions
molecule. Removal of the epoxy bridge, as well
hydroxy and 6-keto groups of naloxone $[IC_{50}$ vs. $[^{3}]$
3-PPP > 100 Of greater importance than relative bulk of the mole-
cule is relative lipophilicity of certain regions of the
molecule. Removal of the epoxy bridge, as well as 3 it
hydroxy and 6-keto groups of naloxone (IC₅₀ vs. $[^{3}$ molecule. Removal of the epoxy bridge, as well as 3
hydroxy and 6-keto groups of naloxone (IC₅₀ vs. $[^{3}H]$ (+)-
3-PPP > 100,000 nM), results in the greater potency of
levallorphan (IC₅₀ vs. $[^{3}H]$ (+)-3-PPP > 1890 n $3-PPP > 100,000$ nM), results in the greater potency of hydroxy and 6-keto groups of naloxone $(IC_{50} \text{ vs. }[^{3}H](+))$
3-PPP > 100,000 nM), results in the greater potency of
levallorphan $(IC_{50} \text{ vs. }[^{3}H](+)\cdot3\cdot\text{PPP} > 1890 \text{ nM})$. Furthermore, the more lipophilic N-allyl group 3-PPP > 100,000 nM), results in the greater potency of levallorphan (IC₅₀ vs. [³H](+)-3-PPP > 1890 nM). Furthermore, the more lipophilic N-allyl group of levallorphan may account for its greater potency, when compared levallorphan (IC₅₀ vs. [³H](+)-3-PPP > 1890 nM). Fur-
thermore, the more lipophilic N-allyl group of levallor-labe
phan may account for its greater potency, when com-
sele-
pared with levorphanol (IC₅₀ > 10,000 nM), phan may account for its greater potency, when com-
pared with levorphanol $(IC_{60} > 10,000 \text{ nm})$, which pos-
sesses an N-methyl group. Dextrallorphan (fig. 1, 6: R₁ si
= H, R₂ = allyl), the "unnatural" or (+)-isomer o

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SIGMA RECEPTORS
receptors (IC₅₀ = 153 nM) than levallorphan itself. How-
ever, dextrallorphan shows low but significant affinity EPTORS 361
receptors (IC₅₀ = 153 nM) than levallorphan itself. How-
ever, dextrallorphan shows low but significant affinity
for the PCP-binding site ($K_i = 5680$ nM). Addition of FREPTORS 361
receptors ($IC_{50} = 153$ nM) than levallorphan itself. How-
ever, dextrallorphan shows low but significant affinity
for the PCP-binding site $(K_i = 5680$ nM). Addition of
still larger N-alkyl side chains (such a receptors (IC₅₀ = 153 nM) than levallorphan itself. Ho
ever, dextrallorphan shows low but significant affini
for the PCP-binding site ($K_i = 5680$ nM). Addition
still larger N-alkyl side chains (such as 3,3-dimethylall
a receptors (IC₅₀ = 153 nM) than levallorphan itself. How-
ever, dextrallorphan shows low but significant affinity
for the PCP-binding site (K_i = 5680 nM). Addition of
still larger N-alkyl side chains (such as 3,3-dimet ever, dextrallorphan shows low but significant affinity
for the PCP-binding site $(K_i = 5680 \text{ nm})$. Addition of
still larger N-alkyl side chains (such as 3,3-dimethylallyl
and phenethyl) to dextrallorphan might be expected still larger N-alkyl side chains (such as 3,3-dimethylallyl
and phenethyl) to dextrallorphan might be expected to
result in even higher potency at sigma receptors and
reduced potency at the PCP-binding site.
Replacement of ill larger N-alkyl side chains (such as 3,3-dimethyl
d phenethyl) to dextrallorphan might be expecte
sult in even higher potency at sigma receptors
duced potency at the PCP-binding site.
Replacement of the phenolic hydrox

(-)-9: R-Me (+)-9: R-Me 10: Progesterone lipophilicity of the side chain. Similarly, the more lipo-
Fro. 1. Structures of selected sigma ligands (see text).
Fro. 1. Structures of selected sigma ligands (see text).
(ig. 1, sigma receptors. The highest affinity among opioids α -
general in the negligible and negligible and negligible and intervention cyclazocine, result in considerably lowered affinities (1%) and phenethyl) to dextrallorphan might be expected to
result in even higher potency at sigma receptors and
reduced potency at the PCP-binding site.
Replacement of the phenolic hydroxyl of dextrallor-
phan with an O-methyl result in even higher potency at sigma receptors and
reduced potency at the PCP-binding site.
Replacement of the phenolic hydroxyl of dextrallor-
phan with an O-methyl (fig. 1, 6: $R_1 = Me$, $R_2 =$ allyl)
either fails to af reduced potency at the PCP-binding site.
Replacement of the phenolic hydroxyl of dextrallor-
phan with an O-methyl (fig. 1, 6: $R_1 = Me$, $R_2 =$ allyl)
either fails to affect affinity at sigma receptors, indicating
that any Replacement of the phenolic hydroxyl of dextrallor-
phan with an O-methyl (fig. 1, 6: R₁ = Me, R₂ = allyl)
either fails to affect affinity at sigma receptors, indicating
that any hydrogen bonding at this site in the m phan with an O-methyl (fig. 1, 6: $R_1 = Me$, $R_2 =$ allyl)
either fails to affect affinity at sigma receptors, indicating
that any hydrogen bonding at this site in the molecule is
not as important for sigma receptor affinit either fails to affect affinity at sigma receptors, indicating
that any hydrogen bonding at this site in the molecule is
not as important for sigma receptor affinity as it is for
opiate receptor binding in the $(-)$ - or na that any hydrogen bonding at this site in the molecule is
not as important for sigma receptor affinity as it is for
opiate receptor binding in the $(-)$ - or natural series
(unpublished observation). Among the $(+)$ -benzomor not as important for sigma receptor affinity as it is for
opiate receptor binding in the $(-)$ - or natural series
(unpublished observation). Among the $(+)$ -benzomor-
phans (fig. 1, 1), replacement of the N-allyl group of opiate receptor binding in the $(-)$ - or natural series
(unpublished observation). Among the $(+)$ -benzomor-
phans (fig. 1, *1*), replacement of the N-allyl group of $(+)$ -
SKF 10,047 with the more bulky and lipophilic N-3,3 phans (fig. 1, 1), replacement of the N-allyl group of (+)-
SKF 10,047 with the more bulky and lipophilic N-3,3-
dimethylallyl group of (+)-pentazocine (fig. 1, 1: R₁ =
3,3-dimethylallyl) results in a 53-fold increase i SKF 10,047 with the more bulky and lipophilic N-3,3-
dimethylallyl group of (+)-pentazocine (fig. 1, 1: R₁ =
3,3-dimethylallyl) results in a 53-fold increase in sigma
receptor potency $[IC_{50} = 70$ nM for (+)-SKF10,047 v dimethylallyl group of (+)-pentazocine (fig. 1, 1: R₁ = 3,3-dimethylallyl) results in a 53-fold increase in sigma
receptor potency $[IC_{60} = 70 \text{ nM}$ for (+)-SKF10,047 versus
 $IC_{60} = 1.3 \text{ nM}$ for (+)-pentazocine deter 3,3-dimethylallyl) results in a 53-fold increase in sigma
receptor potency $[IC_{50} = 70 \text{ nM}$ for (+)-SKF10,047 versus
 $IC_{50} = 1.3 \text{ nM}$ for (+)-pentazocine determined in guinea
pig brain versus [³H](+)-3-PPP]. A simil $IC_{50} = 1.3$ nM for (+)-pentazocine determined in guinea
pig brain versus [³H](+)-3-PPP]. A similar potency dif-
ference is seen when racemic mixtures of pentazocine
and SKF 10,047 are compared (Largent et al., 1987).
F pig brain versus $[{}^3H](+)$ -3-PPP]. A similar potency difpig brain versus $[{}^{3}H](+)-3-PPP$]. A similar potency difference is seen when racemic mixtures of pentazocine and SKF 10,047 are compared (Largent et al., 1987). Furthermore, unlike $(+)\text{-}SKF$ 10,047, $(+)\text{-}pentazocine$ fails to in ference is seen when racemic mixtures of pentazocir
and SKF 10,047 are compared (Largent et al., 1987
Furthermore, unlike $(+)$ -SKF 10,047, $(+)$ -pentazocir
fails to interact with PCP sites (Rothman et al., 1988
These large and SKF 10,047 are compared (Largent et al., 1987).
Furthermore, unlike $(+)$ -SKF 10,047, $(+)$ -pentazocine
fails to interact with PCP sites (Rothman et al., 1988).
These large differences in comparable potency and selec-
t Furthermore, unlike $(+)$ -SKF 10,047, $(+)$ -pentazocine
fails to interact with PCP sites (Rothman et al., 1988).
These large differences in comparable potency and selec-
tivity of $(+)$ -pentazocine compared with $(+)$ -SKF 10, fails to interact with PCP sites (Rothman et al., 1988)
These large differences in comparable potency and selec-
tivity of (+)-pentazocine compared with (+)-SKF 10,04⁷
can only be accounted for by the increased size and These large differences in comparable potency and selectivity of $(+)$ -pentazocine compared with $(+)$ -SKF 10,04 can only be accounted for by the increased size an lipophilicity of the side chain. Similarly, the more lipoph tivity of $(+)$ -pentazocine compared with $(+)$ -SKF 10,047
can only be accounted for by the increased size and
lipophilicity of the side chain. Similarly, the more lipo-
philic pi-bonding N-phenethyl of $(+/-)$ -phenazocine
(f can only be accounted for by the increased size an lipophilicity of the side chain. Similarly, the more lipophilic pi-bonding N-phenethyl of $(+/-)$ -phenazocine (fig. 1, 1: R = phenethyl) accounts for its comparably potency lipophilicity of the side chain. Similarly, the more lipophilic pi-bonding N-phenethyl of $(+/-)$ -phenazocine (fig. 1, 1: R = phenethyl) accounts for its comparable potency to $(+/-)$ -pentazocine at sigma receptors (Largent e philic pi-bonding N-phenethyl of $(+/-)$ -phenazo (fig. 1, $l: R =$ phenethyl) accounts for its compare potency to $(+/-)$ -pentazocine at sigma receptors () gent et al., 1987). In contrast, lipophilic keto groups seen in the 8-p (fig. 1, 1: R = phenethyl) accounts for its comparable
potency to $(+/-)$ -pentazocine at sigma receptors (Largent et al., 1987). In contrast, lipophilic keto groups, as
seen in the 8-position in ketocyclazocine and ethylket phans (ig. 1, 1, replacement of the N-allyl group of (+)-
pentazocine (fig. 1, 1. R₁ = 3,3-dimethylallyl group of (+)-pentazocine (fig. 1, 1: R₁ = 3,3-dimethylallyl) results in a 53-fold increase in sigma chigh and in gent et al., 1987). In contrast, lipophilic keto groups, as
seen in the 8-position in ketocyclazocine and ethylketo-
cyclazocine, result in considerably lowered affinities (1%
that of pentazocine). In light of the high aff seen in the 8-position in ketocyclazocine and ethylketo-
cyclazocine, result in considerably lowered affinities (1%
that of pentazocine). In light of the high affinity and
selectivity of (+)-pentazocine for sigma receptors

2-(1-pentazocine for sigma receptors,
 2.2-(1-Pyrrolidinyl)cyclohexyll benzeneacetamides a
 2.2-(1-Pyrrolidinyl)cyclohexyll benzeneacetamides a
 2-(1-pyrrolidinyl)cyclohexylamines. The recently identied sigma recep Costa et al. (1989b) synthesized $[^{3}H](+)$ -pentazocine as
a selective sigma receptor probe.
2. 2- $[(1-Pyrrolidinyl/cyclohexylbenzeneacetamides and$
2- $(1-pyrrolidinyl/cyclohexylamines)$. The recently identi-
fied sigma receptor activity in the *cis* diastereoisomer a selective sigma receptor probe.

2. 2- $[(1-Pyrrolidinyl/cyclohexyllbenzeneacetamides and
2-(1-pyrrolidinyl/cyclohexylamines. The recently identi-
fied sigma receptor activity in the cis diastereoisomers of
U50,488 (fig. 1, 8: $R_1 = R_2 = Cl$) was used in a large SAR
study to identify still more potent and selective com-$ 2. 2- $[(1-Pyrrolidinyl)cyclohexyllbenzeneacetamides an
2-(1-pyrrolidinyl/cyclohexylamines. The recently identified sigma receptor activity in the *cis* diastereoisomers c
U50,488 (fig. 1, 8: $R_1 = R_2 = C1$) was used in a large SAL
study to identify still more potent and selective com
pounds (de Costa et al., 1989a; 1990). 1R,2S-(+)-U50,48$ 2-(1-pyrrolidinyl)cyclohexylamines. The recently identified sigma receptor activity in the cis diastereoisomers of U50,488 (fig. 1, 8: $R_1 = R_2 = Cl$) was used in a large SAR study to identify still more potent and selectiv fied sigma receptor activity in the *cis* diastereoisomers of U50,488 (fig. 1, 8: $R_1 = R_2 = Cl$) was used in a large SAR study to identify still more potent and selective compounds (de Costa et al., 1989a; 1990). $1R,2S-(+)$ -U50,488 (fig. 1, 8: $R_1 = R_2 = Cl$) was used in a large SAR
study to identify still more potent and selective com-
pounds (de Costa et al., 1989a; 1990). $1R,2S-(+)$ -U50,488
exhibited a K_i of 250 nM against $[^{3}H](+)$ -3-PPP, study to identify still more potent and selective com-
pounds (de Costa et al., 1989a; 1990). $1R,2S-(+)$ -U50,488
exhibited a K_i of 250 nm against $[^{3}H](+)$ -3-PPP, whereas
its enantiomer $1S,2R-(-)$ -U50,488 exhibited a K_i pounds (de Costa et al., 1989a; 1990). $1R,2S-(+)$ -U50
exhibited a K_i of 250 nm against $[^{3}H](+)$ -3-PPP, whe
its enantiomer $1S,2R-(-)$ -U50,488 exhibited a K_i o
nm in guinea pig brain. Although the compounds fa
to intera exhibited a K_i of 250 nM against $[^{3}H](+)$ -3-PPP, whereas
its enantiomer $1S,2R-(-)$ -U50,488 exhibited a K_i of 81
nM in guinea pig brain. Although the compounds failed
to interact with kappa receptors labeled by $[^{3}H$ nM in guinea pig brain. Although the compounds failed
to interact with kappa receptors labeled by $[^{3}H]$ brema-
zocine and interacted only weakly with kappa receptors
labeled by $(-)-[^{3}H]U69,593$, these diastereomers wer nM in guinea pig brain. Although the compounds failed
to interact with kappa receptors labeled by $[^{3}H]$ brema-
zocine and interacted only weakly with kappa receptors
labeled by $(-)-[^{3}H]U69,593$, these diastereomers wer to interact with kappa receptors labeled by $[^{3}H]$ brema-
zocine and interacted only weakly with kappa receptors
labeled by $(-)$ - $[^{3}H]U69,593$, these diastereomers were
selective for the sigma site to the extent that t zocine and interacted only weakly with kappa receptors
labeled by $(-)-[^3H]U69,593$, these diastereomers were
selective for the sigma site to the extent that they also
failed to interact with PCP or D_2 -dopamine receptors labeled by $(-)$ - $[$ ³H]l
selective for the sign
failed to interact wit
sites that commonly
Costa et al., 1989a).
The 3- and 4-chloi lective for the sigma site to the extent that they also
iled to interact with PCP or D_2 -dopamine receptors,
ces that commonly cross-react with sigma ligands (de
osta et al., 1989a).
The 3- and 4-chlorine atoms of the

WALKER ET AL.
362 **WALKER ET AL.**
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364 **WALKER ET AL.**
364 **WALKER ET AL.**
364 **WALKER ET AL.**
364 **W** enhanced potency and selectivity at the sigma receptor WALKER
of U50,488 could be replaced with a naphthyl ring (fig.
1, 8: R_1 , R_2 = benzo) to give compounds with further
enhanced potency and selectivity at the sigma receptor
(1S,2R-(-)-enantiomer, $K_i = 8.66$ nM against of U50,488 could be replaced with a naphthyl ring (fig.
1, 8: R_1, R_2 = benzo) to give compounds with further
enhanced potency and selectivity at the sigma receptor
(1S,2R-(-)-enantiomer, $K_i = 8.66$ nM against $[^{3}H](+)$ of U50,488 could be replaced with a naphthyl ring (fig. rel
1, 8: R_1, R_2 = benzo) to give compounds with further
enhanced potency and selectivity at the sigma receptor
(1S,2R-(-)-enantiomer, $K_i = 8.66$ nM against $[^{3}$ 1, 8: R_1, R_2 = benzo) to give compounds with further as
enhanced potency and selectivity at the sigma receptor
(1S,2R-(-)-enantiomer, $K_i = 8.66$ nM against [³H](+)-3- y.
PPP; 1R,2S-(+)-enantiomer, $K_i = 1372$ nM). Bec enhanced potency and selectivity at the sigma receptor $(1S, 2R - (-)$ -enantiomer, $K_i = 8.66$ nM against $[^{3}H](+)-3-$ PPP; $1R, 2S- (+)$ -enantiomer, $K_i = 1372$ nM). Because the compound devoid of lipophilic groups in the 3- and (1S,2R-(-)-enantiomer, $K_i = 8.66$ nM against $[{}^3H](+)$ -3-yld PPP; 1R,2S-(+)-enantiomer, $K_i = 1372$ nM). Because the R₂ compound devoid of lipophilic groups in the 3- and 4- P(positions (fig. 1, 8: R₁ = R₂ = H) showe PPP; $1R,2S-(+)$ -enantiomer, $K_i = 1372$ nM). Because the
compound devoid of lipophilic groups in the 3- and 4
positions (fig. 1, 8: $R_1 = R_2 = H$) showed a considerable
decrease in potency ($IC_{60} = 1155$ nM) compared with the compound devoid of lipophilic groups in the 3- and 4-
positions (fig. 1, 8: $R_1 = R_2 = H$) showed a considerable
decrease in potency (IC₅₀ = 1155 nM) compared with the
3,4-dichloro- and naphthyl analogs, it appears that l positions (fig. 1, 8: $R_1 = R_2 = H$) showed a considerable 1
decrease in potency (IC₅₀ = 1155 nM) compared with the ta
3,4-dichloro- and naphthyl analogs, it appears that lipo-
philic groups in the 3- and 4-positions on t decrease in poten
3,4-dichloro- and
philic groups in
ring occupy a li
binding affinity.
The most dran 4-dichloro- and naphthyl analogs, it appears that lipo-
illic groups in the 3- and 4-positions on the benzene
ng occupy a lipophilic pocket that allows increased
nding affinity.
The most dramatic increase in sigma receptor philic groups in the 3- and 4-positions on the benzene varing occupy a lipophilic pocket that allows increased co
binding affinity.
The most dramatic increase in sigma receptor-binding affinity occurred when the amide func

ring occupy a lipophilic pocket that allows increased complicing affinity. The most dramatic increase in sigma receptor-binding and affinity occurred when the amide function of the cis politicate discrepance of U50,488 wa binding affinity. $=$
The most dramatic increase in sigma receptor-binding aff
affinity occurred when the amide function of the *cis* pip
diastereomers of U50,488 was reduced to a tertiary amine H)
to give diamines $1R,2S$ The most dramatic increase in sigma receptor-binding
affinity occurred when the amide function of the cis
diastereomers of U50,488 was reduced to a tertiary amine
to give diamines $1R,2S-(+)$ -9 and $1S,2R-(-)$ -9, both
member affinity occurred when the amide function of the diastereomers of U50,488 was reduced to a tertiary ami
to give diamines $1R,2S-(+)$ -9 and $1S,2R-(-)$ -9, bo
members of a new class of highly potent and selecti
sigma ligands (diastereomers of U50,488 was reduced to a tertiary amine
to give diamines $1R,2S-(+)$ -9 and $1S,2R-(-)$ -9, both
members of a new class of highly potent and selective
sigma ligands (de Costa et al., 1990). $1S,2R-(-)$ -9 exhib-
 to give diamines $1R,2S- (+)-9$ and $1S,2R- (-)-9$, both remembers of a new class of highly potent and selective a
sigma ligands (de Costa et al., 1990). $1S,2R- (-)-9$ exhib-
ited a K_i of 1.3 nM against $[^{3}H](+)$ -3-PPP, represe members of a new class of highly potent and selective
sigma ligands (de Costa et al., 1990). $1S,2R-(-)$ -9 exhib-
ited a K_i of 1.3 nM against $[^{3}H](+)$ -3-PPP, representing
a 60-fold increase in sigma receptor potency com sigma ligands (de Costa et al., 1990). $1S, 2R-(-)$ -9 exhibited a K_i of 1.3 nM against $[^{3}H](+)$ -3-PPP, representing de a 60-fold increase in sigma receptor potency compared to its amide precursor $[1S, 2R-(-)$ -8: $R_1 = R_$ ited a K_i of 1.3 nM against $[^{3}H](+)$ -3-PPP, representing
a 60-fold increase in sigma receptor potency compared
to its amide precursor $[1S,2R-(-)-8: R_1 = R_2 = C]$.
Similarly, $1R,2S-(+)-9$ $(K_1=6$ nM) exhibited a 40-fold
incr a 60-fold increase in sigma receptor potency compared
to its amide precursor $[1S, 2R-(-)-8: R_1 = R_2 = \text{Cl}]$.
Similarly, $1R, 2S-(+)-9$ $(K_i=6 \text{ nM})$ exhibited a 40-fold
increase in potency compared to its amide precursor.
These to its amide precursor $[1S,2R-(-)-8: R_1 = R_2 = C]$. a
Similarly, $1R,2S-(+)-9$ ($K_i=6$ nM) exhibited a 40-fold b
increase in potency compared to its amide precursor. a
These enormous increases in potency for (+)- and (-)-
9, wh Similarly, $1R,2S-(+)$ -9 $(K_i=6 \text{ nm})$ exhibited a 40-fold bincrease in potency compared to its amide precursor.
These enormous increases in potency for $(+)$ - and $(-)$ - p.
9, when compared with their precursors, can be explai increase in potency compared to its amide precursor.
These enormous increases in potency for $(+)$ - and $(-)$ -
9, when compared with their precursors, can be explained
by additional hydrogen bonding from the added amine
fun These enormous increases in potency for $(+)$ - and $(-)$ - pl
9, when compared with their precursors, can be explained bi
by additional hydrogen bonding from the added amine
function. Compounds $(+)$ - and $(-)$ -9 failed to int 9, when compared with their precursors, can be explained
by additional hydrogen bonding from the added amine
function. Compounds $(+)$ - and $(-)$ -9 failed to interact
with any of the other receptor systems tested, making
th by additional hydrogen bonding from the added aminfunction. Compounds $(+)$ - and $(-)$ -9 failed to interace with any of the other receptor systems tested, making them the most potent and selective known sigma recepto ligands with any of the other receptor systems tested, making
them the most potent and selective known sigma receptor
ligands (de Costa et al., 1990; Bowen et al., 1990b; Mat-
sumoto et al., 1990).
The SAR of compounds related to

them the most potent and selective known sigma receptor
ligands (de Costa et al., 1990; Bowen et al., 1990b; Mat-
sumoto et al., 1990). (IC
The SAR of compounds related to $(+)$ - and $(-)$ -9 have Ch
been extended by investi ligands (de Costa et al., 1990; Bowen et al., 1990b; Matsumoto et al., 1990).
sumoto et al., 1990).
The SAR of compounds related to $(+)$ - and $(-)$ -9 have
been extended by investigating the effect of changing the
nitrogen sumoto et al., 1990). (IC

The SAR of compounds related to $(+)$ - and $(-)$ -9 have

been extended by investigating the effect of changing the

mitrogen substituent. Preliminary results suggest that

some loss of affinity oc The SAR of compounds related to $(+)$ - and $(-)$ -9 have
been extended by investigating the effect of changing the
nitrogen substituent. Preliminary results suggest that
some loss of affinity occurs by replacing methyl with
 been extended by investigating the effect of changing the whitrogen substituent. Preliminary results suggest that the some loss of affinity occurs by replacing methyl with a study, propyl, or cyclopropyl methyl (Radesca et nitrogen substituent. Preliminary results suggest that tolsome loss of affinity occurs by replacing methyl with are ethyl, propyl, or cyclopropyl methyl (Radesca et al., The results of this study indicate that the nitrogen some loss of affinity occurs by replacing methyl with
ethyl, propyl, or cyclopropyl methyl (Radesca et al.,
1990). The results of this study indicate that the nitrogen
substituent for potent sigma receptor-binding affinity ethyl, propyl, or cyclopropyl methyl (Radesca et 1990). The results of this study indicate that the nitro, substituent for potent sigma receptor-binding affinit the methyl group. This result appears to be in contraction th 1990). The results of this study
substituent for potent sigma re
the methyl group. This result to
to the trend observed with N-a
zomorphans and $(+)$ -morphina
A clear finding from the SAI bstituent for potent sigma receptor-binding affinity is the methyl group. This result appears to be in contrast vote the trend observed with N-alkyl-substituted $(+)$ -ben-binorphans and $(+)$ -morphinans.
A clear finding fro

the methyl group. This result appears to be in contrast vo
to the trend observed with N-alkyl-substituted (+)-ben-
zomorphans and (+)-morphinans. pli
A clear finding from the SAR studies described above wh
is that sigma re to the trend observed with N-alkyl-substituted (+)-ben-
zomorphans and (+)-morphinans.
A clear finding from the SAR studies described above
is that sigma receptors and kappa receptors bind the
same opiates. However, kappa zomorphans and $(+)$ -morphinans.
A clear finding from the SAR studies described above
is that sigma receptors and kappa receptors bind the
same opiates. However, kappa receptors prefer one iso-
mer, and sigma receptors pre A clear finding from the SAR studies described above wis that sigma receptors and kappa receptors bind the oral same opiates. However, kappa receptors prefer one isomer, and sigma receptors prefer the other. Whereas posta is that sigma receptors and kappa receptors bind the same opiates. However, kappa receptors prefer one isomer, and sigma receptors prefer the other. Whereas kappa opiate receptors bind $(-)$ -benzomorphans, sigma receptors same opiates. However, kappa receptors prefer one isomer, and sigma receptors prefer the other. Whereas kappa opiate receptors bind $(-)$ -benzomorphans. Sigma receptors bind $(+)$ -benzomorphans. Examples are $(-)$ -SKF 10,047, mer, and sigma receptors prefer the other. Whereas
kappa opiate receptors bind $(-)$ -benzomorphans, sigma
receptors bind $(+)$ -benzomorphans. Examples are $(-)$ -
SKF 10,047, $(-)$ -pentazocine, $(-)$ -cyclazocine, and $(-)$ -
ethy kappa opiate receptors bind $(-)$ -benzomorphans, sigma
receptors bind $(+)$ -benzomorphans. Examples are $(-)$ -
SKF 10,047, $(-)$ -pentazocine, $(-)$ -cyclazocine, and $(-)$ -
ethylketocyclazoine, which bind kappa opiate receptors; receptors bind (+)-benzomorphans. Examples are (--)-SKF 10,047, (-)-pentazocine, (-)-cyclazocine, and (-)-
ethylketocyclazoine, which bind kappa opiate receptors;
their (+)-enantiomers bind to sigma receptors. Another
exam SKF 10,047, $(-)$ -pentazocine, $(-)$ -cyclazocine, and $(-)$ -
ethylketocyclazoine, which bind kappa opiate receptors; w
their $(+)$ -enantiomers bind to sigma receptors. Another example is found with *cis* and *trans* isomers o ethylketocyclazoine, which bind kappa opiate receptors; wheir (+)-enantiomers bind to sigma receptors. Another example is found with *cis* and *trans* isomers of U50,488. SW whereas the *trans* isomers show preference for their $(+)$ -enantiomers bind to sigma receptors. Another example is found with *cis* and *trans* isomers of U50,488.
Whereas the *trans* isomers show preference for kappa gopiate receptors, the *cis* isomers show preferenc example is found with *cis* and *trans* isomers of U50,488.
Whereas the *trans* isomers show preference for kappa
opiate receptors, the *cis* isomers show preference for
sigma receptors. Thus, in two chemically unrelated
c Whereas the *trans* isomers show preference for kappa
opiate receptors, the *cis* isomers show preference for is
sigma receptors. Thus, in two chemically unrelated e
classes of compounds, different isomers show preference

relationship between the topography of the kappa opiate
and sigma receptor-binding sites.
3. Phencyclidine-related compounds. Among the phen-

ET AL.
relationship between the topography of the kappa opia
and sigma receptor-binding sites.
3. Phencyclidine-related compounds. Among the phen-
ylcyclohexylamines (fig. 1, 2), PCP (fig. 1, 2: R₁ = 1 relationship between the topography of the kappa opiate
and sigma receptor-binding sites.
3. *Phencyclidine-related compounds*. Among the phen-
ylcyclohexylamines (fig. 1, 2), PCP (fig. 1, 2: $R_1 = H$,
 $R_2, R_3 =$ pentameth relationship between the topography of the kappa opiate
and sigma receptor-binding sites.
3. Phencyclidine-related compounds. Among the phen-
ylcyclohexylamines (fig. 1, 2), PCP (fig. 1, 2: $R_1 = H$,
 $R_2, R_3 =$ pentamethyl and sigma receptor-binding sites.

3. Phencyclidine-related compounds. Among the phen-

ylcyclohexylamines (fig. 1, 2), PCP (fig. 1, 2: $R_1 = H$,
 $R_2, R_3 =$ pentamethylene) exhibits greater affinity for

PCP receptors tha R_2 , R_3 = pentamethylene) exhibits greater affinity for
PCP receptors than it does for sigma receptors $[K_i =$
1,014 nM versus [³H](+)-3-PPP]. Unfortunately, no sys-
tematic studies of this compound have been complete R_2, R_3 = pentamethylene) exhibits greater affinity f
PCP receptors than it does for sigma receptors $[K_i]$
1,014 nM versus [³H](+)-3-PPP]. Unfortunately, no sy
tematic studies of this compound have been complet
at thi PCP receptors than it does for sigma receptors $[K_i = 1,014 \text{ nm}$ versus $[^{3}H](+)$ -3-PPP]. Unfortunately, no systematic studies of this compound have been completed at this time. However, recent data (unpublished observatio 1,014 nM versus $[^{3}H](+)$ -3-PPP]. Unfortunately, no systematic studies of this compound have been completed at this time. However, recent data (unpublished observations) indicate that decreasing the lipophilicity of the c tematic studies of this compound have been completed
at this time. However, recent data (unpublished obser-
vations) indicate that decreasing the lipophilicity of the
compound by addition of a 3-hydroxy group (fig. 1, 2: at this time. However, recent data (unpublished observations) indicate that decreasing the lipophilicity of the compound by addition of a 3-hydroxy group (fig. 1, 2: R₁ = 3-OH, R₂,R₃ = pentamethylene) results in los vations) indicate that decreasing the lipophilicity of the compound by addition of a 3-hydroxy group (fig. 1, 2: R_1 = 3-OH, R_2, R_3 = pentamethylene) results in loss of affinity for sigma receptors. Similarly, openin = 3-OH, R_2 , R_3 = pentamethylene) results in loss of affinity for sigma receptors. Similarly, opening of the piperidinyl group as in PCA (fig. 1, 2: $R_1 = R_2 = R_3 =$ H) results in loss of affinity for both PCP and sigma affinity for sigma receptors. Similarly, opening of the
piperidinyl group as in PCA (fig. 1, 2: $R_1 = R_2 = R_3 =$
H) results in loss of affinity for both PCP and sigma
receptors (K_i versus [³H]DTG = 3133 nM). This is cle piperidinyl group as in PCA (fig. 1, 2: $R_1 = R_2 = R_3 =$ H) results in loss of affinity for both PCP and sigma receptors (K_i versus [³H]DTG = 3133 nM). This is clearly an important area for further investigations becaus H) results in loss of affinit
receptors $(K_i$ versus $[^3H]$ DT
an important area for furth
would appear likely that po
developed from this series.
4. Guanidines. Weber et a ceptors $(K_i$ versus $[^3H]$ DTG = 3133 nM). This is clearly

i important area for further investigations because it

buld appear likely that potent sigma ligands could be

veloped from this series.

4. *Guanidines*. Weber e

with any of the other receptor systems tested, making ing congeners of DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl) has
them the most potent and selective known sigma receptor revealed some interesting SAR data. The potency of
lig an important area for further investigations because it
would appear likely that potent sigma ligands could be
developed from this series.
4. Guanidines. Weber et al. (1986) described the high
affinity and selectivity of D would appear likely that potent sigma ligands could be developed from this series.
4. Guanidines. Weber et al. (1986) described the high affinity and selectivity of DTG for sigma sites in the brain. The rank order of poten developed from this series.
4. Guanidines. Weber et al. (1986) described the laffinity and selectivity of DTG for sigma sites in
brain. The rank order of potency of dopamine rece
agonists, neuroleptics, psychotomimetics, a 4. Guanidines. Weber et al. (1986) described the hilaffinity and selectivity of DTG for sigma sites in thrain. The rank order of potency of dopamine receptagonists, neuroleptics, psychotomimetics, and benzome phan opiates affinity and selectivity of DTG for sigma sites in the
brain. The rank order of potency of dopamine receptor
agonists, neuroleptics, psychotomimetics, and benzomor-
phan opiates in displacing [³H]DTG indicated a sigma-
b brain. The rank order of potency of dopamine recepta
agonists, neuroleptics, psychotomimetics, and benzomo
phan opiates in displacing [³H]DTG indicated a sigmi
binding profile. In contrast, ligands for other recepto:
wer agonists, neuroleptics, psychotomimetics, and benzome
phan opiates in displacing [³H]DTG indicated a sign
binding profile. In contrast, ligands for other receptor
were very weak in displacing [³H]DTG binding. Ad
tiona phan opiates in displacing [³H]DTG indicated a sigma-
binding profile. In contrast, ligands for other receptors
were very weak in displacing [³H]DTG binding. Addi-
tional work by this group (Campbell et al., 1989) inv binding profile. In contrast, ligands for other receptors
were very weak in displacing $[^{3}H]DTG$ binding. Addi-
tional work by this group (Campbell et al., 1989) involv-
ing congeners of DTG (fig. 1, 7: $R_1 = R_2 = 2$ -toly were very weak in displacing [³H]DTG binding. Additional work by this group (Campbell et al., 1989) involving congeners of DTG (fig. 1, 7: R₁ = R₂ = 2-tolyl) has revealed some interesting SAR data. The potency of DT tional work by this group (Campbell et al., 1989) involving congeners of DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl) has revealed some interesting SAR data. The potency of DTG against displacement of $[^8H]DTG$ was doubled (IC₅₀ ing congeners of DTG (fig. 1, 7: $R_1 = R_2 = 2$ -tolyl) has
revealed some interesting SAR data. The potency of
DTG against displacement of [³H]DTG was doubled
 $(C_{50} = 28.0 \text{ nM} \text{ for } DTG \text{ versus } IC_{50} = 13.0 \text{ nM} \text{ for}$
 $ChTG)$ by revealed some interesting SAR data. The potency of DTG against displacement of [³H]DTG was doubled (IC₅₀ = 28.0 nM for DTG versus IC₅₀ = 13.0 nM for ChTG) by replacing one of the aromatic rings of DTG with a cyclohe DTG against displacement of [³H]DTG was doubled (IC₅₀ = 28.0 nM for DTG versus IC₅₀ = 13.0 nM for ChTG) by replacing one of the aromatic rings of DTG with a cyclohexyl ring to give ChTG (fig. 1, 7: R₁ = 2-tolyl R (IC₅₀ = 28.0 nM for DTG versus IC₅₀ = 13.0 nM for ChTG) by replacing one of the aromatic rings of DTG with a cyclohexyl ring to give ChTG (fig. 1, 7: R₁ = 2-tolyl R₂ = cyclohexyl). This result indicates that both ChTG) by replacing one of the aromatic rings of DTG with a cyclohexyl ring to give ChTG (fig. 1, 7: R₁ = 2-tolyl R₂ = cyclohexyl). This result indicates that both aromatic rings are not necessary for high binding affi with a cyclohexyl ring to give ChTG (fig. 1, 7: $R_1 = 2$ -
tolyl R_2 = cyclohexyl). This result indicates that both
aromatic rings are not necessary for high binding affinity.
The fact that the potency is increased when tolyl R_2 = cyclohexyl). This result indicates that both aromatic rings are not necessary for high binding affinity.
The fact that the potency is increased when the aromatic ring is replaced with a cyclohexyl ring provi aromatic rings are not necessary for high binding affinity.
The fact that the potency is increased when the aromatic
ring is replaced with a cyclohexyl ring provides evidence
that a more lipophilic group that occupies a gr The fact that the potency is increased when the aromat
ring is replaced with a cyclohexyl ring provides eviden
that a more lipophilic group that occupies a great
volume in three-dimensional space is more important f
bindi that a more lipophilic group that occupies a greater
volume in three-dimensional space is more important for
binding than an aromatic group. This is further exem-
plified by AdTG (fig. 1, 7: $R_1 = 2$ -tolyl, $R_2 =$ adamant that a more lipophilic group that occupies a greater
volume in three-dimensional space is more important for
binding than an aromatic group. This is further exem-
plified by AdTG (fig. 1, 7: $R_1 = 2$ -tolyl, $R_2 =$ adamant volume in three-dimensional space is more important for
binding than an aromatic group. This is further exem-
plified by AdTG (fig. 1, 7: $R_1 = 2$ -tolyl, $R_2 =$ adamantyl)
which exhibited an IC₅₀ of 7.6 nM against $[^{3}$ binding than an aromatic group. This is further exem-
plified by AdTG (fig. 1, 7: $R_1 = 2$ -tolyl, $R_2 =$ adamantyl)
which exhibited an IC_{60} of 7.6 nM against $[^{3}H](+)$ -3-PPP
or a 4-fold increase in potency compared wit plified by AdTG (fig. 1, 7: $R_1 = 2$ -tolyl, $R_2 =$ adamantyl)
which exhibited an IC_{60} of 7.6 nM against $[^{3}H](+)$ -3-PPP
or a 4-fold increase in potency compared with DTG. The
ortho methyl groups of DTG are important fo which exhibited an IC_{50} of 7.6 nM against $[^{3}H](+)-3$ -PPP
or a 4-fold increase in potency compared with DTG. The
ortho methyl groups of DTG are important for improved
potency at the sigma receptor, because the desmethy ortho methyl groups of DTG are important for improved
potency at the sigma receptor, because the desmethyl
analog (DPG; fig. 1, 7: $R_1 = R_2 =$ phenyl) of DTG (IC₅₀
= 397 nM) exhibits a 14-fold reduction in potency relati potency at the sigma receptor, because the desmethyl
analog (DPG; fig. 1, 7: $R_1 = R_2$ = phenyl) of DTG (IC₅₀
= 397 nM) exhibits a 14-fold reduction in potency relative
to DTG. The methyl group of AdTG can be replaced
w analog (DPG; fig. 1, 7: $R_1 = R_2$ = phenyl) of DTG (IC₆₆ = 397 nM) exhibits a 14-fold reduction in potency relative to DTG. The methyl group of AdTG can be replaced with an iodine atom to make AdIpG which exhibits equiv $=$ 397 nM) exhibits a 14-fold reduction in potency relative
to DTG. The methyl group of AdTG can be replaced
with an iodine atom to make AdIpG which exhibits
equivalent potency, indicating that the iodine atom sub-
stitu to DTG. The methyl group of AdTG can be replaced
with an iodine atom to make AdIpG which exhibits
equivalent potency, indicating that the iodine atom sub-
stitutes in terms of size and lipophilicity for the methyl
group to with an iodine atom to make AdIpG which exhibits
equivalent potency, indicating that the iodine atom sub-
stitutes in terms of size and lipophilicity for the methyl
group to give high sigma receptor affinity. An attempt to equivalent potency, indicating that the iodine atom substitutes in terms of size and lipophilicity for the methy
group to give high sigma receptor affinity. An attempt to
increase the potency of DTG further by adding extra stitutes in terms of size and lipophilicity for the methyl
group to give high sigma receptor affinity. An attempt to
increase the potency of DTG further by adding extra
equivalent (ortho) methyl groups to give the tetrame group to give high sigma receptor affinity. An attempt to
increase the potency of DTG further by adding extra
equivalent (ortho) methyl groups to give the tetramethyl
analog N,N'-di(2,6-dimethylphenyl)guanidine resulted
i

PHARMACOLOGICAL REVIEW!

SIGMA RECEPTORS
explanation for this effect is likely to be steric interfer-
ence to binding, by the additional methyl groups. si
explanation for this effect is likely to be steric intence to binding, by the additional methyl groups.
Replacement of both of the aromatic rings of

SIGMA RECEPTOI
planation for this effect is likely to be steric interfer-
ce to binding, by the additional methyl groups. Potent
Replacement of both of the aromatic rings of DTG
th methyl groups (as in N,N'-di(methyl)guani explanation for this effect is likely to be steric int
ence to binding, by the additional methyl groups.
Replacement of both of the aromatic rings of
with methyl groups (as in N,N'-di(methyl)guani
(fig. 1, 7: $R_1 = R_2 = Me$) explanation for this effect is likely to be steric interfer-
ence to binding, by the additional methyl groups.
Replacement of both of the aromatic rings of DTG
with methyl groups (as in N,N'-di(methyl)guanidine)
(fig. 1, ence to binding, by the additional methyl groups.

Replacement of both of the aromatic rings of DTG

with methyl groups (as in N,N'-di(methyl)guanidine)

(fig. 1, 7: R₁ = R₂ = Me) resulted in total loss of potency

(I Replacement of both of the aromatic rings of DTG
with methyl groups (as in N,N'-di(methyl)guanidine)
(fig. 1, 7: R₁ = R₂ = Me) resulted in total loss of potency
(IC₆₀ > 100,000 nM); this suggests that at least one
a with methyl groups (as in N,N'-di(methyl)guanidine)
(fig. 1, 7: $R_1 = R_2 = Me$) resulted in total loss of potency
(IC₈₀ > 100,000 nM); this suggests that at least one
aromatic ring is important for sigma receptor activity. (fig. 1, 7: $R_1 = R_2 = Me$) resulted in total loss of potency
(IC₅₀ > 100,000 nM); this suggests that at least one
aromatic ring is important for sigma receptor activity.
However, replacement of both of the aromatic rings (IC₅₀ > 100,000 nM); this suggests that at least one
aromatic ring is important for sigma receptor activity.
However, replacement of both of the aromatic rings of
DTG with more bulky and lipophilic adamantyl groups
(fig aromatic ring is important for sigma receptor activity.
However, replacement of both of the aromatic rings of
DTG with more bulky and lipophilic adamantyl groups
(fig. 1, 7: $R_1 = R_2 =$ adamantyl) resulted in DAG. This
com However, replacement of both of the aromatic rings of
DTG with more bulky and lipophilic adamantyl groups
(fig. 1, 7: $R_1 = R_2$ = adamantyl) resulted in DAG. This
compound showed an increase in affinity relative to DTG
(D DTG with more bulky and lipophilic adamantyl groups
(fig. 1, 7: $R_1 = R_2$ = adamantyl) resulted in DAG. This
compound showed an increase in affinity relative to DTG
(DAG: $IC_{50} = 11.8$ nM) which suggests that bulky and
li compound showed an increase in affinity relative to DTG (DAG: $IC_{50} = 11.8$ nM) which suggests that bulky and lipophilic groups are capable of completely substituting for the aryl rings. The minimum number of adamantyl gr compound showed an increase in affinity relative to DTG (DAG: $IC_{50} = 11.8$ nM) which suggests that bulky and lipophilic groups are capable of completely substituting for the aryl rings. The minimum number of adamantyl gr (DAG: $IC_{50} = 11.8$ nM) which suggests that bulky and
lipophilic groups are capable of completely substituting
for the aryl rings. The minimum number of adamantyl
groups required for high binding affinity is one, because
 lipophilic groups are capable of completely substituting
for the aryl rings. The minimum number of adamantyl
groups required for high binding affinity is one, because
the N-adamantyl-N'-cyclohexyl analog showed potency
 $($ groups required for high binding affinity is one, because
the N-adamantyl-N'-cyclohexyl analog showed potency
($IC_{50} = 12.5$ nM) equivalent to the bis adamantyl analog
DAG ($IC_{50} = 11.8$ nM). Because sigma receptor activi groups required for high binding affinity is one, because
the N-adamantyl-N'-cyclohexyl analog showed potency
 $(IC_{50} = 12.5 \text{ nm})$ equivalent to the bis adamantyl analog
DAG $(IC_{50} = 11.8 \text{ nm})$. Because sigma receptor acti the N-adamantyl-N'-cyclohexyl analog showed poter (IC₅₀ = 12.5 nM) equivalent to the bis adamantyl ana DAG (IC₅₀ = 11.8 nM). Because sigma receptor active is totally lost with conformational restriction of boaromatic (IC₅₀ = 12.5 nM) equivalent to the bis adamantyl analog DAG (IC₅₀ = 11.8 nM). Because sigma receptor activity is totally lost with conformational restriction of both aromatic rings as in bridged N,N'-diphenylguanidine DAG (IC₅₀ = 11.8 nM). Because sigma receptor activity
is totally lost with conformational restriction of both
aromatic rings as in bridged N,N'-diphenylguanidine
(IC₅₀ > 100,000 nM), conformational mobility of these
a binding. (IC₅₀ > 100,000 nM), conformational mobility of these

aromatic rings is of utmost importance for sigma receptor

binding.

5. 3-Phenylpiperidines. In a qualitative SAR study by
 5. The IC₅₀ values are presented as

(IC_{so} > 100,000 nM), conformational mobility of these
aromatic rings is of utmost importance for sigma receptor
binding.
5. 3-Phenylpiperidines. In a qualitative SAR study by
Largent et al. (1987), a number of compounds aromatic rings is of utmost importance for sigma receptor
binding.
5. 3-Phenylpiperidines. In a qualitative SAR study by
Largent et al. (1987), a number of compounds which
included opioids, neuroleptics, and phenylpiperidi binding.
5. 3-Phenylpiperidines. In a qualitative SAR study by
Largent et al. (1987), a number of compounds which
included opioids, neuroleptics, and phenylpiperidine do-
paminergics were examined for sigma receptor affini 5. 3-Phenylpiperidines. In a qualitative SAR study by
Largent et al. (1987), a number of compounds which groundled opioids, neuroleptics, and phenylpiperidine do-
paminergics were examined for sigma receptor affinity.
In included opioids, neuroleptics, and phenylpiperidine do-
paminergics were examined for sigma receptor affinity.
In the 3-phenylpiperidine series (fig. 1, 3), many of the
compounds were studied as their individual enantiom included opioids, neuroleptics, and phenylpiperidine do-
paminergics were examined for sigma receptor affinity.
In the 3-phenylpiperidine series (fig. 1, 3), many of the
compounds were studied as their individual enantiom paminergics were examined for sigma receptor affinity.
In the 3-phenylpiperidine series (fig. 1, 3), many of the
compounds were studied as their individual enantiomers
for their ability to compete with $[^{3}H](+)-3-PPP$ in ra In the 3-phenylpiperidine series (fig. 1, 3), many of the
compounds were studied as their individual enantiomers (19
for their ability to compete with $[^{3}H](+)-3-PPP$ in rat
of the *R* enantiomers were more potent than the
 compounds were studied as their individual enantiomers
for their ability to compete with $[^{3}H](+)-3-PPP$ in rat
brain membranes. Generally, among the 3-PPP analogs
(fig. 1, 3), the R enantiomers were more potent than the
S for their ability to compete with $[^{3}H](+)$ -3-PPP in rat
brain membranes. Generally, among the 3-PPP analogs
(fig. 1, 3), the *R* enantiomers were more potent than the
S enantiomers in displacing $[^{3}H](+)$ -3-PPP. Analogs
 brain membranes. Generally, among the 3-PPP analogs

(fig. 1, 3), the R enantiomers were more potent than the

S enantiomers in displacing $[^{3}H](+)$ -3-PPP. Analogs

with larger nitrogen substituents exhibited markedly

hi (fig. 1, 3), the R enantiomers were more potent than th
S enantiomers in displacing $[^{3}H](+)$ -3-PPP. Analog
with larger nitrogen substituents exhibited markedl
higher affinities for the sigma receptor. Larger nitrogen
sub S enantiomers in displacing $[{}^{8}H](+)-3-PPP$. Analogs with larger nitrogen substituents exhibited markedly luer higher affinities for the sigma receptor. Larger nitrogen substituents provide greater hydrophobicity in an ana with larger nitrogen substituents exhibited markedly
higher affinities for the sigma receptor. Larger nitrogen
substituents provide greater hydrophobicity in an anal-
recogous fashion to the $(+)$ -benzomorphans (fig. 1, 1) higher affinities for the sigma receptor. Larger nitrogen
substituents provide greater hydrophobicity in an anal-
ogous fashion to the $(+)$ -benzomorphans (fig. 1, 1) and
 $(+)$ -morphinans (fig. 1, 6). The increase in affini substituents provide greater hydrophobicity in
ogous fashion to the $(+)$ -benzomorphans (fig. 1
 $(+)$ -morphinans (fig. 1, *6*). The increase in affin
increasing size of the R_1 group is seen with bo
and the *S* enantiomer ous fashion to the $(+)$ -benzomorphans (fig. 1, 1) and
 $)$ -morphinans (fig. 1, 6). The increase in affinity with

treasing size of the R_1 group is seen with both the R

d the S enantiomers of (fig. 1, 3) (table 2).

increasing size of the R_1 group is seen with both the R
and the S enantiomers of (fig. 1, 3) (table 2).
The trend for increasing potency of both R and S
reasontiomers with increasing size of R_1 is broken wit and the S enantiomers of (fig. 1, 3) (table 2).

The trend for increasing potency of both R and S

enantiomers with increasing size of R₁ is broken with R₁

= isopropyl (see compounds 9 and 10 in table 2), which

may The trend for increasing potency of both R and S
enantiomers with increasing size of R_1 is broken with R_1
= isopropyl (see compounds 9 and 10 in table 2), which
may indicate differing sensitivities toward steric enantiomers with increasing size of R_1 is broken with R_2 = isopropyl (see compounds 9 and 10 in table 2), which may indicate differing sensitivities toward steric bulk for the two enantiomers. A 3-OH is better for s may indicate differing sensitivities toward steric bulk for
thermore, whereas sigma receptors are insensitive to
the two enantiomers. A 3-OH is better for sigma receptor
affinity than a 4-OH. Furthermore, although the phe the two enantiomers. A 3-OH is better for sigma receptinity than a 4-OH. Furthermore, although the p nolic 3-OH is a requirement for the dopamine agor effects of these compounds, it is not essential for signeceptor activi affinity than a 4-OH. Furthermore, although the phenolic 3-OH is a requirement for the dopamine agonist effects of these compounds, it is not essential for sigma receptor activity, because analogs of $(+)$ -3-PPP possessing nolic 3-OH is a requirement for the dopamine ago:
effects of these compounds, it is not essential for signeceptor activity, because analogs of $(+)$ -3-PPP possing 3-F and 3-CF₃ (fig. 1, 3: R₂ = 3-F or 3-CF₃; compound effects of these compounds, it is not essential for sigma
receptor activity, because analogs of $(+)$ -3-PPP possess-
ing 3-F and 3-CF₃ (fig. 1, 3: R₂ = 3-F or 3-CF₃; compounds
16 and 17 in table 2) are potent sigma l receptor activity, because analogs of $(+)$ -3-PPP possessing 3-F and 3-CF₃ (fig. 1, 3: R₂ = 3-F or 3-CF₃; compounds 16 and 17 in table 2) are potent sigma ligands. Additionally, the methyl ether derivative (fig. 1, 3 ing 3-F and 3-CF₃ (fig. 1, 3: R₂ = 3-F or 3-CF₃; compounds e
16 and 17 in table 2) are potent sigma ligands. Addition-
ally, the methyl ether derivative (fig. 1, 3: R₁ = N-propyl, c
R₂ = OMe) of (+)-3-PPP is twi 16 and 17 in table 2) are potent sigma ligands. Addition-
ally, the methyl ether derivative (fig. 1, 3: $R_1 = N$ -propyl, $R_2 = OMe$) of (+)-3-PPP is twice as potent as the parent dompound, indicating that the 3-OH group of (ally, the methyl ether derivative (fig. 1, 3: $R_1 = N$ -propyl, co $R_2 = OMe$) of (+)-3-PPP is twice as potent as the parent decompound, indicating that the 3-OH group of (+)-3-PPP eris not important for hydrogen-bonding inter

TABLE 2 PTORS
Potencies of compounds in a series of phenylpiperidines for inhibition
of (+)-[⁸H]3-PPP binding to rat whole brain membranes* *of (+)-PHJ3-PPP binding to rat whole brain membranest*

^{*} The IC₅₀ values are presented as the means (nM) \pm SE. The R₁ 16 $n\text{-}Pr$ 3-CF₃ $317 \pm 2\text{+}$

17 $n\text{-}Pr$ 3-F $49 \pm 11\text{+}$

* The IC₂₀ values are presented as the means (nM) \pm SE. The R₁

group represents the nitrogen substituent of the piperidine, and the R₂

group d group represents the nitrogen substituent of the piperidine, and the R₂ group denotes the substituent on the phenyl moiety for the given structure. Abbreviations of substitutions: H, hydrogen; Me, methyl; Et, ethyl; *n*-

(1987).

structure. Abbreviations of substitutions: H, hydrogen; Me, methylethyl; *n*-Pr, *n*-propyl; i-Pr, isopropyl; *n*-Bu, *n*-butyl; Pheth, phenet (1987).

f Compounds 15-17 are racemic mixtures. Data from Largent e

(1987).
 ethyl; n-Pr, n-propyl; 1-Pr, isopropyl; n-Bu, n-Butyl; Pheth, phenethyl.

† Compounds 15-17 are racemic mixtures. Data from Largent et al.

(1987).

of MPTP, which does not possess aromatic electron-

donating or -withdraw (1987) .
of MPTP, which does not possess aromatic electronating or -withdrawing groups, is still a potent signeceptor ligand; this suggests that the aromatic substitutions when the 3-phenylpiperidin of MPTP, which does not possess aromatic elect
donating or -withdrawing groups, is still a potent si
receptor ligand; this suggests that the aromatic sub-
uents may not be important in the 3-phenylpiperidines. MPTP, which does not possess aromatic electron-
nating or -withdrawing groups, is still a potent sigma
ceptor ligand; this suggests that the aromatic substit-
nts may not be important in the 3-phenylpiperidines.
Because th

increasing size of the R_1 group is seen with both the R the cisOHBQs (fig. 1, 4) with large nitrogen substituents
and the S enantiomers of (fig. 1, 3) (table 2).
The trend for increasing potency of both R and S r donating or -withdrawing groups, is still a potent sigma
receptor ligand; this suggests that the aromatic substit-
uents may not be important in the 3-phenylpiperidines.
Because the above studies indicated that the structu uents may not be important in the 3-phenylpiperidines.
Because the above studies indicated that the structural
requirements for sigma receptor and dopamine receptor
activity are divergent, new compounds with better selecuents may not be important in the 3-phenylpiperidines.
Because the above studies indicated that the structural
requirements for sigma receptor and dopamine receptor
activity are divergent, new compounds with better selec-
 Because the above studies indicated that the structural
requirements for sigma receptor and dopamine receptor
activity are divergent, new compounds with better selec-
tivity for sigma receptors can be designed. For example requirements for sigma receptor and dopamine receptor
activity are divergent, new compounds with better selec-
tivity for sigma receptors can be designed. For example,
the *cis*OHBQs (fig. 1, 4) with large nitrogen substit activity are divergent, new compounds with better selectivity for sigma receptors can be designed. For example, the *cisOHBQs* (fig. 1, 4) with large nitrogen substituents have high sigma receptor affinity, compared to do tivity for sigma receptors can be designed. For example,
the *cis*OHBQs (fig. 1, 4) with large nitrogen substituents
have high sigma receptor affinity, compared to dopamine
receptor affinity. In contrast, some of the *tra* the *cis*OHBQs (fig. 1, 4) with large nitrogen substituents have high sigma receptor affinity, compared to dopamine receptor affinity. In contrast, some of the *trans*OHBQs are very potent dopamine D_2 receptor agonists are very potent dopamine D_2 receptor agonists, while are very potent dopamine D_2 receptor agonists, while showing little or no affinity for sigma receptors. Furthermore, whereas sigma receptors are insensitive to increased steric bulk at the nitrogen substituent, dopamin showing little or no affinity for sigma receptors. Fur-
thermore, whereas sigma receptors are insensitive to
increased steric bulk at the nitrogen substituent, dopa-
mine receptor agonists have defined directions for their thermore, whereas sigma receptors are insensitive to
increased steric bulk at the nitrogen substituent, dopa-
mine receptor agonists have defined directions for their
N-alkyl substituents. Because the nonhydroxylated 3-
ph increased steric bulk at the nitrogen substituent, dopa-
mine receptor agonists have defined directions for their
N-alkyl substituents. Because the nonhydroxylated 3-
phenylpiperidines lose dopamine receptor affinity, but
 retain sigma receptor affinity, it was suggested (Largent et al., 1987) that certain of these nonhydroxylated com-
pounds (for example, the fluorinated analog of 3-PPP; N-alkyl substituents. Because the nonhydroxylated 3-
phenylpiperidines lose dopamine receptor affinity, but
retain sigma receptor affinity, it was suggested (Largent
et al., 1987) that certain of these nonhydroxylated comphenylpiperidines lose dopamine receptor affinity, but
retain sigma receptor affinity, it was suggested (Largent
et al., 1987) that certain of these nonhydroxylated com-
pounds (for example, the fluorinated analog of 3-PPP retain sigma receptor affinity, it was suggested (Large et al., 1987) that certain of these nonhydroxylated co
pounds (for example, the fluorinated analog of 3-PF
compound 17 in table 2) may serve as templates for t
develo eration of these nonhydroxylated compounds (for example, the fluorinated analog of 3-PPP;
compound 17 in table 2) may serve as templates for the
development of more selective sigma ligands. In consid-
eration of the number pounds (for example, the fluorinated analog of 3-PPP compound 17 in table 2) may serve as templates for the development of more selective sigma ligands. In consideration of the number of classes of compounds (e.g. phenylpi development of more selective sigma ligands. In consideration of the number of classes of compounds (e.g., phenylpiperidines, OHBQs, butyrophenones, and phenothiazines) which exhibit interactions with both sigma

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d dopamine receptors, it is possible that these two more
ptors have an evolutionary or functional link. agai
Sigma receptor affinity (measured as the potency in mod
splacing [3H](+)-3-PPP) is sensitive to pH, a and dopamine receptors, it is possible that these two meceptors have an evolutionary or functional link. ag Sigma receptor affinity (measured as the potency in m displacing $[^{3}H](+)-3-PPP$) is sensitive to pH, a finding hy and dopamine receptors, it is possible that these two move-
receptors have an evolutionary or functional link. age.
Sigma receptor affinity (measured as the potency in modisplacing $[^{3}H](+)-3-PPP$) is sensitive to pH, a fin receptors have an evolutionary or functional link. a a Sigma receptor affinity (measured as the potency in m displacing $[^{3}H](+)-3-PPP$) is sensitive to pH, a finding hyponistent with the importance of lipophilicity in the Sigma receptor affinity (measured as the potency in
displacing $[^{3}H](+)-3-PPP$) is sensitive to pH, a finding
consistent with the importance of lipophilicity in the
vicinity of the N-alkyl region of the piperidine ring of
displacing $[^{3}H](+)-3-PPP$) is sensitive to pH, a finding hydrox
consistent with the importance of lipophilicity in the 1990).
vicinity of the N-alkyl region of the piperidine ring of of con-
 $(+)-3-PPP$ (Largent et al., 1987). consistent with the importance of lipophilicity in the 199
vicinity of the N-alkyl region of the piperidine ring of of c
 $(+)$ -3-PPP (Largent et al., 1987). As one would expect use
from this, $[^{3}H](+)$ -3-PPP binding is en wicinity of the N-alkyl region of the piperidine ring of of $(+)$ -3-PPP (Largent et al., 1987). As one would expect und from this, $[^{3}H](+)$ -3-PPP binding is enhanced as the pH is increased in the range 7.0–8.9. The effec (+)-3-PPP (Largent et al., 1987). As one would expect use
from this, $[^{3}H](+)-3$ -PPP binding is enhanced as the pH
is increased in the range 7.0–8.9. The effect of pH on
 $[^{3}H](+)-3$ -PPP binding may be mediated through
cha from this, $[{}^3H](+)-3$ -PPP binding is enhanced as the pH
is increased in the range 7.0–8.9. The effect of pH on
 $[{}^3H](+)-3$ -PPP binding may be mediated through In
changes in the charge on both the phenolic group and have
 $[{}^{3}H](+)-3-PPP$ binding may be mediated through In recent years, several models of the sigma receptor
changes in the charge on both the phenolic group and have been proposed. These can be placed into five cate-
the nitroge changes in the charge on both the phenolic group and
the nitrogen atom in 3-PPP (fig. 1, 3: R₁ = N-propyl, R₂ gories: (a) topographic models, (b) distinct allosterically
= 3-OH). However, because substituting the 3-OH changes in the charge on both the phenolic group and
the nitrogen atom in 3-PPP (fig. 1, 3: R₁ = N-propyl, R₂
= 3-OH). However, because substituting the 3-OH of
 $(+)$ -3-PPP with an OMe group results in a doubling of
th the nitrogen atom in 3-PPP (fig. 1, 3: $R_1 = N$ -propyl, $R_2 = 3$ -OH). However, because substituting the 3-OH of $(+)$ -3-PPP with an OMe group results in a doubling of $(+)$ -3-PPP with an OMe group results in a doubling of $[$ $=$ 3-OH). However, because substituting the 3-OH of (+)-3-PPP with an OMe group results in a doubling of the affinity to sigma sites, it is unlikely that ionization of the phenolic at increased pH values accounts for the the affinity to sigma sites, it is unlikely that ionization
of the phenolic at increased pH values accounts for the
changes in affinity. Thus, the increase in affinity at
higher pH values is more likely to be be due to dep the affinity to sigma sites,
of the phenolic at increased
changes in affinity. Thus,
higher pH values is more lik
ation of a piperidine ring.
6. Steroids. Su et al. (198 the phenolic at increased pH values accounts for the
anges in affinity. Thus, the increase in affinity at
gher pH values is more likely to be be due to deproton-
ion of a piperidine ring.
6. *Steroids*. Su et al. (1988a) d

changes in affinity. Thus, the increase in affinity at higher pH values is more likely to be be due to deproton-
ation of a piperidine ring.
6. Steroids. Su et al. (1988a) demonstrated that pro-
gesterone (fig. 1, 10) bin higher pH values is more likely to be be due to deproton-
ation of a piperidine ring.
6. Steroids. Su et al. (1988a) demonstrated that pro-
gesterone (fig. 1, 10) binds with reasonable affinity (K_i
= 268 nM, measured ag ation of a piperidine ring.

6. Steroids. Su et al. (1988a) demonstrated that pro-

gesterone (fig. 1, 10) binds with reasonable affinity (K_i

= 268 nM, measured against [³H]SKF 10,047) to guinea

pig brain tissue. As 6. Steroids. Su et al. (1988a) demonstrated that progesterone (fig. 1, 10) binds with reasonable affinity (K_i = 268 nM, measured against [³H]SKF 10,047) to guinea of the pig brain tissue. As shown in table 1, a limite gesterone (fig. 1, 10) binds with reasonable affinity
= 268 nM, measured against [³H]SKF 10,047) to guin
pig brain tissue. As shown in table 1, a limited sampl
of related compounds revealed that testosterone a
desoxycor $= 268$ nM, measured against [³H]SKF 10,047) to guinea
pig brain tissue. As shown in table 1, a limited sampling
of related compounds revealed that testosterone and
desoxycorticosterone bound with affinities of approxipig brain tissue. As shown in table 1, a limited sampling
of related compounds revealed that testosterone and
desoxycorticosterone bound with affinities of approxi-
mately 1 μ M. These authors speculated that progestero of related compounds revealed that testosterone and
desoxycorticosterone bound with affinities of approxi-
mately 1μ M. These authors speculated that progesterone
may act physiologically at the sigma receptors, serving
 desoxycorticosterone bound with affinities of approximately 1μ M. These authors speculated that progesterone may act physiologically at the sigma receptors, serving as an endogenous ligand. However, Schwarz et al. (1989 mately 1 μ M. These authors speculated that progesterone plane
may act physiologically at the sigma receptors, serving plane
as an endogenous ligand. However, Schwarz et al. (1989)
challenged this idea, countering that may act physiologically at the sigma receptors, serving
as an endogenous ligand. However, Schwarz et al. (1989)
challenged this idea, countering that it has only modest
affinity for sigma receptors and circulates primaril as an endogenous ligand. However, Schwarz et al. (198
challenged this idea, countering that it has only mode
affinity for sigma receptors and circulates primarily ir
bound form. Su et al. maintain that especially duri
preg challenged this idea, countering that it has only modest affinity for sigma receptors and circulates primarily in a bound form. Su et al. maintain that especially during all pregnancy sufficient levels might be achieved f affinity for sigma receptors and circulates primarily in a
bound form. Su et al. maintain that especially during
pregnancy sufficient levels might be achieved for endog-
ical
enous progesterone to achieve significant occu bound form. Su et al. maintain that especially during
pregnancy sufficient levels might be achieved for endog-
enous progesterone to achieve significant occupation of
sigma sites. Furthermore, the concentrations assumed by pregnancy sufficient levels might be achieved for endogenous progesterone to achieve significant occupation of the sigma sites. Furthermore, the concentrations assumed by the high degree of lipophilicity of progesterone. enous progesterone to achieve significant occupation of the co
sigma sites. Furthermore, the concentrations assumed by
Schwartz et al. may be underestimates if one considers
the high degree of lipophilicity of progesteron sigma sites. Furthermore, the concentrations assumed by
Schwartz et al. may be underestimates if one considers
the high degree of lipophilicity of progesterone. The
assumption that progesterone which is bound to serum
pro Schwartz et al. may be underestimates if one considers
the high degree of lipophilicity of progesterone. The
assumption that progesterone which is bound to serum
proteins is unavailable for receptor binding may also be
qu the high degree of lipophilicity of progesterone. The
assumption that progesterone which is bound to serum
proteins is unavailable for receptor binding may also be
questioned. Ke and Ramirez (1990) showed that $[$ ¹²⁵I]
p assumption that progesterone which is bound to serum
proteins is unavailable for receptor binding may also be
questioned. Ke and Ramirez (1990) showed that $[1^{25}I]$
progesterone conjugated with bovine serum albumin st proteins is unavailable for receptor binding may also be
questioned. Ke and Ramirez (1990) showed that $[^{125}]$
progesterone conjugated with bovine serum albumin still
exhibits binding to membrane receptors. Further re-
se questioned. Ke and Ramirez (1990) showed that $[1^{25}]$ and progesterone conjugated with bovine serum albumin still exhibits binding to membrane receptors. Further referench is needed to establish whether sigma receptors s **progesterone.** hibits binding to membrane receptors. Further re-
arch is needed to establish whether sigma receptors
sigma
ay mediate certain central nervous system effects of moiet-
gesterone.
7. Miscellaneous compounds. The piperazines

14802 and rimcazole bind to sigma receptors and may mediate certain central nervous system effects of more proposterone.

2. Miscellaneous compounds. The piperazines BMY are 14802 and rimcazole bind to sigma receptors and may mediate certain central nervous system effects of
progesterone.
7. Miscellaneous compounds. The piperazines BMY
14802 and rimcazole bind to sigma receptors and have
been investigated for antipsychotic potential (Ferri progesterone.

7. Miscellaneous compounds. The piperazines BMY

14802 and rimcazole bind to sigma receptors and have

been investigated for antipsychotic potential (Ferris et

al., 1986; Taylor et al., 1990). One reason fo 7. Miscellaneous compounds. The piperazines BMY graded 14802 and rimcazole bind to sigma receptors and have use been investigated for antipsychotic potential (Ferris et class ol., 1986; Taylor et al., 1990). One reason for 14802 and rimcazole bind to sigma receptors and have
been investigated for antipsychotic potential (Ferris et
al., 1986; Taylor et al., 1990). One reason for the interest
in these compounds is that they lack neuroleptic li been investigated for antipsychotic potential (Ferris ed., 1986; Taylor et al., 1990). One reason for the interes
in these compounds is that they lack neuroleptic like
pharmacological properties. They do not, for example
p al., 1986; Taylor et al., 1990). One reason for the interest in these compounds is that they lack neuroleptic like supharmacological properties. They do not, for example, la produce catalepsy in rats (cf. Taylor et al., 19 in these compounds is that they lack neuroleptic like supharmacological properties. They do not, for example, la produce catalepsy in rats (cf. Taylor et al., 1990). How-
produce catalepsy in rats (cf. Taylor et al., 1990) pharmacological properties. They do not, for example produce catalepsy in rats (cf. Taylor et al., 1990). However, firm conclusions regarding the function of signereceptors cannot be inferred from the actions of the compou produce catalepsy in rats (cf. Taylor et al., 1990). How-
ever, firm conclusions regarding the function of sigma
receptors cannot be inferred from the actions of these
compounds. Rimcazole binds only weakly to sigma recepever, firm conclusions regarding the function of sigma
receptors cannot be inferred from the actions of these
compounds. Rimcazole binds only weakly to sigma recep-
tors, with potency estimates as low as in the micromolar

ET AL.
more potent than rimcazole at sigma receptors $(K_i$
against $[{}^3H]DTG = 32$ nM, table 1), it also binds with ET AL.
more potent than rimcazole at sigma receptors (K_i)
against $[^{3}H]DTG = 32$ nM, table 1), it also binds with
moderate affinity to 5HT1a receptors (K_i) against $[^{3}H]8$ -ET AL.
more potent than rimcazole at sigma receptors (K_i)
against $[^{3}H]DTG = 32$ nM, table 1), it also binds with
moderate affinity to 5HT1a receptors (K_i) against $[^{3}H]8$ -
hydroxydipropylaminotetralin = 151 nM; Taylo more potent than rimcazole at sigma receptors (K_i)
against $[{}^3H]DTG = 32$ nM, table 1), it also binds with
moderate affinity to 5HT1a receptors (K_i) against $[{}^3H]8$ -
hydroxydipropylaminotetralin = 151 nM; Taylor et al more potent than rimcazole at sigma receptors $(K_i$
against [³H]DTG = 32 nM, table 1), it also binds with
moderate affinity to 5HT1a receptors $(K_i$ against [³H]8-
hydroxydipropylaminotetralin = 151 nM; Taylor et al.,
1 against $[^{3}H]DTG = 32$ nM, table 1), it also binds with
moderate affinity to 5HT1a receptors $(K_i$ against $[^{3}H]8$ -
hydroxydipropylaminotetralin = 151 nM; Taylor et al.,
1990). As discussed in more detail below, these dr moderate affinity to 5HT1a receptors $(K_i$ agains
hydroxydipropylaminotetralin = 151 nM; Tayle
1990). As discussed in more detail below, these of
considerable clinical interest but are not sui
use as selective sigma ligand 1990). As discussed in more detail below, these drugs are
of considerable clinical interest but are not suitable for
use as selective sigma ligands in basic research.
II. Molecular Models of Sigma Receptors
In recent years considerable clinical interest but are not suitable for
e as selective sigma ligands in basic research.
II. Molecular Models of Sigma Receptors
In recent years, several models of the sigma receptor
we been proposed. These

use as selective sigma ligands in basic research.
 II. Molecular Models of Sigma Receptors

In recent years, several models of the sigma recepto

have been proposed. These can be placed into five cate

gories: (a) topogr II. Molecular Models of Sigma Receptors
In recent years, several models of the sigma receptor
have been proposed. These can be placed into five cate-
gories: (a) topographic models, (b) distinct allosterically
coupled bind II. MOIGCUIAT MOGEIS OT SIGMA RECEPTOTS
In recent years, several models of the sigma receptor
have been proposed. These can be placed into five cate-
gories: (a) topographic models, (b) distinct allosterically
coupled bin In recent years, several models of the sigma receptor
have been proposed. These can be placed into five cate-
gories: (*a*) topographic models, (*b*) distinct allosterically
coupled binding sites or domains on a single sig have been proposed. These can be placed into five categories: (a) topographic models, (b) distinct allosterically coupled binding sites or domains on a single sigma receptor macromolecule, (c) multiple subtypes of sigm gories: (*a*) topographic models, (*b*) distinct allosterically
coupled binding sites or domains on a single sigma receptor macromolecule, (*c*) multiple subtypes of sigma
receptors differing in affinity for various sigma coupled binding sites or domains on a single sigma receptor macromolecule, (c) multiple subtypes of sigma receptors differing in affinity for various sigma ligands, (d) species variations in the sigma receptor, and (e) states. *A.* Quantitative Considerations in the sigma receptor, and *(e)*
 A. *Quantitative Considerations and Topographic Models*

Several attempts have been made to formulate models

Frame receptors that can exist in high and low affinity
ates.
Quantitative Considerations and Topographic Models
Several attempts have been made to formulate models
the sigma receptor that can explain the SAR data for states.
A. Quantitative Considerations and Topographic Models
Several attempts have been made to formulate models
of the sigma receptor that can explain the SAR data for
various classes of sigma ligands. Largent et al. (19 A. Quantitative Considerations and Topographic Models
Several attempts have been made to formulate models
of the sigma receptor that can explain the SAR data for
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perf A. Quantizative Considerations and Topographic Models

Several attempts have been made to formulate models

of the sigma receptor that can explain the SAR data for

various classes of sigma ligands. Largent et al. (1987)
 Several attempts have been made to formulate models
of the sigma receptor that can explain the SAR data for
various classes of sigma ligands. Largent et al. (1987)
performed conformational calculations on a total of 10
com of the sigma receptor that can explain the SAR data for various classes of sigma ligands. Largent et al. (1987) performed conformational calculations on a total of 10 compounds, which included phenothiazines and other stru various classes of sigma ligands. Largent et al. (1987)
performed conformational calculations on a total of 10
compounds, which included phenothiazines and other
structures, in an attempt to determine the N-(aromatic
pl compounds, which included phenothiazines and other structures, in an attempt to determine the N-(aromatic plane) and N-(polar function) interatomic distances. The calculated minimized conformations of $(-)$ -cyclazocine, *c* compounds, which included phenothiazines and other
structures, in an attempt to determine the N-(aromatic
plane) and N-(polar function) interatomic distances. The
calculated minimized conformations of $(-)$ -cyclazocine,
c plane) and N-(polar function) interatomic distances. The
calculated minimized conformations of $(-)$ -cyclazocine,
cis- and trans-clopenthixol, haloperidol (fig. 1, 5: R₁ =
Cl, R₂ = F), and $(+)$ -dexclamol were found to calculated minimized conformations of $(-)$ -cyclazocine,
cis- and trans-clopenthixol, haloperidol (fig. 1, 5: R_1 =
Cl, R_2 = F), and $(+)$ -dexclamol were found to match
their X-ray conformations. The results of the stu cis- and trans-clopenthixol, haloperidol (fig. 1, 5: R₁ = Cl, R₂ = F), and (+)-dexclamol were found to match their X-ray conformations. The results of the study showed that the N-(aromatic plane) distance is not criti Cl, $R_2 = F$), and (+)-dexclamol were found to match
their X-ray conformations. The results of the study
showed that the N-(aromatic plane) distance is not crit
ical for sigma receptor binding because this distance fo
the their X-ray conformations. The results of the study
showed that the N-(aromatic plane) distance is not crit-
ical for sigma receptor binding because this distance for
the compounds varied substantially $(0.08-2.9 \text{ Å})$. F showed that the N-(aromatic plane) distance is not critical for sigma receptor binding because this distance for
the compounds varied substantially $(0.08-2.9 \text{ Å})$. Fur-
thermore, the N-(midpoint of the aromatic plane) an ical for sigma receptor binding because this distance for
the compounds varied substantially $(0.08-2.9 \text{ Å})$. Fur-
thermore, the N-(midpoint of the aromatic plane) and
N-(polar function) distances varied between 4.3–6.4 the compounds varied substantially $(0.08-2.9 \text{ Å})$. Fur-
thermore, the N-(midpoint of the aromatic plane) and
N-(polar function) distances varied between 4.3–6.4 and
6.5–8.9 Å, respectively. This large degree of variatio thermore, the N-(midpoint of the aromatic plane) and N-(polar function) distances varied between 4.3-6.4 and 6.5-8.9 Å, respectively. This large degree of variation in the N-(aromatic ring) distances may account for the va N-(polar function) distances ve
6.5–8.9 Å, respectively. This la
the N-(aromatic ring) distance
variety of chemical structures
affinity for the sigma receptor.
The study indicated several 5–8.9 Å, respectively. This large degree of variation in
e N-(aromatic ring) distances may account for the
riety of chemical structures which exhibit reasonable
finity for the sigma receptor.
The study indicated several s the N-(aromatic ring) distances may account for the variety of chemical structures which exhibit reasonable affinity for the sigma receptor.
The study indicated several structural requirements for sigma binding. First, the

variety of chemical structures which exhibit reasonable
affinity for the sigma receptor.
The study indicated several structural requirements
for sigma binding. First, the primary pharmacophore at
sigma sites appears to be affinity for the sigma receptor.
The study indicated several structural requirements
for sigma binding. First, the primary pharmacophore at
sigma sites appears to be the 3- or 4-phenylpiperidine
moiety, which is present in The study indicated several structural requirements
for sigma binding. First, the primary pharmacophore at
sigma sites appears to be the 3- or 4-phenylpiperidine
moiety, which is present in most compounds showing
high affi for sigma binding. First, the primary pharmacophore
sigma sites appears to be the 3- or 4-phenylpiperid
moiety, which is present in most compounds show
high affinity for sigma receptors. Second, affinity
greatly influenced sigma sites appears to be the 3- or 4-phenylpiperidine moiety, which is present in most compounds showing high affinity for sigma receptors. Second, affinity is greatly influenced by large hydrophobic N-alkyl substituents. moiety, which is present in most compounds showing
high affinity for sigma receptors. Second, affinity is
greatly influenced by large hydrophobic N-alkyl substit-
uents. Third, compounds from many different structural
clas high affinity for sigma receptors. Second, affinity is
greatly influenced by large hydrophobic N-alkyl substit-
uents. Third, compounds from many different structural
classes exhibit substantial affinity for sigma receptor greatly influenced by large hydrophobic N-alkyl substituents. Third, compounds from many different structural classes exhibit substantial affinity for sigma receptors, indicating that certain interatomic distances are not uents. Third, compounds from many different structural
classes exhibit substantial affinity for sigma receptors,
indicating that certain interatomic distances are not
subject to rigid constraint (e.g., N to aromatic ring). classes exhibit substantial affinity for sigma receptors,
indicating that certain interatomic distances are not
subject to rigid constraint (e.g., N to aromatic ring). This
lack of rigid constraint is further exemplified b indicating that c
subject to rigid const
lack of rigid const
of strict enantioss
of sigma ligands.
Manallack et al. subject to rigid constraint (e.g., N to aromatic ring). This lack of rigid constraint is further exemplified by the lack of strict enantioselectivity between the different classes of sigma ligands.
Manallack et al. (1988)

lack of rigid constraint is further exemplified by the lack
of strict enantioselectivity between the different classes
of sigma ligands.
Manallack et al. (1988) performed a study to determine
the receptor site topography f of strict enantioselectivity between the different class
of sigma ligands.
Manallack et al. (1988) performed a study to determi
the receptor site topography for both PCP and sigm
like drugs by correlating quantitative conf of sigma ligands.
Manallack et al. (1988) performed a study to determine
the receptor site topography for both PCP and sigma-
like drugs by correlating quantitative conformational,
electrostatic potential, and radiorecepto

SIGMA RECEPTORS
The study predicted different receptor site topographies sigma at
for PCP and sigma receptors, adding additional evidence classes. sigma RECI
The study predicted different receptor site topographies
for PCP and sigma receptors, adding additional evidence
in support of distinct sigma and PCP receptors as opsigma RI

The study predicted different receptor site topographies

for PCP and sigma receptors, adding additional evidence

in support of distinct sigma and PCP receptors as op-

posed to a sigma/PCP complex (Manallack an The study predicted different receptor site topographies
for PCP and sigma receptors, adding additional evidence
in support of distinct sigma and PCP receptors as op-
posed to a sigma/PCP complex (Manallack and Beart
1987, The study predicted different receptor site to
for PCP and sigma receptors, adding addition
in support of distinct sigma and PCP recep
posed to a sigma/PCP complex (Manallack
1987, Manallack et al., 1986). *Trans-4aR*,10b
 for PCP and sigma receptors, adding additional evidence
in support of distinct sigma and PCP receptors as op-
posed to a sigma/PCP complex (Manallack and Beart
1987, Manallack et al., 1986). *Trans-4aR*,10b*R*-9-OH-*n*-
P posed to a sigma/PCP complex (Manallack and Beart tive. Thus far, it can be concluded that electronegative 1987, Manallack et al., 1986). Trans-4aR,10bR-9-OH- n -
Pr-OHBQ (fig. 1, 4: R₁ = N-propyl, R₂ = 9-OH), a poten posed to a sigma/PCP complex (Manallack and Beart
1987, Manallack et al., 1986). Trans-4aR,10bR-9-OH-n-
Pr-OHBQ (fig. 1, 4: R₁ = N-propyl, R₂ = 9-OH), a potent
sigma ligand that is a conformationally restricted form
o 1987, Manallack et al., 1986). Trans-4aR,10bR-9-OH-n-

Pr-OHBQ (fig. 1, 4: R₁ = N-propyl, R₂ = 9-OH), a potent O

sigma ligand that is a conformationally restricted form

of (+)-3-PPP, is a relatively rigid molecule. Pr-OHBQ (fig. 1, 4: $R_1 = N$ -propyl, $R_2 = 9$ -OH), a potent
sigma ligand that is a conformationally restricted form
of $(+)$ -3-PPP, is a relatively rigid molecule. The crystal
structure of its tricyclic backbone is consider sigma ligand that is a conformationally restricted form in
of $(+)$ -3-PPP, is a relatively rigid molecule. The crystal
structure of its tricyclic backbone is considered to be its
biologically active conformation. Similarly of $(+)$ -3-PPP, is a relatively rigid molecule. The crystal
structure of its tricyclic backbone is considered to be its
chologically active conformation. Similarly, the crystal
structures of R- $(+)$ -3-PPP, $(+)$ -SKF 10,047 (biologically active conformation. Similarly, the crystal
structures of R-(+)-3-PPP, (+)-SKF 10,047 (from the
structure of cyclazocine) and haloperidol (fig. 1, 5: R₁ =
Cl, R₂ = F) were used to define low energy confor structures of R-(+)-3-PPP, (+)-SKF 10,047 (from the
structure of cyclazocine) and haloperidol (fig. 1, 5: R₁ =
Cl, R₂ = F) were used to define low energy conformations
of these ligands. The structure of DTG was develo structure of cyclazocine) and haloperidol (fig. 1, 5: R_1 = Cl, R_2 = F) were used to define low energy conformations of these ligands. The structure of DTG was developed from standard bond lengths and angles. The pri Cl, $R_2 = F$) were used to define low energy conform
of these ligands. The structure of DTG was devertion standard bond lengths and angles. The pr
pharmacophore for sigma receptor binding was
structed by using the crystal of these ligands. The structure of DTG was developed
from standard bond lengths and angles. The primary
pharmacophore for sigma receptor binding was con-
structed by using the crystal structure of *trans*-4aR,10bR-
9-OH-n from standard bond lengths and ang
pharmacophore for sigma receptor k
structed by using the crystal structure of
9-OH- n -Pr-OHBQ as a template onto
the other structures were superimpose
Although the sigma site defined armacophore for sigma receptor binding was con-

ructed by using the crystal structure of *trans*-4aR,10bR-

OH-n-Pr-OHBQ as a template onto which all four of
 $\frac{1}{t}$ other structures were superimposed.

Although the s

structed by using the crystal structure of *trans*-4aR,10bR-
9-OH-n-Pr-OHBQ as a template onto which all four of
the other structures were superimposed.
Although the sigma site defined by this model accepted
many unrelate the other structures were superimposed.

Although the sigma site defined by this model accepted

many unrelated sigma ligands, it failed to predict the

differences in potency of sigma ligands substituted on

the aromatic Although the sigma site defined by this model accomany unrelated sigma ligands, it failed to predidifferences in potency of sigma ligands substitution of a hygroup on the 7-, 8-, or 9-positions in the *trans-4aR*, 9-OH- n many unrelated sigma ligands, it failed to predict the
differences in potency of sigma ligands substituted on
the aromatic ring. For instance, substitution of a hydroxy
group on the 7-, 8-, or 9-positions in the *trans*-4 differences in potency of sigma ligands substituted on
the aromatic ring. For instance, substitution of a hydroxy
group on the 7-, 8-, or 9-positions in the *trans*-4aR,10bR-
9-OH-n-Pr-OHBQ series increased potency with t the aromatic ring. For instance, substitution of a hydroxy
group on the 7-, 8-, or 9-positions in the *trans*-4aR,10bR-
9-OH-n-Pr-OHBQ series increased potency with the
mank order being 8-OH > 9-OH >7-OH. Similar changes
 group on the 7-, 8-, or 9-positions in the *trans*-4aR,10bR-
9-OH-n-Pr-OHBQ series increased potency with the
rank order being 8-OH > 9-OH >7-OH. Similar changes
to $(+)$ -3-PPP have indicated that the 4-OH derivative is
mu 9-OH-n-Pr-OHBQ series increased potency with the nutrog
rank order being 8-OH > 9-OH >7-OH. Similar changes group
to (+)-3-PPP have indicated that the 4-OH derivative is model
much less potent than (+)-3-PPP. However, thi rank order being $8\text{-OH} > 9\text{-OH} > 7\text{-OH}$. Similar change
to $(+)$ -3-PPP have indicated that the 4-OH derivative i
much less potent than $(+)$ -3-PPP. However, this resul
is inconsistent with the OHBQ series in which the 8-O to $(+)$ -3-PPP have indicated that the 4-OH derivative is much less potent than $(+)$ -3-PPP. However, this result is inconsistent with the OHBQ series in which the 8-OH group corresponds to the 4-OH group of $(+)$ -3-PPP. Sig is inconsistent with the OHBQ series in which the 8-OH group corresponds to the 4-OH group of $(+)$ -3-PPP.
Sigma ligands which have substituents other than hy-
droxy groups include haloperidol, bromoperidol, and $(+)$ is inconsistent with the OHBQ series in which the 8-OH
group corresponds to the 4-OH group of $(+)$ -3-PPP.
Sigma ligands which have substituents other than hy-
droxy groups include haloperidol, bromoperidol, and $(+)$ -
3-(3 group corresponds to the 4-OH group of $(+)$ -3-PPP.
Sigma ligands which have substituents other than hy-
droxy groups include haloperidol, bromoperidol, and $(+)$ -
3-(3-fluorophenyl)-N- $(n$ -propyl)piperidine. The latter s
c Sigma ligands which have substituents other than hy-
droxy groups include haloperidol, bromoperidol, and $(+)$ - of r
3-(3-fluorophenyl)-N- $(n$ -propyl)piperidine. The latter sele
compound is similar in potency to $(+)$ -3-PPP, $3-(3$ -fluorophenyl)-N- $(n$ -propyl)piperidine. The latter compound is similar in potency to $(+)$ -3-PPP, indicating that a fluoro substituent is an acceptable alternative to a hydroxyl group. Similarly, DTG possesses higher $3-(3$ -fluorophenyl)-N- $(n$ -propyl)piperidine. The latter compound is similar in potency to $(+)$ -3-PPP, indicating that a fluoro substituent is an acceptable alternative to a hydroxyl group. Similarly, DTG possesses higher compound is similar in potency to $(+)$ -3-PPP, indicating pl
that a fluoro substituent is an acceptable alternative to
a hydroxyl group. Similarly, DTG possesses higher affin-
ity for sigma receptors than its desmethyl ana that a fluoro substituent is an acceptable alternative to
a hydroxyl group. Similarly, DTG possesses higher affin-
ity for sigma receptors than its desmethyl analog DPG
presumably due to the conformational restraints impos a hydroxyl group. Similarly, DTG possesses higher affinity for sigma receptors than its desmethyl analog DPG,
presumably due to the conformational restraints imposed
by the methyl groups. The greater conformational free-
d ity for sigma receptors than its der
presumably due to the conformation
by the methyl groups. The greater
dom exhibited by DPG would resu
affinity because of loss in entropy.
The electrostatic potentials of esumably due to the conformational restraints imposed
the methyl groups. The greater conformational free-
m exhibited by DPG would result in lowered binding
finity because of loss in entropy.
The electrostatic potentials o

by the methyl groups. The greater conformational free-
dom exhibited by DPG would result in lowered binding
affinity because of loss in entropy.
The electrostatic potentials of the five compounds
chosen to define the prima dom exhibited by DPG would result in lowered binding
affinity because of loss in entropy.
The electrostatic potentials of the five compounds
chosen to define the primary sigma receptor model were
investigated further to ex affinity because of loss in entropy.
The electrostatic potentials of the five compounds
chosen to define the primary sigma receptor model were
investigated further to examine the effect of aromatic
substitution on receptor The electrostatic potentials of the five compounds chosen to define the primary sigma receptor model were investigated further to examine the effect of aromatic substitution on receptor binding. The results of the study in chosen to define the primary sigma receptor model were
investigated further to examine the effect of aromatic
substitution on receptor binding. The results of the study
indicated that haloperidol, the most potent in the se investigated further to examine the effect of aromatic substitution on receptor binding. The results of the study indicated that haloperidol, the most potent in the series, possessed a deep potential energy well in the re substitution on receptor binding. The results of the studendicated that haloperidol, the most potent in the serie possessed a deep potential energy well in the region neareholds and the chlorine atom. DTG did not produce a indicated that haloperidol, the most potent in the series, possessed a deep potential energy well in the region near
the chlorine atom. DTG did not produce a potential
energy well and $(+)$ -SKF 10,047 and $trans\text{-}4aR,10bR\text{$ possessed a deep potential energy well in the region near
the chlorine atom. DTG did not produce a potentia
energy well and (+)-SKF 10,047 and *trans*-4aR,10bR-{
OH-n-Pr-OHBQ produced shallow to negligible potentia
energy the chlorine atom. DTG did not produce a potential
energy well and $(+)$ -SKF 10,047 and *trans*-4aR,10bR-9-
OH-n-Pr-OHBQ produced shallow to negligible potential
energy wells in the region of their hydroxy substituents.
Th energy well and $(+)$ -SKF 10,047 and *trans*-4aR,10bR-9-
OH-n-Pr-OHBQ produced shallow to negligible potential
energy wells in the region of their hydroxy substituents.
The higher potency of bromoperidol and haloperidol ma OH-n-Pr-OHBQ produced shallow to negligible potential penergy wells in the region of their hydroxy substituents.
The higher potency of bromoperidol and haloperidol may period be partly explained by their possessing potent energy wells in the region of their hydroxy substituents.

The higher potency of bromoperidol and haloperidol may

be partly explained by their possessing potential energy

wells; however, the high potency of DTG cannot b The higher potency of bromoperidol and haloperidol may
be partly explained by their possessing potential energy
wells; however, the high potency of DTG cannot be
explained this way. Unlike the PCP analogs examined
by Manal

EPTORS
sigma analogs examined are all from different structural
classes, which makes interpretation of the effects of EPTORS 365
sigma analogs examined are all from different structural
classes, which makes interpretation of the effects of
electrostatic potential subjective rather than quantita-EPTORS
sigma analogs examined are all from different struct
classes, which makes interpretation of the effect
electrostatic potential subjective rather than quant
tive. Thus far, it can be concluded that electronega sigma analogs examined are all from different structural classes, which makes interpretation of the effects of electrostatic potential subjective rather than quantitative. Thus far, it can be concluded that electronegative sigma analogs examined are all from different structurelasses, which makes interpretation of the effects electrostatic potential subjective rather than quantit tive. Thus far, it can be concluded that electronegatif substi electrostatic potential subjective rather than quantitaelectrostatic
tive. Thus fa
substituents
OH-n-Pr-OI
ing affinity.
The incre Free. Thus far, it can be concluded that electronegative
bstituents on the C-9 position of *trans*-4aR,10bR-9-
H-n-Pr-OHBQ appear to increase sigma receptor-bind-
g affinity.
The increases in sigma receptor potency seen w

substituents on the C-9 position of *trans*-4a R ,10
OH- n -Pr-OHBQ appear to increase sigma receptor-
ing affinity.
The increases in sigma receptor potency seen
changing the nitrogen substituent in $(+)$ -benzo
phans, $(+)$ OH-n-Pr-OHBQ appear to increase sigma receptor-bind-
ing affinity.
The increases in sigma receptor potency seen with
changing the nitrogen substituent in $(+)$ -benzomor-
phans, $(+)$ -morphinans, and 3-phenylpiperidines can ing affinity.
The increases in sigma receptor potency seen with
changing the nitrogen substituent in $(+)$ -benzomor-
phans, $(+)$ -morphinans, and 3-phenylpiperidines can be
explained by the presence of a lipophilic cleft. W The increases in sigma receptor potency seen with
changing the nitrogen substituent in $(+)$ -benzomor-
phans, $(+)$ -morphinans, and 3-phenylpiperidines can be
explained by the presence of a lipophilic cleft. With the
 $(+)$ -3 changing the nitrogen substituent in $(+)$ -benzomor-
phans, $(+)$ -morphinans, and 3-phenylpiperidines can be
explained by the presence of a lipophilic cleft. With the
 $(+)$ -3-PPP series (table 2), the most potent compounds
i phans, (+)-morphinans, and 3-phenylpiperidines carexplained by the presence of a lipophilic cleft. With (+)-3-PPP series (table 2), the most potent compour in the series are those that have the largest nitrogendstituents. explained by the presence of a lipophilic cleft. With the $(+)-3$ -PPP series (table 2), the most potent compounds in the series are those that have the largest nitrogen substituents. The rank order of potency for nitrogen-s (+)-3-PPP series (table 2), the most potent compounds
in the series are those that have the largest nitrogen-
substituents. The rank order of potency for nitrogen-
substituted derivatives of (+)-3-PPP is N-phenethyl >
N-b in the series are those that have the largest nitrogen
substituents. The rank order of potency for nitrogen-
substituted derivatives of $(+)-3$ -PPP is N-phenethyl >
N-butyl > N-propyl > N-ethyl > N-methyl. A similar
rank or $trans-4aR,10bR-9-OH-n-Pr-OHBQ.$ bstituted derivatives of $(+)$ -3-PPP is N-phenethyl $>$ -butyl $>$ N-propyl $>$ N-ethyl $>$ N-methyl. A similar nk order of potencies has also been demonstrated for ins -4a R ,10b R -9-OH- n -Pr-OHBQ.
The hypothetical recept

the other structures were superimposed.

Although the sigma site defined by this model accepted

many unrelated sigma ligands, it failed to predict the

many pharmacophore were found to be R_1 (0.00, 3.50,

differences N-butyl > N-propyl > N-ethyl > N-methyl. A similar
rank order of potencies has also been demonstrated for
trans-4aR,10bR-9-OH-n-Pr-OHBQ.
The hypothetical receptor points (R_1, R_2, R_3) for the
primary pharmacophore were rank order of potencies has also been demonstrated for

trans-4aR,10bR-9-OH-n-Pr-OHBQ.

The hypothetical receptor points (R_1, R_2, R_3) for the

primary pharmacophore were found to be R_1 (0.00, 3.50,

0.00), R_2 (0.0 trans-4aR,10bR-9-OH-n-Pr-OHBQ.
The hypothetical receptor points (R_1, R_2, R_3) for the
primary pharmacophore were found to be R_1 (0.00, 3.50,
0.00), R_2 (0.00, -3.50, 0.00), R_3 (6.09, 2.09, 0.00), and N
(4.9, -0.1 The hypothetical receptor points (R_1, R_2, R_3) for the
primary pharmacophore were found to be R_1 (0.00, 3.50,
0.00), R_2 (0.00, -3.50, 0.00), R_3 (6.09, 2.09, 0.00), and N
(4.9, -0.12, -1.25). Secondary binding re primary pharmacophore were found to be R_1 (0.00, 3.50, 0.00), R_2 (0.00, -3.50, 0.00), R_3 (6.09, 2.09, 0.00), and N (4.9, -0.12, -1.25). Secondary binding requirements for sigma ligands were proposed with interact 0.00), R_2 (0.00, -3.50 , 0.00), R_3 (6.09, 2.09, 0.00), and N (4.9, -0.12 , -1.25). Secondary binding requirements for sigma ligands were proposed with interaction of the nitrogen substituent and aromatic group w $(4.9, -0.12, -1.25)$. Secondary binding requirements fo
sigma ligands were proposed with interaction of the
nitrogen substituent and aromatic group with lipophili
groups on the receptor. The proposed sigma recepto
model di sigma ligands were proposed with interaction of the nitrogen substituent and aromatic group with lipophilic groups on the receptor. The proposed sigma receptor model differs from the PCP receptor model in (a) position of nitrogen substituent and aromatic group with lipophilic
groups on the receptor. The proposed sigma receptor
model differs from the PCP receptor model in (*a*) posi-
tion of the nitrogen atom, (*b*) direction of the lone pa groups on the receptor. The proposed sigma receptor
model differs from the PCP receptor model in (a) posi-
tion of the nitrogen atom, (b) direction of the lone pair
vector, and (c) secondary binding requirements. These model differs from the PCP receptor model in (a) position of the nitrogen atom, (b) direction of the lone pair vector, and (c) secondary binding requirements. These differing quantitative SARs of PCP and sigma ligands tion of the nitrogen atom, (b) direction of the lone pair
vector, and (c) secondary binding requirements. These
differing quantitative SARs of PCP and sigma ligands
allow definition of discrete receptors, as well as the vector, and (c) secondary binding requirements. These
differing quantitative SARs of PCP and sigma ligands
allow definition of discrete receptors, as well as the design
of novel PCP and sigma ligands of high potency and
se differing quantitative SARs of PCP and sigma ligands
allow definition of discrete receptors, as well as the design
of novel PCP and sigma ligands of high potency and
selectivity. In figs. 2 and 3 the hypothetical primary
p allow definition of discrete receptors, as well as the design
of novel PCP and sigma ligands of high potency and
selectivity. In figs. 2 and 3 the hypothetical primary
pharmacophore formulated with the secondary binding
r the secondary bindin
* trans-4aR,10bR-n-Pr-OHB
* R-(+)-PPP

periodic CHBQ
FIG. 2. Diagrammatic representation of the location of various ar-
omatic substituents of molecules from the benzomorphan, phenylpi-
peridine, and OHBQ drug classes. For reference purposes, the phenyl
ring FIG. 2. Diagrammatic representation of the location of various aromatic substituents of molecules from the benzomorphan, phenylpiperidine, and OHBQ drug classes. For reference purposes, the phenyl ring of (*trans*)-(4aR,10 omatic substituents of molecules from the benzomorphan, phenylpi-
peridine, and OHBQ drug classes. For reference purposes, the phenyl
ring of (*trans*)-(4aR,10bR)-9-OH-*n*-Pr-OHBQ and the carbon-oxygen
or carbon-chloride b ring of (*trans*)-(4aR,10bR)-9-OH-n-Pr-OHBQ and the carbon-oxygen
or carbon-chloride bonds for each molecule are shown. Optimal sigma
receptor affinity appears to require electronegative aromatic substit-
uents residing in

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REVIEW

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FIG. 3. Diagrammatic representation of the sigma receptor model
detailing the position of receptor points R₁, R₂, and R₄, lipophilic clefts,
and a site for electronegative substituents. *Dashed line*, R₁-R₂ and N FIG. 3. Diagrammatic representation of the sigma receptor model of detailing the position of receptor points R_1 , R_2 , and R_3 , lipophilic clefts, and a site for electronegative substituents. Dashed line, R_1 - R_2 and a site for electronegative substituents. *Dashed line*, R_1 - R_2 and N - R_3 vectors. Hydrogen atoms have been deleted for clarity. Each unit on the scale bar represents 1 Å. *a*, Sigma receptor model viewed down Example a new order of the scale bar represents a have been deleted for clarity. Each unit the on the scale bar represents 1 Å. a, Sigma receptor model viewed down the y axis, showing the molecules haloperidol, (*trans*)-(on the scale bar represents 1 Å. *a*, Sigma receptor model viewed d
the y axis, showing the molecules haloperidol, $(trans)-(4aR,10bI$
OH-n-Pr-OHBQ, $(R)-(+)$ -[³H]-3-PPP, DTG, and $(+)$ -SKF 10,04
their best fit low energy conformat on the scale bar represents 1 Å. a , Sigma receptor model viewed down the y axis, showing the molecules haloperidol, $(trans)$ - $(4aR,10bR)$ -9-
OH-n-Pr-OHBQ, (R) - $(+)$ -[³H]-3-PPP, DTG, and $(+)$ -SKF 10,047 in b
their best fi the y axis, showing the molecules haloperidol, $(trains)$ - $(4aR,10bR)$ -9-
OH-n-Pr-OHBQ, (R) - $(+)$ -[³H]-3-PPP, DTG, and $(+)$ -SKF 10,047 in be di
their best fit low energy conformations to the primary pharmacophore. light.
b, State their best fit low energy
their best fit low energy
b, Sigma receptor model
of the receptor points l
Manallack et al., 1988. *b*, Sigma receptor model view
of the receptor points R₁, F
Manallack et al., 1988.
B. Allosteric Models
1 Allosteric interact

of the receptor points R₁, R₂, and R₆ and the lipophilic cleft. From
 Manallack et al., 1988.
 B. Allosteric Models
 1. Allosteric interactions between (+)-benzomorphan-
 and non-benzomorphan-binding domains. B. Allosteric Models
1. Allosteric interactions between (+)-benzomorphan-
and non-benzomorphan-binding domains. In a markedly
different approach to modeling the sigma receptor,
Bowen et al. (1989a) found evidence supportin B. Aubsteric interactions between $(+)$ -benzomorphan-
and non-benzomorphan-binding domains. In a markedly
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Bowen et al. (1989a) found evidence supporting a model
of distinc 1. Allosteric interactions between $(+)$ -benzomorphan-
and non-benzomorphan-binding domains. In a markedly C
different approach to modeling the sigma receptor, the
Bowen et al. (1989a) found evidence supporting a model
of and non-benzomorphan-binding domains. In a markedly different approach to modeling the sigma receptor, Bowen et al. (1989a) found evidence supporting a model of distinct, allosterically coupled binding domains for non-benz different approach to modeling the sigma receptor, the Bowen et al. (1989a) found evidence supporting a model the of distinct, allosterically coupled binding domains for pernon-benzomorphan sigma ligands and sigma-related Bowen et al. (1989a) found evidence supporting a mode of distinct, allosterically coupled binding domains for
non-benzomorphan sigma ligands and sigma-related $(+)$
benzomorphans. Studies of the sensitivity of rat brai
sig of distinct, allosterically coupled binding domains for
non-benzomorphan sigma ligands and sigma-related (+)-
benzomorphans. Studies of the sensitivity of rat brain
sigma receptors to UV irradiation revealed unusual bind-
 non-benzomorphan sigma ligands and sigma-related $(+)$ - and
benzomorphans. Studies of the sensitivity of rat brain PP!
sigma receptors to UV irradiation revealed unusual bind-
ing interactions of the various radiolabeled s benzomorphans. Studies of the sensitivity of rat brain Plagma receptors to UV irradiation revealed unusual bind-
ing interactions of the various radiolabeled sigma probes. Un
As shown in fig. 4, irradiation of membranes w sigma receptors to UV irradiation revealed unusual bind-
ing interactions of the various radiolabeled sigma probes.
As shown in fig. 4, irradiation of membranes with 254
nm light produced a time-dependent decrease in the
 ing interactions of the various radiolabeled sigma probes. Unk shown in fig. 4, irradiation of membranes with 254 comm light produced a time-dependent decrease in the zoi binding of both $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$, an e

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FIG. 4. Effect of UV irradiation on binding of ligands to the sigma
receptor. Rat brain membranes were irradiated using a high intensity
UV lamp of 254 nm. Aliquots were taken at each time point and FIG. 4. Effect of UV irradiation on binding of ligands to the sigma
receptor. Rat brain membranes were irradiated using a high intensity
UV lamp of 254 nm. Aliquots were taken at each time point and
pelleted. After resuspe **FIG. 4. Effect of UV irradiation on binding of ligands to the sigma receptor. Rat brain membranes were irradiated using a high intensity UV lamp of 254 nm. Aliquots were taken at each time point and pelleted. After resusp** EV lamp of 254 nm. Aliquots were taken at each time point an pelleted. After resuspension in the assay buffer, the ability of the membranes to bind $[^2H]DTG$ (\bullet), $[^2H](+)-3-PPP$ (\circ), and $[^2H](+)$ SKF 10,047 (\bullet) was d pelleted. After resuspension in the assay buffer, the ability of the
membranes to bind [³H]DTG ([●]), [³H](+)-3-PPP (○), and [³H](+)-
SKF 10,047 (■) was determined. Values are expressed as percentages
of the specifi the averages of two experiments carried out in duplicate \pm SEM. Time-

zero specific binding: [³H]OTG, 1472 \pm 296 cpm; [³H](+)-3-PPP, 1462
 \pm 404 cpm; [³H](+)-SKF 10,047, 299 \pm 36 cpm. Nonspecific bindin \pm 404 cpm; $[{}^{3}H](+)-SKF$ 10,047, 299 \pm 36 cpm. Nonspecific binding for each ligand was determined in the presence of 10 μ M $(+/-)-cycl$ azocine. Identical results were obtained when 1 μ M haloperidol was used to det cyclazocine. Identical results were obtained when $1 \mu M$ haloperidol was used to determine specific binding of $[{}^{3}H]DTG$ and $[{}^{3}H](+)$ -3-PPP. Irradiation had no effect on nonspecific binding. Reprinted from Bowen et a symmetric interaction of the binding of $(^3H]DTG$ and $(^3H)(+)$ -3-PPP.
Irradiation had no effect on nonspecific binding. Reprinted from Bowen
et al., 1989a.
other hand, the binding of $(^3H)(+)$ -SKF 10,047 was
markedly enhanc **Fig. 14.1**
 be distinguished by the matrices were irradiated using a figured by the signal receptor. Rat brain membranes were irradiated using a high intensity of the points of 264 nm. Aliquots were taken at each time p

Irradiation had no effect on nonspecific binding. Reprinted from Bowen
et al., 1989a.

other hand, the binding of $[^{3}H](+)$ -SKF 10,047 was

markedly enhanced by irradiation, due to an increase in

the binding affinity. T et al., 1989a.

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markedly enhanced by irradiation, due to an increas

the binding affinity. The data suggest that benzon

phan and non-benzomorphan sigma ligands interact v other hand, the binding of $[^{3}H](+)$ -SKF 10,047 was
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phan and non-benzomorphan sigma ligands interact with
differ other hand, the binding of $[^{3}H](+)$ -SKF 10,047 was
markedly enhanced by irradiation, due to an increase in
the binding affinity. The data suggest that benzomor-
phan and non-benzomorphan sigma ligands interact with
diffe light. phan and non-benzomorphan sigma ligands interact with
different sites on the receptor macromolecule that can
be distinguished by their different sensitivities to UV
light.
Other studies also yielded results consistent with

B. Allosteric Models
DTG or haloperidol are added to the incubation, an
increase in the K_d occurs without a change in the B_{max} ;
1. Allosteric interactions between (+)-benzomorphan-
and non-benzomorphan-bin different sites on the receptor macromolecule that can
be distinguished by their different sensitivities to UV
light.
Other studies also yielded results consistent with an
allosteric model. Scatchard analysis (fig. 5) of l be distinguished by their different sensitivities to UV
light.
Other studies also yielded results consistent with an
allosteric model. Scatchard analysis (fig. 5) of labeled
[³H](+)-3-PPP binding revealed that, when unla light.

Other studies also yielded results consistent with an

allosteric model. Scatchard analysis (fig. 5) of labeled

[³H](+)-3-PPP binding revealed that, when unlabeled

DTG or haloperidol are added to the incubatio Other studies also yielded results consistent with an allosteric model. Scatchard analysis (fig. 5) of labeled $[^{3}H](+)-3$ -PPP binding revealed that, when unlabeled DTG or haloperidol are added to the incubation, an incre allosteric model. Scatchard analysis (fig. 5) of labeled $[^{3}H](+)-3-PPP$ binding revealed that, when unlabeled DTG or haloperidol are added to the incubation, an increase in the K_d occurs without a change in the B_{max} [³H](+)-3-PPP binding revealed that, when unlabeled
DTG or haloperidol are added to the incubation, an
increase in the K_d occurs without a change in the B_{max} ;
this pattern is consistent with competitive inhibitio DTG or haloperidol are added to the incubation, an increase in the K_d occurs without a change in the B_{max} ; this pattern is consistent with competitive inhibition.
On the other hand, when the experiment is performed increase in the K_d occurs without a change in the B_t , this pattern is consistent with competitive inhibition the other hand, when the experiment is performed the presence of unlabeled $(+)$ -opiates, both the K_d a the this pattern is consistent with competitive inhibition.
On the other hand, when the experiment is performed in
the presence of unlabeled $(+)$ -opiates, both the K_d and
the B_{max} are decreased, a finding suggestive of On the other hand, when the experiment is performed in
the presence of unlabeled $(+)$ -opiates, both the K_d and
the B_{max} are decreased, a finding suggestive of uncom-
petitive inhibition. Thus, the non-benzomorphans the presence of unlabeled $(+)$ -opiates, both the K_d and
the B_{max} are decreased, a finding suggestive of uncom-
petitive inhibition. Thus, the non-benzomorphans DTG
and haloperidol are competitive inhibitors of $[^3H$ the B_{max} are decreased, a finding suggestive of uncompetitive inhibition. Thus, the non-benzomorphans DTG and haloperidol are competitive inhibitors of $[^{3}H](+)-3$ -PPP binding, whereas the benzomorphans $(+)-SKF$ 10,047 petitive inhibition. Thus, the non-benzomorphans DTG
and haloperidol are competitive inhibitors of $[^{3}H](+)-3$ -
PPP binding, whereas the benzomorphans $(+)$ -SKF
10,047 and $(+)$ -pentazocine are uncompetitive inhibitors.
Unc and haloperidol are competitive inhibitors of $[{}^{3}H](+)-3-$
PPP binding, whereas the benzomorphans $(+)$ -SKF
10,047 and $(+)$ -pentazocine are uncompetitive inhibitors.
Uncompetitive inhibition is consistent with allosteric
 zomorphan-binding site. A ,047 and $(+)$ -pentazocine are uncompetitive inhibitors.

accompetitive inhibition is consistent with allosteric

upling of a benzomorphan-binding site to a non-ben-

morphan-binding site.

A third line of evidence favo Uncompetitive inhibition is consistent with allosteric
coupling of a benzomorphan-binding site to a non-ben-
zomorphan-binding site.
A third line of evidence favoring an allosteric model
was again derived from studies of m

3-PPP binding was carried out in the absence *(closed circles)* and the presence *(open symbols)* of a fixed concentration of the specified unlabeled sigma ligands inhibit binding of $(^{3}H)(+)-3-PPP$. Scatchard analysis of **competing ligand using orientation** of the mechanism by which unlabeled sigma ligands inhibit binding of $[{}^{3}H](+)-$ 3-PPP. Scatchard analysis of $[{}^{3}H](+)-$ 3-PPP binding was carried out in the absence (*closed circles*) a FIG. 5. Determination of the mechanism by which unlabeled sigma ligands inhibit binding of $[{}^{3}H](+)-3-PPP$. Scatchard analysis of $[{}^{3}H](+)-3-PPP$ binding was carried out in the absence (*closed circles*) and the presence (FIG. 5. Determination of the mechanism by which unlabeled sigma ligands inhibit binding of $[{}^{3}H](+)-3-PPP$. Scatchard analysis of $[{}^{3}H](+)-3-PPP$ binding was carried out in the absence (closed circles) and the presence (ope competing ligand using nonirradiated membranes. Non-specific binding was determined in the presence of 1 μ M haloperidol. The binding of [³H] (+)-3-PPP alone (\bullet) was repeated for comparison in all 4 panels. As illu illustrated in C and D, the simultaneous alterations in apparent K_d and B_{max} of $[^3H](+)$ -3-PPP induced by addition of unlabeled 300 nM (+)subtype **of sigma receptor.** Reprinted from **Bowen et a!., 1989a.** illustrated in C and D, the simultaneous alterations in apparent K_d and SKF 10,047 (\square) or 50 nM (+)-pentazocine (\diamond) demonstrates uncompetify subtype of sigma receptor. Reprinted from Bowen et al., 1989a.
irradiate

SKF 10,047 (\square) or 50 nM (+)-pentazocine (\diamond) demonstrates uncompetistively of sigma receptor. Reprinted from Bowen et al., 1989a.

irradiated with UV light. This treatment markedly reduced the ability of DTG and (+)subtype or sigma receptor. Reprinted from Bowen et al., 1989a.

irradiated with UV light. This treatment markedly re-

duced the ability of DTG and $(+)$ -3-PPP to inhibit

binding of $[^{3}H](+)$ -SKF 10,047 but had no effect o irradiated with UV light. This treatment markedly re-
duced the ability of DTG and $(+)$ -3-PPP to inhibit
binding of $[^{3}H](+)$ -SKF 10,047 but had no effect on the
potency of $(+)$ -pentazocine and $(+)$ -SKF 10,047. Similar
re irradiated with UV light. This treatment markedly
duced the ability of DTG and $(+)$ -3-PPP to inh
binding of $[^{3}H](+)$ -SKF 10,047 but had no effect on
potency of $(+)$ -pentazocine and $(+)$ -SKF 10,047. Sin
results have been binding of $[^{3}H](+)$ -SKF 10,047 but had no effect on the potency of $(+)$ -pentazocine and $(+)$ -SKF 10,047. Similar results have been obtained with $[^{3}H](+)$ -pentazocine. These findings imply that the binding site of the potency of $(+)$ -pentazocine and $(+)$ -SKF 10,047. Similar potency of $(+)$ -pentazocine and $(+)$ -SKF 10,047. Similar
results have been obtained with $[^{3}H](+)$ -pentazocine.
These findings imply that the binding site of the neuro-
leptic type compounds was disrupted by the UV light, intact. hose findings imply that the binding site of the neurotic type compounds was disrupted by the UV light, sile the binding site for the $(+)$ -opiate ligands remained tact.
A model (fig. 6) consistent with all the data cited

leptic type compounds was disrupted by the UV light,
while the binding site for the $(+)$ -opiate ligands remained
intact.
A model (fig. 6) consistent with all the data cited above
is one in which benzomorphans bind to a do while the binding site for the $(+)$ -opiate ligands remained
intact.
A model (fig. 6) consistent with all the data cited above
is one in which benzomorphans bind to a domain on the
receptor macromolecule that is resistant intact.

A model (fig. 6) consistent with all the data cited above

is one in which benzomorphans bind to a domain on the

receptor macromolecule that is resistant to the effects of

UV light. This domain is allostericall A model (fig. 6) consistent with all the data cited abis one in which benzomorphans bind to a domain on receptor macromolecule that is resistant to the effect UV light. This domain is allosterically coupled to binding doma is one in which benzomorphans bind to a domain on the receptor macromolecule that is resistant to the effects of UV light. This domain is allosterically coupled to a binding domain for non-benzomorphans. The non-benzomorph receptor macromolecule that is resistant to the effects of UV-light. This domain is allosterically coupled to a highlning domain for non-benzomorphans. The non-ben-
zomorphan domain is sensitive to UV-sensitive residue wh binding domain for non-benzomorphans. The non-benzomorphan domain is sensitive to UV irradiation, perhaps because of the presence of a UV-sensitive residue such as tryptophan.
An allosteric model may have implications for nding domain for non-benzomorphans. The non-ben-
morphan domain is sensitive to UV irradiation, per-
ps because of the presence of a UV-sensitive residue with
ch as tryptophan.
An allosteric model may have implications for

zomorphan domain is sensitive to UV irradiation, perhaps because of the presence of a UV-sensitive residue with
such as tryptophan.
An allosteric model may have implications for an where
endogenous sigma ligand. The marke haps because of the presence of a UV-sensitive residue
such as tryptophan.
An allosteric model may have implications for an
endogenous sigma ligand. The marked enhancement in
 $[^{3}H](+)-SKF$ 10,047 binding following UV irrad such as tryptophan.

An allosteric model may have implications for an whendogenous sigma ligand. The marked enhancement in
 $[^{3}H](+)$ -SKF 10,047 binding following UV irradiation

was intriguing. Conceivably, an endogenous An allosteric model may have implications for an when
endogenous sigma ligand. The marked enhancement in
 $[^{3}H](+)$ -SKF 10,047 binding following UV irradiation
was intriguing. Conceivably, an endogenous sigma ligand
and no endogenous sigma ligand. The marked enhancement in $[^{3}H](+)$ -SKF 10,047 binding following UV irradiation was intriguing. Conceivably, an endogenous sigma ligand normally occupies the neuroleptic like binding site and inhi [$^{\circ}$ H](+)-SKF 10,047 binding following UV irradiation ers
was intriguing. Conceivably, an endogenous sigma ligand an
normally occupies the neuroleptic like binding site and bin
inhibits the binding of (+)-opiates. In s was intriguing. Conceivably, an endogenous sigma ligand
normally occupies the neuroleptic like binding site and
inhibits the binding of $(+)$ -opiates. In such a case, dis-
ruption of the neuroleptic site by UV irradiation normally occupies the neuroleptic like binding site
inhibits the binding of (+)-opiates. In such a case,
ruption of the neuroleptic site by UV irradiation w
remove the inhibition, thereby increasing the bindi
(+)-opiate li *sant compounds the neuroleptic site by UV irradiation work-*
sant compounds igands. 2. Allosteric interactions of antitussive and anticonvent compounds with sigma sites. Musacchio and cowork-
sant compounds with sigma

interaction
FIG. 6. Schematic of an allosteric model of sigma-bindi
hypothesized by Bowen et al. (1988a). Various sigma ligar
interact with either a neuroleptic binding site or (+)-benzom
binding site on a sigma receptor FIG. 6. Schematic of an allosteric model of sigma-binding sites hypothesized by Bowen et al. (1988a). Various sigma ligands may interact with either a neuroleptic binding site or $(+)$ -benzomorphan-binding site on a sigma r interact with either a neuroleptic binding site or $(+)$ -benzomorph
binding site on a sigma receptor macromolecule. Ligands that inter
with the same site exhibit competitive inhibition; ligands interact
with different site interaction. The neuroleptic site is readily destroyed by the same site on a sigma receptor macromolecule. Ligands that interaction which the same site exhibit binding by an allosteric (noncompetitive with different sites with different sites inhibit binding by an allosteric (noncompetitive)
interaction. The neuroleptic site is readily destroyed by UV irradiation,
whereas the (+)-benzomorphan site is relatively unaffected.
ers (Musacchio et

interaction. The neuroleptic site is readily destroyed by UV irradiation,
whereas the (+)-benzomorphan site is relatively unaffected.
ers (Musacchio et al., 1989a,b; Klein et al., 1989; Klein
and Musacchio, 1989; Canoll et whereas the (+)-benzomorphan site is relatively unaffected.
ers (Musacchio et al., 1989a,b; Klein et al., 1989; Klein
and Musacchio, 1989; Canoll et al., 1989) identified a
binding site for the non-opioid antitussive DM in ers (Musacchio et al., 1989a,b; Klein et al., 1989; Klein
and Musacchio, 1989; Canoll et al., 1989) identified a
binding site for the non-opioid antitussive DM in guinea
pig, rat, and mouse brain. [³H]DM binds to high a ers (Musacchio et al., 1989a,b; Klein et al., 1989; Kland Musacchio, 1989; Canoll et al., 1989) identified binding site for the non-opioid antitussive DM in guir pig, rat, and mouse brain. [³H]DM binds to high and laffi and Musacchio, 1989; Canoll et al., 1989) identified a
binding site for the non-opioid antitussive DM in guinea
pig, rat, and mouse brain. [³H]DM binds to high and low
affinity sites with K_d values of 57 nM and 24 μ binding site for the non-opioid antitussive DM in guinea
pig, rat, and mouse brain. [³H]DM binds to high and low
affinity sites with K_d values of 57 nM and 24 μ M, respec-
tively (Klein and Musacchio, 1989). Prototy pig, rat, and mouse brain. [³H]DM binds to high and low
affinity sites with K_d values of 57 nM and 24 μ M, respec-
tively (Klein and Musacchio, 1989). Prototypic sigma
ligands, such as haloperidol, (+)-pentazocine, affinity sites with K_d values of 57 nM and 24 μ M, respectively (Klein and Musacchio, 1989). Prototypic sigma ligands, such as haloperidol, (+)-pentazocine, and (+)-SKF 10,047, displace [³H]DM from the high affinity

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site (Klein et al., 1989). Similarly, there is a high corre-
lation between the potency of compounds in displacing WALKER E
site (Klein et al., 1989). Similarly, there is a high corre-
lation between the potency of compounds in displacing
[³H](+)-3-PPP and [³H]DM (table 3). These data sup-WALKI
site (Klein et al., 1989). Similarly, there is a high corre-
lation between the potency of compounds in displacing
[³H](+)-3-PPP and [³H]DM (table 3). These data sup-
port the contention of Musacchio et al. that site (Klein et al., 1989). Similarly, there is a high correlation between the potency of compounds in displacing $[^{3}H](+)-3$ -PPP and $[^{3}H]DM$ (table 3). These data support the contention of Musacchio et al. that the sigm site (Klein et al., 1989). Similarly, there is a high correlation between the potency of compounds in displacing $[^{3}H](+)-3$ -PPP and $[^{3}H]DM$ (table 3). These data support the contention of Musacchio et al. that the sigma entity. port the contention of Musacchio et al. that the sigma site and the high affinity DM-binding site are the same
entity.
Support for an allosteric model of sigma sites comes
from the effect of antitussive and anticonvulsant

port the contention of Musacchio et al. that the sigm-
site and the high affinity DM-binding site are the same
entity.
Support for an allosteric model of sigma sites come
from the effect of antitussive and anticonvulsant c site and the high affinity DM-binding site are the same
entity.
Support for an allosteric model of sigma sites comes
from the effect of antitussive and anticonvulsant com-
pounds on binding of $[^3H]DM$ (Musacchio et al., 19 entity.

Support for an allosteric model of sigma sites comes

from the effect of antitussive and anticonvulsant com-

pounds on binding of $[^{3}H]DM$ (Musacchio et al., 1989b).

The anticonvulsants phenytoin and ropizine p Support for an allosteric model of sigma sites comes
from the effect of antitussive and anticonvulsant com-
pounds on binding of $[^{3}H]DM$ (Musacchio et al., 1989b).
The anticonvulsants phenytoin and ropizine produce
dose from the effect of antitussive and anticonvulsant compounds on binding of $[^3H]DM$ (Musacchio et al., 1989b).
The anticonvulsants phenytoin and ropizine produce
dose-dependent enhancement of $[^3H]DM$ binding to
guinea pig b pounds on binding of [³H]DM (Musacchio et al., 1989b).
The anticonvulsants phenytoin and ropizine produce
dose-dependent enhancement of [³H]DM binding to
guinea pig brain membranes. The increase in binding is
biphasic, The anticonvulsants phenytoin and ropizine produce
dose-dependent enhancement of $[^8H]DM$ binding to
guinea pig brain membranes. The increase in binding is
biphasic, shows an inhibitory phase after a peak of
enhancement, a dose-dependent enhancement of [³H]DM binding to
guinea pig brain membranes. The increase in binding is
biphasic, shows an inhibitory phase after a peak of
enhancement, and appears to be related to a 3-fold
increase in b guinea pig brain membranes. The increase in binding is
biphasic, shows an inhibitory phase after a peak of
enhancement, and appears to be related to a 3-fold
increase in binding affinity without a change in the (*tr*
numbe biphasic, shows an inhibitory phase after a peak of enhancement, and appears to be related to a 3-fold increase in binding affinity without a change in the number of sites. Both ropizine and phenytoin were shown to slow t or phasic, shows an inhibitory phase after a peak of $[{}^{4}H]$ $(+)$ -3-PPP (solid lines) and $[{}^{4}H]$ DM (dashed lines) in guinea pig
enhancement, and appears to be related to a 3-fold
increase in binding affinity without a number of sites. Both ropizine and phenytoin were shown
to slow the dissociation of [³H]DM. These results suggest
that [³H]DM binds to a macromolecule that contains a
distinct but allosterically coupled binding site fo to slow the dissociation of $[^{3}H]DM$. These results suggest
that $[^{3}H]DM$ binds to a macromolecule that contains a
distinct but allosterically coupled binding site for ropi-
zine and phenytoin.
Perhaps the strongest evi slow the dissociation of $[^{3}H]DM$. These results suggest of i
at $[^{3}H]DM$ binds to a macromolecule that contains a from
stinct but allosterically coupled binding site for ropi-
e and phenytoin.
Perhaps the strongest e that $[^{3}H]DM$ binds to a macromolecule that contains
distinct but allosterically coupled binding site for ro
zine and phenytoin.
Ferhaps the strongest evidence that sigma sites a
identical with at least one of the $[^{3}H$

distinct but allosterically coupled binding site for ropi-
zine and phenytoin.
Perhaps the strongest evidence that sigma sites are
identical with at least one of the [³H]DM sites charac-
terized by Musacchio and coworker zine and phenytoin.

Perhaps the strongest evidence that sigma sites are

identical with at least one of the $[^3H]DM$ sites charac-

terized by Musacchio and coworkers is the finding that
 $[^3H](+)-3-PPP$ binding shows alloste Perhaps the strongest evidence that sigma sites are
identical with at least one of the [³H]DM sites charac-
terized by Musacchio and coworkers is the finding that
[³H](+)-3-PPP binding shows allosteric modulations
tha identical with at least one of the [³H] DM sites characterized by Musacchio and coworkers is the finding that $[^3H](+)-3$ -PPP binding shows allosteric modulations that are similar to those of $[^3H]$ DM. As shown in fig. 7 terized by Musacchio and coworkers is the finding that $[^{3}H](+)-3$ -PPP binding shows allosteric modulations that are similar to those of $[^{3}H]DM$. As shown in fig. 7, ropizine and phenytoin enhanced binding of $[^{3}H] (+)-3$ ropizine and phenytoin enhanced binding of $[^{3}H]$ (+)-3-
PPP to guinea pig brain membranes (Musacchio et al.,
1989b). The effect was biphasic and occurred over a
nearly identical dose range of both ropizine and pheny-
t ropizine and phenytoin enhanced binding of $[{}^{3}H]$ (+)-3-
PPP to guinea pig brain membranes (Musacchio et al.,
1989b). The effect was biphasic and occurred over a
nearly identical dose range of both ropizine and pheny-
 PPP to guinea pig brain membranes (Musacchio et al., 1989b). The effect was biphasic and occurred over a nearly identical dose range of both ropizine and phenytoin. This phenomenon is quite dramatic; ropizine caused nearl 1989b). The effect was biphasic and occurred over a
nearly identical dose range of both ropizine and pheny-
toin. This phenomenon is quite dramatic; ropizine caused
nearly a 3-fold increase in the binding affinity of $[^{3$ mearly identical dose range of both ropizine and phen
toin. This phenomenon is quite dramatic; ropizine cause
nearly a 3-fold increase in the binding affinity of $[^3]$
 $(+)-3-PPP$ without a change in the number of site
These toin. This phenomenon is quite dramatic; ropizine cause
nearly a 3-fold increase in the binding affinity of $[^3H$
 $(+)$ -3-PPP without a change in the number of sites
These results support a model in which the sigma recep
t $(+)$ -3-PPP without a change in the number of sites.
These results support a model in which the sigma receptor macromolecule possesses allosterically coupled binding sites for $(+)$ -opiates, neuroleptics, and certain anti-
 These results support a model in which the sigma receptor macromolecule possesses allosterically coupled binding sites for (+)-opiates, neuroleptics, and certain antitiussives and anticonvulsants.
TABLE 3
Effect of dextro

Effect of dextromethorphan and sigma ligands on the binding of [⁸H]

	("HIDM		(+)-[[*] H]3-PPP		
DRUG	$K1$ (nM)	$D_{\rm NL}$ and (τ) -[11] σ - τ τ w gained ρ is order nomes not K2 (MM) 24 0.7 3 3.3 386 0.16 0.40 225 4.5 9.9 220	K.1 (nM)	K,2 (MM)	
Dextromethorphan	57		37	0.78	
Caramiphen	9.5		9.4	15	
Carbetapentane	11.3		11		
(+)-3-PPP	27		25.4	0.93	
(+)-SKF 10,047	44		40	0.9	
(-)-SKF 10,047	2.620				
Opipramol	0.41		0.92		
Cinnarizine	22		28.9		
Quinidine	1,090		20,050		
Haloperidol	1.4				
$(+)$ -Pentazocine	1.9				
$(-)$ -Pentazocine	71				
(+)-Cyclazocine	11	67			
$(-)$ -Cyclazocine	395	12			
(-)-Butaclamol	81	9			
(+)-Butaclamol	290				

^S Data from Musacchio et al. (1989b).

['H](+)-3-PPP (solid *lines)* **and ['HJDM** *(dashed lines)* **in guinea pig** brain. **Increasing concentrations of ropizine** *(circles)* **and phenytoin** FIG. 7. Effects of ropizine and phenytoin on the specific binding of $[{}^{4}H](+)-3-PPP$ (solid lines) and $[{}^{3}H]DM$ (dashed lines) in guinea pig brain. Increasing concentrations of ropizine (circles) and phenytoin (triangles) ^{[3}H](+)-3-PPP (solid lines) and ^{[3}H]DM (dashed lines) in guinea pig brain. Increasing concentrations of ropizine (circles) and phenytoin (*triangles*) enhanced the binding of both radioligands suggesting (*a*) a common brain. Increasing concentrations of ropizine (circles) and phenytoin (*triangles*) enhanced the binding of both radioligands suggesting (*a*) a common binding site for DM and sigma ligands and (*b*) the presence of alloste

1989b). The effect was biphasic and occurred over a
nearly identical dose range of both ropizine and pheny-
nearly identical dose range of both ropizine and pheny-
nearly identical dose range of both ropizine and pheny-
n support from physiological studies showing that rela-
support from Mussachio et al. (1989b) with permission of the authors.
The model of Musacchio et al. has received some
support from physiological studies showing that re from Mussachio et al. (1989b) with permission of the authors.
The model of Musacchio et al. has received some
support from physiological studies showing that rela-
tively low doses of DM or carbetapentane potentiate the
an The model of Musacchio et al. has received some support from physiological studies showing that relatively low doses of DM or carbetapentane potentiate the anticonvulsant activity of phenytoin by decreasing its ED_{50} (T The model of Musacchio et al. has received some support from physiological studies showing that relatively low doses of DM or carbetapentane potentiate the anticonvulsant activity of phenytoin by decreasing its ED_{so} (To support from physiological studies showing that rela-
tively low doses of DM or carbetapentane potentiate the
anticonvulsant activity of phenytoin by decreasing its
 ED_{60} (Tortella and Musacchio, 1986; Choi and Peters,
 tively low doses of DM or carbetapentane potentiate the anticonvulsant activity of phenytoin by decreasing its ED_{50} (Tortella and Musacchio, 1986; Choi and Peters, 1987). These findings imply that sigma ligands and DM anticonvulsant activity of phenytoin by decreasing its ED_{so} (Tortella and Musacchio, 1986; Choi and Peters, 1987). These findings imply that sigma ligands and DM would produce similar pharmacological effects, because th ED_{50} (Tortella and Musacchio, 1986; Choi and Peters, 1987). These findings imply that sigma ligands and DM would produce similar pharmacological effects, because they presumably induce the same conformation of the rece 1987). These findings imply that sigma ligands and DM
would produce similar pharmacological effects, because
they presumably induce the same conformation of the
receptor. Whether the antitussive, anticonvulsant, and
neurop would produce similar pharmacological
they presumably induce the same confreceptor. Whether the antitussive, anti-
neuroprotective properties of DM are
ligands is an important line of inquiry.

C. Species Differences in Sigma Sites

Several studies have shown differences in sigma recepligands is an important line of inquiry.

C. Species Differences in Sigma Sites

Several studies have shown differences in sigma recep-

tors among species. Sigma receptors from rat and guinea

pig brain exhibit marked dif C. Species Differences in Sigma Sites
Several studies have shown differences in sigma recep-
tors among species. Sigma receptors from rat and guinea
pig brain exhibit marked differences in their sensitivity
to the effects C. Species Differences in Sigma Sues
Several studies have shown differences in sigma recep-
tors among species. Sigma receptors from rat and guinea
pig brain exhibit marked differences in their sensitivity
to the effects Several studies have shown differences in sigma receptors among species. Sigma receptors from rat and guinea
pig brain exhibit marked differences in their sensitivity
to the effects of UV irradiation (Bowen et al. 1989a;
 tors among species. Sigma receptors from rat and guinea
pig brain exhibit marked differences in their sensitivity
to the effects of UV irradiation (Bowen et al. 1989a;
Bowen and Hellewell, 1988): (a) $[^{3}H]DTG$ and $[^{3}H$ to the effects of UV irradiation (Bowen et al. 1989a;
Bowen and Hellewell, 1988): (a) [³H]DTG and [³H](+)-
3-PPP binding to guinea pig brain membranes is de-
creased by irradiation but at a much less rapid rate than
i Bowen and Hellewell, 1988): (a) $[^{3}H]DTG$ and $[^{3}H]$ $(+)$ -3-PPP binding to guinea pig brain membranes is de-
creased by irradiation but at a much less rapid rate than
in rat brain membranes, (b) the marked increase in $[^{3}H]$
(+)-SKF 10,047 binding following UV irradiation ob-
 3-PPP binding to guinea pig brain membranes is decreased by irradiation but at a much less rapid rate than
in rat brain membranes, (b) the marked increase in [³H]
(+)-SKF 10,047 binding following UV irradiation ob-
serv creased by irradiation but at a much less rapid rate than
in rat brain membranes, (b) the marked increase in $[^3H]$
(+)-SKF 10,047 binding following UV irradiation ob-
served in rat brain is not observed in guinea pig bra in rat brain membranes, (b) the marked increase in [³H] (+)-SKF 10,047 binding following UV irradiation observed in rat brain is not observed in guinea pig brain membranes, and (c) [³H](+)-pentazocine binding is incre (+)-SKF 10,047 binding following UV irradiation observed in rat brain is not observed in guinea pig brain membranes, and (c) $[^{3}H](+)$ -pentazocine binding is increased by irradiation in rat brain membranes but decreased served in rat brain is not observed in guinea pig brain
membranes, and (c) $[^{3}H](+)$ -pentazocine binding is in-
creased by irradiation in rat brain membranes but de-
creased in guinea pig brain (unpublished observation). membranes, and (c) $[^{3}H](+)$ -pentazocine binding is increased by irradiation in rat brain membranes but decreased in guinea pig brain (unpublished observation).
The different sensitivities of guinea pig and rat brain sig creased by irradiation in rat brain membranes
creased in guinea pig brain (unpublished obser
The different sensitivities of guinea pig and re
sigma receptors suggest that they differ in comp
or position of UV-sensitive ami eased in guinea pig brain (unpublished observation).
he different sensitivities of guinea pig and rat brain
gma receptors suggest that they differ in composition
position of UV-sensitive amino acid residues.
Allosteric int

The different sensitivities of guinea pig and rat brain
sigma receptors suggest that they differ in composition
or position of UV-sensitive amino acid residues.
Allosteric interactions also differ among species. Mu-
sacchi sigma receptors suggest that they differ in composition of UV-sensitive amino acid residues.
Allosteric interactions also differ among species. Misacchio and coworkers reported that the allosteric encement of $[^8H]DM$ bindi Allosteric interactions also differ among species. Mu-
sacchio and coworkers reported that the allosteric en-
hancement of $[^{3}H]DM$ binding by the anticonvulsant
diphenylhydantoin or the antitussive, noscapine, ob-
serve Allosteric interactions also differ among species. Mu-
sacchio and coworkers reported that the allosteric en-
hancement of [³H]DM binding by the anticonvulsant
diphenylhydantoin or the antitussive, noscapine, ob-
served sacchio and coworkers reported that the allosteric enhancement of [³H]DM binding by the anticonvulsant diphenylhydantoin or the antitussive, noscapine, observed in guinea pig brain does not occur in rat or mouse brain (C hancement of $[^{3}H]DM$ binding by the anticonvulsant
diphenylhydantoin or the antitussive, noscapine, ob-
served in guinea pig brain does not occur in rat or mouse
brain (Craviso and Musacchio, 1983b). From this it ap-
pe diphenylhydantoin or the antitussive, noscapine, ob-
served in guinea pig brain does not occur in rat or mouse
brain (Craviso and Musacchio, 1983b). From this it ap-
pears that the rat and mouse brain receptor do not
posse served in guinea pig brain does not occur in rat or mouse
brain (Craviso and Musacchio, 1983b). From this it ap-
pears that the rat and mouse brain receptor do not
possess the allosteric site that regulates binding of $[^3H$

PHARMACOLOGICAL REVIEW

PHARMACOLOGICAL REVIEWS

siGMA REC
ability of carbetapentane, caramiphen, and dextrorphan
to displace [³H]DM from rat, guinea pig, and mouse SIGMA RECE
ability of carbetapentane, caramiphen, and dextrorphan F
to displace [³H]DM from rat, guinea pig, and mouse 10
brain membranes (Craviso and Musacchio, 1983b). SIGMA RECEPTORS
ability of carbetapentane, caramiphen, and dextrorphan For exat
to displace $[^3H]DM$ from rat, guinea pig, and mouse 1000 nM
brain membranes (Craviso and Musacchio, 1983b). have K_i
Prototypic sigma ligand From Figure 3.1 Text of carbetapentane, caramiphen, and dextrorphan

displace [³H]DM from rat, guinea pig, and mouse

ain membranes (Craviso and Musacchio, 1983b).

Prototypic sigma ligands also exhibit different binding

ability of carbetapentane, caramiphen, and dextrorphan For to displace [³H]DM from rat, guinea pig, and mouse 1000 brain membranes (Craviso and Musacchio, 1983b). have Prototypic sigma ligands also exhibit different bind to displace $[^{3}H]DM$ from rat, guinea pig, and mouse
brain membranes (Craviso and Musacchio, 1983b).
Prototypic sigma ligands also exhibit different binding
affinities in rat and guinea pig brain. Whereas $[^{3}H]DTG$
bind brain membranes (Craviso and Musacchio, 1983b). ha

Prototypic sigma ligands also exhibit different binding 4).

affinities in rat and guinea pig brain. Whereas $[^{3}H]DTG$ res

binds with similar affinity in both species, Prototypic sigma ligands also exhibit different bindiaffinities in rat and guinea pig brain. Whereas $[^{3}H]/+$)
binds with similar affinity in both species, $[^{3}H]/+$)
PPP binds with 3.5-fold lower affinity in rat brainer affinities in rat and guinea pig brain. Whereas $[{}^{3}H]DTG$
binds with similar affinity in both species, $[{}^{3}H](+)-3-$
PPP binds with 3.5-fold lower affinity in rat brain
(Bowen and Hellewell, 1988; Bowen et al., 1989a; H binds with similar affinity in both species, $[^{3}H]$ (PPP binds with 3.5-fold lower affinity in rat (Bowen and Hellewell, 1988; Bowen et al., 1989a; Hell and Bowen, 1990). There is an even more pronot loss of affinity of PPP binds with 3.5-fold lower affinity in rat brain
(Bowen and Hellewell, 1988; Bowen et al., 1989a; Hellew-
ell and Bowen, 1990). There is an even more pronounced
loss of affinity of (+)-morphinans and (+)-benzomor-
phans (Bowen and Hellewell, 1988; Bowen et al., 1989a; Hellew-pold and Bowen, 1990). There is an even more pronounced (+ loss of affinity of $(+)$ -morphinans and $(+)$ -benzomor-affinities of these drugs in the rat SF brain are 4ell and Bowen, 1990). There is an even more pronounced
loss of affinity of (+)-morphinans and (+)-benzomor-
phans in the rat. The affinities of these drugs in the rat
brain are 4- to 30-fold lower than in the guinea pig br loss of affinity of $(+)$ -morphinans and $(+)$ -benzomorphans in the rat. The affinities of these drugs in the rat brain are 4- to 30-fold lower than in the guinea pig brain (table 1; Bowen and Hellewell, 1988; Matsumoto et phans in the rat. The affinities of these drugs in the rat S
brain are 4- to 30-fold lower than in the guinea pig brain
(table 1; Bowen and Hellewell, 1988; Matsumoto et al.,
1990). It appears that either sigma receptors a brain are 4- to 30-fold lower than in the guinea pig brain (table 1; Bowen and Hellewell, 1988; Matsumoto et al., 1990). It appears that either sigma receptors are different in rats and guinea pigs or the brains of these t (table 1; Bowen and Hellewell, 1988; Matsumoto et al., 1990). It appears that either sigma receptors are different in rats and guinea pigs or the brains of these two species have different proportions of sigma receptor ty 1990). It appe
in rats and g
have differen
discriminate
(see below).
When thes rats and guinea pigs or the brains of these two species
we different proportions of sigma receptor types that
scriminate (+)-morphinans and (+)-benzomorphans
se below).
When these data are viewed as a whole, it is apparent

have different proportions of sigma receptor types that discriminate $(+)$ -morphinans and $(+)$ -benzomorphans (see below).
When these data are viewed as a whole, it is apparent that sigma receptor structure or organization discriminate (+)-morphinans and (+)-benzomorphans pol

(see below). bre

When these data are viewed as a whole, it is apparent cell

that sigma receptor structure or organization must differ dat

in important ways among sp (see below).
When these data are viewed as a whole, it is appare
that sigma receptor structure or organization must differ-
in important ways among species. As a consequence,
wust assume the presence of concomitant specie When these data are viewed as a whole, it is apparent that sigma receptor structure or organization must differ in important ways among species. As a consequence, we must assume the presence of concomitant species differe receptors. must assume the presence of concomitant species differences in the in vivo pharmacology and function of sigma
receptors.
D. Multiple Sigma Receptor Types
Studies showing different binding profiles in various

species and tissues and mathematical analysis of binding
data within particular tissues have led investigators to
data within particular tissues have led investigators to D. Multiple Sigma Receptor Types years

Studies showing different binding profiles in various

species and tissues and mathematical analysis of binding

data within particular tissues have led investigators to

hypothesize D. Multiple Sigma Receptor Types

Studies showing different binding profiles in various

species and tissues and mathematical analysis of binding

data within particular tissues have led investigators to

hypothesize mult Studies showing different binding profiles in various
species and tissues and mathematical analysis of binding
data within particular tissues have led investigators to
hypothesize multiple forms of sigma receptors. Bowen
a species and tissues and mathematical analysis of binding
data within particular tissues have led investigators to
hypothesize multiple forms of sigma receptors. Bowen
and coworkers (Bowen and Hellewell, 1988; Hellewell
and data within particular tissues have led investigators to
hypothesize multiple forms of sigma receptors. Bowen
and coworkers (Bowen and Hellewell, 1988; Hellewell
produced binding of the prototypic
sigma ligands [³H]DTG hypothesize multiple forms of sigma receptors. Bowen
and coworkers (Bowen and Hellewell, 1988; Hellewell
and Bowen, 1990) reported binding of the prototypic
sigma ligands [³H]DTG and [³H](+)-3-PPP to rat PC12
cells. P and coworkers (Bowen and Hellewell, 1988; Hellewel
and Bowen, 1990) reported binding of the prototypis
igma ligands [³H]DTG and [³H](+)-3-PPP to rat PC1:
cells. PC12 cells are a tumor cell line derived from the
rat adr and Bowen, 1990) reported binding of the prototypic
sigma ligands [³H]DTG and [³H](+)-3-PPP to rat PC12
cells. PC12 cells are a tumor cell line derived from the
rat adrenal medulla which attains the phenotype of sym-
 sigma ligands $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ to rat PC12 cells. PC12 cells are a tumor cell line derived from the rat adrenal medulla which attains the phenotype of sympathetic neurons when stimulated with nerve growth fact cells. PC12 cells are a tumor cell line derived from the rat adrenal medulla which attains the phenotype of sympathetic neurons when stimulated with nerve growth factor (Greene and Tischler, 1976). These cells exhibit many rat adrenal medulla which attains the phenotype of spathetic neurons when stimulated with nerve greeds factor (Greene and Tischler, 1976). These cells ex many of the properties of neurons in culture, inclusively neurite fo pathetic neurons when stimulat
factor (Greene and Tischler, 197
many of the properties of neuron
neurite formation and expression
mitter receptors (Guroff, 1985).
The presence of sigma-binding ctor (Greene and Tischler, 1976). These cells exhibit any of the properties of neurons in culture, including ($\frac{1}{2}$ unite formation and expression of several neurotrans-
itter receptors (Guroff, 1985).
The presence of

many of the properties of neurons in culture, including the neurite formation and expression of several neurotrans-
mitter receptors (Guroff, 1985).
The presence of sigma-binding sites in PC12 cells was are
first suggeste meurite formation and expression of several neurotransmitter receptors (Guroff, 1985).
The presence of sigma-binding sites in PC12 cells was
first suggested by the relatively large number of high
affinity binding sites fo mitter receptors (Guroff, 1985).
The presence of sigma-binding sites in PC12 cells wa
first suggested by the relatively large number of hight
affinity binding sites for $[^{3}H]DTG$ and $[^{3}H](+)-3-PP1$
 $(K_{d} = 23.7$ and 86.3 The presence of sigma-binding sites in PC12 cells was
first suggested by the relatively large number of high
affinity binding sites for $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$
($K_d = 23.7$ and 86.3 nM, respectively). For some com-
po first suggested by the relatively large number of high
affinity binding sites for $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$
($K_{d} = 23.7$ and 86.3 nM, respectively). For some com-
pounds, the typical sigma-binding profile was observed affinity binding sites for $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ wh
($K_d = 23.7$ and 86.3 nM, respectively). For some com-
pounds, the typical sigma-binding profile was observed.
Binding of $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ is potently $(K_d = 23.7$ and 86.3 nM, respectively). For some com-
pounds, the typical sigma-binding profile was observed.
Binding of $[^3H]DTG$ and $[^3H] (+)-3-PPP$ is potently energy
displaced by haloperidol, weakly displaced by PCP, and $($ pounds, the typical sigma-binding profile was observed.
Binding of [³H]DTG and [³H](+)-3-PPP is potently elisplaced by haloperidol, weakly displaced by PCP, and (tunaffected by high concentrations of apomorphine and dM Binding of $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ is potently displaced by haloperidol, weakly displaced by PCP, and (unaffected by high concentrations of apomorphine and dMK-801, further evidence of a relationship between this F s displaced by haloperidol, weakly displaced by PCP, and
unaffected by high concentrations of apomorphine and
MK-801, further evidence of a relationship between this
site and sigma receptors. Similar results were obtained
by unaffected by high concentrations of apomorphine and MK-801, further evidence of a relationship between this site and sigma receptors. Similar results were obtained by Yang et al. (1989) using $[^{3}H](+)-3-PPP$. In addition, MK-801, further evidence of a relationship between this
ite and sigma receptors. Similar results were obtaine
by Yang et al. (1989) using $[^{3}H](+)-3-PPP$. In addition
binding of $[^{3}H]TCP$ is undetectable, demonstrating at
 is and sigma receptors. Similar results were obtained has Yang et al. (1989) using $[^{3}H]/(+)-3-PPP$. In addition, site of $[^{3}H]TCP$ is undetectable, demonstrating ab-
nce of PCP receptors (Hellewell and Bowen, 1990). fice

by Yang et al. (1989) using $[^{3}H](+)-3-PPP$. In addition,
binding of $[^{3}H]TCP$ is undetectable, demonstrating absence of PCP receptors (Hellewell and Bowen, 1990).
However, the PC12 sigma-like site differs from the
guinea binding of [³H]TCP is undetectable, demonstrating a sence of PCP receptors (Hellewell and Bowen, 1990).
However, the PC12 sigma-like site differs from the guinea pig brain sigma site in its substantially low
affinity for sence of PCP receptors (Hellewell and Bowen, 1990).
However, the PC12 sigma-like site differs from the
guinea pig brain sigma site in its substantially lower
affinity for (+)-morphinans and (+)-benzomorphans
(Bowen and Hel

EPTORS 369
For example, in PC12 cells, $(+)$ -pentazocine has a K_i of 1000 nm, and $(+)$ -SKF 10,047 and dextrallorphan both EPTORS 369

For example, in PC12 cells, (+)-pentazocine has a K_i of

1000 nM, and (+)-SKF 10,047 and dextrallorphan both

have K_i values >10,000 nM (versus [³H](+)-3-PPP; table EPTORS 369

For example, in PC12 cells, $(+)$ -pentazocine has a K_i of
 1000 nM, and $(+)$ -SKF 10,047 and dextrallorphan both

have K_i values >10,000 nM (versus $[^{3}H](+)$ -3-PPP; table

4). The corresponding values in For example, in PC12 cells, $(+)$ -pentazocine has a K_i of 1000 nM, and $(+)$ -SKF 10,047 and dextrallorphan both have K_i values >10,000 nM (versus $[^{3}H](+)$ -3-PPP; table 4). The corresponding values in guinea pig brain For example, in PC12 cells, $(+)$ -pentazocine has a K_i of 1000 nM, and $(+)$ -SKF 10,047 and dextrallorphan both have K_i values >10,000 nM (versus $[^{3}H](+)$ -3-PPP; table 4). The corresponding values in guinea pig brain 1000 nM, and $(+)$ -SKF 10,047 and dextrallorphan both
have K_i values $>10,000$ nM (versus $[^{3}H](+)$ -3-PPP; table
4). The corresponding values in guinea pig brain are,
respectively, 1.2, 62.5, and 16.1 nM. Similar result have K_i values >10,000 nM (versus $[^{3}H](+)$ -3-PPP; table 4). The corresponding values in guinea pig brain are, respectively, 1.2, 62.5, and 16.1 nM. Similar results were obtained when $[^{3}H]DTG$ was used as probe (table 4). The corresponding values in guinea pig brain are, respectively, 1.2, 62.5, and 16.1 nM. Similar results were obtained when $[^{3}H]DTG$ was used as probe (table 4). The PC12 site also differs from the guinea pig site in respectively, 1.2, 62.5, and 16.1 nM. Similar results were
obtained when [³H]DTG was used as probe (table 4).
The PC12 site also differs from the guinea pig site in
possessing greater affinity for (-)-benzomorphans than obtained when [³H]DTG was used as probe (table 4).
The PC12 site also differs from the guinea pig site in
possessing greater affinity for (-)-benzomorphans than
(+)-benzomorphans (table 4). Consistent with the low
affin The PC12 site also differs from the guinea pig site in
possessing greater affinity for $(-)$ -benzomorphans than
 $(+)$ -benzomorphans (table 4). Consistent with the low
affinity of $(+)$ -benzomorphans, binding of 5 nM $[^{3}H](+$ possessing greater affinity for $(+)$ -benzomorphans (table 4). C
affinity of $(+)$ -benzomorphans, b
SKF 10,047 and $[^{3}H](+)$ -pentazo
in membranes from these cells.
Affinity labeling studies in w)-benzomorphans (table 4). Consistent with the low
finity of (+)-benzomorphans, binding of 5 nM $[^{3}H](+)$ -
 \angle F 10,047 and $[^{3}H](+)$ -pentazocine cannot be detected
membranes from these cells.
Affinity labeling studies

SKF 10,047 and $[{}^{3}H](+)$ -pentazocine cannot be detected
in membranes from these cells.
Affinity labeling studies in which $[{}^{3}H]Az$ -DTG was
used (see below) also revealed differences in the sigma-
like binding sites of SKF 10,047 and $[^{3}H](+)$ -pentazocine cannot be detected
in membranes from these cells.
Affinity labeling studies in which $[^{3}H]Az$ -DTG was
used (see below) also revealed differences in the sigma-
like binding sites of gu in membranes from these cells.

Affinity labeling studies in which $[^{3}H]Az-DTG$ was

used (see below) also revealed differences in the sigma-

like binding sites of guinea pig brain and PC12 cells

(Hellewell and Bowen, 19 Affinity labeling studies in which $[^{3}H]Az-DTG$ was
used (see below) also revealed differences in the sigma-
like binding sites of guinea pig brain and PC12 cells
(Hellewell and Bowen, 1988; 1990). This probe labeled a
pol used (see below) also revealed differences in the sigma-
like binding sites of guinea pig brain and PC12 cells
(Hellewell and Bowen, 1988; 1990). This probe labeled a
polypeptide of 25 kDa in membranes from guinea pig
brai like binding sites of guinea pig brain and PC12 cells
(Hellewell and Bowen, 1988; 1990). This probe labeled a
polypeptide of 25 kDa in membranes from guinea pig
brain but labeled polypeptides of 18 and 21 kDa in PC12
cell (Hellewell and Bowen, 1988; 1990). This probe labeled a polypeptide of 25 kDa in membranes from guinea pig brain but labeled polypeptides of 18 and 21 kDa in PC12 cell membranes (fig. 8). Taken with the ligand-binding data polypeptide of 25 kDa in membranes
brain but labeled polypeptides of 18 and
cell membranes (fig. 8). Taken with tl
data, these results argue for the exist
molecular forms of the sigma receptor.
The existence of sigma-like ain but labeled polypeptides of 18 and 21 kDa in PC12
Il membranes (fig. 8). Taken with the ligand-binding
ta, these results argue for the existence of different
plecular forms of the sigma-receptor.
The existence of sigma

ences in the in vivo pharmacology and function of sigma $(+)$ -benzomorphans in various tissue sources raises the receptors.

D. Multiple Sigma Receptor Types vears, sigma sites have been defined pharmacologically

Studies data, these results argue for the existence of different
molecular forms of the sigma receptor.
The existence of sigma-like sites with low affinity for
(+)-benzomorphans in various tissue sources raises the
question of how data, these results argue for the existence of different
molecular forms of the sigma receptor.
The existence of sigma-like sites with low affinity for
(+)-benzomorphans in various tissue sources raises the
question of how molecular forms of the sigma receptor.
The existence of sigma-like sites with low affinity for $(+)$ -benzomorphans in various tissue sources raises the question of how sigma sites are to be defined. In recent years, sigma The existence of sigma-like sites with low affini $(+)$ -benzomorphans in various tissue sources raise
question of how sigma sites are to be defined. In r
years, sigma sites have been defined pharmacolog
by their high affini $(+)$ -benzomorphans in various tissue sources raises the question of how sigma sites are to be defined. In recen years, sigma sites have been defined pharmacologically by their high affinity for haloperidol and $(+)$ -benzom question of how sigma sites are to be defined. In recent
years, sigma sites have been defined pharmacologically
by their high affinity for haloperidol and (+)-benzomor-
phans and their low affinity for PCP-related compound years, sigma sites have been defined pharmacologically
by their high affinity for haloperidol and (+)-benzomor-
phans and their low affinity for PCP-related compounds.
According to this definition, the sites described abov by their high affinity for haloperidol and (+)-benzomor-
phans and their low affinity for PCP-related compounds.
According to this definition, the sites described above
could not be considered sigma sites. However, when ot phans and their low affinity for PCP-related compounds.
According to this definition, the sites described above
could not be considered sigma sites. However, when other
prototypic sigma ligands are taken into account, the
 According to this definition, the sites described above could not be considered sigma sites. However, when other prototypic sigma ligands are taken into account, the marked overlap in their pharmacologic properties suggest could not be considered sigma sites. However, when other prototypic sigma ligands are taken into account, the marked overlap in their pharmacologic properties suggests a close relationship. As a result it appears that the prototypic sigma ligands are taken into account, the marked overlap in their pharmacologic properties sugests a close relationship. As a result it appears that the current definition is inadequate and should be modifical i marked overlap in their pharmacologic properties suggests a close relationship. As a result it appears that the current definition is inadequate and should be modified In light of this, the terminology "sigma-1" and "sigma gests a close relationship. As a result it appears that the current definition is inadequate and should be modified.
In light of this, the terminology "sigma-1" and "sigma-2" was suggested for the guinea pig brain traditio current definition is inadequate and should be modified.
In light of this, the terminology "sigma-1" and "sigma-2" was suggested for the guinea pig brain traditional
sigma site and the PC12 cell sigma-like sites, respectiv In light of this, the terminology "sigma-1" and "sigma-2" was suggested for the guinea pig brain traditional sigma site and the PC12 cell sigma-like sites, respectively (Hellewell and Bowen, 1990). The properties of these 2" was suggested for the guinea pig brain traditional
sigma site and the PC12 cell sigma-like sites, respectively
(Hellewell and Bowen, 1990). The properties of these
putative sigma receptor types are summarized in table 5 sigma site and the PC12 cell sigma-like sites, respectively
(Hellewell and Bowen, 1990). The properties of these
putative sigma receptor types are summarized in table 5,
and the apparent biological correlates to these two (Hellewell and Bowen, 1990). The properties of these
putative sigma receptor types are summarized in table 5,
and the apparent biological correlates to these two sites
are discussed below. Because PC12 cells appear to lac and the apparent biological correlates to these two sites are discussed below. Because PC12 cells appear to lack the sigma-1 receptor, this may be an ideal system in which to study the properties and function of the sigmaare discussed below. Because PC12 cells appear to lack e discussed below. Because PC12 cells appear to lack
e sigma-1 receptor, this may be an ideal system in
inch to study the properties and function of the sigma-
ite.
The tissue variation in stereoselectivity ratio with
anti

the sigma-1 receptor, this may be an ideal system in
which to study the properties and function of the sigma-
2 site.
The tissue variation in stereoselectivity ratio with
enantiomeric pairs of opiates (when $[^{3}H]DTG$ or which to study the properties and function of the sigma-
2 site.
The tissue variation in stereoselectivity ratio with
enantiomeric pairs of opiates (when $[^{3}H]DTG$ or $[^{3}H]$
(+)-3-PPP are used as sigma receptor probes) 2 site.
The tissue variation in stereoselectivity ratio with
enantiomeric pairs of opiates (when $[^{3}H]DTG$ or $[^{3}H]$
 $(+)-3-PPP$ are used as sigma-receptor probes) may be
due to varying proportions of sigma-1 and sigma-2 s The tissue variation in stereoselectivity ratio wienantiomeric pairs of opiates (when $[^{3}H]DTG$ or $[^{3}$) $(+)-3-PPP$ are used as sigma receptor probes) may due to varying proportions of sigma-1 and sigma-2 site Furthermore, enantiomeric pairs of opiates (when $[^{3}H]DTG$ or $[^{3}H]$ (+)-3-PPP are used as sigma receptor probes) may be due to varying proportions of sigma-1 and sigma-2 sites.
Furthermore, it is interesting that (-)-benzomorphans (+)-3-PPP are used as sigma receptor probes) may be
due to varying proportions of sigma-1 and sigma-2 sites.
Furthermore, it is interesting that (-)-benzomorphans
have equal affinity at the putative sigma-1 and sigma-2
si due to varying proportions of sigma-1 and sigma-2 sites
Furthermore, it is interesting that $(-)$ -benzomorphan
have equal affinity at the putative sigma-1 and sigma-
sites (table 4). This might explain observations in whic Furthermore, it is interesting that $(-)$ -benzomorphans
have equal affinity at the putative sigma-1 and sigma-2
sites (table 4). This might explain observations in which
 $(-)$ -opiates produce steep displacement curves (Hill have equal affinity at the putative sigma-1 and sigma-2
sites (table 4). This might explain observations in which
 $(-)$ -opiates produce steep displacement curves (Hill coef-
ficients of unity) against $[^{3}H](+)$ -3-PPP or $[^$ sites (table 4). This might explain observations in which $(-)$ -opiates produce steep displacement curves (Hill coefficients of unity) against $[^{3}H](+)$ -3-PPP or $[^{3}H]DTG$, whereas $(+)$ -benzomorphans often produce shallow (-)-opiates produce steep displacement curves (Hill coefficients of unity) against $[^{3}H](+)-3$ -PPP or $[^{3}H]DTG$,
whereas (+)-benzomorphans often produce shallow or
biphasic curves (Largent et al., 1984; Matsumoto et al., whereas $(+)$ -benzomorphans often produce shallow or biphasic curves (Largent et al., 1984; Matsumoto et al., 1990). $(-)$ -Benzomorphans would not differentiate the sigma-1 and sigma-2 sites labeled by these probes.

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SEM from two or three experiments, each carried out in duplicate.
inhibition of control binding at 10,000 and 5,000 nM, respectively; ND,
none. Data from Hellewell and Bowen (1990).
and $[^{3}H](+)-3-PPP$ bound to sites with Apomorphine No inhibn¹ No (-)-Sulpiride No inhibn¹ (²H)(+)-3-PPP (3 nM) or [³H)DTG (5 nM) was incubated with various concentrations of unlabeled ligan

20.1 – EXEC EXEC EXEC EXECUTE:
FIG. 8. Photolabeling of guinea pig (GP) brain membranes an
PC12 cell membranes with [⁴H]Az-DTG. Membranes from guinea pi
brain or PC12 cells were photolabeled with 10 nM [⁴H]Az-DTG, so FIG. 8. Photolabeling of guinea pig (GP) brain membranes and

PC12 cell membranes with [³H]Az-DTG. Membranes from guinea pig

brain or PC12 cells were photolabeled with 10 nM [³H]Az-DTG, solu-

bilized, and analyzed by PC12 cell membranes with [³H]Az-DTG. Membranes from guines
brain or PC12 cells were photolabeled with 10 nM [³H]Az-DTG, s
bilized, and analyzed by polyacrylamide gel electrophoresis. Ordin
positions of molecular weight billized, and analyzed by polyacrylamide gel electrophoresis. Ordinate,
positions of molecular weight markers in kilodaltons (KD): bovine
albumin, 66; egg albumin, 45; glyceraldehyde-3-phosphate dehydroge-
nase, 36; carbon mase, 36; carbonic anhydrase, 29; trypainogen, 24; soybean trypain winhibitor, 20.1. NSB, the nonspecific binding control; TB, total binding.
['H]Az-DTG labels a 25-kDa polypeptide in guinea pig brain. By contrast, ['H]Az-**PC12** cells. The nonspecific binding control; TB, total binding.

[²H]Az-DTG labels a 25-kDa polypeptide in guinea pig brain. By contrast, [²H]Az-DTG labels an 18-kDa and a 21-kDa polypeptide in PC12 cells. The differ with differing molecular verified in guinea pig brain. By

contrast, [³H]Az-DTG labels an 18-kDa and a 21-kDa polypeptide in
 PC12 cells. The differing molecular weight polypeptides correspond

with differing pharmacol **porting the Hypothesis of multiple sigma receptor subtyperties in**
PC12 cells. The differing molecular weight polypeptides correspond
with differing pharmacological profiles of sites in these tissues, sup-
porting the hyp From and Bowen and Bowen and Bowen and Bowen periods of From PC12 cells. The differing molecular weight polypeptides correspond
with differing pharmacological profiles of sites in these tissues, sup-
porting the hypothesis

with differing pharmacological profiles of sites in these tissues, supporting the hypothesis of multiple sigma receptor subtypes. Reprinted from Hellewell and Bowen, 1990.

Binding of sigma ligands to certain peripheral t portang the hypothesis of multiple sigma receptor subtypes. Reprint
from Hellewell and Bowen, 1990.
Of the rat also suggests the possibility of multiple form
of sigma-like binding sites. Hellewell et al. (1990) inve
tigate site
Binding of sigma ligands to certain peripheral tissues
of the rat also suggests the possibility of multiple forms
PP
of sigma-like binding sites. Hellewell et al. (1990) inves-
tigated the binding of $[^{3}H]DTG$, $[^{3}$ Binding of sigma ligands to certain peripheral tissues obset
of the rat also suggests the possibility of multiple forms PPP
of sigma-like binding sites. Hellewell et al. (1990) inves-
the *L*
figated the binding of $[^{3}H$

inhibition of control binding at 10,000 and 5,000 nM, respectively; ND,
none. Data from Hellewell and Bowen (1990).
and $[^{3}H](+)-3$ -PPP bound to sites with K_{d} values of 17.9
and 51.9 nM. The two probes labeled the sam one. Data from Hellewell and Bowen (1990).

and $[{}^3H](+)$ -3-PPP bound to sites with K_d values of 17.9

and 51.9 nM. The two probes labeled the same number

of sites, with a density much higher than guinea pig

brain; i and $[^{3}H](+)-3-PPP$ bound to sites with K_{d} values of 17.
and 51.9 nM. The two probes labeled the same number of sites, with a density much higher than guinea pi
brain; i.e., approximately 11,500 fmol/mg protein. Com
pet and $[^{3}H](+)-3$ -PPP bound to sites with K_d values of 17.9
and 51.9 nM. The two probes labeled the same number
of sites, with a density much higher than guinea pig
brain; i.e., approximately 11,500 fmol/mg protein. Com-
 and 51.9 nM. The two probes labeled the same number
of sites, with a density much higher than guinea pig
brain; i.e., approximately 11,500 fmol/mg protein. Com-
petition of various ligands against $[^{3}H]DTG$ revealed the
 $>$ fluphenazine $>$ (+)-3-PPP $>$ haloperidol $>$ (-)-3-PPP brain; i.e., approximately 11,500 fmol/mg protein. Competition of various ligands against $[{}^3H]DTG$ revealed the following rank order of potency: $DTG = (-)$ -pentazocine $>$ fluphenazine $> (+)$ -3-PPP $>$ haloperidol $> (-)$ -3-P petition of various ligands against [³H]DTG revealed the
following rank order of potency: DTG = (-)-pentazocine
> fluphenazine > (+)-3-PPP > haloperidol > (-)-3-PPP
> dextrallorphan > (-)-SKF 10,047 > (+)-pentazocine
= (following rank order of potency: $DTG = (-)$ -pentazocin

> fluphenazine > $(+)$ -3-PPP > haloperidol > $(-)$ -3-PP

> dextrallorphan > $(-)$ -SKF 10,047 > $(+)$ -pentazocin

= $(+)$ -SKF 10,047. Opioid peptides, $(-)$ -sulpiride, apamorp $>$ fluphenazine $>$ (+)-3-PPP $>$ haloperidol $>$ (-)-3-PPP
 $>$ dextrallorphan $>$ (-)-SKF 10,047 $>$ (+)-pentazocine
= (+)-SKF 10,047. Opioid peptides, (-)-sulpiride, apo-
morphine, and MK-801 were inactive. This ligand $>$ dextrallorphan $>$ (-)-SKF 10,047 > (+)-p
= (+)-SKF 10,047. Opioid peptides, (-)-sulp
morphine, and MK-801 were inactive. This li
tivity is similar to that observed in PC12 c
scribed above (Hellewell and Bowen, 1990). (+)-SKF 10,047. Opioid peptides, (-)-sulpiride, apo-
orphine, and MK-801 were inactive. This ligand selec-
rity is similar to that observed in PC12 cells as de-
ribed above (Hellewell and Bowen, 1990).
The selective sigma

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FIG. 8. Photolabeling of guinea pig *(GP)* brain membranes and
PC12 cell membranes with [³H]Az-DTG. Membranes from guinea pig
PC12 cell membranes with [³H]Az-DTG. Membranes from guinea pig
prain studies revealed the ty morphine, and MK-801 were inactive. This ligand selectivity is similar to that observed in PC12 cells as described above (Hellewell and Bowen, 1990).
The selective sigma probe, $[^{3}H](+)$ -pentazocine, bound to hepatic mem tivity is similar to that observed in PC12 cells as de-
scribed above (Hellewell and Bowen, 1990).
The selective sigma probe, $[^{3}H](+)-$ pentazocine, bound
to hepatic membranes with $K_d = 7.5$ nM and exhibited a
 B_{max} that scribed above (Hellewell and Bowen, 1990).
The selective sigma probe, $[^{3}H](+)$ -pentazocine, bound
to hepatic membranes with $K_d = 7.5$ nM and exhibited a
 B_{max} that was only 25% of that for $[^{3}H]DTG$ and $[^{3}H]$
(+) The selective sigma probe, $[^{3}H](+)$ -pentazocine, bound
to hepatic membranes with $K_d = 7.5$ nM and exhibited a
 B_{max} that was only 25% of that for $[^{3}H]DTG$ and $[^{3}H]$
 $(+)-3-PPP$. The K_d determined by direct Scatcha to hepatic membranes with $K_d = 7.5$ nM and exhibited B_{max} that was only 25% of that for [³H]DTG and [³H(+)-3-PPP. The K_d determined by direct Scatchan analysis is in marked contrast to the K_i of 1058 nideterm B_{max} that was only 25% of that for [³H]DTG and [¹)-3-PPP. The K_d determined by direct Scatch analysis is in marked contrast to the K_i of 1058 determined by competition with [³H]DTG. Furthermowhen [³H](+)analysis is in marked contrast to the K_i of 1058 nM
determined by competition with [³H]DTG. Furthermore,
when [³H](+)-pentazocine was used as probe, competi-
tion studies revealed the typical sigma ligand selectivit tion studies revealed the typical sigma ligand selectivity determined by competition with $[^{3}H]DTG$. Furthermore,
when $[^{3}H](+)$ -pentazocine was used as probe, competi-
tion studies revealed the typical sigma ligand selectivity
observed in guinea pig brain, including potent disp when $[^{3}H](+)$ -pentazocine was used as probe, competi-
tion studies revealed the typical sigma ligand selectivity
observed in guinea pig brain, including potent displace-
ment by haloperidol, DTG, and $(+).3$ -PPP. These dat tion studies revealed the typical sigma ligand selectivity
observed in guinea pig brain, including potent displace-
ment by haloperidol, DTG, and $(+)-3$ -PPP. These data
suggest that $[^{3}H]DTG$ and $[^{3}H](+)-3$ -PPP label sit observed in guinea pig brain, including potent displacement by haloperidol, DTG, and $(+)$ -3-PPP. These data suggest that $[^{3}H]DTG$ and $[^{3}H](+)$ -3-PPP label sites with both high and low affinity for $(+)$ -opiates in this ment by haloperidol, DTG, and (+)-3-PPP. These data
suggest that [³H]DTG and [³H](+)-3-PPP label sites
with both high and low affinity for (+)-opiates in this
tissue. These sites may be synonymous with the sigma-1
and suggest that $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ label sites
with both high and low affinity for $(+)$ -opiates in this
tissue. These sites may be synonymous with the sigma-1
and sigma-2 sites of guinea pig brain and PC12 cells,
r with both high and low affinity for $(+)$ -opiates in this
tissue. These sites may be synonymous with the sigma-1
and sigma-2 sites of guinea pig brain and PC12 cells,
respectively, as proposed by Hellewell and Bowen (table tissue. These sites may be synonymous with the sigma-1
and sigma-2 sites of guinea pig brain and PC12 cells,
respectively, as proposed by Hellewell and Bowen (table
4). In the nomenclature scheme proposed in table 5,
 $[^{3$ and sigma-2 sites of guinea pig brain and PC12 cells,
respectively, as proposed by Hellewell and Bowen (table
4). In the nomenclature scheme proposed in table 5,
 $[^{3}H](+)$ -pentazocine would selectively label the sigma-1
 respectively, as proposed by Hellewell and Bowen (table 4). In the nomenclature scheme proposed in table 5, $[^{3}H](+)$ -pentazocine would selectively label the sigma-1 site in the liver, giving the ligand selectivity profile [³H](+)-pentazocine would selectively label the sigma-1 site in the liver, giving the ligand selectivity profile observed in guinea pig brain. [³H]DTG and [³H](+)-3 - PPP would label both sigma-1 and sigma-2 sites. site in the liver, giving the ligand selectivity profile
observed in guinea pig brain. [³H]DTG and [³H](+)-3 -
PPP would label both sigma-1 and sigma-2 sites. Because
the B_{max} of [³H](+)-pentazocine is only 25% observed in guinea pig brain. [³H]DTG
PPP would label both sigma-1 and sigma
the B_{max} of [³H](+)-pentazocine is only
DTG and [³H](+)-3-PPP, it appears the
binding in liver is to the sigma-2 site.

^C From the model developed by Hellewell and Bowen (1990).

Affinity labeling of liver membranes with $[{}^{3}H]Az-DTG$ sites for $[{}^{3}H]DTG$, termed "site 1" and "site 2" (table (see below) reveals labeling of two distinct polypeptides Although site 1 and site 2 have comparable affini Affinity labeling of liver membranes with $[^{3}H]Az-DTG$ sites for $[^{3}H]DTG$, termed "site 1" and "site 2" (table 6) (see below) reveals labeling of two distinct polypeptides Although site 1 and site 2 have comparable affin whereas the other (21.5 kDa) is comparable to the proteins labeled in PC12 cells. This confirms the presence of two $[^3H]DTG$ -binding sites in the liver. Notably, labeling of the higher molecular weight polypeptide can teins labeled in PC12 cells. This confirms the presence with high affinity, whereas site 2 has very low affinity
of two [³H]DTG-binding sites in the liver. Notably, for these compounds. Also, although possessing high
la not two [³H]DTG-binding sites in the liver. Notably, for these compounds. Also, although possessing high
labeling of the higher molecular weight polypeptide can affinity for both sites, haloperidol binds with a lower
be whereas labeling of the lower molecular weight band is
not affected. This strongly supports the notion that the
 $25-\text{kDa}$ protein represents the high affinity $(+)$ -opiate-
binding site (sigma-1) and the lower molecular we be completely blocked by 100 nM dextrallorphan, affinity to site 2. $(+)-3$ -PPP binds w
whereas labeling of the lower molecular weight band is
not affected. This strongly supports the notion that the has not yet been invest whereas labeling of the lower molecular weight band is
not affected. This strongly supports the notion that the has not yet been investigated. A surprising finding from
25-kDa protein represents the high affinity $(+)$ -opi (sigma-2). -kDa protein represents the high affinity $(+)$ -opiate-
nding site (sigma-1) and the lower molecular weight
lypeptide represents the low affinity $(+)$ -opiate site
gma-2).
Based on differing drug selectivity profiles, Musac

Squires, 1977).

There is evidence that guinea pig brain contains two

types of sigma receptors. Results from ligand-binding

surface analysis led Rothman and coworkers (Reid et al.,

1988) to argue for the existence of tw

(kDa)]

* From the model developed by Hellewell and Bowen (1990).

Affinity labeling of liver membranes with $[^{3}H]Az-DTG$ sites for $[^{3}H]DTG$, termed "site 1" and "site 2" (table 6).

(see below) reveals labeling of two d * From the model developed by Hellewell and Bowen (1990).

Affinity labeling of liver membranes with $[{}^{3}H]Az-DTG$ sites for $[{}^{3}H]DTG$, termed "site 1" and "site 2" (table 6).

(see below) reveals labeling of two distinc (see below) reveals labeling of two distinct polypeptides Although site 1 and site 2 have comparable affinities for (Hellewell et al., 1990). One polypeptide (25 kDa) is DTG, there are marked differences in the affinity o Although site 1 and site 2 have comparable affinities for DTG, there are marked differences in the affinity of the two sites for $(+)$ -benzomorphans and $(+)$ -morphinans.
Site 1 binds $(+)$ -benzomorphans and $(+)$ -morphinans DTG, there are marked differences in the affinity of the
two sites for (+)-benzomorphans and (+)-morphinans.
Site 1 binds (+)-benzomorphans and (+)-morphinans
with high affinity, whereas site 2 has very low affinity
for th comparable to the protein labeled in guinea pig brain, two sites for $(+)$ -benzomorphans and $(+)$ -morphinans.
whereas the other (21.5 kDa) is comparable to the pro-
stite 1 binds $(+)$ -benzomorphans and $(+)$ -morphinans
tein whereas the other (21.5 kDa) is comparable to the pro-
teins labeled in PC12 cells. This confirms the presence with high affinity, whereas site 2 has very low affinity
of two [³H]DTG-binding sites in the liver. Notably,

in guinea pig brain'

phinning site (signing-1) and the lower molecular weight		IADLL 0			
polypeptide represents the low affinity $(+)$ -opiate site	Inhibitory dissociation constants of test drugs for DTG site 1 and site 2 in guinea pig brain*				
$(sigma-2).$					
Based on differing drug selectivity profiles, Musacchio	Drug	Site 1 $(K_4 \pm SEM)$	Site 2 $(K_4 \pm \text{SEM})$	Site 2/ site 1	
et al. (1988) have also hypothesized multiple types of	Haloperidol	0.30 ± 0.01	36.1 ± 1.6	120	
³ H]DM-binding sites in guinea pig liver, kidney, and	$(+)$ -Pentazocine	2.0 ± 0.06	456 ± 11	228	
adrenal medulla. The anticonvulsants carbetapentane	$R-(+)$ -PPP	5.1 ± 0.3	442 ± 34	86	
and caramiphen potently inhibited [³ H]DM binding to	Carbetapentane	5.2 ± 0.3	1523 ± 85	292	
guinea pig brain and kidney medulla membranes but	BD738	6.4 ± 0.1	188 ± 6	29.4	
were virtually inactive in liver and kidney cortex. Adrenal	BD737	8.0 ± 0.3	502 ± 29	62.8	
	Fluzphenazine	7.6 ± 0.5	440 ± 30	58	
sites were sensitive to carbetapentane, although not as	Dextrallorphan	8.4 ± 0.4	1861 ± 94	221	
sensitive as the brain sites. In contrast, the antidepres-	Perphenazine	8.9 ± 0.5	429 ± 27	48	
sant drug opipramol potently inhibited [³ H]DM binding	DTG	11.9 ± 0.1	37.6 ± 0.6	3	
in brain, liver, and adrenal tissues. This suggests that	$S-(-)$ -PPP	30.5 ± 0.6	1544 ± 37	50	
the receptors from these tissues have different molecular	KCR-11-240.1	33.5 ± 1.4	1399 ± 68	42	
forms. In view of the evidence that the brain contains	BMY 14802	41.4 ± 2.0	728 ± 52	18	
	$(+)$ -SKF 10.047	44.8 ± 1.6	4263 ± 190	95	
$[$ ³ H $]$ DM-binding sites that appear to be identical with	BD446	47.4 ± 3.0	1383 ± 96	29	
sigma receptors, these results with peripheral tissues may	$(-)$ -Butaclamol	47.4 ± 2.9	3646 ± 312	77	
suggest heterogeneity of sigma sites. The finding of high	Caramiphen	65.3 ± 3.8	2864 ± 224	44	
densities of sigma-like sites in peripheral tissues with	(+)-Cyclazocine	77.6 ± 6.4	1238 ± 108	16	
characteristics different from the brain sites may suggest	Buspirone	95.7 ± 2.3	744 ± 19	8	
	Dextromethorphan	121 ± 6	53503 ± 3962	442	
the existence of peripheral- and central-type sigma sites,	BD445	126 ± 7	4144 ± 265	33	
analogous to the benzodiazepine receptor (Braestrup and	KCR-12-83.1	154 ± 4	18245 ± 657	118	
Squires, 1977).	KCR-12-84.1	179 ± 11	29258 ± 2081	163	
There is evidence that guinea pig brain contains two	Dextrorphan	202 ± 10	11386 ± 719	56	
	Levallorphan	721 ± 20	13686 ± 422	19	
types of sigma receptors. Results from ligand-binding	KCR-11-239.1	1245 ± 85	18705 ± 1373	15	
surface analysis led Rothman and coworkers (Reid et al.,	KCR-12-69.1	9064 ± 1289	>1 mM	>110	
1988) to argue for the existence of two classes of binding	* From Rothman et al. (1990).				

evidence that sigma sites are allosterically modulated

(Bowen et al., 1989a; Musacchio et al., 1989b).

Guinea pig brain, therefore, appears to contain sigma

sites that differ mainly in their affinity for $(+)$ -opiates.
 (Bowen et al., 1989a; Musacchio et al., 1989b).

Guinea pig brain, therefore, appears to contain sigma

sites that differ mainly in their affinity for $(+)$ -opiates.

It will be interesting to learn whether the low affinit Guinea pig brain, therefore, appears to contain sigma
sites that differ mainly in their affinity for (+)-opiates.
It will be interesting to learn whether the low affinity
 $(+)$ -opiate site of guinea pig brain is the same a sites that differ mainly in their affinity for $(+)$ -opiates.
It will be interesting to learn whether the low affinity
 $(+)$ -opiate site of guinea pig brain is the same as that
described in PC12 cells and liver (sigma-2). F It will be interesting to learn whether the low affinity
 $(+)$ -opiate site of guinea pig brain is the same as that

described in PC12 cells and liver (sigma-2). Failure of
 $[^{3}H]Az-DTG$ to photolabel a polypeptide in the 2 (+)-opiate site of guinea pig brain is the same as that
described in PC12 cells and liver (sigma-2). Failure of
 $[^{3}H]Az-DTG$ to photolabel a polypeptide in the 21-kDa
al.,
molecular weight range (fig. 8) and the relatively described in PC12 cells and liver (sigma-2). Failure $[^{3}H]Az-DTG$ to photolabel a polypeptide in the 21-kI molecular weight range (fig. 8) and the relatively lot affinity for $(+)$ -3-PPP (table 6) suggest that this man ot b [³H]Az-DTG to photolabel a polypeptide in the 21-kl molecular weight range (fig. 8) and the relatively leaffinity for $(+)$ -3-PPP (table 6) suggest that this m not be the case. Further studies will be needed to det mine molecular
affinity for
not be the
mine the re
like sites. *E. High and Low Affinity States of the Same Receptor*

Was

The sites.

High and Low Affinity States of the Same Receptor

Another possible model of the sigma receptor is one in the

hich the receptor can exist in interconvertible high and cree stee

E. High and Low Affinity States of the Same Receptor

Another possible model of the sigma receptor is one in

which the receptor can exist in interconvertible high and

low affinity states. This possibility is discus E. High and Low Affinity States of the Same Receptor in the Another possible model of the sigma receptor is one in the which the receptor can exist in interconvertible high and cree low affinity states. This possibility is E. High and Low Affling States of the sigma receptor is one in
Another possible model of the sigma receptor is one in
which the receptor can exist in interconvertible high and
low affinity states. This possibility is discu

F. Summary

At the present time, there does not appear to be a
integral term of sigma receptors to G proteins.
At the present time, there does not appear to be a
inifying hypothesis capable of reconciling these different (Cr F. Summary
At the present time, there does not appear to be a
unifying hypothesis capable of reconciling these different
topographic and structural models of the sigma receptor. At the present time, there does not appear to be a unifying hypothesis capable of reconciling these different topographic and structural models of the sigma receptor. However, the evidence clearly points to interaction of At the present time, there does not appear to be a
unifying hypothesis capable of reconciling these different topographic and structural models of the sigma receptor.
However, the evidence clearly points to interaction of At the present time, there does not appear to be a
unifying hypothesis capable of reconciling these different
topographic and structural models of the sigma receptor.
However, the evidence clearly points to interaction of
 unifying hypothesis capable of reconciling these different topographic and structural models of the sigma receptor.
However, the evidence clearly points to interaction of sigma ligands with a heterogeneous population of si topographic and structural models of the sigma receptor.
However, the evidence clearly points to interaction of sigma ligands with a heterogeneous population of sites.
It is also important to note that one model does not
n However, the evidence clearly points to interaction of sigma ligands with a heterogeneous population of sites.
It is also important to note that one model does not B necessarily preclude another (i.e., allosteric models sigma ligands with a heterogeneous population of sites.
It is also important to note that one model does not
necessarily preclude another (i.e., allosteric models ver-
sus multiple receptor models versus multiple state
mo It is also important to note that one model does not B ,
necessarily preclude another (i.e., allosteric models ver-
sus multiple receptor models versus multiple state
models). For example, it is conceivable that there ar necessarily preclude another (i.e., allosteric models ver-
sus multiple receptor models versus multiple state
models). For example, it is conceivable that there are at
least two sigma receptor macromolecules, one of which sus multiple receptor models versus multiple state
models). For example, it is conceivable that there are at
least two sigma receptor macromolecules, one of which
consisting of distinct allosterically coupled binding sites models). For example, it is conceivable that there are at
least two sigma receptor macromolecules, one of which
consisting of distinct allosterically coupled binding sites
and the other consisting of a single ligand bindi least two sigma receptor macromolecules, one of which
consisting of distinct allosterically coupled binding sites
and the other consisting of a single ligand binding do-
main. Superimposed on these general schemes might b and the other consisting of a single ligand binding domain. Superimposed on these general schemes might be subtle species or tissue differences in the structure of receptor proteins that might affect the ligand-binding profiles. subtle species or tissue differences in the structure of receptor proteins that might affect the ligand-binding profiles.
Additional studies in the area of quantitative SAR relationships will allow further refinement of pr

receptor proteins that might affect the ligand-bind
profiles.
Additional studies in the area of quantitative S
relationships will allow further refinement of predicti
regarding topographical features of the ligand recep
co profiles.
Additional studies in the area of quantitative SA
relationships will allow further refinement of prediction
regarding topographical features of the ligand recepto
combining site(s) (fig. 3). Elucidation of overal Additional studies in the area of quantitative SAR
relationships will allow further refinement of predictions
regarding topographical features of the ligand receptor-
combining site(s) (fig. 3). Elucidation of overall str relationships will allow further refinement of predic
regarding topographical features of the ligand rece
combining site(s) (fig. 3). Elucidation of overall s
tural features, such as possible subunit composition
organizati regarding topographical features of the ligand receptor-
combining site(s) (fig. 3). Elucidation of overall struc-
tural features, such as possible subunit composition and
organization, must await purification and characte combining site(s) (fig. 3). Elucidatic
tural features, such as possible subun
organization, must await purification
tion of the receptor proteins. Progres
goal is discussed in the next section. reduction, must await purification and characterization of the receptor proteins. Progress toward this latter coal is discussed in the next section.
III. Physical and Chemical Properties of Sigma
Receptors

Receptors

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Receptors
Molecular characterization of sigma sites has pro-
eded slowly. However, steady progress is being made III. Physical and Chemical Properties of Sigma

Receptors

Molecular characterization of sigma sites has pro-

ceeded slowly. However, steady progress is being made

and the data have confirmed that the sigma site is a and Chemical Properties of Sigma
Receptors 150
Molecular characterization of sigma sites has pro-
eeded slowly. However, steady progress is being made molecular
and the data have confirmed that the sigma site is a poly
pro Molecular characterization of sigma sites has
ceeded slowly. However, steady progress is being
and the data have confirmed that the sigma sit
protein and that it differs from the PCP receptor.

A. Proteinaceous Nature of the Sigma Receptor

man et al., 1990). These data add to the growing body of
evidence that sigma sites are allosterically modulated
(Bowen et al., 1989a; Musacchio et al., 1989b).
Guinea pig brain, therefore, appears to contain sigma
and $[{}$ AL.
Proteinaceous Nature of the Sigma Receptor
Converging lines of evidence from several laboratories
pport the protein nature of sigma-binding sites. First, ET AL.
A. Proteinaceous Nature of the Sigma Receptor
Converging lines of evidence from several laboratories
support the protein nature of sigma-binding sites. First,
sigma-binding sites appear to be heat labile. Binding to A. Proteinaceous Nature of the Sigma Receptor
Converging lines of evidence from several laboratories
support the protein nature of sigma-binding sites. First,
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sigma **Share of the Sigma Receptor**
Converging lines of evidence from several laboratories
support the protein nature of sigma-binding sites. First,
sigma-binding sites appear to be heat labile. Binding to
sigma sites labeled by Converging lines of evidence from several laborators
support the protein nature of sigma-binding sites. Fir
sigma-binding sites appear to be heat labile. Binding
sigma sites labeled by both $[^{3}H]SKF 10,047$ (Su, 198
and icantly reduced following heat treatment of guinea pig sigma-binding sites appear to be heat labile. Binding to
sigma sites labeled by both $[^{3}H]SKF 10,047$ (Su, 1982)
and $[^{3}H]DM$ (Craviso and Musacchio, 1983a) was signif-
icantly reduced following heat treatment of guinea sigma sites labeled by both [³H]SKF 10,047 (Su, 1982)
and [³H]DM (Craviso and Musacchio, 1983a) was signif-
icantly reduced following heat treatment of guinea pig
brain membranes. Second, the pH optimum for both
[³H] and $[^{3}H]DM$ (Craviso and Musacchio, 1983a) was significantly reduced following heat treatment of guinea pig brain membranes. Second, the pH optimum for both $[^{3}H](+)-3-PPP$ and $[^{3}H]DM$ binding was between pH 8.0 and 8.9 icantly reduced following heat treatment of guinea pig
brain membranes. Second, the pH optimum for both
[³H](+)-3-PPP and [³H]DM binding was between pH
8.0 and 8.9 (Craviso and Musacchio, 1983a; Largent et
al., 1987). brain membranes. Second, the pH optimum for both $[^{3}H](+)-3-PPP$ and $[^{3}H]DM$ binding was between pH 8.0 and 8.9 (Craviso and Musacchio, 1983a; Largent et al., 1987). For $[^{3}H]DM$ sites in guinea pig brain, there was a sh 8.0 and 8.9 (Craviso and Musacchio, 1983a; Largent et al., 1987). For $[^{3}H]$ DM sites in guinea pig brain, there was a sharp decrease in specific binding below pH 8.0 and a gradual decline above pH 8.5 (Craviso and Musac 8.0 and 8.9 (Craviso and Musacchio, 1983a; Largent et al., 1987). For $[^{3}H]DM$ sites in guinea pig brain, there was a sharp decrease in specific binding below pH 8.0 and a gradual decline above pH 8.5 (Craviso and Musacc al., 1987). For $[^{3}H]DM$ sites in guinea pig brain, there was a sharp decrease in specific binding below pH 8.0 and a gradual decline above pH 8.5 (Craviso and Musacchio, 1983a). For $[^{3}H](+)-3$ -PPP sites in rat brain, t was a sharp decrease in specific binding below pH 8.0 and a gradual decline above pH 8.5 (Craviso and Musacchio, 1983a). For $[^{3}H](+)-3$ -PPP sites in rat brain, there was an increase over the pH range 7.0–8.9 with a fairl and a gradual decline above pH 8.5 (Craviso and Musacchio, 1983a). For $[^{3}H](+)$ -3-PPP sites in rat brain, there was an increase over the pH range 7.0–8.9 with a fairly steep increase between pH 8.0 and 8.9; higher pH was steep increase between pH 8.0 and 8.9; higher pH was not tested. The increases in binding were due to decreases in the K_d and are attributed to the protonation state of the ligand (Largent et al., 1987). Third, protease was an increase over the pH range 7.0–8.9 with a fairly
steep increase between pH 8.0 and 8.9; higher pH was
not tested. The increases in binding were due to decreases
in the K_d and are attributed to the protonation sta steep increase between pH 8.0 and 8.9; higher pH was
not tested. The increases in binding were due to decreases
in the K_d and are attributed to the protonation state of
the ligand (Largent et al., 1987). Third, protease not tested. The increases in binding were due to decreases
in the K_d and are attributed to the protonation state of
the ligand (Largent et al., 1987). Third, proteases de-
creased the binding of both $[^3H]SKF 10,047$ and in the K_d and are attributed to the protonation state the ligand (Largent et al., 1987). Third, proteases decreased the binding of both [³H]SKF 10,047 and [³HDM to guinea pig brain membranes. [³H]SKF 10,04 binding the ligand (Largent et al., 1987). Third, proteases d
creased the binding of both [³H]SKF 10,047 and [³H
DM to guinea pig brain membranes. [³H]SKF 10,0₂
binding was significantly reduced by trypsin and pho
pholipas creased the binding of both $[^{3}H]SKF$ 10,047 and $[^{3}H]$ DM to guinea pig brain membranes. $[^{3}H]SKF$ 10,047 binding was significantly reduced by trypsin and phospholipase C (Su, 1982). Similarly, incubation of membranes DM to guinea pig brain membranes. [³H]SKF 10,047
binding was significantly reduced by trypsin and phos-
pholipase C (Su, 1982). Similarly, incubation of mem-
branes with trypsin or alpha-chymotrypsin attenuated
[³H]DM binding was significantly reduced by trypsin and phos-
pholipase C (Su, 1982). Similarly, incubation of mem-
branes with trypsin or alpha-chymotrypsin attenuated
[³H]DM binding (Craviso and Musacchio, 1983a). Also,
sulfh pholipase C (Su, 1982). Similarly, incubation of mem-
branes with trypsin or alpha-chymotrypsin attenuated
[³H]DM binding (Craviso and Musacchio, 1983a). Also,
sulfhydryl reagents significantly reduced sigma binding
(Cra branes with trypsin or alpha-chymotrypsin attenuated [³H]DM binding (Craviso and Musacchio, 1983a). Also, sulfhydryl reagents significantly reduced sigma binding (Craviso and Musacchio, 1983a). The sensitivity of these b [³H]DM binding (Craviso and Musacchio, 1983a). A sulfhydryl reagents significantly reduced sigma bind (Craviso and Musacchio, 1983a). The sensitivity of the binding sites to temperature, pH, and protein-modifiagents str *A. Craviso and Musacchio, 1983a). The sensitity binding sites to temperature, pH, and prote agents strongly suggest that these sites are* B *. Affinity Labeling and Molecular Weight Determination*

Determination

with properties nearly indistinguishable from those of
receptor proteins that might affect the ligand-binding
profiles.
Additional studies in the area of quantitative SAR the ligand to the sigma receptor. Sodium dodecyl su agents strongly suggest that these sites are proteins.

B. Affinity Labeling and Molecular Weight

Determination

Affinity labeling has been a useful tool in characteriz-

ing sigma sites, as it has with other receptor sys B. Affinity Labeling and Molecular Weight
Determination
Affinity labeling has been a useful tool in characteriz-
ing sigma sites, as it has with other receptor systems.
Kavanaugh et al. (1988) developed a radiolabeled azid B. Affinity Labeung and Molecular Weight
Determination
Affinity labeling has been a useful tool in characteriz-
ing sigma sites, as it has with other receptor systems.
Kavanaugh et al. (1988) developed a radiolabeled azido Determination
Affinity labeling has been a useful tool in characteriz-
ing sigma sites, as it has with other receptor systems.
Kavanaugh et al. (1988) developed a radiolabeled azido
derivative of the selective sigma ligand Affinity labeling has been a useful tool in characteriz-
ing sigma sites, as it has with other receptor systems.
Kavanaugh et al. (1988) developed a radiolabeled azido
derivative of the selective sigma ligand, DTG. In the ing sigma sites, as it has with other receptor systems.
Kavanaugh et al. (1988) developed a radiolabeled azido
derivative of the selective sigma ligand, DTG. In the
dark, $[^{3}H]Az-DTG$ binds to guinea pig brain sigma sites
w Kavanaugh et al. (1988) developed a radiolabeled azido
derivative of the selective sigma ligand, DTG. In the
dark, [³H]Az-DTG binds to guinea pig brain sigma sites
with properties nearly indistinguishable from those of
[derivative of the selective sigma ligand, DTG. In the dark, [³H]Az-DTG binds to guinea pig brain sigma sites with properties nearly indistinguishable from those of [³H]DTG. Irradiation of the ligand-receptor complex wi dark, [³H]Az-DTG binds to guinea pig brain sigma si
with properties nearly indistinguishable from those
[³H]DTG. Irradiation of the ligand-receptor comp
with light of 366 nm produced covalent attachment
the ligand to t with properties nearly indistinguishable from those of [³H]DTG. Irradiation of the ligand-receptor complex with light of 366 nm produced covalent attachment of the ligand to the sigma receptor. Sodium dodecyl sulfatepoly $[^3H]DTG.$ Irradiation of the ligand-receptor complex with light of 366 nm produced covalent attachment of the ligand to the sigma receptor. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis revealed labeling of a with light of 366 nm produced covalent attachment of
the ligand to the sigma receptor. Sodium dodecyl sulfate-
polyacrylamide gel electrophoresis revealed labeling of a
single polypeptide of 29 kDa. Labeling of this band w the ligand to the sigma receptor. Sodium dodecyl sulfate-
polyacrylamide gel electrophoresis revealed labeling of a
single polypeptide of 29 kDa. Labeling of this band was
blocked by haloperidol but not by PCP, suggesting polyacrylamide gel ele
single polypeptide of 2
blocked by haloperido.
this protein is a compo
not the PCP receptor.
When photolabeled ngle polypeptide of 29 kDa. Labeling of this band was
ocked by haloperidol but not by PCP, suggesting that
is protein is a component of the sigma-binding site and
t the PCP receptor.
When photolabeled membranes were solubi

blocked by haloperidol but not by PCP, suggesting that
this protein is a component of the sigma-binding site and
not the PCP receptor.
When photolabeled membranes were solubilized with
sodium cholate and subjected to chrom this protein is a component of the sigma-binding site and
not the PCP receptor.
When photolabeled membranes were solubilized with
sodium cholate and subjected to chromatography on
Sepharose Cl-6B, radioactivity was associa not the PCP receptor.
When photolabeled membranes were solubilized with
sodium cholate and subjected to chromatography on
Sepharose Cl-6B, radioactivity was associated with a
major protein peak with Stokes radius of 4.6 nm When photolabeled membranes were solubilized with
sodium cholate and subjected to chromatography on
Sepharose Cl-6B, radioactivity was associated with a
major protein peak with Stokes radius of 4.6 nm. This
corresponded to sodium cholate and subjected to chromatography
Sepharose Cl-6B, radioactivity was associated with
major protein peak with Stokes radius of 4.6 nm. T
corresponded to an approximate molecular weight
150,000 Da (uncorrected f Sepharose Cl-6B, radioactivity was associated with a major protein peak with Stokes radius of 4.6 nm. This corresponded to an approximate molecular weight of 150,000 Da (uncorrected for bound detergent). Kavanaugh et al. (major protein peak with Stokes radius of 4.6 nm. This corresponded to an approximate molecular weight of 150,000 Da (uncorrected for bound detergent). Kavanaugh et al. (1988) suggested that the lack of higher molecular wei corresponded to an approximate molecular weight of 150,000 Da (uncorrected for bound detergent). Kavanaugh et al. (1988) suggested that the lack of higher molecular weight proteins on sodium dodecyl sulfate-polyacrylamide 150,000 Da (uncorrected for bound detergent). Kavanaugh et al. (1988) suggested that the lack of higher molecular weight proteins on sodium dodecyl sulfate-polyacrylamide gel electrophoresis indicated that the 29-kDa polyp

PHARMACOLOGICAL REVIEWS

SIGMA RECEPT
plex. No disulfide bridges appeared to be involved in because
stabilizing the structure because the same 29-kDa protein com stabilizing the structure because the same 29-kDa protein
stabilizing the structure because the same 29-kDa protein correlations of
was observed under both reducing and nonreducing con-SIGMA I
plex. No disulfide bridges appeared to be involved in
stabilizing the structure because the same 29-kDa protein
was observed under both reducing and nonreducing con-
ditions. ditions. Ex. No disulfide bridges appeared to be involved is
abilizing the structure because the same 29-kDa prote
is observed under both reducing and nonreducing con-
ions.
 $[^{8}H]Az-DTG$ also labels a 29-kDa polypeptide in NCI
cell

stabilizing the structure because the same 29-kDa protein con-
was observed under both reducing and nonreducing con-
ditions.
[³H]Az-DTG also labels a 29-kDa polypeptide in NCB-
20 cells (Adams et al., 1987a). NCB-20 cel was observed under both reducing and nonreducing conditions.

[³H]Az-DTG also labels a 29-kDa polypeptide in NCl

20 cells (Adams et al., 1987a). NCB-20 cells have bee

shown to have sigma receptors with pharmacologic

c ditions.

[³H]Az-DTG also labels a 29-kDa polypeptide in NCB

20 cells (Adams et al., 1987a). NCB-20 cells have been

shown to have sigma receptors with pharmacologics

characteristics similar to those of guinea pig brai $[^{3}H]Az-DTG$ also labels a 29-kDa polypeptide in NCE
20 cells (Adams et al., 1987a). NCB-20 cells have bee
shown to have sigma receptors with pharmacologics
characteristics similar to those of guinea pig brain (Langent et 20 cells (Adams et al., 1987a). NCB-20 cells have been tion due to failure to remove noncovalently bound Meshown to have sigma receptors with pharmacological taphit cannot account for this effect, because equivalent charac shown to have sigma receptors with pharmacological
characteristics similar to those of guinea pig brain (Lar-
gent et al., 1986; Kushner et al., 1988). Thus, the phar-
macological similarity between sigma receptors from
NC characteristics similar to those of guinea pig brain (Lar-
gent et al., 1986; Kushner et al., 1988). Thus, the phar-
macological similarity between sigma receptors from sugg
NCB-20 cells and guinea pig brain also extends t gent et al., 1986; Kushner et al., 1988). Thus, the phar-
macological similarity between sigma receptors from st
NCB-20 cells and guinea pig brain also extends to their
physical properties. The labeling of a 29-kDa protein macological similarity between sigma receptors from sum.
NCB-20 cells and guinea pig brain also extends to their
physical properties. The labeling of a 29-kDa protein in va
membranes of both guinea pig brain and NCB-20 cel membranes of both guinea pig brain and NCB-20 cells
lends support to the notion that this protein is the
binding site of the sigma receptor, or at least a protein
near the binding domain of the receptor.
Hellewel and Bowen

binding site of the sigma receptor, or at least a protein current the binding domain of the receptor. D'
Hellewel and Bowen (1990) used $[^{3}H]Az-DTG$ to study the
the physical properties of sigma receptors from rat PC12 me
 near the binding domain of the receptor. DT
Hellewel and Bowen (1990) used [³H]Az-DTG to study
the physical properties of sigma receptors from rat PC12 mot
cells. In contrast to the guinea pig brain, which yielded ent
a Hellewel and Bowen (1990) used [³H]Az-DTG to study
the physical properties of sigma receptors from rat PC12
cells. In contrast to the guinea pig brain, which yielded
a single polypeptide of 29 kDa, PC12 cells yielded two the physical properties of sigma receptors from rat PC12 cells. In contrast to the guinea pig brain, which yielded a single polypeptide of 29 kDa, PC12 cells yielded two polypeptides with molecular weights of 18 and 21 kDa cells. In contrast to the guinea pig brain, which yielded (a single polypeptide of 29 kDa, PC12 cells yielded two looplypeptides with molecular weights of 18 and 21 kDa. (It is unlikely that the lower molecular weight prot a single polypeptide of 29 kDa, PC12 cells yielded two papelypeptides with molecular weights of 18 and 21 kDa. difference in the lower molecular weight proteins in were generated by proteolysis, because similar results we polypeptides with molecular weights of 18 and 21 kDa. different that the lower molecular weight proteins nowere generated by proteolysis, because similar results were obtained in the presence of protease inhibitors. As ind It is unlikely that the lower molecular weight proteins non
were generated by proteolysis, because similar results States were obtained in the presence of protease inhibitors. As inhi-
discussed above, PC12 cells possess a were generated by proteolysis, because similar results Surprisingly, like DIGIT, Metaphit was a competitive
were obtained in the presence of protease inhibitors. As
discussed above, PC12 cells possess a sigma-like binding discussed above, PC12 cells possess a sigma-like binding contrast to effects on [^oH]^T site that differs from the guinea pig brain receptor in the phit produced the expected having low affinity for sigma-related morphin site that differs from the guinea pig brain receptor in having low affinity for sigma-related morphinans and benzomorphans. The lower molecular weight of the sigma site in PC12 cells is thus consistent with the different p site that differs from the guinea pig brain receptor in provide that the neutron of the neutron or pharmacology of this receptor and strengthens the notion of the notion that there may be multiple types of sigma receptors having low affinity for sigma-related morphinans
benzomorphans. The lower molecular weight of the signite in PC12 cells is thus consistent with the different
pharmacology of this receptor and strengthens the no
that there site in PC12 cells is thus consistent with the different
pharmacology of this receptor and strengthens the notion
that there may be multiple types of sigma receptors.
Sigma receptors have also been examined with several

site in PC12 cells is thus consistent with the different

pharmacology of this receptor and strengthens the notion

that there may be multiple types of sigma receptors.

Sigma receptors have also been examined with several pharmacology of this receptor and strengthens the notion
that there may be multiple types of sigma receptors.
Sigma receptors have also been examined with several
isothiocyanate probes. The isothiocyanate moiety is a
chemi that there may be multiple types of sigma receptors.

Sigma receptors have also been examined with several

isothiocyanate probes. The isothiocyanate moiety is a

chemically reactive electrophilic group that may be at-

ta Sigma receptors have also been examined with several
isothiocyanate probes. The isothiocyanate moiety is a
chemically reactive electrophilic group that may be at-
tacked by amine- or thiol-type nucleophiles at or near
the isothiocyanate probes. The isothiocyanate moiety is a chemically reactive electrophilic group that may be attacked by amine- or thiol-type nucleophiles at or near the ligand-binding site of the receptor, forming thiourea o chemically reactive electrophilic group that may be attacked by amine- or thiol-type nucleophiles at or near
the ligand-binding site of the receptor, forming thiourea
or dithiocarbamate links, respectively. Adams et al.
(1 derivative of DTG, DIGIT. Competition studies in which

derivative of DTG, DIGIT. Competition studies in which

derivative of DTG, DIGIT. Competition studies in which

derivative of DTG, DIGIT. Competition studies in which the ligand-binding site of the receptor, forming thiourea

or dithiocarbamate links, respectively. Adams et al.

(1987b) synthesized and characterized an isothiocyanate

derivative of DTG, DIGIT. Competition studies in wh or dithiocarbamate links, respectively. Adams et al. (1987b) synthesized and characterized an isothiocyanate derivative of DTG, DIGIT. Competition studies in which $[^3H]DTG$ was used revealed high affinity binding of DIGIT (1987b) synthesized and characterized an isothiocyanate
derivative of DTG, DIGIT. Competition studies in which
[³H]DTG was used revealed high affinity binding of
DIGIT to sigma sites $(K_i = \sim 28 \text{ nm})$. Membranes pre-
trea derivative of DTG, DIGIT. Competition studies in which [³H]DTG was used revealed high affinity binding of DIGIT to sigma sites $(K_i = \sim 28 \text{ nM})$. Membranes pretreated with DIGIT showed virtually no sigma-binding sites ev [³H]DTG was used revealed high affinity binding DIGIT to sigma sites $(K_i = \sim 28 \text{ nm})$. Membranes presented with DIGIT showed virtually no sigma-bindinaties even after repeated washing, suggesting covales attachment to th DIGIT to sigma sites $(K_i = \sim 28 \text{ nm})$. Membranes pre-
treated with DIGIT showed virtually no sigma-binding
sites even after repeated washing, suggesting covalent
attachment to the receptor. DIGIT acylates sigma recep-
tors treated with DIGIT showed virtually no sigma-binding for
sites even after repeated washing, suggesting covalent
attachment to the receptor. DIGIT acylates sigma recep-
tors with an IC₅₀ of 50 nM. Furthermore, the effect sites even after repeated washing, suggesting covalent attachment to the receptor. DIGIT acylates sigma receptors with an IC_{50} of 50 nM. Furthermore, the effect was selective for sigma sites, because binding of ligands attachment to the receptor. DIGIT acylates sigma receptors with an IC_{50} of 50 nM. Furthermore, the effect was selective for sigma sites, because binding of ligands for PCP, dopamine D_2 , benzodiazepine, and mu-opioid tors with an IC₅₀ of 50 nM. Furthermore, the effect was
selective for sigma sites, because binding of ligands for
PCP, dopamine D_2 , benzodiazepine, and mu-opioid re-
ceptors was unaffected. DIGIT produced competitive selective for sigma sites, because binding of ligands for

PCP, dopamine D_2 , benzodiazepine, and mu-opioid receptors was unaffected. DIGIT produced competitive

inhibition of $[^{3}H]DTG$ binding, which is quite surprisi PCP, dopamine D_2 , benzodiazepine, and mu-opioid receptors was unaffected. DIGIT produced competitive inhibition of $[^8H]$ DTG binding, which is quite surprising because noncompetitive inhibition would be expected of an ceptors was unaffected. DIGIT produced competitive
inhibition of $[{}^{8}H]DTG$ binding, which is quite surprising
because noncompetitive inhibition would be expected of
an agent that covalently occludes the ligand-binding s inhibition of [³H]DTG binding, which is quite surprising because noncompetitive inhibition would be expected of an agent that covalently occludes the ligand-binding site.
Bluth et al. (1989) used another irreversible iso

because noncompetitive inhibition would be expected of
an agent that covalently occludes the ligand-binding site.
Bluth et al. (1989) used another irreversible isothio-
cyanate ligand, Metaphit, to study the sigma receptor an agent that covalently occludes the ligand-binding site.
Bluth et al. (1989) used another irreversible isothio-
cyanate ligand, Metaphit, to study the sigma receptor.
Metaphit was previously shown to produce irreversible Bluth et al. (1989) used another irreversible isothio-
cyanate ligand, Metaphit, to study the sigma receptor.
Metaphit was previously shown to produce irreversible
blockade of PCP receptors in rat brain (Contreras et al.,

EPTORS
because of the known interaction of some PCP-related
compounds with sigma sites. Pretreatment of guinea pig EPTORS 373
because of the known interaction of some PCP-related
compounds with sigma sites. Pretreatment of guinea pig
brain membranes with Metaphit produced a concentra-EPTORS
because of the known interaction of some PCP-rel
compounds with sigma sites. Pretreatment of guines
brain membranes with Metaphit produced a concertion-dependent loss of sigma binding that was not because of the known interaction of some PCP-related compounds with sigma sites. Pretreatment of guinea pig brain membranes with Metaphit produced a concentration-dependent loss of sigma binding that was not reversed by re because of the known interaction of some PCP-relat
compounds with sigma sites. Pretreatment of guinea p
brain membranes with Metaphit produced a concent
tion-dependent loss of sigma binding that was not
versed by repeated compounds with sigma sites. Pretreatment of guinea pig
brain membranes with Metaphit produced a concentra-
tion-dependent loss of sigma binding that was not re-
versed by repeated washing. Residual receptor occupa-
tion du brain membranes with Metaphit produced a concentra-
tion-dependent loss of sigma binding that was not re-
versed by repeated washing. Residual receptor occupa-
tion due to failure to remove noncovalently bound Me-
taphit c versed by repeated washing. Residual receptor occupaversed by repeated washing. Residual receptor occupation due to failure to remove noncovalently bound Metaphit cannot account for this effect, because equivalent concentrations of PCP could be efficiently removed from the tion due to failure to remove noncovalently bound Me-
taphit cannot account for this effect, because equivalent
concentrations of PCP could be efficiently removed from
the receptor by the washing procedure. These data thus phit cannot account for this effect, because equivalent
ncentrations of PCP could be efficiently removed from
e receptor by the washing procedure. These data thus
ggest that Metaphit irreversibly labels sigma receptors.
Me

physical properties. The labeling of a 29-kDa protein in various radiolabeled sigma ligands. The order of sensitiv-
membranes of both guinea pig brain and NCB-20 cells ity to Metaphit was $[^{3}H]DTG >[^{3}H](+)-3-PPP >>[^{3}H]$
len lends support to the notion that this protein is the $(+)$ -SKF 10,047, with half-maximal loss of binding oc-
binding site of the sigma receptor, or at least a protein curring at 2, 10, and 50 μ M, respectively. In fact, binding site of the sigma receptor, or at least a protein curring at 2, 10, and 50 μ M, respectively. In fact, [⁹H] near the binding domain of the receptor. DTG binding was more sensitive to Metaphit than was Hellewel concentrations of PCP could be efficiently removed fr
the receptor by the washing procedure. These data the
suggest that Metaphit irreversibly labels sigma recept
Metaphit had a differential effect on the binding
various the receptor by the washing procedure. These data thus
suggest that Metaphit irreversibly labels sigma receptors.
Metaphit had a differential effect on the binding of
various radiolabeled sigma ligands. The order of sensit suggest that Metaphit irreversibly labels sigma receptors.
Metaphit had a differential effect on the binding of
various radiolabeled sigma ligands. The order of sensitiv-
ity to Metaphit was $[^{3}H]DTG > [^{3}H] (+)-3-PPP >> [^{3}H]$
 Metaphit had a differential effect on the binding of
various radiolabeled sigma ligands. The order of sensitiv-
ity to Metaphit was $[^{3}H]DTG > [^{3}H](+)-3-PPP >> [^{3}H]$
(+)-SKF 10,047, with half-maximal loss of binding oc-
curri various radiolabeled sigma ligands. The order of sensitiv-
ity to Metaphit was $[^{3}H]DTG > [^{3}H](+)-3-PPP >> [^{3}H]$
(+)-SKF 10,047, with half-maximal loss of binding oc-
curring at 2, 10, and 50 μ M, respectively. In fact, $[^{$ ity to Metaphit was $[^{3}H]DTG > [^{3}H](+)-3-PPP >> [^{3}H]$
(+)-SKF 10,047, with half-maximal loss of binding oc-
curring at 2, 10, and 50 μ M, respectively. In fact, $[^{3}H]$
DTG binding was more sensitive to Metaphit than was
t (+)-SKF 10,047, with half-maximal loss of binding c
curring at 2, 10, and 50 μ M, respectively. In fact, [³]
DTG binding was more sensitive to Metaphit than w
the binding of [³H]TCP, suggesting that Metaphit
more po curring at 2, 10, and 50 μ M, respectively. In fact, [³H]DTG binding was more sensitive to Metaphit than wa
the binding of [³H]TCP, suggesting that Metaphit i
more potent at sigma than at PCP receptors. The differ
e DTG binding was more sensitive to Metaphit than was
the binding of [³H]TCP, suggesting that Metaphit is
more potent at sigma than at PCP receptors. The differ-
ential sensitivity of [³H]DTG and [³H](+)-3-PPP com-
pa the binding of $[^{3}H]TCP$, suggesting that Metaphit is
more potent at sigma than at PCP receptors. The differ-
ential sensitivity of $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ com-
pared to $[^{3}H](+)$ - SKF 10,047 again seems to reflect more potent at sigma than at PCP recepto-
ential sensitivity of $[^{3}H]DTG$ and $[^{3}H](+)$ -
pared to $[^{3}H](+)$ - SKF 10,047 again seems
different modes of interaction of benzon-
non-benzomorphans with sigma receptors.
Surpr tial sensitivity of $[^{3}H]DTG$ and $[^{3}H](+)$ -3-PPP com-
red to $[^{3}H](+)$ -SKF 10,047 again seems to reflect the
fferent modes of interaction of benzomorphans and
n-benzomorphans with sigma receptors.
Surprisingly, like DIG pared to $[^{3}H](+)-$ SKF 10,047 again seems to reflect the
different modes of interaction of benzomorphans and
non-benzomorphans with sigma receptors.
Surprisingly, like DIGIT, Metaphit was a competitive
inhibitor of the b

different modes of interaction of benzomorphans are
non-benzomorphans with sigma receptors.
Surprisingly, like DIGIT, Metaphit was a competiti
inhibitor of the binding of sigma ligands. This is
contrast to effects on $[^{3}$ non-benzomorphans with sigma receptors.

Surprisingly, like DIGIT, Metaphit was a competitive

inhibitor of the binding of sigma ligands. This is in

contrast to effects on [³H]TCP binding, in which Meta-

phit produced Surprisingly, like DIGIT, Metaphit was a competitive
inhibitor of the binding of sigma ligands. This is in
contrast to effects on [³H]TCP binding, in which Meta-
phit produced the expected noncompetitive inhibition in
th inhibitor of the binding of sigma ligands. This is in contrast to effects on $[^{3}H]TCP$ binding, in which Meta-
phit produced the expected noncompetitive inhibition in
the same membranes. Reid et al. (1990) showed that
sev contrast to effects on [³H]TCP binding, in which Meta-
phit produced the expected noncompetitive inhibition in
the same membranes. Reid et al. (1990) showed that
several other electrophilic derivatives of PCP-related
com phit produced the expected
the same membranes. Reiseveral other electrophilic
compounds also irreversibly
varying degrees of potency.
From their studies of se e same membranes. Reid et al. (1990) showed the veral other electrophilic derivatives of PCP-relat mpounds also irreversibly bound to sigma sites w rying degrees of potency.
From their studies of several isothiocyanate der

several other electrophilic derivatives of PCP-related
compounds also irreversibly bound to sigma sites with
varying degrees of potency.
From their studies of several isothiocyanate deriva-
tives of (+)-3-PPP, Grayson et a compounds also irreversibly bound to sigma sites with varying degrees of potency.

From their studies of several isothiocyanate deriva-

tives of $(+)$ -3-PPP, Grayson et al. (1988) added to the

list of sigma receptor acyla varying degrees of potency.
From their studies of several isothiocyanate deriva-
tives of (+)-3-PPP, Grayson et al. (1988) added to the
list of sigma receptor acylators that form covalent at-
tachment but inhibit binding c From their studies of several isothiocyanate derivatives of $(+)$ -3-PPP, Grayson et al. (1988) added to the list of sigma receptor acylators that form covalent at tachment but inhibit binding competitively. Although there tives of (+)-3-PPP, Grayson et al. (1988) added to the list of sigma receptor acylators that form covalent attachment but inhibit binding competitively. Although there is no unequivocal explanation for the several demonstr list of sigma receptor acylators that form covalent at-
tachment but inhibit binding competitively. Although
there is no unequivocal explanation for the several dem-
onstrations of this phenomenon, a plausible explanation
 tachment but inhibit binding competitively. Although
there is no unequivocal explanation for the several dem-
onstrations of this phenomenon, a plausible explanation
is that the nucleophile may lie close to, but outside o there is no unequivocal explanation for the several demonstrations of this phenomenon, a plausible explanation
is that the nucleophile may lie close to, but outside of,
the ligand-binding site. This arrangement could allow constrations of this phenomenon, a plausible explanation
is that the nucleophile may lie close to, but outside of,
the ligand-binding site. This arrangement could allow
the ligand to attach in such a way that it is free t curring at 2, 10, and 80 μ M, respectively. In fact, [14] and the binding vas more sensitive to Metaphit than was
the binding of [³H]TCP, suggesting that Metaphit is more potent at sigma than at PCP receptors. The dif the ligand-binding site. This arrangement could allow
the ligand to attach in such a way that it is free to move
in and out of the binding site. This, in turn, would allow
a competing ligand to enter the binding site when the ligand to attach in such a way that it is free to move
in and out of the binding site. This, in turn, would allow
a competing ligand to enter the binding site when it is
present in sufficient concentration. The differe in and out of the binding site. This, in turn, would all a competing ligand to enter the binding site when i
present in sufficient concentration. The differential
fect of acylation on the various classes of sigma liga
may a competing ligand to enter the binding site when it is
present in sufficient concentration. The differential ef-
fect of acylation on the various classes of sigma ligands
may reflect the complexities of the structural org present in sufficient concentration. The differential fect of acylation on the various classes of sigma ligan may reflect the complexities of the structural organizion of sigma receptors as described above (i.e., texistenc fect of acylation on the various classes of sigma ligands may reflect the complexities of the structural organization of sigma receptors as described above (i.e., the existence of allosteric binding sites on the sigma macr may reflect the complexities of the structural organition of sigma receptors as described above (i.e., existence of allosteric binding sites on the sigma mac molecule or the existence of multiple types of recepto:
Although tion of sigma receptors as described above (i.e., the existence of allosteric binding sites on the sigma macromolecule or the existence of multiple types of receptors). Although a clear understanding of the mode of interac existence of allosteric binding sites on the sigma macromolecule or the existence of multiple types of receptors).
Although a clear understanding of the mode of interaction of isothiocyanates with sigma receptors is presen molecule or the existence of multiple types of receptors).
Although a clear understanding of the mode of interaction of isothiocyanates with sigma receptors is presently
lacking, further study of these compounds may provid Although a clear understanding of the mode of interaction of isothiocyanates with sigma receptors is presently lacking, further study of these compounds may provide important clues to the organization and structure of sigm receptor and increase with sigma receptors is present lacking, further study of these compounds may provide important clues to the organization and structure sigma receptors and may provide novel long-acting signeceptor an Furtherman receptors and may provide novel long-acting sigma
reptor antagonists.
Solubilization and Purification of Active Receptors
Purification of active sigma receptors must follow sol-
ilization in active form. Kavanau

receptor antagonists.
C. Solubilization and Purification of Active Receptors
Purification of active sigma receptors must follow solu-
ubilization in active form. Kavanaugh et al. (1989) solu-

³⁷⁴ **WALKER ET AL.** bilized sigma receptors from guinea pig brain using so-WALKER ET
bilized sigma receptors from guinea pig brain using so-
dium cholate. The solubilized receptors possess binding tr
properties that are similar to those of intact brain mem- de waLl
bilized sigma receptors from guinea pig brain using section
dium cholate. The solubilized receptors possess bindir
properties that are similar to those of intact brain mem-
branes. [³H]DTG and [³H](+)-3-PPP bound bilized sigma receptors from guinea pig brain using dium cholate. The solubilized receptors possess bindiproperties that are similar to those of intact brain meeting branes. $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$ bound to solubized bilized sigma receptors from guinea pig brain using so-
dium cholate. The solubilized receptors possess binding
properties that are similar to those of intact brain mem-
branes. [³H]DTG and [³H](+)-3-PPP bound to solub dium cholate. The solubilized receptors possess binding treproperties that are similar to those of intact brain mem-
branes. [³H]DTG and [³H](+)-3-PPP bound to solubi-
nized preparations with K_d values of 31 and 33 properties that are similar to those of intact brain membranes. [³H]DTG and [³H](+)-3-PPP bound to solubi-
lized preparations with K_d values of 31 and 33 nM,
respectively. Competition of [³H]DTG with a series of
c lized preparations with K_d values of 31 and 33 nM,
respectively. Competition of [³H]DTG with a series of
compounds revealed a ligand selectivity pattern indistin-
guishable from that of brain. Size exclusion chromatolized preparations with K_d values of 31 and 33 nM,
respectively. Competition of [³H]DTG with a series of
compounds revealed a ligand selectivity pattern indistin-
guishable from that of brain. Size exclusion chromatorespectively. Competition of [³H]DTG with a series of compounds revealed a ligand selectivity pattern indistinguishable from that of brain. Size exclusion chromatograpy on Sepharose Cl-6B showed that the binding activity compounds revealed a ligand selectivity pattern indistinguishable from that of brain. Size exclusion chromatograpy on Sepharose Cl-6B showed that the binding activity has an estimated Stokes radius of 8.7 Å. Similar resul guishable from that of brain. Size exclusion chromatograpy on Sepharose Cl-6B showed that the binding activity has an estimated Stokes radius of 8.7 Å. Similar results were obtained with membranes solubilized after photola grapy on Sepharose Cl-6B showed that the binding activity has an estimated Stokes radius of 8.7 Å. Similar m results were obtained with membranes solubilized after cyphotolabeling with $[^{3}H]Az-DTG$. However, this high mo-
 tivity has an estimated Stokes radius of 8.7 Å. Similar results were obtained with membranes solubilized after photolabeling with $[^{3}H]Az-DTG$. However, this high molecular weight may reflect aggregation of receptors or ass results were obtained with membranes solubilized after cy
photolabeling with [³H]Az-DTG. However, this high mo-
lecular weight may reflect aggregation of receptors or
massociation with other membrane proteins or detergen possibilities. Exploration with other membrane proteins or detergent sociation with other membrane proteins or detergent is
celles. Further work will be needed to exclude these
ssibilities.
Sigma receptors have also been solubilized from

association with other membrane proteins or detergent micelles. Further work will be needed to exclude these
possibilities. a
Sigma receptors have also been solubilized from rat seed and bovine cerebellum by Arnold et al. micelles. Further work will be needed to exclude the possibilities.
Sigma receptors have also been solubilized from
and bovine cerebellum by Arnold et al. (1988). The
investigators reported solubilization with 3-(3-chola-
 possibilities.

Sigma receptors have also been solubilized from and bovine cerebellum by Arnold et al. (1988). The

investigators reported solubilization with 3-(3-cho

midopropyl)dimethylammonio-1-propanesulfona

(CHAPS) Sigma receptors have also been solubilized from rat so
and bovine cerebellum by Arnold et al. (1988). These so
investigators reported solubilization with 3-(3-chola- el
midopropyl)dimethylammonio-1-propanesulfonate or
(CHA and bovine cerebellum by Arnold et al. (1988). The
investigators reported solubilization with 3-(3-ch
midopropyl)dimethylammonio-1-propanesulfon
(CHAPS) and a 6000-fold purification on an affin
column derivatized with a 3investigators reported solubilization with 3-(3-chola-
midopropyl)dimethylammonio-1-propanesulfonate op
(CHAPS) and a 6000-fold purification on an affinity the
column derivatized with a 3-PPP analog. After reconsti-
pretut midopropyl)dimethylammonio-1-propanesulfonate
(CHAPS) and a 6000-fold purification on an affinity
column derivatized with a 3-PPP analog. After reconsti-
tution into lipid vesicles, the purified material showed
the charact (CHAPS) and a 6000-fold purification on an affinity the column derivatized with a 3-PPP analog. After reconstitution into lipid vesicles, the purified material showed the characteristic ligand selectivity of the sigma sit column derivatized with a 3-PPP analog. After reconstitution into lipid vesicles, the purified material showed the characteristic ligand selectivity of the sigma site: high affinity for haloperidol and DTG, preference for tution into lipid vesicles, the purified material showed
the characteristic ligand selectivity of the sigma site:
high affinity for haloperidol and DTG, preference for the
 $(+)$ -isomer of SKF 10,047, and preference for the the characteristic ligand selectivity of the sigma site: pling
high affinity for haloperidol and DTG, preference for the of rat
 $(+)$ -isomer of SKF 10,047, and preference for the $(-)$ - nonse
isomer of butaclamol. Ligands f high affinity for haloperidol and DTG, preference for the $(+)$ -isomer of SKF 10,047, and preference for the $(-)$ -isomer of butaclamol. Ligands for other receptors, including PCP receptors, had little or no affinity. Sodiu (+)-isomer of SKF 10,047, and preference for the $(-)$ -
isomer of butaclamol. Ligands for other receptors, in-
cluding PCP receptors, had little or no affinity. Sodium
dodecyl sulfate-polyacrylamide gel electrophoresis reisomer of butaclamol. Ligands for other receptors, in-
cluding PCP receptors, had little or no affinity. Sodium
dodecyl sulfate-polyacrylamide gel electrophoresis re-
the vealed two polypeptides of 63 and 65 kDa. This diff cluding PCP receptors, had little or no affinity. Sodiu
dodecyl sulfate-polyacrylamide gel electrophoresis is
vealed two polypeptides of 63 and 65 kDa. This differ-
from the 29-kDa band photolabeled with $[^{3}H]Az-DT$
in gui dodecyl sulfate-polyacrylamide gel electrophoresis revealed two polypeptides of 63 and 65 kDa. This differs from the 29-kDa band photolabeled with [³H]Az-DTG in guinea pig brain and may again suggest species differences from the 29-kDa band photolabeled with $[{}^{3}H]$ Az-DTG in guinea pig brain and may again suggest species differences in sigma sites, as described above. Further studies must be carried out to investigate this possibility.

Mechanisms

must be carried out to investigate this possibility.
 IV. Sigma Receptors and Signal Transduct
 A. Coupling of Sigma Receptors to Guanine Nucleot

binding Proteins **bigma Rec**
A. Coupling of Signaling Proteins
G. proteins also

Mechanisms
Coupling of Sigma Receptors to Guanine Nucleotide-
nding Proteins
G proteins play a central role in several types of
grading mechanisms (Gilman, 1987). In some systems, d A. Coupling of Sigma Receptors to Guanine Nucleotide-
binding Proteins
G proteins play a central role in several types of
signaling mechanisms (Gilman, 1987). In some systems,
the first step in the cascade of biochemical e A. Coupling of Sigma Receptors to Guantine Pucteoine-
binding Proteins
G proteins play a central role in several types of
sigmaling mechanisms (Gilman, 1987). In some systems, dence f
the first step in the cascade of bioch omaing Proteins

G proteins play a central role in several types

signaling mechanisms (Gilman, 1987). In some system

the first step in the cascade of biochemical events, from

the formation of a transmitter-receptor comp G proteins play a central role in several types
signaling mechanisms (Gilman, 1987). In some system
the first step in the cascade of biochemical events, fro
the formation of a transmitter-receptor complex to mer
brane cond signaling mechanisms (Gilman, 1987). In some systems,
the first step in the cascade of biochemical events, from
the formation of a transmitter-receptor complex to mem-
brane conductance changes, is the coupling of the rec the first step in the cascade of biochemical events, from
the formation of a transmitter-receptor complex to mem
brane conductance changes, is the coupling of the receptor
tor to a G protein. G proteins play a role in cycl the formation of a transmitter-receptor complex to mem-
brane conductance changes, is the coupling of the recep-
tor to a G protein. G proteins play a role in cyclic
adenosine monophosphate-related systems, PPI turn-
over, brane conductance changes, is the coupling of the receptor to a G protein. G proteins play a role in cyclic adenosine monophosphate-related systems, PPI turnover, direct coupling to some ion channels, arachidonic acid-deri tor to a G protein. G proteins
adenosine monophosphate-relate
over, direct coupling to some ion
acid-derived systems, and protein
1987; Casey and Gilman, 1988).
Itzhak and coworkers (Itzhak Enosine monophosphate-related systems, PPI turn-
er, direct coupling to some ion channels, arachidonic
id-derived systems, and protein translocation (Gilman,
87; Casey and Gilman, 1988).
Itzhak and coworkers (Itzhak and Kh

over, direct coupling to some ion channels, arachidonic
acid-derived systems, and protein translocation (Gilman,
1987; Casey and Gilman, 1988).
Itzhak and coworkers (Itzhak and Khouri, 1988; It-
zhak, 1989) obtained eviden acid-derived systems, and protein translocation (Gilm
1987; Casey and Gilman, 1988).
Itzhak and coworkers (Itzhak and Khouri, 1988;
zhak, 1989) obtained evidence that sigma receptors
teract with G proteins. As observed wit 1987; Casey and Gilman, 1988). $\frac{1}{2}$ is n
Itzhak and coworkers (Itzhak and Khouri, 1988; It-
zhak, 1989) obtained evidence that sigma receptors in-
teract with G proteins. As observed with other G protein-
coupled rec Itzhak and coworkers (Itzhak and Khouri, 1988; It-

zhak, 1989) obtained evidence that sigma receptors in-

teract with G proteins. As observed with other G protein-

coupled receptors, guanosine triphosphate and

Gpp(NH) zhak, 1989) obtained evidence that sigma receptors in-
teract with G proteins. As observed with other G protein-
coupled receptors, guanosine triphosphate and
Gpp(NH)p inhibited the binding of $[^{3}H](+)-3-PPP$ to B.
rat brai teract with G proteins. As observed with other G protein-
coupled receptors, guanosine triphosphate and
Gpp(NH)p inhibited the binding of $[^{3}H](+)$ -3-PPP to
rat brain membranes. Binding of $[^{3}H](+)$ -SKF 10,047
was also in

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ing so- PPP binding. Guanosine monophosphate and adenosine
inding triphosphate had no effect on $[^{3}H](+)$ -3-PPP binding, ET AL.
PPP binding. Guanosine monophosphate and adenosine
triphosphate had no effect on $[^{3}H](+)-3-PPP$ binding,
demonstrating specificity for G protein-active guanine ET AL.
PPP binding. Guanosine monophosphate and adenosine
triphosphate had no effect on $[^{3}H](+)$ -3-PPP binding,
demonstrating specificity for G protein-active guanine
nucleotides. In the absence of $Gpp(NH)p$, $(+)$ -SKF PPP binding. Guanosine monophosphate and adenosine
triphosphate had no effect on $[^{3}H](+)$ -3-PPP binding,
demonstrating specificity for G protein-active guanine
nucleotides. In the absence of $Gpp(NH)p$, (+)-SKF
10,047 displ PPP binding. Guanosine monophosphate and adenosine
triphosphate had no effect on $[^{3}H](+)-3$ -PPP binding,
demonstrating specificity for G protein-active guanine
nucleotides. In the absence of $Gpp(NH)p$, $(+)-SKF$
10,047 displa triphosphate had no effect on $[^{3}H](+)$ -3-PPP binding,
demonstrating specificity for G protein-active guanine
nucleotides. In the absence of Gpp(NH)p, $(+)$ -SKF
10,047 displaced $[^{3}H](+)$ -3-PPP in a biphasic manner
from h nucleotides. In the absence of Gpp(NH)p, $(+)$ -SKF
10,047 displaced $[^{3}H](+)$ -3-PPP in a biphasic manner
from high and low affinity sites. Gpp(NH)p eliminated
the high affinity phase, suggesting conversion to a low
affini nucleotides. In the absence of Gpp(NH)p, (+)-SKF
10,047 displaced [³H](+)-3-PPP in a biphasic manner
from high and low affinity sites. Gpp(NH)p eliminated
the high affinity phase, suggesting conversion to a low
affinity 10,047 displaced $[^{3}H](+)$ -3-PPP in a biphasic man
from high and low affinity sites. Gpp(NH)p elimina
the high affinity phase, suggesting conversion to a
affinity state (Itzhak and Khouri, 1988). Further stude
revealed th from high and low affinity sites. Gpp(NH)p eliminated
the high affinity phase, suggesting conversion to a low
affinity state (Itzhak and Khouri, 1988). Further studies
revealed that Gpp(NH)p had a similar effect on displa the high affinity phase, suggesting conversion to a low
affinity state (Itzhak and Khouri, 1988). Further studies
revealed that Gpp(NH)p had a similar effect on displace-
ment of $[^{3}H](+)-3-PPP$ by $(+)-3-PPP$, pentazocine, and affinity state (Itzhak and Khouri, 1988). Further studies
revealed that Gpp(NH)p had a similar effect on displace-
ment of $[^{3}H](+)$ -3-PPP by $(+)$ -3-PPP, pentazocine, and
cyclazocine. However, haloperidol displaced $[^{3}H$ revealed that Gpp(NH)p had a similar effect on displament of $[^{3}H](+)$ -3-PPP by $(+)$ -3-PPP, pentazocine, cyclazocine. However, haloperidol displaced $[^{3}H](+$ PPP from a single state and was not affected by guan nucleotide ment of $[^{3}H](+)$ -3-PPP by (+ cyclazocine. However, halope
PPP from a single state and w
nucleotides (Itzhak, 1989). E
mazine was also not affected.
Kinetic studies revealed tha clazocine. However, haloperidol displaced $[^{3}H](+)-3$ -

²P from a single state and was not affected by guanine

cleotides (Itzhak, 1989). Displacement by chlorpro-

zine was also not affected.

Kinetic studies revealed

PPP from a single state and was not affected by guanine
nucleotides (Itzhak, 1989). Displacement by chlorpro-
mazine was also not affected.
Kinetic studies revealed that $Gpp(NH)p$ decreased the
association rate of $[^{3}H](+)$ nucleotides (Itzhak, 1989). Displacement by chlorpro-
mazine was also not affected.
Kinetic studies revealed that Gpp(NH)p decreased the
association rate of $[^{3}H](+)-3-PPP$ by about 5-fold. Dis-
sociation experiments demons mazine was also not affected.

Kinetic studies revealed that Gpp(NH)p decreased the

association rate of $[^{3}H](+)-3$ -PPP by about 5-fold. Dis-

sociation experiments demonstrated biexponential dis-

sociation of $[^{3}H](+)-$ Kinetic studies revealed that Gpp(NH)p decreased thas
association rate of $[^{3}H](+)-3$ -PPP by about 5-fold. Dis
sociation experiments demonstrated biexponential dis
sociation of $[^{3}H](+)-3$ -PPP. Inclusion of Gpp(NH)
elimin association rate of $[^{3}H](+)$ -3-PPP by about 5-fold. Dissociation experiments demonstrated biexponential dissociation of $[^{3}H](+)$ -3-PPP. Inclusion of $Gpp(NH)p$ eliminated the slower phase, leaving only the rapid monophasic sociation experiments demonstrated biexponential dissociation of $[^{3}H](+)-3-PPP$. Inclusion of $Gpp(NH)p$
eliminated the slower phase, leaving only the rapid mon-
ophasic component intact (Itzhak, 1989). This suggested
that th sociation of $[{}^{3}H](+)-3-PPP$. In
eliminated the slower phase, leavi
ophasic component intact (Itzhak
that the formation of a high aff
prevented by guanine nucleotides
Other agents known to affect r minated the slower phase, leaving only the rapid mon-
hasic component intact (Itzhak, 1989). This suggested
at the formation of a high affinity receptor state is
evented by guanine nucleotides.
Other agents known to affec

ophasic component intact (Itzhak, 1989). This suggested
that the formation of a high affinity receptor state is
prevented by guanine nucleotides.
Other agents known to affect receptor-G protein cou-
pling also inhibited that the formation of a high affinity receptor state is
prevented by guanine nucleotides.
Other agents known to affect receptor-G protein cou-
pling also inhibited $[^{3}H](+)-3-PPP$ binding. Treatment
of rat brain membranes w prevented by guanine nucleotides.

Other agents known to affect receptor-G protein cou-

pling also inhibited $[^{3}H](+)$ -3-PPP binding. Treatment

of rat brain membranes with either N-ethylmaleimide (a

nonselective agent) Other agents known to affect receptor-G protein coupling also inhibited $[^{3}H](+)-3-PPP$ binding. Treatment of rat brain membranes with either N-ethylmaleimide (a nonselective agent) or pertussis toxin (which selectively alt pling also inhibited $[^{3}H](+)$ -3-PPP binding. Treatment
of rat brain membranes with either N-ethylmaleimide (a
nonselective agent) or pertussis toxin (which selectively
alters G proteins) significantly decreased $[^{3}H](+)$ of rat brain membranes with either N-ethylmaleimide (a
nonselective agent) or pertussis toxin (which selectively
alters G proteins) significantly decreased $[^{3}H](+)-3-PPP$
binding (Itzhak, 1989). These reagents also elimina nonselective agent) or pertussis toxin (which selectively
alters G proteins) significantly decreased $[^{3}H](+)$ -3-PPP
binding (Itzhak, 1989). These reagents also eliminated
the effect of Gpp(NH)p on $[^{3}H](+)$ -3-PPP binding alters G proteins) significantly decreased $[^{3}H](+)-3-PPP$
binding (Itzhak, 1989). These reagents also eliminated
the effect of Gpp(NH)p on $[^{3}H](+)-3-PPP$ binding.
These results are similar to those obtained with other G
pro binding (Itzhak, 1989). These reagents also eliminated
the effect of $Gpp(NH)p$ on $[^{3}H](+)$ -3-PPP binding.
These results are similar to those obtained with other G-
protein-coupled receptors where these reagents are be-
lie the effect of Gpp(NH)p on $[^{3}H](+)-3$ -PPP bind
These results are similar to those obtained with othe
protein-coupled receptors where these reagents are
lieved to cause uncoupling of the receptor from the
protein unit. Beca These results are similar to those obtained with other G protein-coupled receptors where these reagents are be-
lieved to cause uncoupling of the receptor from the G-
protein unit. Because pertussis toxin adenosine diphoslieved to cause uncoupling of the receptor from the G-
protein unit. Because pertussis toxin adenosine diphos-
phate ribosylates Gi and Go, coupling to these particular
G proteins is suggested.
Taken together, these result wed to cause uncoupling of the receptor from the G-
otein unit. Because pertussis toxin adenosine diphos-
ate ribosylates Gi and Go, coupling to these particular
proteins is suggested.
Taken together, these results strongl

protein unit. Because pertussis toxin adenosine diphos-
phate ribosylates Gi and Go, coupling to these particular
G proteins is suggested.
Taken together, these results strongly suggest that the
sigma receptor labeled by phate ribosylates Gi and Go, coupling to these particular G proteins is suggested.
Taken together, these results strongly suggest that the sigma receptor labeled by $[^{3}H](+)-3$ -PPP can exist in a high and low affinity sta G proteins is suggested.
Taken together, these results strongly suggest that the sigma receptor labeled by $[^{8}H](+)-3-PPP$ can exist in a high and low affinity state, with the high affinity state coupled to a G protein. Thi Taken together, these results strongly suggest that the sigma receptor labeled by $[{}^{3}H](+)-3-PPP$ can exist in a high and low affinity state, with the high affinity state coupled to a G protein. This has important implicat sigma receptor labeled by $[{}^{3}H](+)-3-PPP$ can exist in a
high and low affinity state, with the high affinity state
coupled to a G protein. This has important implications
for the function of sigma sites, because it suggest high and low affinity state, with the high affine
coupled to a G protein. This has important im
for the function of sigma sites, because it sugg
sigma receptors are involved in signal transduc
dence for this is discussed i upled to a G protein. This has important implications
r the function of sigma sites, because it suggests that
gma receptors are involved in signal transduction. Evi-
nce for this is discussed in the next section.
The failu for the function of sigma sites, because it suggests that sigma receptors are involved in signal transduction. Evidence for this is discussed in the next section.
The failure of guanine nucleotides to alter haloperidol bin

(because are involved in signal transduction. Evidence for this is discussed in the next section.
The failure of guanine nucleotides to alter haloperidol
binding suggests that it is an antagonist at sigma sites
(because an dence for this is discussed in the next section.
The failure of guanine nucleotides to alter haloperid
binding suggests that it is an antagonist at sigma sit
(because antagonist binding is not sensitive to guanin
nucleotid The failure of guanine nucleotides to alter haloperi-
binding suggests that it is an antagonist at sigma si
(because antagonist binding is not sensitive to guan-
nucleotides, Gilman, 1987), whereas $(+)$ -benzomorpha
and $(+$ binding suggests that it is an antagonist at sigma sites (because antagonist binding is not sensitive to guanine nucleotides, Gilman, 1987), whereas (+)-benzomorphans and (+)-3-PPP would be agonists. However, this contradi (because antagonist binding is not sensitive to guanine nucleotides, Gilman, 1987), whereas $(+)$ -benzomorphans and $(+)$ -3-PPP would be agonists. However, this contradicts the results from several functional systems discus nucleotides, Gilman, 1987), whereas (+)-benzomorphans
and (+)-3-PPP would be agonists. However, this contra-
dicts the results from several functional systems dis-
cussed below. The reason for the apparent discrepancy
is n and $(+)$ -3-PPP would be agonists. However, this contra-
dicts the results from several functional systems dis-
cussed below. The reason for the apparent discrepancy
is not clear but may be related to the presence of multi dicts the results from several functional systems discussed below. The reason for the apparent discrepancy is not clear but may be related to the presence of multiple sigma-binding sites. Conceivably, haloperidol is an ancussed below. The reason for the apparent discress is not clear but may be related to the presence of m sigma-binding sites. Conceivably, haloperidol is a tagonist at one of the sites and an agonist at the This question cl Sigma-binding sites. Conceivably, haloperidol is an antagonist at one of the sites and an agonist at the other.
This question clearly calls for further investigation.
B. Modulation of Phosphoinositide Turnover
Although the

Although the biochemical systems acted on by sigma

PHARMACOLOGICAL REVIEWS

sig at the sections of sigma ligands on second messengers are now this powell established. Bowen and coworkers investigated the 1 (table SIGMA RECEF
actions of sigma ligands on second messengers are now this
well established. Bowen and coworkers investigated the 1 (
effects of sigma ligands on PPI turnover (Bowen et al., an sigma ligands on second messengers are now
well established. Bowen and coworkers investigated the
effects of sigma ligands on PPI turnover (Bowen et al.,
1988a; 1989b; Bowen et al., 1990b; Bowen and Tolentino, actions of sigma ligands on second messengers are now
well established. Bowen and coworkers investigated the
effects of sigma ligands on PPI turnover (Bowen et al.,
1988a; 1989b; Bowen et al., 1990b; Bowen and Tolentino,
1 actions of sigma ligands on second messengers are now well established. Bowen and coworkers investigated the effects of sigma ligands on PPI turnover (Bowen et al. 1988a; 1989b; Bowen et al., 1990b; Bowen and Tolentine (1 well established. Bowen and coworkers investigated the 1 (effects of sigma ligands on PPI turnover (Bowen et al., an 1988a; 1989b; Bowen et al., 1990b; Bowen and Tolentino, D7
1990). Sigma ligands did not significantly al 1988a; 1989b; Bowen et al., 1990b; Bowen and Tolentino, 1990). Sigma ligands did not significantly alter PPI turnover at concentrations up to 100 μ M in a rat brain synaptoneurosome preparation; although at higher conce 1990). Sigma ligands did not significantly alter PPI turn-1990). Sigma ligands did not significantly alter PPI turn-
over at concentrations up to $100 \mu M$ in a rat brain resynaptoneurosome preparation; although at higher con-
centrations there was slight depression of basal inos ligands do not directly stimulate PPI turnover in the manner of a number of based in the manner of a number of brain neurotransmitters. as a sight depression of based in the low directly stimulate PPI turnover in the low synaptoneurosome preparation; although at
centrations there was slight depression of be
phosphate production with some ligands. I
ligands do not directly stimulate PPI turn
manner of a number of brain neurotransmitt
Althou ntrations there was slight depression of basal inositol littles osphate production with some ligands. Thus, sigma (Bo ands do not directly stimulate PPI turnover in the louse anner of a number of brain neurotransmitters. a phosphate production with some ligands. Thus, sigma
ligands do not directly stimulate PPI turnover in the
manner of a number of brain neurotransmitters.
Although sigma ligands do not have direct effects on
PPI turnover, th

ligands do not directly stimulate PPI turnover if manner of a number of brain neurotransmitters.
Although sigma ligands do not have direct effect PPI turnover, they do modulate the actions of light for the cholinergic rece manner of a number of brain neurotransmitters.
Although sigma ligands do not have direct effects on
PPI turnover, they do modulate the actions of ligands
for the cholinergic receptor. In rat brain synaptoneuro-
somes, sigm Although sigma ligands do not have direct effects of PPI turnover, they do modulate the actions of ligand for the cholinergic receptor. In rat brain synaptoneur somes, sigma ligands attenuated the ability of both capachol PPI turnover, they do modulate the actions of ligands negrot for the cholinergic receptor. In rat brain synaptoneuro-
somes, sigma ligands attenuated the ability of both car-
bachol and oxotremorine-M to stimulate inositol for the cholinergic receptor. In rat brain synaptoneuro-
somes, sigma ligands attenuated the ability of both car-
bachol and oxotremorine-M to stimulate inositol phos-
sense phate production. The effect was dose dependent somes, sigma ligands attenuated the ability of both carbachol and oxotremorine-M to stimulate inositol phos-
phate production. The effect was dose dependent and
occurred at concentrations less than those required to
produc bachol and oxotremorine-M to stimulate inositol phos-

phate production. The effect was dose dependent and

occurred at concentrations less than those required to

produce the minor changes in basal activity. This effect
 phate production. The effect was dose dependent and tune occurred at concentrations less than those required to approduce the minor changes in basal activity. This effect symptom of sigma ligands was observed for compounds occurred at concentrations less than those required to aproduce the minor changes in basal activity. This effect so of sigma ligands was observed for compounds from varied nehemical classes. The rank order of potency of s produce the minor changes in basal activity. This effect
of sigma ligands was observed for compounds from varied
chemical classes. The rank order of potency of sigma
ligands at attenuating the PPI stimulatory effects of
o of sigma ligands was observed for compounds from varied no
chemical classes. The rank order of potency of sigma the
ligands at attenuating the PPI stimulatory effects of hy
oxotremorine-M correlated highly $(r = 0.92)$ with chemical classes. The rank order of potency of sigma
ligands at attenuating the PPI stimulatory effects of
oxotremorine-M correlated highly $(r = 0.92)$ with their
ability to displace $[^{3}H](+)-3$ -PPP from guinea pig brain
s ligands at attenuating the PPI stimulatory effects of oxotremorine-M correlated highly $(r = 0.92)$ with their ability to displace $[^{3}H](+)-3$ -PPP from guinea pig brain sigma receptors (Bowen et al., 1990b; fig. 9). A simil oxotremorine-M correlated highly $(r = 0.92)$ with their
ability to displace $[^{3}H](+)$ -3-PPP from guinea pig brain
sigma receptors (Bowen et al., 1990b; fig. 9). A similar
correlation was obtained with carbachol as the chol ability to displace $[^{3}H](+)$ -3-PPP from guinea pig brain site sigma receptors (Bowen et al., 1990b; fig. 9). A similar (B correlation was obtained with carbachol as the cholinergic agonist (Bowen et al., 1988a). This con sigma receptors (Bowen et al., 1990b; fig. 9). A similar correlation was obtained with carbachol as the cholinergic agonist (Bowen et al., 1988a). This constitutes strong evidence for sigma receptor moduluation of the PPI

inhibiting the cholinergic PPI response. Sigma-binding affinity and potency at inhibiting the cholinergic PPI response. Sigma-binding affinity was determined using $[{}^{3}H](+)-3-PPP$ **in guinea pig brain membranes. Sim-
ilar** FIG. 9. Correlation between sigma-binding affinity and potency at

inhibiting the cholinergic PPI response. Sigma-binding affinity was

determined using [³H](+)-3-PPP in guinea pig brain membranes. Sim-

ilar results are determined using [³H](+)-3-PPP in guinea pig brain membranes. Similar results are obtained if carbachol (rather than oxotremorine-M) is used to stimulate the response. The least squares correlation coefficient is 0.92. R Extra mixed are obtained if carbachol (rather than oxotremorine-
used to stimulate the response. The least squares correlation coefi
is 0.92. Reprinted from Bowen et al., 1990b. Abbreviations: KCF
N-cyclopropylmethyl-nordi trant vocales and vocales of the response. The least squares correlation coefficient
is 0.92. Reprinted from Bowen et al., 1990b. Abbreviations: KCR, (+)-
N-cyclopropylmethyl-nordihydrocodeinone; MDEX, 3-methoxydex-
trallo duced burname and a superior of al., 1990b. Abbreviations: KCN-cyclopropylmethyl-nordihydrocodeinone; MDEX, 3-methorallorphan; FLU, fluphenazine; DEX, dextrallorphan; Red. Haloperidol; HAL, haloperidol; (+)-PENT, (+)-penta

EPTORS
this potency profile is consistent with actions at sigm
1 (table 5) and not sigma-2, because (+)-benzomorpha EPTORS

this potency profile is consistent with actions at sigm

1 (table 5) and not sigma-2, because (+)-benzomorpha

and (+)-morphinans are in the same potency range 375
this potency profile is consistent with actions at sigma-
1 (table 5) and not sigma-2, because (+)-benzomorphans
and (+)-morphinans are in the same potency range as
DTG and haloperidol. this potency profile is
1 (table 5) and not signad (+)-morphinans
DTG and haloperidol
The only sigma con is potency profile is consistent with actions at sigma-
(table 5) and not sigma-2, because $(+)$ -benzomorphans
d $(+)$ -morphinans are in the same potency range as
TG and haloperidol.
The only sigma compound tested that gave

1 (table 5) and not sigma-2, because (+)-benzomorphans
and (+)-morphinans are in the same potency range as
DTG and haloperidol.
The only sigma compound tested that gave anomalous
results was (+)-3-PPP. This compound produ and $(+)$ -morphinans are in the same potency range as
DTG and haloperidol.
The only sigma compound tested that gave anomalous
results was $(+)$ -3-PPP. This compound produced 40%
inhibition at concentrations up to 100μ DTG and haloperidol.

The only sigma compound tested that gave anomalous

results was $(+)$ -3-PPP. This compound produced 40%

inhibition at concentrations up to 100 μ M and produced

little additional inhibition at conc The only sigma compound tested that gave anomalous
results was $(+)$ -3-PPP. This compound produced 40%
inhibition at concentrations up to 100 μ M and produced
little additional inhibition at concentrations up to 1 mM
(Bo inhibition at concentrations up to 100μ M and produce
little additional inhibition at concentrations up to 1 m!
(Bowen et al., 1990b). $(+)$ -3-PPP also exhibited anoma
lous effects in other assays of sigma receptor funct (Bowen et al., 1990b). (+)-3-PPP also exhibited anomalous effects in other assays of sigma receptor function, as discussed in more detail below.
Sigma ligands also attenuated the action of norepi-
nephrine via the α_1 lous effects in other assays of sigma receptor function,

lous effects in other assays of sigma receptor function,
as discussed in more detail below.
Sigma ligands also attenuated the action of norepi-
nephrine via the α_1 -adrenergic receptor, but at concen-
trations 15-fold as discussed in more detail below.
Sigma ligands also attenuated the action of norepi-
nephrine via the α_1 -adrenergic receptor, but at concen-
trations 15-fold greater than those needed to affect cho-
linergic activit Sigma ligands also attenuated the action of norepi-
nephrine via the α_1 -adrenergic receptor, but at concen-
trations 15-fold greater than those needed to affect cho-
linergic activity (Bowen et al., 1990b). The differ nephrine via the α_1 -adrenergic receptor, but at concentrations 15-fold greater than those needed to affect cho-
linergic activity (Bowen et al., 1990b). The differential
sensitivity of cholinergic and adrenergic stimu linergic activity (Bowen et al., 1990b). The differential
sensitivity of cholinergic and adrenergic stimulated PPI
turnover suggests receptor specificity in the effect and
argues against actions on a component common to bo linergic activity (Bowen et al., 1990b). The differential
sensitivity of cholinergic and adrenergic stimulated PPI
turnover suggests receptor specificity in the effect and
argues against actions on a component common to bo sensitivity of cholinergic and adrenergic stimulated PPI
turnover suggests receptor specificity in the effect and
argues against actions on a component common to both
systems. Consistent with this notion, sigma ligands did turnover suggests receptor specificity in the effect and argues against actions on a component common to both systems. Consistent with this notion, sigma ligands did not appear to affect incorporation of myoinositol into t argues against actions on a component common to both
systems. Consistent with this notion, sigma ligands did
not appear to affect incorporation of myoinositol into
the inositol phospholipid pool. They also did not affect
h systems. Consistent with this notion, sigma ligands did
not appear to affect incorporation of myoinositol into
the inositol phospholipid pool. They also did not affect
hydrolysis of inositol trisphosphate, an effect that w not appear to affect incorporation of myoinositol into
the inositol phospholipid pool. They also did not affect
hydrolysis of inositol trisphosphate, an effect that would
decrease accumulation of inositol-1-phosphate, the the inositol phospholipid pool. They also did not affect
hydrolysis of inositol trisphosphate, an effect that would
decrease accumulation of inositol-1-phosphate, the ino-
sitol phosphate monitored in the studies described hydrolysis of inositol trisphosphate, an effect that would
decrease accumulation of inositol-1-phosphate, the ino-
sitol phosphate monitored in the studies described above
(Bowen et al. 1989b). Sigma ligands blocked format decrease accumulation of in
sitol phosphate monitored i
(Bowen et al. 1989b). Sign
of all three inositol phosph
phospholipase C activation
The effects on both cholin col phosphate monitored in the studies described above
fowen et al. 1989b). Sigma ligands blocked formation
all three inositol phosphates, suggesting blockade of
ospholipase C activation.
The effects on both cholinergic an

(Bowen et al. 1989b). Sigma ligands blocked formation
of all three inositol phosphates, suggesting blockade of
phospholipase C activation.
The effects on both cholinergic and adrenergic activity
were noncompetitive, with s of all three inositol phosphates, suggesting blockade of
phospholipase C activation.
The effects on both cholinergic and adrenergic activity
were noncompetitive, with sigma ligands reducing the
maximal stimulation (Bowen e phospholipase C activation.
The effects on both cholinergic and adrenergic active
were noncompetitive, with sigma ligands reducing
maximal stimulation (Bowen et al., 1990b). This sugge
that the effect does not occur throug The effects on both cholinergic and adrenergic activity
were noncompetitive, with sigma ligands reducing the
maximal stimulation (Bowen et al., 1990b). This suggests
that the effect does not occur through a simple compet-
 were noncompetitive, with sigma ligands reducing the
maximal stimulation (Bowen et al., 1990b). This suggests
that the effect does not occur through a simple compet-
itive interaction of sigma ligands with cholinergic or
a that the effect does not occur through a simple competitive interaction of sigma ligands with cholinergic or adrenergic receptors. All of the active sigma ligands possess micromolar affinity for cholinergic receptors label itive interaction of sigma ligands with cholinergic c
adrenergic receptors. All of the active sigma liganc
possess micromolar affinity for cholinergic receptors la
beled by [³H]oxotremorine-M. However, direct recepto
ant possess micromolar affinity for cholinergic receptors labeled by [³H]oxotremorine-M. However, direct receptor antagonism was ruled out by a series of pretreatment experiments which demonstrated that sigma inhibition possess micromolar affinity for cholinergic receptors labeled by [³H]oxotremorine-M. However, direct receptor antagonism was ruled out by a series of pretreatment experiments which demonstrated that sigma inhibition of t beled by [³H]oxotremorine-M. However, direct receptor
antagonism was ruled out by a series of pretreatment
experiments which demonstrated that sigma inhibition
of the cholinergic PPI response could be observed when
there antagonism was ruled out by a series of pretreatme experiments which demonstrated that sigma inhibition of the cholinergic PPI response could be observed when there was no occupation of cholinergic receptors by sigma ligan linergic activity (Bowen et al., 1990b). The differential
sensitivity of columergic and adrenargic stimulated PPI
turnover suggests receptor specificity in the effect and
argues against actions on a component common to bo of the cholinergic PPI response could be observed when
there was no occupation of cholinergic receptors by
sigma ligand (Bowen et al., 1990b). An interesting observation in the course of these studies was that despite th
 there was no occupation of cholinergic receptors lagrama ligand (Bowen et al., 1990b). An interesting obvation in the course of these studies was that despite order of magnitude lower binding affinity of sigma c pounds at sigma ligand (Bowen et al., 1990b). An interesting observation in the course of these studies was that despite the order of magnitude lower binding affinity of sigma compounds at cholinergic receptors labeled by $[^{3}H]$ o vation in the course of these studies was that despite the order of magnitude lower binding affinity of sigma compounds at cholinergic receptors labeled by $[^{3}H](+)-3-PPP$ *(r* = 0.89; Bowen et al., 1990b). This suggests som pounds at cholinergic receptors labeled by $[^{3}H]$ oxotremorine-M, the rank order of affinity was very similar to that at sigma receptors labeled by $[^{3}H](+)-3-PPP$ ($r = 0.89$; Bowen et al., 1990b). This suggests some rela morine-M, the rank order of affinity was very similar to
that at sigma receptors labeled by $[^{3}H](+)-3-PPP$ ($r = 0.89$; Bowen et al., 1990b). This suggests some relation-
ship between sigma and cholinergic receptor topograp that at sigma receptors labeled by $[{}^3H](+)-3-PPP$ ($r=$

0.89; Bowen et al., 1990b). This suggests some relation-
0 1 2 and deserves further study.
FIG. 9. Correlation between sigma-binding affinity and potency at
hibiting the cholinergic PPI response. Sigma-binding affinity was 0.89; Bowen et al., 1990b). This suggests some relation-
ship between sigma and cholinergic receptor topography
and deserves further study.
Further investigation of the mechanism of sigma-ac-
tion demonstrated that activat ship between sigma and cholinergic receptor topography
and deserves further study.
Further investigation of the mechanism of sigma ac-
tion demonstrated that activation of sigma-binding sites
affects cholinergic receptor b and deserves further study.
Further investigation of the mechanism of sigma-
tion demonstrated that activation of sigma-binding s
affects cholinergic receptor binding (Bowen et al., 199
Bowen and Tolentino, 1990). Pretreat Further investigation of the mechanism of sigmation demonstrated that activation of sigma-binding affects cholinergic receptor binding (Bowen et al., 19
Bowen and Tolentino, 1990). Pretreatment of synaneurosomes with the s Bowen and Tolentino, 1990). Pretreatment of synapto-
neurosomes with the selective sigma ligand $(+)$ -penta-
zocine resulted in a decrease in the binding of $[^{3}H]$
oxotremorine-M. This was due to a marked decrease in affects cholinergic receptor binding (Bowen et al., 1990b;
Bowen and Tolentino, 1990). Pretreatment of synapto-
neurosomes with the selective sigma ligand (+)-penta-
zocine resulted in a decrease in the binding of $[^{3}H]$ Bowen and Tolentino, 1990). Pretreatment of synapto-
neurosomes with the selective sigma ligand $(+)$ -penta-
zocine resulted in a decrease in the binding of $[^{3}H]$
oxotremorine-M. This was due to a marked decrease in
the

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(fig. 10). However, the pretreatment did not affect the red
binding parameters of the membrane-permeant cholin-red WAI
(fig. 10). However, the pretreatment did not affect t
binding parameters of the membrane-permeant choli
ergic ligand [³H]quinuclidinyl benzylate ([³H]QN wALKE
(fig. 10). However, the pretreatment did not affect the
binding parameters of the membrane-permeant cholin-
ergic ligand [³H]quinuclidinyl benzylate ([³H]QNB)
(Bowen and Tolentino, 1990). This suggested that sigm (fig. 10). However, the pretreatment did not affect the rebinding parameters of the membrane-permeant cholin-
ergic ligand [³H]quinuclidinyl benzylate ([³H]QNB) P.
(Bowen and Tolentino, 1990). This suggested that sigma (fig. 10). However, the pretreatment did not affect the identicing parameters of the membrane-permeant cholinergic ligand $[^{3}H]$ quinuclidinyl benzylate $([^{3}H]QNB)$ ligands heterologously desensitize the cholinergic PPI binding parameters of the membrane-permeant cholivergic ligand [³H]quinuclidinyl benzylate ([³H]QN] (Bowen and Tolentino, 1990). This suggested that signigands heterologously desensitize the cholinergic P? response by ergic ligand $[{}^{3}H]$ quinuclidinyl benzylate $([{}^{3}H]$ QNB) PH
(Bowen and Tolentino, 1990). This suggested that sigma
receptors are internalization of cholinergic PPI curresponse by causing internalization of cholinergic (Bowen and Tolentino, 1990). This suggested that sigma
ligands heterologously desensitize the cholinergic PPI
response by causing internalization of cholinergic recep-
tors. A mechanism involving receptor internalization i ligands heterologously desensitize the cholinergic PPI
response by causing internalization of cholinergic recep-
tors. A mechanism involving receptor internalization is
consistent with the observation that sigma ligands de response by causing internalization of cholinergic recep-
tors. A mechanism involving receptor internalization is
in v
consistent with the observation that sigma ligands de-
sigm
crease the maximal stimulation produced by tors. A mechanism involving receptor internalization is in consistent with the observation that sigma ligands de-
crease the maximal stimulation produced by cholinergic the
agonists. More work will be needed to verify this consistent with
crease the maxi
agonists. More
determine what
sigma receptor.
It should be ease the maximal stimulation produced by cholinergic thouists. More work will be needed to verify this and to time
termine what signal is produced by activation of the max receptor.
It should be noted that, despite nanomol

agonists. More work will be needed to verify this and to determine what signal is produced by activation of the sigma receptor.
It should be noted that, despite nanomolar binding affinities at sigma receptors, micromolar c determine what signal is produced by activation of the sigma receptor.
It should be noted that, despite nanomolar binding affinities at sigma receptors, micromolar concentrations of sigma ligands are required to affect the sigma receptor.
It should be noted that, despite nanomolar binding
affinities at sigma receptors, micromolar concentrations
of sigma ligands are required to affect the PPI system
This might, at first glance, be somewhat di It should be noted that, despite nanomolar binding
affinities at sigma receptors, micromolar concentrations
of sigma ligands are required to affect the PPI system.
This might, at first glance, be somewhat disturbing.
Howev affinities at sigma receptors, micromolar concentration
of sigma ligands are required to affect the PPI system
This might, at first glance, be somewhat disturbing
However, it is also true that micromolar concentration
of o of sigma ligands are required to affect the PPI system.
This might, at first glance, be somewhat disturbing.
However, it is also true that micromolar concentrations
of oxotremorine-M are required to stimulate PPI turn-
ov This might, at first glance, be somewhat disturbing.
However, it is also true that micromolar concentrations
of oxotremorine-M are required to stimulate PPI turn-
over, despite nanomolar affinity at cholinergic receptors
 However, it is also true that micromolar concentrations signal of oxotremorine-M are required to stimulate PPI turn-
over, despite nanomolar affinity at cholinergic receptors cheretic $(K_d = 39 \text{ nM})$. This is also true for of oxotremorine-M are required to stimulate PPI turn-
over, despite nanomolar affinity at cholinergic receptors $(K_d = 39 \text{ nM})$. This is also true for some other agonists a
linked to second messenger systems. Consequently, over, despite nanomolar affinity at cholinergic receptors change $(K_d = 39 \text{ nM})$. This is also true for some other agonists a bi-
linked to second messenger systems. Consequently, the site
discrepancy between sigma-binding linked to second messenger systems. Consequently, the discrepancy between sigma-binding affinity and effective dose may be indicative of coupling of sigma receptors to a signaling system.
Recently, several neurotransmitter ked to second messenger systems. Consequently, the site
screpancy between sigma-binding affinity and effective fu-
se may be indicative of coupling of sigma receptors to accrigaing system.
Recently, several neurotransmitte discrepancy between sigma-binding affinity and effect
dose may be indicative of coupling of sigma receptors
a signaling system.
Recently, several neurotransmitters have been sho
to inhibit agonist-stimulated PPI turnover i

dose may be indicative of coupling of sigma receptors to
a signaling system.
Recently, several neurotransmitters have been shown
to inhibit agonist-stimulated PPI turnover in a heterol-
ogous manner (Linden and Delahunty,

Control: $K_d = 39$ nM; $B_{\text{max}} = 151$ fmol/mg P				
Pretreated: K _d = 32 nM; B _{max} = 78 fmol/mg P				

Pretreated: $K_d = 39 \text{ nN}$; $B_{\text{max}} = 151 \text{ fmol/mg P}$
 Pro. 10. Reduction in the density of muscarinic receptors in syn-

aptoneurosomes following pretreatment with (+)-pentazocine. Intact

synaptoneurosomes were pretre **Example 1998 Example 1999 We also the Pretreated:** $K_d = 32$ mH; $B_{max} = 78$ fmol/mg P
FIG. 10. Reduction in the density of muscarinic receptors in syn-
aptoneurosomes following pretreated with 50 μ M (+)-pentazoci FIG. 10. Reduction in the density of muscarinic receptors in syn-
aptoneurosomes following pretreatment with $(+)$ -pentazocine. Intact
synaptoneurosomes were pretreated with 50 μ M $(+)$ -pentazocine under
conditions ident aptoneurosomes following pretreatment with $(+)$ -pentazocine. Intactynaptoneurosomes were pretreated with 50 μ M $(+)$ -pentazocine undeconditions identical with those used in PPI assays. After the membranes were washed and synaptoneurosomes were pretreated with 50 μ M (+)-pentazocine und
conditions identical with those used in PPI assays. After the men
branes were washed and resuspended in fresh medium that was free
(+)-pentazocine, [³H conditions identical with those used in PPI assays. After the mem-
branes were washed and resuspended in fresh medium that was free of
 $(+)$ -pentazocine, [³H]oxotremorine-M binding was examined. Scat-
chard analysis reve unaffected by pretreatment with sigma ligands are minded. Scatchard analysis revealed that pretreatment with $(+)$ -pentazocine markedly decreases the B_{max} of muscarinic binding. The K_d is relatively unaffected by pr the sigma ligands in the sigma ligands affect cholinergic induced by decreases the B_{max} of muscarinic binding. The K_d is relatively unaffected by pretreatment with sigma ligands. These findings suggest that sigma l East a miny survey and product antary product and in the state of the state of

ET AL.
receptor may thus be a member of a growing family of
receptors that are coupled to negative modulation of the ET AL.
receptor may thus be a member of a growing family of
receptors that are coupled to negative modulation of the
PPI response. It remains to be seen whether sigma ET AL.
receptor may thus be a member of a growing family of
receptors that are coupled to negative modulation of the
PPI response. It remains to be seen whether sigma
receptors affect other PPI-linked receptor systems. The receptor may thus be a member of a growing family of
receptors that are coupled to negative modulation of the
PPI response. It remains to be seen whether sigma
receptors affect other PPI-linked receptor systems. The
curren receptor may thus be a member of a growing family of receptors that are coupled to negative modulation of the PPI response. It remains to be seen whether sigma receptors affect other PPI-linked receptor systems. The curren receptors that are coupled to negative modulation of the PPI response. It remains to be seen whether sigma receptors affect other PPI-linked receptor systems. The current state of understanding is, however, sufficient to c PPI response. It remains to be seen whether sigma
receptors affect other PPI-linked receptor systems. The
current state of understanding is, however, sufficient to
conclude that sigma ligands may produce certain effects
in receptors affect other PPI-linked receptor systems. The
current state of understanding is, however, sufficient to
conclude that sigma ligands may produce certain effects
in vivo by modulating the efficacy of transmitters t current state of understanding is, however, sufficient t conclude that sigma-ligands may produce certain effect
in vivo by modulating the efficacy of transmitters that
signal through the PPI system. These findings add t
th conclude that s
in vivo by mod
signal through
the body of evi
tional entities.
V Free V. Functions of the Sigma Receptor
hrough the PPI system. These findings a
y of evidence that sigma-binding sites are
tities.
V. Functions of the Sigma Receptor
adical modifications of Martin's original hy e body of evidence that sigma-binding sites are fuorthermal entities.

V. Functions of the Sigma Receptor

The radical modifications of Martin's original hypoter

is of sigma opiate receptors (1976) raise many que

tional entities.

V. Functions of the Sigma Receptor

The radical modifications of Martin's original hypothesis

of sigma opiate receptors (1976) raise many ques-

tions about the pharmacology and function of this sys-V. Functions of the Sigma Receptor
The radical modifications of Martin's original hypothesis of sigma opiate receptors (1976) raise many ques-
tions about the pharmacology and function of this sys-
tem. Several questions V. Functions of the Sigma Receptor
The radical modifications of Martin's original hypothesis of sigma opiate receptors (1976) raise many ques-
tions about the pharmacology and function of this sys-
tem. Several questions m The radical modifications of Martin's original hypothesis of sigma opiate receptors (1976) raise many questions about the pharmacology and function of this system. Several questions must be addressed: (a) Is the sigmaesis of sigma opiate receptors (1976) raise many questions about the pharmacology and function of this system. Several questions must be addressed: (a) Is the sigma-binding site a true biologically active receptor, an (ina tions about the pharmacology and function of this system. Several questions must be addressed: (a) Is the sigma-binding site a true biologically active receptor, an (inactive) acceptor site, or some other entity $(e.g.,$ io sigma-binding site a true biologically active receptor, an (inactive) acceptor site, or some other entity (e.g., ion channel or enzyme)? (b) Assuming that the sigma site is a biologically functional receptor, are the liga (inactive) acceptor site, or some other entity (e.g., ion (inactive) acceptor site, or some other entity (e.g., ion channel or enzyme)? (b) Assuming that the sigma site is a biologically functional receptor, are the ligands for this site acting as agonists or antagonists? (c) Wh channel or enzyme)? (b) Assuming that the sigma site is
a biologically functional receptor, are the ligands for this
site acting as agonists or antagonists? (c) What are the
functions of the sigma receptor? (d) Are some o a biologically functional receptor, are the ligands for this site acting as agonists or antagonists? (c) What are the functions of the sigma receptor? (d) Are some of the actions of antipsychotic drugs that are traditiona receptors? nctions of the sigma receptor? (d) Are some of the
tions of antipsychotic drugs that are traditionally as-
ibed to dopamine receptors mediated instead by sigma
ceptors?
Until recently, finding answers to these questions actions of antipsychotic drugs that are traditionally ascribed to dopamine receptors mediated instead by sigma
receptors?
Until recently, finding answers to these questions has
been hampered by the lack of selective ligand

cribed to dopamine receptors mediated instead by sigm
receptors?
Until recently, finding answers to these questions ha
been hampered by the lack of selective ligands for th
sigma receptor. For example, conclusions about th receptors?
Until recently, finding answers to these questions has
been hampered by the lack of selective ligands for the
sigma receptor. For example, conclusions about the func-
tions of the sigma receptor based on the act Until recently, finding answers to these questions has
been hampered by the lack of selective ligands for the
sigma receptor. For example, conclusions about the func-
tions of the sigma receptor based on the actions of SKF been hampered by the lack of selective ligands for the sigma receptor. For example, conclusions about the functions of the sigma receptor based on the actions of SKF 10,047 must be viewed with caution because it acts at a sigma receptor. For example, conclusions about the functions of the sigma receptor based on the actions of SKF 10,047 must be viewed with caution because it acts at a number of receptors. Consequently, a reexamination of t 10,047 must be viewed with caution because
number of receptors. Consequently, a reexa
the functions of sigma receptors using mo
ligands has been an important recent thrust. *A.* Putative External With Cattion Because in the functions of sigma receptors using religends has been an important recent thru A. Putative Endogenous Sigma Ligands
To prove beyond any doubt that a bin e functions of sigma receptors using more selective

ands has been an important recent thrust.

Putative Endogenous Sigma Ligands

To prove beyond any doubt that a binding site is a

ue receptor requires identification of

ligands has been an important recent thrust.

A. Putative Endogenous Sigma Ligands

To prove beyond any doubt that a binding site

true receptor requires identification of the neuroti

mitter. Although this has not yet occ A. Putative Endogenous Sigma Ligands
To prove beyond any doubt that a binding site is
true receptor requires identification of the neurotrans
mitter. Although this has not yet occurred, several labo
ratories have isolated A. Putative Endogenous Sigma Ligands
To prove beyond any doubt that a binding site is a
true receptor requires identification of the neurotrans-
mitter. Although this has not yet occurred, several labo-
ratories have isola To prove beyond any doubt that a binding site is a
true receptor requires identification of the neurotrans-
mitter. Although this has not yet occurred, several labo-
ratories have isolated substances from brain extracts th true receptor requires identification of the neurotrans-

mitter. Although this has not yet occurred, several laboratories have isolated substances from brain extracts that

inhibit the binding of sigma radioligands. Cont mitter. Although this has not yet occurred, several laboratories have isolated substances from brain extracts that inhibit the binding of sigma radioligands. Contreras et al. $(1987a,b)$ reported on a polypeptide isolated ratories have isolated substances from brain extracts that
inhibit the binding of sigma radioligands. Contreras et
al. (1987a,b) reported on a polypeptide isolated from
porcine brain designated β -endopsycosin, and Sond inhibit the binding of sigma radioligands. Contreras et al. $(1987a,b)$ reported on a polypeptide isolated from porcine brain designated β -endopsycosin, and Sonders et al. (1986) reported on a low molecular weight mat al. (1987a,b) reported on a polypeptide isolated from
porcine brain designated β -endopsycosin, and Sonders et
al. (1986) reported on a low molecular weight material
from bovine brain extracts that inhibits sigma bindin porcine brain designated β -endopsycosin, and Sonders et
al. (1986) reported on a low molecular weight material
from bovine brain extracts that inhibits sigma binding.
Su and colleagues (1986; 1988) reported on a possib al. (1986) reported on a low molecular weight material from bovine brain extracts that inhibits sigma binding Su and colleagues (1986; 1988) reported on a possible ndogenous ligand (molecular weight ~ 500 Da) from guin from bovine brain extracts the
Su and colleagues (1986; 198
endogenous ligand (molecular
guinea pig brain that inhibits
ing but not $[^{3}H]PCP$ binding.
In what may be a crucial disc In and colleagues (1986; 1988) reported on a possible dogenous ligand (molecular weight \sim 500 Da) from inea pig brain that inhibits $[^{3}H](+)$ -SKF 10,047 bind-
g but not $[^{3}H]PCP$ binding.
In what may be a crucial disco

endogenous ligand (molecular weight \sim 500 Da) from
guinea pig brain that inhibits $[{}^8H](+)$ -SKF 10,047 bind-
ing but not $[{}^8H]$ PCP binding.
In what may be a crucial discovery, Roman et al. (1989)
reported that two end guinea pig brain that inhibits $[^{3}H](+)$ -SKF 10,047 bind-
ing but not $[^{3}H]PCP$ binding.
In what may be a crucial discovery, Roman et al. (1989)
reported that two endogenous peptides, NPY and peptide
YY, have high affini ing but not $[^{3}H]PCP$ binding.
In what may be a crucial discovery, Roman et al. (1989)
reported that two endogenous peptides, NPY and peptide
YY, have high affinity for rat brain sigma receptors
labeled with $[^{3}H](+)-SKF$ In what may be a crucial discovery, Roman et al. (1989)
reported that two endogenous peptides, NPY and peptide
YY, have high affinity for rat brain sigma receptors
labeled with $[^{3}H](+)-SKF$ 10,1047. In fact, with IC_{50}
 reported that two endogenous peptides, NPY and peptide YY, have high affinity for rat brain sigma receptors labeled with $[^{3}H](+)-SKF 10,1047$. In fact, with IC_{50} values of 9.8 and 4.9 nM respectively, these compounds w YY, have high affinity for rat brain sigma receptors
labeled with $[^{3}H](+)$ -SKF 10,1047. In fact, with IC_{50}
values of 9.8 and 4.9 nM respectively, these compounds
were 2.5-5 times more potent than haloperidol in the
ra labeled with $[^{3}H](+)-SKF$ 10,1047. In fact, with IC_{50} values of 9.8 and 4.9 nM respectively, these compounds were 2.5-5 times more potent than haloperidol in the rat. The distribution of NPY in rat brain (Allen et al., values of 9.8 and 4.9 nM respectively, these compounds
were 2.5–5 times more potent than haloperidol in the
rat. The distribution of NPY in rat brain (Allen et al.,
1983) corresponds reasonably well with the distribution
o

HARMACOLOGICAL REVIEW!

SIGM.
McLean and Weber, 1988), except in the nucleus accumbens where there is a great deal of NPY but very f SIGMA RECEPTOR
McLean and Weber, 1988), except in the nucleus accum-little e
bens where there is a great deal of NPY but very few these sigma sites. 1988), except in the nucleus accum-
http bens where there is a great deal of NPY but very few
sigma sites. NPY may be the most abundant peptide in
the central nervous system (Adrian et al., 1983; Tatemoto prod McLean and Weber, 1988), except in the nucleus accum-
bens where there is a great deal of NPY but very few
sigma sites. NPY may be the most abundant peptide in
the central nervous system (Adrian et al., 1983; Tatemoto
1982 McLean and Weber, 1988), except in the nucleus accumbens where there is a great deal of NPY but very few sigma sites. NPY may be the most abundant peptide in the central nervous system (Adrian et al., 1983; Tatemoto 1982), bens where there is a great deal of NPY but very few
sigma sites. NPY may be the most abundant peptide in
the central nervous system (Adrian et al., 1983; Tatemoto
1982), and the possibility that it serves as the endogenou sigma sites. NPY may be
the central nervous system
1982), and the possibility t
ligand for sigma receptors
needs further investigation
Although they have not i e central nervous system (Adrian et al., 1983; Tatemoto
82), and the possibility that it serves as the endogenous
and for sigma receptors is a very exciting prospect that
eds further investigation.
Although they have not i

1982), and the possibility that it serves as the endogenous
ligand for sigma receptors is a very exciting prospect that
needs further investigation.
Although they have not identified a chemical structure,
Chavkin and cowo ligand for sigma receptors is a very exciting prospect the
needs further investigation.
Although they have not identified a chemical structure
Chavkin and coworkers have presented a strong case if
the existence of an endog needs further investigation.
Although they have not identified a chemical structure,
Chavkin and coworkers have presented a strong case for
the existence of an endogenous sigma ligand in a hippo-
campal slice preparation m Although they have not identified a chemical structure Chavkin and coworkers have presented a strong case f
the existence of an endogenous sigma ligand in a hipp
campal slice preparation maintained in vitro (Neumai
and Cha Chavkin and coworkers have presented a strong case
the existence of an endogenous sigma ligand in a hip
campal slice preparation maintained in vitro (Neuma
and Chavkin, 1989; Connor and Chavkin, 1990). Dep
larization of ph the existence of an endogenous sigma ligand in a hippo-
campal slice preparation maintained in vitro (Neumaier Th
and Chavkin, 1989; Connor and Chavkin, 1990). Depo-
larization of physiologically intact slices by focal ele campal slice preparation maintained in vitro (Neumaier Ti
and Chavkin, 1989; Connor and Chavkin, 1990). Depo-
larization of physiologically intact slices by focal electri-
cal stimulation, veratridine, or potassium reduce and Chavkin, 1989; Connor and Chavkin, 1990). Depo-
larization of physiologically intact slices by focal electrical stimulation, veratridine, or potassium reduced the way
binding of $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ in the slic larization of physiologically intact slices by focal electrical stimulation, veratridine, or potassium reduced the was binding of $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ in the slice. As proshown in fig. 11, the effect was calcium de cal stimulation, veratridine, or potassium reduced the w
binding of $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ in the slice. As pishown in fig. 11, the effect was calcium dependent and endissipated over a 90-min period, findings consist shown in fig. 11, the effect was calcium dependent and endogenous neurotransmitter for the sigma receptor.
dissipated over a 90-min period, findings consistent with An interesting feature of these investigations is the
the inhibited the binding of sigma radioligands.

the investigators' conclusion that depolarization induced
the release of an endogenous sigma ligand that then
inhibited the binding of sigma radioligands. grave
Evidence that the inhibition of binding is caused by
of
the r the release of an endogenous sigma ligand that then
inhibited the binding of sigma radioligands.
Evidence that the inhibition of binding is caused by
the release of an endogenous sigma ligand is found in the
selective effe inhibited the binding of sigma radioligands.
Evidence that the inhibition of binding is caused by
the release of an endogenous sigma ligand is found in the
selective effects of electrically stimulating different re-
gions Evidence that the inhibition of binding is caused by of
the release of an endogenous sigma ligand is found in the
selective effects of electrically stimulating different re-
gions of the hippocampus. Connor and Chavkin (19 the release of an endogenous sigma ligand is found in the selective effects of electrically stimulating different regions of the hippocampus. Connor and Chavkin (1990; personal communication) found that stimulation of the selective effects of electrically stimulating different re-
gions of the hippocampus. Connor and Chavkin (1990; Hippersonal communication) found that stimulation of the 30
mossy fibers or the perforant path produced the st gions of the hippocampus. Connor and Chavkin (1990;
personal communication) found that stimulation of the
mossy fibers or the perforant path produced the strongest
reduction in binding. The perforant path and the mossy
fib personal communication) found that stimulation of the 3
mossy fibers or the perforant path produced the strongest
reduction in binding. The perforant path and the mossy
(fibers interact mainly with granule cells in the den reduction in binding. The perforant path and the mossy (DeGroat et al., 1984; DeGroat and Kawatani, 1985; fibers interact mainly with granule cells in the dentate Lundberg and Hökfelt, 1986; Lundberg et al., 1986) gyrus an fibers interact mainly with granule cells in the dentate Lundberg and Hökfelt, 1986; Lundberg et al., 1986) gyrus and with pyramidal cells in CA1 and CA3, areas showing that the rate of stimulation is an important that are fibers interact mainly with granule cells in the dentate
gyrus and with pyramidal cells in CA1 and CA3, areas
that are rich in sigma receptors. By contrast, stimulation
of the stratum radiatum or the alvius/oriens regions gyrus and with pyramidal cells in CA1 and CA3, areas shothat are rich in sigma receptors. By contrast, stimulation varies of the stratum radiatum or the alvius/oriens regions of tranched CA1, loci where stimulation should

zation relative [⁹H]DTG addition (arrow); ordinate, percentage of for an action of an endogenous sigma ligand. These
control-specific binding (undepolarized slices). The initation of vera-experiments constitute the best Triding tridine-induced displacement of

[³H] DTG binding to hippocampal slices. Abscissa, times of depolari-

zation relative [³H]DTG addition (arrow); ordinate, percentage of

control-specific binding (undepolarized zation relative [³H]DTG addition (arrow); ordinate, percentage of for control-specific binding (undepolarized slices). The initation of vera-
tridine-induced depolarization was varied, but the period of depolari-
action control-specific binding (undepolarized slices). The initation of vera-
tridine-induced depolarization was varied, but the period of depolari-
zation was held constant by terminating the action of veratridine with
the addi tridine-induced depolarization was varied, but the period of depolarization was held constant by terminating the action of veratridine with the addition of tetrodotoxin 30 min later. Depolarization induced a transient redu printed from Neumain by variance with a distinct of the addition of the
rolotoxin 30 min later. Depolarization induced a
transient reduction of $[$ ²H]DTG binding suggestive of release of an
endogenous ligand that inhibit

EPTORS 377
little effect. The high degree of specificity observed in
these experiments provides solid evidence that the ob-EPTORS
little effect. The high degree of specificity observed in
these experiments provides solid evidence that the ob-
served effects represent a physiologically significant served a 377
ittle effect. The high degree of specificity observed in
these experiments provides solid evidence that the ob-
served effects represent a physiologically significant
process. process. the effect. The high degree of specificity observed in ese experiments provides solid evidence that the ob-
rved effects represent a physiologically significant
ocess.
In addition to being confined to particular loci withi

these experiments provides solid evidence that the observed effects represent a physiologically significar
process.
In addition to being confined to particular loci withi
the hippocampus, this response shows considerable p served effects represent a physiologically significant
process.
In addition to being confined to particular loci within
the hippocampus, this response shows considerable phar-
macological specificity. Inhibition of sigma b process.
In addition to being confined to particular loci within
the hippocampus, this response shows considerable phar-
macological specificity. Inhibition of sigma binding fol-
lowing perforant path stimulation, but not In addition to being confined to particular loci within
the hippocampus, this response shows considerable phar-
macological specificity. Inhibition of sigma binding fol-
lowing perforant path stimulation, but not mossy fib the hippocampus, this response shows considerable phar-
macological specificity. Inhibition of sigma binding fol-
lowing perforant path stimulation, but not mossy fiber
stimulation, is blocked by CNQX, an antagonist at the macological specificity. Inhibition of sigma binding following perforant path stimulation, but not mossy fiber stimulation, is blocked by CNQX, an antagonist at the kainate and quisqualate excitatory amino acid receptors. lowing perforant path stimulation, but not mossy fiber
stimulation, is blocked by CNQX, an antagonist at the
kainate and quisqualate excitatory amino acid receptors.
The effect of mossy fiber stimulation is blocked by AP4, stimulation, is blocked by CNQX, an antagonist at th
kainate and quisqualate excitatory amino acid receptor
The effect of mossy fiber stimulation is blocked by AP-
a selective NMDA receptor antagonist. The different
pharma kainate and quisqualate excitatory amino acid receptors.
The effect of mossy fiber stimulation is blocked by AP4,
a selective NMDA receptor antagonist. The different
pharmacological susceptibilities of the different path-
 The effect of mossy fiber stimulation is blocked by AP4,
a selective NMDA receptor antagonist. The different
pharmacological susceptibilities of the different path-
ways in the hippocampus adds further support to the
propo a selective NMDA receptor antagonist. The different parameter of the sigma receptor is ways in the hippocampus adds further support to proposed inhibition of binding through release of endogenous neurotransmitter for the s narmacological susceptibilities of the different path-
hys in the hippocampus adds further support to the
oposed inhibition of binding through release of an
dogenous neurotransmitter for the sigma receptor.
An interesting

Evidence that the inhibition of binding is caused by of 50-Hz stimulation, one train every 10 s, 300 μ A) was
the release of an endogenous sigma ligand is found in the effective in causing up to 50% inhibition of bindin ways in the hippocampus adds further support to the proposed inhibition of binding through release of an endogenous neurotransmitter for the sigma receptor.
An interesting feature of these investigations is the possible si group found that high frequency stimulation (1-s trains of 50-Hz stimulation, one train every 10 s, 300 μ A) was An interesting feature of these investigations is the possible significance of the stimulation parameters necessary to produce an inhibition of binding. Chavkin's group found that high frequency stimulation (1-s trains of possible significance of the stimulation parameters nec-
essary to produce an inhibition of binding. Chavkin's
group found that high frequency stimulation (1-s trains
of 50-Hz stimulation, one train every 10 s, 300 μ A) essary to produce an inhibition of binding. Chavkin's
group found that high frequency stimulation (1-s trains
of 50-Hz stimulation, one train every 10 s, 300 μ A) was
effective in causing up to 50% inhibition of binding group found that high frequency stimulation $(1-s \text{ trains})$
of 50-Hz stimulation, one train every 10 s, $300 \mu\text{A}$) was
effective in causing up to 50% inhibition of binding after
30 min. However, constant stimulation at of 50-Hz stimulation, one train every 10 s, 300 μ A) was effective in causing up to 50% inhibition of binding afte 30 min. However, constant stimulation at the rate of Hz , which produces the same number of pulses over effective in causing up to 50% inhibition of binding after 30 min. However, constant stimulation at the rate of 5 Hz, which produces the same number of pulses over the 30-min stimulation period, was not effective. These fi 30 min. However, constant stimulation at the rate of 5
Hz, which produces the same number of pulses over the
30-min stimulation period, was not effective. These find-
ings corroborate reports from a number of laboratories
 Hz, which produces the same number of pulses over the 30-min stimulation period, was not effective. These findings corroborate reports from a number of laboratories (DeGroat et al., 1984; DeGroat and Kawatani, 1985; Lundbe 30-min stimulation period, was not effective. These find-
ings corroborate reports from a number of laboratories ings corroborate reports from a number of laborator (DeGroat et al., 1984; DeGroat and Kawatani, 198
Lundberg and Hökfelt, 1986; Lundberg et al., 198
showing that the rate of stimulation is an imports
variable in determini Lundberg and Hökfelt, 1986; Lundberg et al., 1986) Lundberg and Hökfelt, 1986; Lundberg et al., 1986)
showing that the rate of stimulation is an important
variable in determining whether or not certain neuro-
transmitters are released. Notably, peptides have con-
sistently variable in determining whether or not certain neuro-
transmitters are released. Notably, peptides have con-
sistently required relatively high rates of stimulation for
release to occur, raising the speculation that the en variable in determining whether or not certain neuro-
transmitters are released. Notably, peptides have con-
sistently required relatively high rates of stimulation for
release to occur, raising the speculation that the en transmitters are released. Notably, peptides have consistently required relatively high rates of stimulation for release to occur, raising the speculation that the endogenous sigma ligand may be a peptide. Because NPY is a sistently required relatively high rates of stimulation for
release to occur, raising the speculation that the endog-
enous sigma ligand may be a peptide. Because NPY is
abundant in the hippocampus (Allen et al., 1983), fu release to occur, raising the speculation that the endogenous sigma ligand may be a peptide. Because NPY is abundant in the hippocampus (Allen et al., 1983), further work with this preparation may reveal whether it is rele enous sigma ligand may be a per
abundant in the hippocampus (Alwork with this preparation mas
released under these conditions a
sigma binding in this preparation
Although Connor and Chavkin undant in the hippocampus (Allen et al., 1983), further
prk with this preparation may reveal whether it is
leased under these conditions and whether it can affect
ma binding in this preparation.
Although Connor and Chavkin work with this preparation may reveal whether it is
released under these conditions and whether it can affect
sigma binding in this preparation.
Although Connor and Chavkin (1990) have cautioned
that these data may reflect

FIG. 11. Time course of depolarization-induced displacement of

THE DTG addition

FIG. 11. Time course of depolarization-induced displacement of

("He DTG binding to hippocampal slices. Abecises, times of depolari-

THE DT released under these conditions and whether it can affect
sigma binding in this preparation.
Although Connor and Chavkin (1990) have cautioned
that these data may reflect voltage-induced alterations
in receptor conformatio sigma binding in this preparation.

Although Connor and Chavkin (1990) have cautioned

that these data may reflect voltage-induced alterations

in receptor conformation leading to changes in binding

of the radioligand, th Although Connor and Chavkin (1990) have cautioned
that these data may reflect voltage-induced alterations
in receptor conformation leading to changes in binding
of the radioligand, there are several reasons why this
seems that these data may reflect voltage-induced alterations
in receptor conformation leading to changes in binding
of the radioligand, there are several reasons why this
seems much less likely than inhibition of binding due to in receptor conformation leading to changes in binding
of the radioligand, there are several reasons why this
seems much less likely than inhibition of binding due to
release of a neurotransmitter or modulator. As this gr of the radioligand, there are several reasons why this
seems much less likely than inhibition of binding due to
release of a neurotransmitter or modulator. As this group
has noted, (a) depolarization alone does not inhibi seems much less likely than inhibition of binding du
release of a neurotransmitter or modulator. As this gr
has noted, (a) depolarization alone does not inhibit sig
binding and (b) concentrates of the superfusion med
conta release of a neurotransmitter or modulator. As this group has noted, (a) depolarization alone does not inhibit sigma binding and (b) concentrates of the superfusion medium
contain a factor that inhibits sigma binding. Further-
more, the lack of the effect in the presence of tetrodo-
toxin or in the absence of calcium argues convincingl contain a factor that inhibits sigma binding. Furthermore, the lack of the effect in the presence of tetrodotoxin or in the absence of calcium argues convincingly for an action of an endogenous sigma ligand. These experime more, the lack of the effect in the presence of tetrodotoxin or in the absence of calcium argues convincingly for an action of an endogenous sigma ligand. These experiments constitute the best evidence to date that an endo central or in the absence of

for an action of an ender

experiments constitute the

endogenous sigma ligand

central nervous system.
 B. Receptor Regulation

Chronic haloperidol tre dogenous sigma ligand is secreted by neurons in the
ntral nervous system.
Receptor Regulation
Chronic haloperidol treatment in rats differentially
fects sigma-binding sites labeled by (+)-opiate-related

Example and the state of the state of the central nervous system.

B. Receptor Regulation

Chronic haloperidol treatment in rats differentially

affects sigma-binding sites labeled by (+)-opiate-related

WALKER ET AL.
and non-opiate-related probes, providing further evi- was a
dence for the existence of multiple types of sigma-binding sites. walker walkers
and non-opiate-related probes, providing further evi-
dence for the existence of multiple types of sigma-binding
sites. Furthermore, these alterations suggest the mode of sites. Furthermore, these alternations suggest the mode of action of ligands at the sigma receptor and support the mode of action of ligands at the sigma receptor and support the and non-opiate-related probes, providing further evi-
dence for the existence of multiple types of sigma-binding sit
sites. Furthermore, these alterations suggest the mode of
action of ligands at the sigma receptor and su and non-opiate-related probes, providence for the existence of multiple types sites. Furthermore, these alterations su action of ligands at the sigma receptors.
biological relevance of sigma receptors.
Although both sites nce for the existence of multiple types of sigma-bind
tes. Furthermore, these alterations suggest the mod
tion of ligands at the sigma receptor and support
ological relevance of sigma receptors.
Although both sites are dow

sites. Furthermore, these alterations suggest the mode of action of ligands at the sigma receptor and support the biological relevance of sigma receptors.
Although both sites are down-regulated/desensitized variably chron action of ligands at the sigma receptor and support the
biological relevance of sigma receptors.
Although both sites are down-regulated/desensitized
by chronic haloperidol treatment, the magnitude and
time course of the c biological relevance of sigma receptors.
Although both sites are down-regulated/desensitized
by chronic haloperidol treatment, the magnitude and
time course of the changes differ. Binding sites labeled
by either $[^{3}H]DTG$ by chronic haloperidol treatment, the magnitude and
time course of the changes differ. Binding sites labeled
by either $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ are depressed fol-
lowing 10-21 days of chronic haloperidol treatment (fig by chronic haloperidol treatment, the magnitude and time course of the changes differ. Binding sites labele by either $[^{3}H]DTG$ or $[^{3}H](+)$ -3-PPP are depressed folowing 10–21 days of chronic haloperidol treatment (fi
12) time course of the changes differ. Binding sites labeled
by either [³H]DTG or [³H](+)-3-PPP are depressed fol-
lowing 10–21 days of chronic haloperidol treatment (fig.
12) (Bremer et al., 1989; Matsumoto et al., 1989b by either [³H]DTG or [³H](+)-3-PPP are depressed fol-
lowing 10–21 days of chronic haloperidol treatment (fig.
12) (Bremer et al., 1989; Matsumoto et al., 1989b). How-
ever, after longer periods of treatment (up to 60 lowing 10–21 days of chronic haloperidol treatmothlency.

12) (Bremer et al., 1989; Matsumoto et al., 1989b)

ever, after longer periods of treatment (up to 6

the B_{max} and K_d values compensate to maintain t

of ra If Christian contrast to the transient down-regulation
 B_{max} and K_d values compensate to maintain

radioligand bound (Matsumoto et al., 1989b

In contrast to the transient down-regulation

ation observed with $[^3H]$

the B_{max} and K_d values compensate to maintain the level
of radioligand bound (Matsumoto et al., 1989b).
In contrast to the transient down-regulation/desensi-
tization observed with [³H]DTG and [³H](+)-3-PPP,
(+ tization observed with $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$,
(+)-opiate binding to sigma sites using $[^{3}H](+)$ -penta-
zocine as the radiolabeled probe is virtually eliminated Exampled to the autoradiographic procedures; conse-
of radioligand bound (Matsumoto et al., 1989b).
In contrast to the transient down-regulation/desensi-
tization observed with $[^{3}H]DTG$ and $[^{3}H](+)-3-PPP$,
(+)-opiate bi In contrast to the transient down-regulation/desensi-
tization observed with $[^{3}H]DTG$ and $[^{3}H](+)$ -3-PPP,
(+)-opiate binding to sigma sites using $[^{3}H](+)$ -penta-
zocine as the radiolabeled probe is virtually eliminate tization observed with [³H]DTG and [³H](+)-3-PPP,
(+)-opiate binding to sigma sites using [³H](+)-penta-
zocine as the radiolabeled probe is virtually eliminated
with haloperidol. This effect, observed in the same b (+)-opiate binding to sigma sites using $[{}^{3}H](+)$ -pents
zocine as the radiolabeled probe is virtually eliminate
with haloperidol. This effect, observed in the same batc
of membranes as the $[{}^{3}H]DTG$ binding, occurs fa zocine as the radiolabeled probe is virtually eliminated function and the same batch of membranes as the $[^{3}H]DTG$ binding, occurs fairly requickly (seen after 5 days of treatment) and is long-
lasting (binding is still with haloperidol. This effect, observed in the same ba
of membranes as the [³H]DTG binding, occurs fa
quickly (seen after 5 days of treatment) and is lo
lasting (binding is still depressed after 60 days of chro
treatment of membranes as the [³H]DTG binding, occurs fairly m
quickly (seen after 5 days of treatment) and is long-
lasting (binding is still depressed after 60 days of chronic
treatment)(Matsumoto et al., 1989b). A similar elim quickly (seen after 5 days of treatment) and is long
lasting (binding is still depressed after 60 days of chronic
treatment)(Matsumoto et al., 1989b). A similar elimina
tion of binding to sigma sites labeled by $(+)$ -opiat lasting (binding is still depressed after 60 days of chronic surfreatment)(Matsumoto et al., 1989b). A similar elimina-
tion of binding to sigma sites labeled by $(+)$ -opiates was nuo
observed in mice using $[^{3}H](+)$ -SKF 1 treatment)(Matsumoto et al., 1989b). A similar elimition of binding to sigma sites labeled by $(+)$ -opiates w
observed in mice using $[^{3}H](+)$ -SKF 10,047 as the ra
oligand (Itzhak and Alerhand, 1989). These results m
refle tion of binding to sigma sites labeled by $(+)$ -opiates was
observed in mice using $[^{3}H](+)$ -SKF 10,047 as the radi-
oligand (Itzhak and Alerhand, 1989). These results may
reflect differences in the regulation of the putat observed in mice using $[{}^{3}H](+)$ -SKF 10,047 as the rad oligand (Itzhak and Alerhand, 1989). These results material reflect differences in the regulation of the putative sigma-1 and sigma-2 receptors (table 5), because (+ oligand (Itzhak and Alerhand, 1989). These results may an reflect differences in the regulation of the putative sigma-
1 and sigma-2 receptors (table 5), because (+)-opiates low
ould selectively label the sigma-1 site. Al reflect differences in the regulation of the putative 1 and sigma-2 receptors (table 5), because $(+)$ would selectively label the sigma-1 site. Alternation there may be differential effects on allosterically sites for $(+)$ would selectively label the sigma-1 site. Alternatively,
there may be differential effects on allosterically coupled
sites for (+)-benzomorphan- and non-benzomorphan-
related ligands (Bowen et al., 1989a).
The ability of h there may be differential effects on allosterically coupled
sites for $(+)$ -benzomorphan- and non-benzomorphan-
related ligands (Bowen et al., 1989a).
The ability of haloperidol to down-regulate/desensitize
sigma receptors

sites for (+)-benzomorphan- and non-benzomorphan-
related ligands (Bowen et al., 1989a).
The ability of haloperidol to down-regulate/desensitize
sigma-receptors appears to be related to its sigma-binding
properties because sites for (+)-benzomorphan- and non-benzomorphan-
related ligands (Bowen et al., 1989a).
The ability of haloperidol to down-regulate/desensitize
sigma receptors appears to be related to its sigma-binding
properties because related ligands (Bowen et al., 1989a).
The ability of haloperidol to down-regulate/desensitiz
sigma receptors appears to be related to its sigma-bindin
properties because dopamine receptors were up-regulate
in the same ani The ability of haloperidol to down-regulate/desensitize
sigma receptors appears to be related to its sigma-binding
properties because dopamine receptors were up-regulated
in the same animals (Itzhak and Alerhand, 1989; Ma sigma receptors appears to be related to its sigma-binding
properties because dopamine receptors were up-regulated
in the same animals (Itzhak and Alerhand, 1989; Mat-
sumoto et al., 1989b). Furthermore, PCP receptors wer properties because dopamine receptors were up-regulated
in the same animals (Itzhak and Alerhand, 1989; Maturet and
sumoto et al., 1989b). Furthermore, PCP receptors were
al., 1989; Itzhak and Alerhand, 1989) and chronic in the same animals (Itzhak and Alerhand, 1989; Matsumoto et al., 1989b). Furthermore, PCP receptors were unaffected by chronic haloperidol treatment (Bremer et al., 1989; Itzhak and Alerhand, 1989) and chronic PCP treatme sumoto et al., 1989b). Furthermore, PCP receptors were
unaffected by chronic haloperidol treatment (Bremer et
al., 1989; Itzhak and Alerhand, 1989) and chronic PCP
treatment had no effect on binding to sigma receptors
lab unaffected by chronic haloperidol treatment (Bremer et al., 1989; Itzhak and Alerhand, 1989) and chronic PCP treatment had no effect on binding to sigma receptors labeled by $[^{3}H](+)-SKF$ 10,047 (Itzhak and Alerhand, 1989) al., 1989; Itzhak and Alerhand, 1989) and chronic P
treatment had no effect on binding to sigma recept
labeled by $[^{3}H](+)$ -SKF 10,047 (Itzhak and Alerhan
1989). Although the molecular mechanisms that under
these changes treatment had no effect on binding to sigma receptors
labeled by $[^{3}H](+)$ -SKF 10,047 (Itzhak and Alerhand,
1989). Although the molecular mechanisms that underlie
these changes are still in question, the selective regulalabeled by $[{}^3H](+)$ -SKF 10,047 (Itzhak and Alerhand,
1989). Although the molecular mechanisms that underlie
these changes are still in question, the selective regula-
tion of the sigma site by its ligands provides furthe 1989). Although the mold
these changes are still in
tion of the sigma site
evidence that they are u
physiologically relevant.
The only study to dat ese changes are still in question, the selective regula-
on of the sigma site by its ligands provides further
idence that they are unique physical entities that are
universible to date that appears to contradict the
guove

evidence that they are unique physical entities that are
physiologically relevant.
The only study to date that appears to contradict the
above interpretation of the data involves the apparent
up-regulation of sigma recepto evidence that they are unique physical entities that are
physiologically relevant.
The only study to date that appears to contradict the
above interpretation of the data involves the apparent
up-regulation of sigma recepto physiologically relevant.
The only study to date that appears to contradict the
above interpretation of the data involves the apparent
up-regulation of sigma receptors following subchronic
treatment (up to 5 days) with the The only study to date that appears to contradict the above interpretation of the data involves the apparent up-regulation of sigma receptors following subchronic treatment (up to 5 days) with the sigma ligand, rimcazole (above interpretation of the data involves the appartup-regulation of sigma receptors following subchrotreatment (up to 5 days) with the sigma ligand, rimcaz (Beart et al., 1989). In the study by Beart et al., s chronic tr up-regulation of sigma receptors following subchronic
treatment (up to 5 days) with the sigma ligand, rimcazol
(Beart et al., 1989). In the study by Beart et al., sub
chronic treatment with rimcazole produced a simulta
ne treatment (up to 5 days) with the sigma ligand, rimcazole (Beart et al., 1989). In the study by Beart et al., sub-
chronic treatment with rimcazole produced a simulta-
neous increase in B_{max} and K_d of $[^{3}H](+)-3$ -P (Beart et al., 1989). In the study by Beart et al., sub-
chronic treatment with rimcazole produced a simulta-
neous increase in B_{max} and K_d of $[^{3}H](+)-3$ -PPP-labeled
sites. Because of the 30% increase in B_{max}

was a simultaneous 97% decrease in the affinity of the sites.

C. Anatomical Distribution of Sigma Receptors

Sigma receptors as a simultaneous 97% decrease in the affinity of the

Sigma receptors have been labeled and visualized with

rious radiolabeled ligands using receptor autoradivarious.
C. Anatomical Distribution of Sigma Receptors
Sigma receptors have been labeled and visualized v
various radiolabeled ligands using receptor autora
ographic procedures similar to those detailed by Herk C. Anatomical Distribution of Sigma Receptors
Sigma receptors have been labeled and visualized w
various radiolabeled ligands using receptor autors
ographic procedures similar to those detailed by Herk
ham and Pert (1982) C. Anatomical Distribution of Sigma Receptors
Sigma receptors have been labeled and visualized with
various radiolabeled ligands using receptor autoradi-
ographic procedures similar to those detailed by Herken-
ham and Per Sigma receptors have been labeled and visualized with
various radiolabeled ligands using receptor autoradi-
ographic procedures similar to those detailed by Herken-
ham and Pert (1982) (Aanonsen and Seybold, 1989;
Gundlach various radiolabeled ligands using receptor autoradi-
ographic procedures similar to those detailed by Herken-
ham and Pert (1982) (Aanonsen and Seybold, 1989;
Gundlach et al., 1986; McLean and Weber, 1988; Walker
et al. 1 ographic procedures similar to those detailed by Herkenham and Pert (1982) (Aanonsen and Seybold, 1989;
Gundlach et al., 1986; McLean and Weber, 1988; Walker
et al. 1990; Sircar et al., 1986). As shown in table 7, sigma
re ham and Pert (1982) (Aanonsen and Seybold, 19.
Gundlach et al., 1986; McLean and Weber, 1988; Wall
et al. 1990; Sircar et al., 1986). As shown in table 7, sign
receptors are unevenly distributed throughout ma
brain areas. Gundlach et al., 1986; McLean and Weber, 1988; Walker
et al. 1990; Sircar et al., 1986). As shown in table 7, sigma
receptors are unevenly distributed throughout many
brain areas. The procedures that have led to the identi et al. 1990; Sircar et al., 1986). As shown in table 7, signeceptors are unevenly distributed throughout ma
brain areas. The procedures that have led to the iden
fication of multiple sigma-binding sites have yet to
applied receptors are unevenly distributed throughout many
brain areas. The procedures that have led to the identi-
fication of multiple sigma-binding sites have yet to be
applied to the autoradiographic procedures; conse-
quently brain areas. The procedures that have led to the identification of multiple sigma-binding sites have yet to be applied to the autoradiographic procedures; consequently, nothing is known about any differences that may exist types. quently, nothing is known about any differences that
may exist between the regional distributions of the sub-
types.
1. Cellular localization of sigma binding. As shown in
fig. 13, sigma receptors are highly concentrated i

Example 12. All the state of sigma binding. As shown in the state of the sub-
 1. Cellular localization of sigma binding. As shown in
 1. Cellular localization of sigma binding. As shown in
 1. Cellular localization may exist between the regional distributions of the sub-
types.
1. Cellular localization of sigma binding. As shown in
fig. 13, sigma receptors are highly concentrated in gray
matter regions, with little binding occurring types.

1. Cellular localization of sigma binding. As shown in

fig. 13, sigma receptors are highly concentrated in gray

matter regions, with little binding occurring in white

matter areas. Conspicuously high levels are 1. Cellular localization of sigma binding. As shown in fig. 13, sigma receptors are highly concentrated in gray matter regions, with little binding occurring in white matter areas. Conspicuously high levels are found in ma fig. 13, sigma receptors are highly concentrated in gray matter regions, with little binding occurring in white matter areas. Conspicuously high levels are found in many areas populated by large neuronal cell bodies (e.g. matter regions, with little binding occurring in white matter areas. Conspicuously high levels are found in many areas populated by large neuronal cell bodies (e.g., supraoptic nucleus, Purkinje cell layer of the cerebellu matter areas. Conspicuously high levels are found in
many areas populated by large neuronal cell bodies (e.g.,
supraoptic nucleus, Purkinje cell layer of the cerebellum,
pyramidal cell layer of the hippocampus, cranial ner many areas populated by large neuronal cell bodies (e.g., supraoptic nucleus, Purkinje cell layer of the cerebellum, pyramidal cell layer of the hippocampus, cranial nerve nuclei, and the red nucleus). The location of sigm supraoptic nucleus, Purkinje cell layer of the cerebellum,
pyramidal cell layer of the hippocampus, cranial nerve
nuclei, and the red nucleus). The location of sigma re-
ceptors relative to neuronal cell bodies was further pyramidal cell layer of the hippocampus, cranial nerve
nuclei, and the red nucleus). The location of sigma re-
ceptors relative to neuronal cell bodies was further ex-
amined in the hippocampus by Gundlach et al. (1986).
T nuclei, and the red nucleus). The location of sigma receptors relative to neuronal cell bodies was further examined in the hippocampus by Gundlach et al. (1986). They found that quinolinic acid lesions caused a marked loss ceptors relative to neuronal cell bodies was further examined in the hippocampus by Gundlach et al. (1986).
They found that quinolinic acid lesions caused a marked
loss of binding in the hippocampal pyramidal cell layer,
w amined in the hippocampus by Gundlach et al. (1986).
They found that quinolinic acid lesions caused a marked
loss of binding in the hippocampal pyramidal cell layer,
whereas lesions of the entorhinal cortex and lateral se They found that quinolinic acid lesions caused a marked
loss of binding in the hippocampal pyramidal cell layer,
whereas lesions of the entorhinal cortex and lateral sep-
tum, major inputs to the hippocampus, had no effec loss of binding in the hippocampal pyramidal cell layer,
whereas lesions of the entorhinal cortex and lateral sep-
tum, major inputs to the hippocampus, had no effect on
the density of $[^3H](+)$ -3-PPP binding. These results
 whereas lesions of the entorhinal cortex and lateral septum, major inputs to the hippocampus, had no effect on the density of $[^{3}H](+)$ -3-PPP binding. These results suggest that sigma receptors in this region are localize

suggest that sigma receptors in this region are localized
on pyramidal cells rather than on the terminals of input
neurons.
However, some binding may occur on axons or termi-
nals because 6-hydroxydopamine lesions of the c on pyramidal cells rather than on the terminals of input
neurons.
However, some binding may occur on axons or termi-
nals because 6-hydroxydopamine lesions of the corpus
striatum caused a loss of sigma binding. Because the neurons.
However, some binding may occur on axons or terminals because 6-hydroxydopamine lesions of the corpus
striatum caused a loss of sigma binding. Because the
caudate is a terminal region for the ascending midbrain
do However, some binding may occur on axons or terminals because 6-hydroxydopamine lesions of the corpus striatum caused a loss of sigma binding. Because the caudate is a terminal region for the ascending midbrain dopamine sy nals because 6-hydroxydopamine lesions of the corpus
striatum caused a loss of sigma binding. Because the
caudate is a terminal region for the ascending midbrain
dopamine system, the reduced binding (approximately
20%) was terminals.

The subcellular localization of sigma receptors has also
been investigated (Craviso and Musacchio, 1983a; Mcdopamine system, the reduced binding (approximately 20%) was attributed to sigma binding to dopamine nerve terminals.
The subcellular localization of sigma receptors has also been investigated (Craviso and Musacchio, 1983a 20%) was attributed to sigma binding to dopamine nerve
terminals.
The subcellular localization of sigma receptors has also
been investigated (Craviso and Musacchio, 1983a; Mc-
Cann et al., 1989). Craviso and Musacchio (19 terminals.
The subcellular localization of sigma receptors has also
been investigated (Craviso and Musacchio, 1983a; Mc-
Cann et al., 1989). Craviso and Musacchio (1983a)
showed that [³H]DM binding displaceable by 10 $\$ The subcellular localization of sigma receptors has al
been investigated (Craviso and Musacchio, 1983a; M
Cann et al., 1989). Craviso and Musacchio (1983
showed that [³H]DM binding displaceable by 10 μ
unlabeled DM i been investigated (Craviso and Musacchio, 1983a; Mc-Cann et al., 1989). Craviso and Musacchio (1983a) showed that $[^{3}H]DM$ binding displaceable by 10 μ M unlabeled DM is found in the nuclear, mitochondrial, synaptic pl Cann et al., 1989). Craviso and Musacchio (1983a)
showed that [³H]DM binding displaceable by 10 μ M
unlabeled DM is found in the nuclear, mitochondrial,
synaptic plasma membrane, and microsomal fractions of
guinea pig showed that $[^{3}H]DM$ binding displaceable by 10 μ M
unlabeled DM is found in the nuclear, mitochondrial,
synaptic plasma membrane, and microsomal fractions of
guinea pig brain. However, high affinity $[^{3}H]DM$ binding
 unlabeled DM is found in the nuclear, mitochondrial,
synaptic plasma membrane, and microsomal fractions of
guinea pig brain. However, high affinity [³H]DM binding
(presumably synonymous with sigma) is found only in
the m synaptic plasma membrane, and microsomal fraction
guinea pig brain. However, high affinity $[{}^{3}H]DM$ bind
(presumably synonymous with sigma) is found only
the microsomal fraction. $[{}^{3}H]DM$ binding in the ot
fractions w guinea pig brain. However, high affinity [³H]DM binding (presumably synonymous with sigma) is found only in the microsomal fraction. [³H]DM binding in the other fractions was of low affinity and high capacity. Subfract (presumably synonymous with sigma) is found only in
the microsomal fraction. [³H]DM binding in the other
fractions was of low affinity and high capacity. Subfrac-
tionation of the microsomal fraction showed that [³H]
 the microsomal fraction. [³H]DM binding in the other
fractions was of low affinity and high capacity. Subfrac-
tionation of the microsomal fraction showed that [³H]
DM binding closely paralleled the distribution of the fractions was of low affinity and high capacity. Subfractionation of the microsomal fraction showed that $[^{3}H]$ DM binding closely paralleled the distribution of the smooth endoplasmic reticulum marker, the reduced form

PHARMACOLOGICAL REVIEWS

Regional distribution of binding in guinea pig brain for various sigma radiotigands' **TABLE 7**

Regional distribution of binding in guinea pig brain for various sigma radioligands* Ratios Labeling ligand								
Region	$(+)$ -3-PPP (fmol/mg protein)	DTG (fmol/mg tissue)	$(+)$ -Pent (fmol/mg tissue)	DTG/3-PPP	Pent/3-PPP	DTG/Pent		
Cortex		88						
Frontal	85		152	1.0	1.8	0.58		
Frontoparietal	94							
Pyramidal cell layer	125							
Entorhinal	84		138		1.6			
Cingulate (anterior)	88		205		2.3			
Cingulate (posterior)	190		338		1.8			
Basal ganglia								
Caudate putamen	73	69	191	0.95	2.6	0.36		
Nucleus accumbens	70		177		2.5			
Globus pallidus	77		63		.81			
Septal area								
Lateral septal nucleus	130	150	236	1.2	1.8	0.63		
Medial septal nucleus	223	198	249	0.89	1.1	0.80		
Dorsal diagonal band	182	213	315	1.2	1.7	0.68		
Septohypothalamic nucleus	217							
Ventral pallidum	138		206		1.5			
Septofimbrial nucleus	116							
Hippocampal formation								
Stratum pyramidale	144							
Stratum radiatum	46		123		2.7			
Dentate gyrus	126	98	329	0.77	2.6	0.30		
Subicilum	144		235		1.6			
Amygdala								
Central nucleus	107		183		1.7			
Medial nucleus	108							
Anterior cortical nucleus	98							
Thalamus								
Habenula	184	220		1.2				
Medial geniculate nucleus	93		76		0.82			
Lateral geniculate nucleus	100	126						
Reticular nucleus	206							
Anteromedial nucleus	123							
Ventral thalamic nucleus	76							
Zona incerta	155	129	323	0.83	2.1	0.4		
Hypothalamus								
Anterior hypo. area	182	184		1.0				
Paraventricular nucleus	150	296		$2.0\,$				
Lateral preoptic area	161	192		$\mathbf{1.2}$				
Medial preoptic area	221	213	274	0.96	1.2	0.78		
Supraoptic nucleus	221	252		1.1				
Mamillary nucleus	107							
Lateral mamillary nucleus	160		399		2.5			
Med. forebrain bundle	134							
Midbrain								
Superior colliculus	159	117	269	0.74	1.7	0.44		
Inferior colliculus	118	68		0.58				
Red nerve	291	158	432	0.54	1.5	0.37		
Substantia nigra	172	86	279	0.5	1.6	0.31		
Interpeduncular nucleus	121	123	279	1.0	2.3	0.44		
Lateral tegmental nucleus	182							
Dorsal tegmental nucleus	207	173	601	0.84	2.9	0.29		
Anterior pretectal area	325		323		0.99 ₀			
Central gray	268	144	476	0.54	1.8	0.30		
Dorsal raphe nucleus	251	209		0.83				
Deep mesencephalic nucleus	178		247		1.4			
Cranial nerve nuclei								
Oculomotor nucleus	392	309	590	0.79	1.5	0.52		
Motor trigeminal nucleus	523	178	597	0.34	1.1	0.3		
Facial nucleus	802	215	541	0.27	0.67	0.4		
Medial vestibular nucleus	275		487		1.8			
Superior vestibular nucleus	305							
Nucleus ambiguus	301	349		1.2				
Hypoglossal nucleus	784	279		0.36				

Nucleus interpositus

• Data from the following sources: [³H](+)-3-PPP from Gundlach et al

(Pent) from Walker et al. (1990).

(1989) using [³H](+)-SKF 10,047 as a sigma receptor

probe and Wong et al. (1990) using [³ **Probe and Wong sources:** [³H](+)-3-PPP from
(Pent) from Walker et al. (1990).
(1989) using [³H](+)-SKF 10,047 as a sigma
probe and Wong et al. (1990) using [³H]DTG.
These findings have led to the speculation t

Fraction Walker et al. (1990).

1989) using $[^{3}H](+)$ -SKF 10,047 as a sigma receptor as

1989) using $[^{3}H][+)-SKF$ 10,047 as a sigma receptor as

1990) using $[^{3}H]DTG$.

1990) using $[^{3}H]DTG$.

1990 using $[^{3}H]DTG$. (1989) using $[^{3}H](+)$ -SKF 10,047 as a sigma receptor a
probe and Wong et al. (1990) using $[^{3}H]DTG$. d
These findings have led to the speculation that sigma o
sites may represent a type of drug-metabolizing enzyme
or ot (1989) using $[{}^{3}H](+)-SKF$ 10,047 as a sigma receptor as well as in the anterior horn of the spinal cord. These
probe and Wong et al. (1990) using $[{}^{3}H]DTG$. data form one of several lines of evidence for a function
The probe and Wong et al. (1990) using [³H]DTG.

These findings have led to the speculation that sigma

sites may represent a type of drug-metabolizing enzyme

or other nonreceptor-related protein (McCann et al.,

1989). How These findings have led to the speculation that signites may represent a type of drug-metabolizing enzy
or other nonreceptor-related protein (McCann et
1989). However, although liver microsomes metaboli:
^{[3}H]DM in the pr sites may represent a type of drug-metabolizing enzyme
or other nonreceptor-related protein (McCann et al., of t
1989). However, although liver microsomes metabolized (Gra
[³H]DM in the presence of the reduced form of ni or other nonreceptor-related protein (McCann et al., of 1989). However, although liver microsomes metabolized (G

[³H]DM in the presence of the reduced form of nicotin-

amide adenine dinucleotide, brain microsomes faile 1989). However, although liver microsomes metabolized ((³H)DM in the presence of the reduced form of nicotincamide adenine dinucleotide, brain microsomes failed to (so continuous continuous continuous microsomes were sho amide adenine dinucleotide, brain microsomes failed to (striosomal compartment) that receive inputs from cer-
do so (Craviso and Musacchio, 1983a). Because brain in limbic structures such as the amygdala, midline
microsom amide adenine dinucleotide, brain microsomes failed
do so (Craviso and Musacchio, 1983a). Because bra
microsomes were shown to metabolize other drugs, the
investigators argued that [³H]DM does not bind to
drug-metabolizi do so (Craviso and Musacchio, 1983a). Because brain
microsomes were shown to metabolize other drugs, these
investigators argued that [³H]DM does not bind to a
drug-metabolizing enzyme in the brain. Thus, the signif-
ican microsomes were shown to metabolize other drugs, these the investigators argued that $[^{3}H]DM$ does not bind to a correct drug-metabolizing enzyme in the brain. Thus, the significiance of the microsomal localization of sig drug-metabolizing enzyme in the brain. Thus, the signif-
imbic and motor system, together with the motor effects
icance of the microsomal localization of sigma receptors
is not clear. It is conceivable that these microsoma icance of the microsomal localization of sigma receptors icance of the microsomal localization of sigma receptors
is not clear. It is conceivable that these microsomal sites
represent nascent receptors undergoing synthesis or
transport, as is believed to be the case with other r

represent nascent receptors undergoing synthesis or
transport, as is believed to be the case with other recep-
tors (Wamsley et al., 1984).
2. *Regional distribution of sigma receptors in the central*
nervous system transport, as is believed to be the case with other receptors (Wamsley et al., 1984).

2. Regional distribution of sigma receptors in the central and nervous system. McLean and Weber (1988) noted that origina receptors ar tors (Wamsley et al., 1984).
2. Regional distribution of sigma receptors in the central
nervous system. McLean and Weber (1988) noted that
sigma receptors are concentrated in (a) brainstem areas
that primarily subserve mot 2. Regional distribution of sigma receptors in the central
nervous system. McLean and Weber (1988) noted that
sigma receptors are concentrated in (a) brainstem areas
that primarily subserve motor functions, (b) certain nervous system. McLean and Weber (1988) noted that
sigma receptors are concentrated in (a) brainstem areas
that primarily subserve motor functions, (b) certain lim-
bic structures, (c) some predominantly sensory areas,
and sigma receptors are concentrated in (a) brainstem areas
that primarily subserve motor functions, (b) certain lim-
bic structures, (c) some predominantly sensory areas
and (d) brain areas associated with endocrine func that primarily subserve motor functions, (b) certain lim-
bic structures, (c) some predominantly sensory areas,
and (d) brain areas associated with endocrine function.
As illustrated in fig. 14, sigma receptors are mor bic structures, (c) some predominantly sensory areas, me
and (d) brain areas associated with endocrine function.
As illustrated in fig. 14, sigma receptors are more con-
centrated in motor areas than in limbic areas. Th and (d) brain areas associated with endocrine function.
As illustrated in fig. 14, sigma receptors are more concentrated in motor areas than in limbic areas. The distribution in the motor system is marked by the high den As illustrated in fig. 14, sigma receptors are more concertrated in motor areas than in limbic areas. The dis-
tribution in the motor system is marked by the high by
densities found in brainstem motor circuits. For example centrated in motor areas than in limbic areas. The dis-
tribution in the motor system is marked by the high by
densities found in brainstem motor circuits. For example, late
the cerebellum and its closely associated circui tribution in the motor system is marked by the high by
densities found in brainstem motor circuits. For example, lat
the cerebellum and its closely associated circuits, the red
winucleus, inferior olive, and locus coeruleu densities found in brainstem motor circuits. For example,
the cerebellum and its closely associated circuits, the red
nucleus, inferior olive, and locus coeruleus, are all rich
in sigma receptors. Furthermore, sigma bindin the cerebellum and its closely associated circuits, the requirement change in the mucleus, inferior olive, and locus coeruleus, are all ricin sigma receptors. Furthermore, sigma binding is found in cranial nerve nuclei tha

as well as in the anterior horn of the spinal cord. These
data form one of several lines of evidence for a function (1986); $[^1 H] DTG$ from McLean and Weber (1988); $[^1 H] (+)$ -pentazocine
as well as in the anterior horn of the spinal cord. These
data form one of several lines of evidence for a function
of the sigma receptor in motor functi $\frac{1}{2}$ and $\frac{1}{2}$ is the sigma receptor in motor function.
In the cat, sigma receptor in motor function.
In the cat, sigma receptors are concent well as in the anterior horn of the spinal cord. These ta form one of several lines of evidence for a function the sigma receptor in motor function.
In the cat, sigma receptors are concentrated in an area the substantia ni

as well as in the anterior horn of the spinal cord. These
data form one of several lines of evidence for a function
of the sigma receptor in motor function.
In the cat, sigma receptors are concentrated in an area
of the su data form one of several lines of evidence for a function
of the sigma receptor in motor function.
In the cat, sigma receptors are concentrated in an area
of the substantia nigra termed the densocellular zone
(Graybiel et of the sigma receptor in motor function.
In the cat, sigma receptors are concentrated in an area
of the substantia nigra termed the densocellular zone
(Graybiel et al., 1989). This subdivision of the pars
compacta projects In the cat, sigma receptors are concentrated in an area
of the substantia nigra termed the densocellular zone
(Graybiel et al., 1989). This subdivision of the pars
compacta projects selectively to regions in the caudate
(s of the substantia nigra termed the densocellular zone (Graybiel et al., 1989). This subdivision of the pars compacta projects selectively to regions in the caudate (striosomal compartment) that receive inputs from certain (Graybiel et al., 1989). This subdivision of the paracompacta projects selectively to regions in the caudate (striosomal compartment) that receive inputs from certain limbic structures such as the amygdala, midline thalamu compacta projects selectively to regions in the caudate
(striosomal compartment) that receive inputs from cer-
tain limbic structures such as the amygdala, midline
thalamus, and the prefrontal and insular cortex. A con-
ce (striosomal compartment) that receive inputs from certain limbic structures such as the amygdala, midline thalamus, and the prefrontal and insular cortex. A concentration of sigma receptors at an interface between the limb tain limbic structures such as the amygdala, midline
thalamus, and the prefrontal and insular cortex. A con-
centration of sigma receptors at an interface between the
limbic and motor system, together with the motor effect thalamus, and the prefrontal and insular cortex. A co
centration of sigma receptors at an interface between t
limbic and motor system, together with the motor effec
of sigma ligands, suggests that sigma receptors m
modulat centration of sigma rece
limbic and motor systen
of sigma ligands, sugg
modulate behavioral reent affective conditions
Several limbic structu of sigma ligands, suggests that sigma receptors may
modulate behavioral responses differently under differ-
ent affective conditions.
Several limbic structures are labeled by sigma radioli-309 1.2

16 6.45 $\frac{1}{2}$

16 6.45 $\frac{1}{2}$

173 107

18 19 0.61 1.7

173 107

18 19 0.61 1.7

18 19 0.61 1.7

18 19 0.61 1.7

18 19 0.61 1.7

18 19 107 2.4

11996); $[H1]DTG G from McLean and Weber (1988); [H1(+)-pentaxocine
as well as in the anterior horn of the spinal cord. These
of the sigma receptor in$

of sigma ligands, suggests that sigma receptors may
modulate behavioral responses differently under differ-
ent affective conditions.
Several limbic structures are labeled by sigma radioli-
gands. These areas include the c modulate behavioral responses differently under different affective conditions.

Several limbic structures are labeled by sigma radioli-

gands. These areas include the cingulate cortex, lateral

and medial septum, hippoca ent affective conditions.
Several limbic structures are labeled by sigma radioli-
gands. These areas include the cingulate cortex, lateral
and medial septum, hippocampus, hypothalamus, parts
of the limbic thalamus, habenul Several limbic structures are labeled by sigma radioli-
gands. These areas include the cingulate cortex, lateral
and medial septum, hippocampus, hypothalamus, parts
of the limbic thalamus, habenula, and anterodorsal nu-
cl memory. the limbic thalamus, habenula, and anterodorsal nu-
pus. The presence of sigma receptors in limbic systems
ight suggest a role of sigma receptors in emotion and
emory.
Sigma receptors are found in certain areas that are
ea

cleus. The presence of sigma receptors in limbic systems
might suggest a role of sigma receptors in emotion and
memory.
Sigma receptors are found in certain areas that are
clearly related to sensory processing. Most notabl might suggest a role of sigma receptors in emotion and
memory.
Sigma receptors are found in certain areas that are
clearly related to sensory processing. Most notable
among these is the heavy labeling of dorsal root gangli memory.

Sigma receptors are found in certain areas that are

clearly related to sensory processing. Most notable

among these is the heavy labeling of dorsal root ganglia

by $[^{3}H](+)-3-PPP$ (Gundlach et al., 1986). The dor Sigma receptors are found in certain areas that are
clearly related to sensory processing. Most notable
among these is the heavy labeling of dorsal root ganglia
by $[^{3}H](+)-3-PPP$ (Gundlach et al., 1986). The dorsal
lateral clearly related to sensory processing. Most notable among these is the heavy labeling of dorsal root ganglia
by $[^{3}H](+)-3-PPP$ (Gundlach et al., 1986). The dorsal
lateral geniculate and anterior pretectal areas (associated among these is the
by $[^{3}H](+)$ -3-PPP
lateral geniculate an
with visual informa
beled by $[^{3}H]DTG.$
Although the bra lateral geniculate and anterior pretectal areas (associated
with visual information processing) are also heavily la-
beled by $[^{3}H]DTG$.
Although the brain distribution of sigma receptors is
unique, some associations wit

lateral geniculate and anterior pretectal areas (associated with visual information processing) are also heavily beled by $[^{3}H]DTG$.
Although the brain distribution of sigma receptors unique, some associations with the d with visual information processing) are also heavily labeled by [³H]DTG.
beled by [³H]DTG.
Although the brain distribution of sigma receptors is
unique, some associations with the distribution of cholin-
ergic neurons

PHARMACOLOGICAL REVIEW!

FIG. 12. Down-regulation/desensitization of sigma receptors by chronic administration of haloperidol. Rats were given 5 mg/kg once daily for the times shown. A, ['H](+)-pentazocine binding is rapidly land profoundly reduc FIG. 12. Down-regulation/desensitization of sigma receptors by
chronic administration of haloperidol. Rats were given 5 mg/kg once
daily for the times shown. A, [⁵H](+)-pentazocine binding is rapidly
and profoundly reduc chronic administration of haloperidol. Rats were given 5 mg/kg once
daily for the times shown. A, $[{}^{4}H](+)+$ pentazocine binding is rapidly F
and profoundly reduced by chronic administration of haloperidol.
Whether the o and profoundly reduced by chronic administration of haloperidol. Whether the observed changes are due to a decreased affinity or number or both was impossible to determine because the level of binding was so low. B, Chroni and profoundly reduced by chronic administration of haloperidol. ta
Whether the observed changes are due to a decreased affinity or number
or both was impossible to determine because the level of binding was
so low. B, Chr so low. *B*, Chronic administration of haloperidol produced tipendent alterations in both affinity and density. In this summ
the data, the binding parameters were used to calculate the ameligand bound at a subseturating co the data, the binding parameters were used to calculate the amount of ligand bound at a subsaturating concentration of 3 nM. As shown, the changes were all in the direction of down-regulation/decensitization.
These data fu ligand bound at a subsaturating concentration of 3 nM. As shown, the
changes were all in the direction of down-regulation/decensitization.
These data further demonstrate the differences between neuroleptic
like compounds These data further demonstrate the differences between neuroleptic These data further demonstrate the differences between neuroleptic
like compounds (DTG) and (+)-opiates in their interactions with sigma
receptors. Data from Matsumoto et al., 1989b, 1990.
notable. For example sigma recept

like compounds (DTG) and (+)-opiates in their interactions with sigma
receptors. Data from Matsumoto et al., 1989b, 1990.
notable. For example sigma receptors are rich in cranial
nerve motor nuclei, spinal ventral horns, d receptors. Data from Matsumoto et al., 1989b, 1990.

notable. For example sigma receptors are rich in cranial

nerve motor nuclei, spinal ventral horns, dorsal diagonal

band of Broca, and septal region, all of which posse notable. For example sigma receptors are rich in cranial
nerve motor nuclei, spinal ventral horns, dorsal diagonal
band of Broca, and septal region, all of which possess
cholinergic neurons. These two receptor systems do n notable. For example sigma receptors are rich in cranial density of the new motor nuclei, spinal ventral horns, dorsal diagonal proband of Broca, and septal region, all of which possess videolinergic neurons. These two rec nerve motor nuclei, spinal ventral horns, dorsal diagonal
band of Broca, and septal region, all of which possess
cholinergic neurons. These two receptor systems do not
overlap completely, however, because the caudate, whic nd of Broca, and septal region, all of which possess vidently oblinergic neurons. These two receptor systems do not signal echap completely, however, because the caudate, which will receptor in accetylcholine, has low leve

cholinergic neurons. These two receptor systems do not overlap completely, however, because the caudate, which wis rich in acetylcholine, has low levels of sigma receptors. The heavy labeling dassociated with endocrine fun overlap completely, however, because the caudate, which
is rich in acetylcholine, has low levels of sigma receptors. The
Sigma receptors are found in many areas of the brain
dessociated with endocrine function. The heavy is rich in acetylcholine, has low levels of sigma receptom Sigma receptors are found in many areas of the brassociated with endocrine function. The heavy labelies over the supraoptic and paraventricular nuclei with the hyp Sigma receptors are found in many areas of the brain
associated with endocrine function. The heavy labeling
over the supraoptic and paraventricular nuclei within
the hypothalamus suggests that sigma receptors partici-
pate associated with endocrine function. The heavy labeli
over the supraoptic and paraventricular nuclei with
the hypothalamus suggests that sigma receptors parti
pate in the regulation of vasopressin (and/or dynorphi
secretion over the supraoptic and paraventricular nuclei within
the hypothalamus suggests that sigma receptors partici-
pate in the regulation of vasopressin (and/or dynorphin)
secretion. Dense labeling was also found in the adeno-
 the hypothalamus suggests that sigma receptors partici-
pate in the regulation of vasopressin (and/or dynorphin)
secretion. Dense labeling was also found in the adeno-
hypophysis (Gundlach et al. 1986; Wolfe et al. 1989),
 pate in the regulation of vasopressin (and/or dynorphin)
secretion. Dense labeling was also found in the adeno-
hypophysis (Gundlach et al. 1986; Wolfe et al. 1989),
suggesting regulation of anterior pituitary hormones.
Us secretion. Dense labeling was also found in the adeno-
hypophysis (Gundlach et al. 1986; Wolfe et al. 1989),
suggesting regulation of anterior pituitary hormones.
Using [³H](+)-3-PPP, Jansen et al. (1990) demonstrated
hi hypophysis (Gundlach et al. 1986; Wolfe et al. 1989),
suggesting regulation of anterior pituitary hormones. sy
Using $[^{3}H](+)-3-PPP$, Jansen et al. (1990) demonstrated the
high levels of sigma receptors in the rat pineal gla suggesting regulation of anterior pituitary hormones.
Using $[^{3}H](+)-3-PPP$, Jansen et al. (1990) demonstrated
high levels of sigma receptors in the rat pineal gland,
again linking sigma receptors to endocrine function. The

EPTORS 381
ther supported by the presence of sigma receptors in
many peripheral endocrine tissues discussed below. EPTORS
ther supported by the presence of sigma receptors
many peripheral endocrine tissues discussed below.
3. Species differences in the regional distribution

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 EXECUTE: 3. **Species** differences in the regional distribution of

3. Species differences in the regional distribution of
 tima receptors. The above discussion focussed mainly ther supported by the presence of sigma receptors in
many peripheral endocrine tissues discussed below.
3. Species differences in the regional distribution of
sigma receptors. The above discussion focussed mainly
on guinea ther supported by the presence of sigma receptors in
many peripheral endocrine tissues discussed below.
3. Species differences in the regional distribution of
sigma receptors. The above discussion focussed mainly
on guinea many peripheral endocrine tissues discussed below.
3. Species differences in the regional distribution of
sigma receptors. The above discussion focussed mainly
on guinea pig because several complete studies have been
condu 3. Species differences in the regional distribution of sigma receptors. The above discussion focussed mainly on guinea pig because several complete studies have been conducted in that species. However, it is clear from oth on guinea pig because several complete studies have been conducted in that species. However, it is clear from other work that sigma receptors occur in many different species including sea anemone, smooth dogfish, goldfish, on guinea pig because several complete studies have been
conducted in that species. However, it is clear from other
work that sigma receptors occur in many different species
including sea anemone, smooth dogfish, goldfish, conducted in that species. However, it is clear from other
work that sigma receptors occur in many different species
including sea anemone, smooth dogfish, goldfish, frog,
turtle, chicken, squirrel monkey, and man (Vu et a work that sigma receptors occur in many different species
including sea anemone, smooth dogfish, goldfish, frog,
turtle, chicken, squirrel monkey, and man (Vu et al.,
1990; Weismann et al., 1988). The conservation of sigma including
turtle, chia
1990; Weis
receptors a
this site.
The reg rtle, chicken, squirrel monkey, and man (Vu et al., 90; Weismann et al., 1988). The conservation of sigma ceptors across species suggests important functions for is site.
The regional distribution of sigma receptors differ

1990; Weismann et al., 1988). The conservation of sigma
receptors across species suggests important functions for
this site.
The regional distribution of sigma receptors differs
among species to some extent. For example, a receptors across species suggests important functions for
this site.
The regional distribution of sigma receptors differs
among species to some extent. For example, a comparison
of the autoradiographs from rats and guinea this site.
The regional distribution of sigma receptors differs
among species to some extent. For example, a comparison
of the autoradiographs from rats and guinea pigs reveals
markedly greater sigma binding in cerebellum The regional distribution of sigma receptors differs
among species to some extent. For example, a comparison
of the autoradiographs from rats and guinea pigs reveals
markedly greater sigma binding in cerebellum (relative
t of the autoradiographs from rats and guinea pigs reveals
markedly greater sigma binding in cerebellum (relative
to other areas) in guinea pig compared to rat (Gundlach
et al. 1986) . By contrast, compared to the guinea pig of the autoradiographs from rats and guinea pigs reveals
markedly greater sigma binding in cerebellum (relative
to other areas) in guinea pig compared to rat (Gundlach
et al. 1986) . By contrast, compared to the guinea pig markedly greater sigma binding in cerebellum (relative
to other areas) in guinea pig compared to rat (Gundlach
et al. 1986). By contrast, compared to the guinea pig,
humans apparently have even higher levels of sigma
bindi to other areas) in guinea pig compared to rat (Gundlach
et al. 1986). By contrast, compared to the guinea pig,
humans apparently have even higher levels of sigma
binding in cerebellum relative to other structures, being
th et al. 1986). By contrast, compared to the guinea pig,
humans apparently have even higher levels of sigma
binding in cerebellum relative to other structures, being
the most densely labeled structure in humans (Weissman
et humans apparently have even higher levels of sigma
binding in cerebellum relative to other structures, being
the most densely labeled structure in humans (Weissman
et al., 1988). The human brain is also marked by having
re binding in cerebellum relative to other structures, being
the most densely labeled structure in humans (Weissman
et al., 1988). The human brain is also marked by having
relatively high levels of sigma binding in the nucleu the most densely labeled structure in humans (Weissman et al., 1988). The human brain is also marked by having relatively high levels of sigma binding in the nucleus accumbens and cortex, a pattern not observed in lower an al., 1988). The human brain is also marked by having latively high levels of sigma binding in the nucleus cumbens and cortex, a pattern not observed in lower imals (Weissman et al., 1988; Tam and Zhang, 1988).
4. *Distribu*

relatively high levels of sigma binding in the nucleus
accumbens and cortex, a pattern not observed in lower
animals (Weissman et al., 1988; Tam and Zhang, 1988).
4. Distribution of sigma receptors in the periphery.
Sigma accumbens and cortex, a pattern not observed in low
animals (Weissman et al., 1988; Tam and Zhang, 1984
4. Distribution of sigma receptors in the periphe
Sigma receptors are quite rich in many peripheral tissue
Peripheral animals (Weissman et al., 1988; Tam and Zhang, 1988).
4. Distribution of sigma receptors in the periphery.
Sigma receptors are quite rich in many peripheral tissues.
Peripheral binding of sigma ligands might have impor-
ta 4. Distribution of sigma receptors in the periphery.
Sigma receptors are quite rich in many peripheral tissues.
Peripheral binding of sigma ligands might have impor-
tant implications for side effect profiles when consider Sigma receptors are quite rich in many peripheral tissues.
Peripheral binding of sigma ligands might have important implications for side effect profiles when considering
potential therapeutic actions of sigma drugs. As di Peripheral binding of sigma ligands might have important implications for side effect profiles when considering potential therapeutic actions of sigma drugs. As discussed earlier, the sigma receptors found in some tissues tant implications for side effect profiles when considering
potential therapeutic actions of sigma drugs. As dis-
cussed earlier, the sigma receptors found in some tissues
differ in their drug selectivity patterns, raising potential therapeutic actions of sigma drugs. As discussed earlier, the sigma receptors found in some tissued differ in their drug selectivity patterns, raising questions about nomenclature and hypotheses of subtypes. For nition. ffer in their drug selectivity patterns, raising questions
out nomenclature and hypotheses of subtypes. For the
esent purposes, we will continue with the broad defi-
tion.
Wolfe et al. (1989) using [³H]haloperidol, [³H

about nomenclature and hypotheses of subtypes. For the
present purposes, we will continue with the broad defi-
nition.
Wolfe et al. (1989) using [³H]haloperidol, [³H]DTG,
and [³H](+)-3-PPP, found sigma-binding sites present purposes, we will continue with the broad definition.

Wolfe et al. (1989) using [³H]haloperidol, [³H]DTG,

and [³H](+)-3-PPP, found sigma-binding sites in the

adrenal gland, the testis, and the ovary, with nition.
Wolfe et al. (1989) using [³H]haloperidol, [³H]DTG,
and [³H](+)-3-PPP, found sigma-binding sites in the
adrenal gland, the testis, and the ovary, with the highest
density in the ovary. The reasonably high aff Wolfe et al. (1989) using [³H]haloperidol, [³H]DTG, and [³H](+)-3-PPP, found sigma-binding sites in the adrenal gland, the testis, and the ovary, with the highest density in the ovary. The reasonably high affinity o and $[^{3}H](+)-3$ -PPP, found sigma-binding sites in the adrenal gland, the testis, and the ovary, with the highest density in the ovary. The reasonably high affinity of progesterone for sigma receptors (Su et al., 1988a) pr adrenal gland, the testis, and the ovary, with the highest
density in the ovary. The reasonably high affinity of
progesterone for sigma receptors (Su et al., 1988a) pro-
vides further support for this view. The localizatio density in the ovary. The reasonably high affinity of
progesterone for sigma receptors (Su et al., 1988a) pro-
vides further support for this view. The localization of
sigma receptors in the endocrine system is consistent progesterone for sigma receptors (Su et al., 1988a) provides further support for this view. The localization of sigma receptors in the endocrine system is consistent with the varied effects of $(+)$ -SKF 10,047 and PCP on e vides further support for this view. The localization of
sigma receptors in the endocrine system is consistent
with the varied effects of $(+)$ -SKF 10,047 and PCP on
endocrine function, especially in light of the failure t sigma receptors in the endocrine system is consistent
with the varied effects of $(+)$ -SKF 10,047 and PCP on
endocrine function, especially in light of the failure to
detect PCP receptors in endocrine organs with either
[with the varied effects of $(+)$ -SKF 10,047 and PCP on
endocrine function, especially in light of the failure to
detect PCP receptors in endocrine organs with either
[³H]TCP or [³H]MK-801 (Wolfe et al., 1989). These
fi endocrine function, especially in light of the failure to detect PCP receptors in endocrine organs with either [³H]TCP or [³H]MK-801 (Wolfe et al., 1989). These findings raise the possibility that some of the endocrine detect PCP receptors in endocrine organs with either [³H]TCP or [³H]MK-801 (Wolfe et al., 1989). These findings raise the possibility that some of the endocrine effects of neuroleptics, previously attributed to action receptors. dings raise the possibility that some of the endocrine
fects of neuroleptics, previously attributed to actions
dopamine D_2 receptors, may be mediated by sigma
reptors.
Sigma ligands also bind to tissues of the immune
s

effects of neuroleptics, previously attributed to actions
at dopamine D_2 receptors, may be mediated by sigma
receptors.
Sigma ligands also bind to tissues of the immune
system. Su et al. (1988b) and Wolfe et al. (1988) at dopamine D_2 receptors, may be mediated by sigma
receptors.
Sigma ligands also bind to tissues of the immune
system. Su et al. (1988b) and Wolfe et al. (1988) showed
that sigma ligands bind with high affinity to sple receptors.

Sigma ligands also bind to tissues of the immune

system. Su et al. (1988b) and Wolfe et al. (1988) showed

that sigma ligands bind with high affinity to spleen and

to human peripheral blood leukocytes. Thus, Sigma ligands also bind to tissues of the immune
system. Su et al. (1988b) and Wolfe et al. (1988) showed
that sigma ligands bind with high affinity to spleen and
to human peripheral blood leukocytes. Thus, endogenous
or e that sigma ligands bind with high affinity to spleen and
to human peripheral blood leukocytes. Thus, endogenous
or exogenous sigma ligands could play some role in
immune responses. The binding of progesterone to sigma

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FIG. 13. Autoradiographic distribution of sigma receptors labeled with [³H]DTG in coronal sections of guinea pig brain. Abbeviations: ad, anterodorsal n. thalamus; lg, lateral geniculate; ah, anterior hypothalamus; lh, l **CA2, field CA2 of Ammons horn; m, mitral cell layer; CA3, field CA3 of Ammons horn; mh, medial habenula; cg, central gray; mpo, medial** F1G. 13. Autoradiographic distribution of sigma receptors labeled with [³H]DTG in coronal sections of guinea pig brain. Abbeviations: ad, anterodorsal n. thalamus; lg, lateral geniculate; ah, anterior hypothalamus; lh, l preoptic area; ci, centrolateral thalamic n.; the, nucleus tractus solitarius; cm, central medial thalamic n.; pit, pituitary gland; cp, caudate putamen; pk, Purkinje cell layer; cpl, choroid plexus; pn, pontine nuclei; db plotamer; pk, Purkinje cell layer; cpl, choroid plexus; bn, bontine nuclei; db, diagonal band of Broca; po, primary olfactory cortex; dg, dentate gyrus; pv, paraventricular thalamic n.; dm, dorsal motor n. vagus; pvn, para parasion, paraventricular thalamic n.; dm, dorsal motor n. vagus; pun, paraventricular n. hypothalamus; dmh, dorsomedial n. hypothalamus; rn, red nucleus; dr, dorsal raphe; rs, retrosplenial cortex; dt, dorsal tegmentum; s red nucleus; dr. dorsal raphe; rs. retrosplenial cortex; dt. dorsal tegmentum; sc. superior colliculus; ep. ependymal cells; sfo. subfornical organ; glomerular layer; sn. substantia nigra; gp. globus pallidus; so. superior glomerular layer; sn, substantia nigra; gp, globus pallidus; so, superior olive; hg, hypoglossal n.; v, vestibular n.; ic, inferior colliculus; vmh, ventromedial hypothalamus; io, inferior olive; zi, zona incerta; ipn, int

receptors of spleen (Su et al., 1988a,b) suggests that hepatic and renal tissue. Musacchio et al. (1988) inves-
hormones might modulate immune functions via sigma tigated these tissues using [³H]DM and Samovilova et
rec

receptors of spleen (Su et al., 1988a,b) suggests that hepatic and renal tissue. Musacchio et al. (1988) inves-
receptors of spleen (Su et al., 1988a,b) suggests that hepatic and renal tissue. Musacchio et al. (1988) inves receptors of spleen (Su et al., 1988a,b) suggests that hepatic and renal tissue. Musacchio et al. (1988) inves-
hormones might modulate immune functions via sigma tigated these tissues using [³H]DM and Samovilova et
rec hormones might modulate immune functions via sigma tigated these tissues using [³H]DM and Samovilova et receptors. The high concentrations of sigma receptors al. (1988) studied [³H](+)-SKF 10,047 binding in rat and ab receptors. The high concentrations of sigma receptors al. (1988) studied $[^{3}H](+)-SKF10,047$ binding in rat
and absence of PCP receptors in human peripheral blood liver membranes. [³H](+)-SKF10,047 was displaced with
leu d absence of PCP receptors in human peripheral blood liver membranes. [³H](+)-SKF 10,047 was displaced v
ukocytes led Wolfe et al. (1988) to suggest that PCP a ligand selectivity similar to sigma sites of guinear
ay exe

FIG. 13.

was used to label hepatic sites. However, as described hepatic $[{}^{3}H](+)$ -SKF 10,047 binding. Further character-
above, a different ligand selectivity pattern suggesting ization of this substance may help elucidate this f FIG. 13.
was used to label hepatic sites. However, as described habove, a different ligand selectivity pattern suggesting is
the presence of sigma-1 and sigma-2 sites is revealed Fro. 13.
was used to label hepatic sites. However, as described habove, a different ligand selectivity pattern suggesting iz
the presence of sigma-1 and sigma-2 sites is revealed
when either $[^{3}H]DTG$ or $[^{3}H](+)-3$ -PPP was used to label hepatic sites. However, as described above, a different ligand selectivity pattern suggesting the presence of sigma-1 and sigma-2 sites is revealed when either [³H]DTG or [³H](+)-3-PPP is used to labe was used to label hepatic sites. However, as de
above, a different ligand selectivity pattern sug
the presence of sigma-1 and sigma-2 sites is r
when either $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ is used
hepatic sigma-like sites (He ove, a different ligand selectivity pattern suggesting
e presence of sigma-1 and sigma-2 sites is revealed
len either $[^{3}H]DTG$ or $[^{3}H](+)-3-PPP$ is used to label
patic sigma-like sites (Hellewell et al., 1990).
As mentio the presence of sigma-1 and sigma-2 sites is revealed
when either $[{}^{3}H]DTG$ or $[{}^{3}H](+)$ -3-PPP is used to label
hepatic sigma-like sites (Hellewell et al., 1990).
As mentioned earlier, very high levels of sigma binding

when either $[^{3}H]DTG$ or $[^{3}H](+)$ -3-PPP is used to label behind the beat is dependent of the sites (Hellewell et al., 1990). As mentioned earlier, very high levels of sigma binding the occur in the liver as evidenced b hepatic sigma-like sites (Hellewell et al., 1990).
As mentioned earlier, very high levels of sigma binding
occur in the liver as evidenced by the B_{max} of eithe
^{[3}H]DTG or [³H](+)-3-PPP (Hellewell et al., 1990). I As mentioned earlier, very high levels of sigma binding the occur in the liver as evidenced by the B_{max} of either 0¹H]DTG or $[^{3}H](+)$ -3-PPP (Hellewell et al., 1990). In class fact, the levels are nearly 10 times h occur in the liver as evidenced by the B_{max} of either onl
[³H]DTG or [³H](+)-3-PPP (Hellewell et al., 1990). In charact, the levels are nearly 10 times higher in liver com-
pared to guinea pig brain. Although the [³H]DTG or $[^{3}H](+)-3$ -PPP (Hellewell et al., 1990). In fact, the levels are nearly 10 times higher in liver compared to guinea pig brain. Although the function of sigma-like binding sites in liver is unknown, the high fact, the levels are nearly 10 times higher in liver compared to guinea pig brain. Although the function of sigma-like binding sites in liver is unknown, the high levels of binding suggest a role in hepatic physiology. Alt pared to guinea pig brain. Although the function
sigma-like binding sites in liver is unknown, the hi
levels of binding suggest a role in hepatic physiolo
Alternatively, as noted above, these findings may refle
binding of iloguity is unknown, the high the vels of binding suggest a role in hepatic physiology.

Alternatively, as noted above, these findings may reflect is

binding of sigma ligands to a metabolic enzyme. Samov-

ilova et al. (1 levels of binding suggest a role in hepatic physiology. receptor types with which nonselective sigma ligands
Alternatively, as noted above, these findings may reflect interact. Although we cannot be certain that sigma re-

ization of this substance may help elucidate this function.
 D. Electrophysiological Effects

Although in a number of electrophysiological studies patic $[^{3}H](+)$ -SKF 10,047 binding. Further character-
tion of this substance may help elucidate this function.
Electrophysiological Effects
Although in a number of electrophysiological studies
e actions of sigma compou

ization of this substance may help elucidate this function.
 D. Electrophysiological Effects

Although in a number of electrophysiological studies

the actions of sigma compounds have been examined,

only one study clear D. Electrophysiological Effects
Although in a number of electrophysiological stud
the actions of sigma compounds have been examin
only one study clearly links the electrophysiologi
changes to a sigma-like binding site. In D. Electrophysiological Effects
Although in a number of electrophysiological studies
the actions of sigma compounds have been examined,
only one study clearly links the electrophysiological
changes to a sigma-like binding Although in a number of electrophysiological studies
the actions of sigma compounds have been examined,
only one study clearly links the electrophysiological
changes to a sigma-like binding site. In most of the
studies onl the actions of sigma compounds have been examined
only one study clearly links the electrophysiologics
changes to a sigma-like binding site. In most of the
studies only a limited number of compounds were examined, some of only one study clearly links the electrophysiological
changes to a sigma-like binding site. In most of the
studies only a limited number of compounds were ex-
amined, some of the sigma ligands were nonselective,
and most o changes to a sigma-like binding site. In most of the studies only a limited number of compounds were examined, some of the sigma ligands were nonselective, and most of the preparations contained a plethora of receptor type studies only a limited number of compounds were examined, some of the sigma ligands were nonselective, and most of the preparations contained a plethora of receptor types with which nonselective sigma ligands interact. Alt amined, some of the sigma ligands were nonselectiand most of the preparations contained a plethora receptor types with which nonselective sigma ligar
interact. Although we cannot be certain that sigma
ceptors mediated the receptor types with which nonselective sigma ligands interact. Although we cannot be certain that sigma receptors mediated the effects observed in these experiments, these studies nonetheless suggest some common properties interact. Although we canno
ceptors mediated the effects
ments, these studies nonethe
properties of sigma compoun

Areas
Fro. 14. Autoradiographic distribution of sigma receptors (labeled
with [³H](+)-3-PPP) in motor areas compared to limbic areas of the
brain. Abbreviations: cerebellum, pk, Purkinje cell layer of cerebellum;
cingula FIG. 14. Autoradiographic distribution of sigma receptors (labeled
with [³H](+)-3-PPP) in motor areas compared to limbic areas of the
brain. Abbreviations: cerebellum, pk, Purkinje cell layer of cerebellum;
cingulate ctx with [³H](+)-3-PPP) in motor areas compared to limbic areas of the brain. Abbreviations: cerebellum, pk, Purkinje cell layer of cerebellum; ^{D8} cingulate ctx, cingulate cortex; pyriform ctx, py, pyramidal cell layer of brain. Abbreviations: cerebe
cingulate ctx, cingulate cort
pyriform cortex; Med. Sep.,
band of Broca; Amygdala, c
from Largent et al., 1986.

ration in which the electrophysiological effects of a series 1. Intracellular electrophysiology and effects on ion channels. a. EFFECTS ON NCB-20 CELLS. The only preparation in which the electrophysiological effects of a series is of sigma ligands correlated with binding potency is 1. Intracellular electrophysiology and effects on ion side channels. a. EFFECTS ON NCB-20 CELLS. The only preparation in which the electrophysiological effects of a series ite of sigma ligands correlated with binding pote 1. Intracellular electrophysiology and effects on ion
channels. a. EFFECTS ON NCB-20 CELLS. The only prepa-
ration in which the electrophysiological effects of a series
of sigma ligands correlated with binding potency is channels. a. EFFECTS ON NCB-20 CELLS. The only preparation in which the electrophysiological effects of a series ite
of sigma ligands correlated with binding potency is the $NCB-20$ cell line investigated using whole-cell ration in which the electrophysiological effects of a series
of sigma ligands correlated with binding potency is the
NCB-20 cell line investigated using whole-cell patch
clamp by Bell et al. (1988). These investigators fou of sigma ligands correlated with binding potency is the NCB-20 cell line investigated using whole-cell patch clamp by Bell et al. (1988). These investigators found that a tonic potassium current was blocked by numerous si NCB-20 cell line investigated using whole-cell patch clamp by Bell et al. (1988). These investigators found that a tonic potassium current was blocked by numerous sigma ligands. The potencies of the drugs in producing thi clamp by Bell et al. (1988). These investigators found
that a tonic potassium current was blocked by numerous
sigma-ligands. The potencies of the drugs in producing
this effect correlated highly $(r = 0.96)$ with their affi that a tonic potassium current was blocked by numerous
sigma ligands. The potencies of the drugs in producing
this effect correlated highly $(r = 0.96)$ with their affinities
at a sigma-like site in these cells (Wu et al., sigma ligands. The potencies of the drugs in producing in
this effect correlated highly $(r = 0.96)$ with their affinities
at a sigma-like site in these cells (Wu et al., 1990).
However, this is not the typical sigma recept this effect correlated highly $(r = 0.96)$ with their affinities
at a sigma-like site in these cells (Wu et al., 1990).
However, this is not the typical sigma receptor because (+
the order of potency was haloperidol > BMY 1 at a sigma-like site in these cells (Wu et al., 1990). Similarly, Bobker et al. (1989) found that DTG and
However, this is not the typical sigma receptor because (+)-3-PPP inhibited ligand-activated hyperpolarizations
the However, this is not the typical sigma receptor because
the order of potency was haloperidol > BMY 14802 >
 $(-)$ -pentazocine > $(+)$ -pentazocine > $(-)$ -SKF 10,047 >
 $(-)$ -3-PPP > $(+)$ -SKF 10,047 > $(+)$ -3-PPP > PCP >
TCP. Bec the order of potency was haloperidol > BMY 1480 (-)-pentazocine > (+)-pentazocine > (-)-SKF 10,0 (-)-3-PPP > PC TCP. Because the site exhibits a low affinity for SKF 10,047 (K_d = 6997 nM), and because its stereose tivit (-)-pentazocine > (+)-pentazocine > (-)-SKF 10,047 > ple

(-)-3-PPP > (+)-SKF 10,047 > (+)-3-PPP > PCP > evers

TCP. Because the site exhibits a low affinity for (+)-

SKF 10,047 ($K_d = 6997$ nM), and because its stereosel TCP. Because the site exhibits a low affinity for $(+)$ - cep SKF 10,047 (K_d = 6997 nM), and because its stereoselec- sig tivity is the reverse of that shown by the sigma receptor ity as currently defined $[(-)$ -opiates ar SKF 10,047 (K_d = 6997 nM), and because its stereoselec-
tivity is the reverse of that shown by the sigma receptor
as currently defined $[(-)$ -opiates are more potent than
 $(+)$ -opiates in the NCB-20 cells], it may be iden tivity is the reverse of that shown by the sigma receptor
as currently defined $[(-)$ -opiates are more potent than
 $(+)$ -opiates in the NCB-20 cells], it may be identical with
the sigma-2 site discussed above (table 5), whi as currently defined $[(-)$ -opiates are more potent than $(+)$ -opiates in the NCB-20 cells], it may be identical with an the sigma-2 site discussed above (table 5), which shows a similar binding profile. This finding may th $(+)$ -opiates in the N
the sigma-2 site dis
a similar binding pi
the first known fun
the sigma receptor.
b. SIGMA RECEPT similar binding profile. This finding may thus provide first known function of a newly identified subtype e sigma receptor.
b. SIGMA RECEPTORS AND CALCIUM CHANNELS. See al lines of evidence suggest a possible relationship a similar binding profile. This finding may thus provide
the first known function of a newly identified subtype of
the sigma receptor.
b. SIGMA RECEPTORS AND CALCIUM CHANNELS. Several lines of evidence suggest a possible r

the first known function of a newly identified subtype of ability
the sigma receptor. efflux
b. SIGMA RECEPTORS AND CALCIUM CHANNELS. Sev-
effect
eral lines of evidence suggest a possible relationship of (Fletc
sigma recep channels. Sev-
channels. Sev-
eral lines of evidence suggest a possible relationship of (larger al. (1985) demonstrated inhibition of
channels. Klein et al. (1985) demonstrated inhibition of (1998)
(PH]DM binding to guinea b. SIGMA RECEPTORS AND CALCIUM CHANNELS. Several lines of evidence suggest a possible relationship of (F sigma receptors (and/or [³H]DM sites) and calcium also hannels. Klein et al. (1985) demonstrated inhibition of (the eral lines of evidence suggest a possible relationship of sigma receptors (and/or [³H]DM sites) and calcium channels. Klein et al. (1985) demonstrated inhibition of [³H]DM binding to guinea pig brain membranes by the sigma receptors (and/or $[^{3}H]DM$ sites) and calciu
channels. Klein et al. (1985) demonstrated inhibition
 $[^{3}H]DM$ binding to guinea pig brain membranes by t
calcium antagonists prenylamine, cinnarizine, and l
droxyzine channels. Klein et al. (1985) demonstrated inhibition of $[{}^3H]DM$ binding to guinea pig brain membranes by the calcium antagonists prenylamine, cinnarizine, and hydroxyzine with K_i values of 17, 22, and 46 nM, respecti

ET AL.
pine (diltiazem)-type calcium channel blockers were
much less potent. Carpenter et al. (1988) further showed ET AL.
pine (diltiazem)-type calcium channel blockers were
much less potent. Carpenter et al. (1988) further showed
that micromolar concentrations of DM and dextrorphan ET AL.
pine (diltiazem)-type calcium channel blockers were
much less potent. Carpenter et al. (1988) further showed
that micromolar concentrations of DM and dextrorphan
inhibit potassium-stimulated calcium uptake into rat pine (diltiazem)-type calcium channel blockers were
much less potent. Carpenter et al. (1988) further showed
that micromolar concentrations of DM and dextrorphan
inhibit potassium-stimulated calcium uptake into rat
brain s pine (diltiazem)-type calcium channel blockers were
much less potent. Carpenter et al. (1988) further showed
that micromolar concentrations of DM and dextrorphan
inhibit potassium-stimulated calcium uptake into rat
brain s much less potent. Carpenter et al. (1988) further showed
that micromolar concentrations of DM and dextrorphan
inhibit potassium-stimulated calcium uptake into rat
brain synaptosomes (N-type channels) and PC12 cells
(L-type that micromolar concentrations of DM and dextrorphan
inhibit potassium-stimulated calcium uptake into rat
brain synaptosomes (N-type channels) and PC12 cells
(L-type channels). In both systems, DM was more potent
than dext brain synaptosomes (N-type channels) and PC12 cells (L-type channels). In both systems, DM was more potent than dextrorphan, arguing against the involvement of PCP/NMDA receptors. Furthermore, the concentrations required a brain synaptosomes (N-type channels) and PC12 cells (L-type channels). In both systems, DM was more potent than dextrorphan, arguing against the involvement of PCP/NMDA receptors. Furthermore, the concentrations required a (L-type channels). In both systems, DM was more potent
than dextrorphan, arguing against the involvement of
PCP/NMDA receptors. Furthermore, the concentrations
required are higher than would be expected for actions
at eith than dextrorphan, arguing against the involvement of
PCP/NMDA receptors. Furthermore, the concentrations
required are higher than would be expected for actions
at either high affinity [³H]DM sites or PCP/NMDA
receptors, PCP/NMDA receptors. Furthermore, the concentrations
required are higher than would be expected for actions
at either high affinity [³H]DM sites or PCP/NMDA
receptors, and PC12 cells have been shown to lack PCP
receptors required are higher than would be expected for actions
at either high affinity $[^{3}H]DM$ sites or PCP/NMDA
receptors, and PC12 cells have been shown to lack PCP
receptors (Hellewell and Bowen, 1990; Yang et al., 1989).
In at either high affinity $[{}^{3}H]DM$ sites or PCP/NMDA
receptors, and PC12 cells have been shown to lack PCP
receptors (Hellewell and Bowen, 1990; Yang et al., 1989).
Inorganic calcium channel blockers such as Li^{2+} , Ni^{2 receptors, and PC12 cells have been shown to lack PCP
receptors (Hellewell and Bowen, 1990; Yang et al., 1989).
Inorganic calcium channel blockers such as Li^{2+} , Ni^{2+} ,
and Cd^{2+} selectively accelerated dissociation receptors (Hellewell and Bowen, 1990; Yang et al., 1989).
Inorganic calcium channel blockers such as Li^{2+} , Ni^{2+} , and Cd^{2+} selectively accelerated dissociation of $[^{3}H]DTG$ from binding site 2 (table 6), suggesti Inorganic calcium channel blockers such as Li^{2+} , Ni^{2+} , and Cd^{2+} selectively accelerated dissociation of $[^{3}H]DTG$ from binding site 2 (table 6), suggesting an association of site 2 with calcium channels (Rothman and Cd^{2+} selectively accelerated dissociation of $[^{3}H]DTG$ from binding site 2 (table 6), suggesting an association of site 2 with calcium channels (Rothman et al., 1990). Taken together, these results suggest a possi from binding site 2 (table 6), suggesting an association
of site 2 with calcium channels (Rothman et al., 1990).
Taken together, these results suggest a possible link
between sigma-like sites with low affinity for $(+)$ -op of site 2 with calcium channels (Rothman et al., 1990).
Taken together, these results suggest a possible link
between sigma-like sites with low affinity for $(+)$ -opiates
and modulation of calcium channels. These results a Taken together, these results suggest a possible link
between sigma-like sites with low affinity for $(+)$ -opiates
and modulation of calcium channels. These results are
particularly interesting in view of the existence in between sigma-like sites with low affinity for (+)-opiates
and modulation of calcium channels. These results are
particularly interesting in view of the existence in PC12
cells (Hellewell and Bowen, 1990) and brain (Reid e and modulation of calcium channels. These results are particularly interesting in view of the existence in PC12 cells (Hellewell and Bowen, 1990) and brain (Reid et al., 1988) of sigma-like sites with low affinity for $(+)$ particularly interesting in view of the existence in PC12
cells (Hellewell and Bowen, 1990) and brain (Reid et al.,
1988) of sigma-like sites with low affinity for (+)-opiates
(tables 4 and 6). This warrants further invest from binding site 2 (table 6), suggesting an association
of site 2 with calcum channels (Rothman et al., 1999).
Taken together, these results suggest a possible link
between sigma-like sites with low affinity for $(+)$ -opi

n pyriform cortex; Med. Sep., medial septum; Diag. Band, dorsal diagonal 1988) of sigma-like sites with low affinity for (+)-opiates

band of Broca; Amygdala, cen., central nucleus of the amygdala. Data (tables 4 and 6). 1988) of sigma-like sites with low affinity for (+)-opiates (tables 4 and 6). This warrants further investigation with other sigma ligands.

c. CONDUCTANCE CHANGES NOT CLEARLY RELATED TO

SIGMA BINDING. Using intracellular (tables 4 and 6). This warrants further investigation wi
other sigma ligands.
c. CONDUCTANCE CHANGES NOT CLEARLY RELATED 7
SIGMA BINDING. Using intracellular recordings, Gallign
et al. (1989) found that DTG and $(+)$ -SKF 1 other sigma ligands.

c. CONDUCTANCE CHANGES NOT CLEARLY RELATED TO

SIGMA BINDING. Using intracellular recordings, Galligan

et al. (1989) found that DTG and (+)-SKF 10,047 inhib-

ited acetylcholine-induced depolarizatio c. CONDUCTANCE CHANGES NOT CLEARLY RELATED TO
SIGMA BINDING. Using intracellular recordings, Galligan
et al. (1989) found that DTG and (+)-SKF 10,047 inhib-
ited acetylcholine-induced depolarization of guinea pig
myenteric SIGMA BINDING. Using intracellular recordings, Gallig
et al. (1989) found that DTG and $(+)$ -SKF 10,047 inh
ited acetylcholine-induced depolarization of guinea
myenteric neurons. However, several structurally relat
compoun et al. (1989) found that DTG and $(+)$ -SKF 10,047 inhibited acetylcholine-induced depolarization of guinea pig myenteric neurons. However, several structurally related compounds with no sigma-binding affinity were equipote ited acetylcholine-induced depolarization of guinea pig
myenteric neurons. However, several structurally related
compounds with no sigma-binding affinity were equipo-
tent. Therefore, it is unclear at this time whether DTG compounds with no sigma-binding affinity
tent. Therefore, it is unclear at this time
and (+)-SKF 10,047 acted through a non-
nism or whether the other compounds proc
effect through an independent mechanism
Similarly, Bobke nt. Therefore, it is unclear at this time whether DTG
id (+)-SKF 10,047 acted through a non-sigma mecha-
sm or whether the other compounds produced a similar
fect through an independent mechanism.
Similarly, Bobker et al.

and $(+)$ -SKF 10,047 acted through a non-sigma mechanism or whether the other compounds produced a simile effect through an independent mechanism.
Similarly, Bobker et al. (1989) found that DTG an $(+)$ -3-PPP inhibited liga nism or whether the other compounds produced a similar
effect through an independent mechanism.
Similarly, Bobker et al. (1989) found that DTG and
 $(+)$ -3-PPP inhibited ligand-activated hyperpolarizations
in three separate effect through an independent mechanism.

Similarly, Bobker et al. (1989) found that DTG an

(+)-3-PPP inhibited ligand-activated hyperpolarization

in three separate preparations: the guinea pig submucos

plexus, the dors Similarly, Bobker et al. (1989) found that DTG and $(+)$ -3-PPP inhibited ligand-activated hyperpolarizations in three separate preparations: the guinea pig submucosal plexus, the dorsal raphe, and the locus coeruleus. Howe in three separate preparations: the guinea pig submucosal plexus, the dorsal raphe, and the locus coeruleus. However, haloperidol, which has high affinity for sigma receptors, was inactive. The authors thus questioned a si plexus, the dorsal raphe, and the locus coeruleus. How-
ever, haloperidol, which has high affinity for sigma re-
ceptors, was inactive. The authors thus questioned a
sigma-mediated mechanism but also raised the possibil-
i ever, haloperidol, which has high affinity for sigma receptors, was inactive. The authors thus questioned a sigma-mediated mechanism but also raised the possibility that the lack of effect of haloperidol may be related to ceptors, was inactive. The authors thus questioned a sigma-mediated mechanism but also raised the possibility that the lack of effect of haloperidol may be related to its affinity for other receptor types [e.g., dopaminerg gma-mediated mechanism but also raised the possibil-
 α that the lack of effect of haloperidol may be related

its affinity for other receptor types [e.g., dopaminergic

d adrenergic sites (Seeman 1981; Peroutka et al. ity that the lack of effect of haloperidol may be related
to its affinity for other receptor types [e.g., dopaminergic
and adrenergic sites (Seeman 1981; Peroutka et al. 1977)].
An interaction between sigma ligands and cer

to its affinity for other receptor types [e.g., dopaminergic
and adrenergic sites (Seeman 1981; Peroutka et al. 1977)].
An interaction between sigma ligands and certain
types of potassium channels is also suggested by the
 and adrenergic sites (Seeman 1981; Peroutka et al. 1977)].
An interaction between sigma ligands and certain
types of potassium channels is also suggested by the
ability of sigma ligands to inhibit potassium-stimulated
effl An interaction between sigma ligands and certain
types of potassium channels is also suggested by the
ability of sigma ligands to inhibit potassium-stimulated
efflux of rubidium from rat cortical synaptosomes, an
effect th types of potassium channels is also suggested by the ability of sigma ligands to inhibit potassium-stimulated efflux of rubidium from rat cortical synaptosomes, an effect that is thought to involve potassium channels (Flet ability of sigma ligands to inhibit potassium-stimulated
efflux of rubidium from rat cortical synaptosomes, an
effect that is thought to involve potassium channels
(Fletcher et al., 1989). Kennedy and Henderson (1989a)
als efflux of rubidium from rat cortical synaptosomes, an
effect that is thought to involve potassium channels
(Fletcher et al., 1989). Kennedy and Henderson (1989a)
also described an inhibition of two potassium currents
(the effect that is thought to involve potassium channel (Fletcher et al., 1989). Kennedy and Henderson (198 also described an inhibition of two potassium curre (the M current and a fast, calcium-activated potassi current) in v (Fletcher et a
also described
(the M current) in vo
tric ganglion.
2. Effects o_i also described an inhibition of two potassium currents

(the M current and a fast, calcium-activated potassium

current) in voltage clamp studies in the mouse hypogas-

tric ganglion.

2. Effects of sigma ligands on the fi *the H n teremi nucleuse clamp studies in the mouse hypogastric ganglion.*
 2. Effects of sigma ligands on the firing of neurons in the red nucleus and cerebellum. Iontophoretic application

CAL REVIEW

PHARMACOLOGIO

aspet

SIGMA RECEPTORS 385

SIGMA REC
of sigma ligands onto neurons in the red nucleus inhibits
the firing of these cells (Matsumoto and Walker, 1988a,b; sigma ligands onto neurons in the red nucleus inhibits
the firing of these cells (Matsumoto and Walker, 1988a,b;
fig. 15). Both DTG and (+)-pentazocine inhibit the firing SIGMA RECEP
of sigma ligands onto neurons in the red nucleus inhibits
the firing of these cells (Matsumoto and Walker, 1988a,b; ing
fig. 15). Both DTG and (+)-pentazocine inhibit the firing the
of rubral neurons in a doseof sigma ligands onto neurons in the red nucleus inhibits
the firing of these cells (Matsumoto and Walker, 1988a,b;
fig. 15). Both DTG and (+)-pentazocine inhibit the firing
of rubral neurons in a dose-dependent and revers of sigma ligands onto neurons in the red nucleus inhibits
the firing of these cells (Matsumoto and Walker, 1988a,b;
fig. 15). Both DTG and (+)-pentazocine inhibit the firing
of rubral neurons in a dose-dependent and revers the firing of these cells (Matsumoto and Walker, 1988a,b; ing
fig. 15). Both DTG and (+)-pentazocine inhibit the firing the
of rubral neurons in a dose-dependent and reversible 5
manner. These actions occur in the absence fig. 15). Both DTG and $(+)$ -pentazocine inhibit the firing
of rubral neurons in a dose-dependent and reversible
manner. These actions occur in the absence of local
anesthetic effects (however, see Malouf et al. 1988) and
 manner. These actions occur in the absence of local rons. The effects of sigma ligands on midbrain dopamine
anesthetic effects (however, see Malouf et al. 1988) and neurons have been the focus of numerous studies. Intra-
 manner. These actions occur in the absence of local
anesthetic effects (however, see Malouf et al. 1988) and
are more frequent in the red nucleus than in the sur-
rounding reticular formation (an area containing a lower
de anesthetic effects (however, see Malouf et al. 1988) and neu
are more frequent in the red nucleus than in the sur-
rounding reticular formation (an area containing a lower PPI
density of sigma-binding sites). As in behavio are more frequent in the red nucleus than in the survenced rounding reticular formation (an area containing a lower PPP density of sigma-binding sites). As in behavioral studies, Tam $(+)$ -3-PPP apparently acts in the red rounding reticular formation (an area containing a lower
density of sigma-binding sites). As in behavioral studies,
(+)-3-PPP apparently acts in the red nucleus, at least in
part, through an unidentified non-sigma mechanis density of sigma-binding sites). As in behavioral studential expansion of the independent, through an unidentified non-sigma mechanged (Matsumoto et al., 1990; Matsumoto and Walker, 198 However, the inhibitory actions of D (+)-3-PPP apparently acts in the red nucleus, at least in Icord, through an unidentified non-sigma mechanism P (Matsumoto et al., 1990; Matsumoto and Walker, 1988b). In However, the inhibitory actions of DTG and (+)-penta part, through an unidentified non-sigma mechanism F
(Matsumoto et al., 1990; Matsumoto and Walker, 1988b). In
However, the inhibitory actions of DTG and (+)-penta-
zocine in the red nucleus may be mediated through sigma
re (Matsumoto et al., 1990; Matsumoto and Walker, 1988b). Iul
However, the inhibitory actions of DTG and $(+)$ -penta-
zocine in the red nucleus may be mediated through sigma
receptors because the ligands are relatively select However, the inhibitory actions of DTG and $(+)$ -penta-
zocine in the red nucleus may be mediated through sigma
receptors because the ligands are relatively selective for
sigma-binding sites, the red nucleus is virtually d zocine in the red nucleus may be mediated through sigma
receptors because the ligands are relatively selective for
sigma-binding sites, the red nucleus is virtually devoid
of the receptors with which nonselective sigma li receptors because the ligands are relatively selective for sigma-binding sites, the red nucleus is virtually devoition of the receptors with which nonselective sigma ligand interact, and the compounds are more efficacious of the receptors with which nonselective sigma ligands
interact, and the compounds are more efficacious in areas
containing a higher density of sigma-binding sites. How-
ever, it must be recognized that not enough compound of the receptors with which nonselective sigma ligands interact, and the compounds are more efficacious in areas containing a higher density of sigma-binding sites. However, it must be recognized that not enough compounds interact, and the
containing a high
ever, it must be
have been tested
in these effects.
Similarly, appl ntaining a higher density of sigma-binding sites. However, it must be recognized that not enough compour we been tested to establish the role of sigma recept these effects.
Similarly, application of sigma ligands in the ce

ever, it must be recognized that not enough compound have been tested to establish the role of sigma receptoin these effects.

Similarly, application of sigma ligands in the cereb

lum tends to inhibit the firing of these have been tested to establish the role of sigma receptors
in these effects.
Similarly, application of sigma ligands in the cerebel-
lum tends to inhibit the firing of these neurons. Micro-
pressure ejection of the relative crease effects. These effects. The signal igends in the cerebel-

lum tends to inhibit the firing of these neurons. Micro-

in pressure ejection of the relatively selective sigma ligand, 19

DTG, onto Purkinje cells inhibi Similarly, application of sigma ligands in the cerebel-
lum tends to inhibit the firing of these neurons. Micro-
inhibit
pressure ejection of the relatively selective sigma ligand, 1988),
DTG, onto Purkinje cells inhibits lum tends to inhibit the firing of these neurons. Micro-
pressure ejection of the relatively selective sigma ligand,
DTG, onto Purkinje cells inhibits the firing of these
neurons in a dose-dependent and reversible manner (pressure ejection of the relatively selective sigma ligand, 19

DTG, onto Purkinje cells inhibits the firing of these to

neurons in a dose-dependent and reversible manner (Kim

et al., 1989). This effect appears to rely o neurons in a dose-dependent and reversible manner (Kim tors (Wachtel and White, 1988). Whether the effects of
et al., 1989). This effect appears to rely on the presence BMY 14802 are due to actions at sigma receptors, howof endogenous norepinephrine because destruction of

EPTORS
lished from an examination of a single drug, these find
ings are suggestive of possible sigma receptor function is EPTORS 385
lished from an examination of a single drug, these find-
ings are suggestive of possible sigma receptor function in
the cerebellum. EPTORS
lished from an
ings are sugges
the cerebellum
3. Effects of

3. Effects of sigma ligands on midbrain dopamine neu-
3. Effects of sigma ligands on midbrain dopamine neu-
rons. The effects of sigma ligands on midbrain dopamine neu-
rons. The effects of sigma ligands on midbrain ings are suggestive of possible sigma receptor function
the cerebellum.
3. Effects of sigma ligands on midbrain dopamine nerons.
The effects of sigma ligands on midbrain dopamin
neurons have been the focus of numerous stu the cerebellum.
3. Effects of sigma ligands on midbrain dopamine neu-
rons. The effects of sigma ligands on midbrain dopamine
neurons have been the focus of numerous studies. Intra-
venous application of DTG, $(+)$ -pentazo 3. Effects of sigma ligands on midbrain dopamine neurons. The effects of sigma ligands on midbrain dopamine neurons have been the focus of numerous studies. Intra-
venous application of DTG, $(+)$ -pentazocine, and $(+)$ -3-
 rons. The effects of sigma ligands on midbrain dopamine
neurons have been the focus of numerous studies. Intra-
venous application of DTG, $(+)$ -pentazocine, and $(+)$ -3-
PPP all inhibit A9 dopamine neurons (Steinfels and
T neurons have been the focus of numerous studies. Intra-
venous application of DTG, $(+)$ -pentazocine, and $(+)$ -3-
PPP all inhibit A9 dopamine neurons (Steinfels and
Tam, 1988; Steinfels et al., 1989; Clark et al., 1985a).
I venous application of DTG, (+)-pentazocine, and (+)
PPP all inhibit A9 dopamine neurons (Steinfels 4
Tam, 1988; Steinfels et al., 1989; Clark et al., 198
Jontophoretic application of (+)-pentazocine and (+)
PPP onto these PPP all inhibit A9 dopamine neurons (Steinfels and
Tam, 1988; Steinfels et al., 1989; Clark et al., 1985a).
Iontophoretic application of (+)-pentazocine and (+)-3-
PPP onto these cells during intracellular and extracel-
lu Tam, 1988; Steinfels et al., 1989; Clark et al., 1985a).
Iontophoretic application of (+)-pentazocine and (+)-3-
PPP onto these cells during intracellular and extracel-
lular recordings suggest that at least some of these PPP onto these cells during intracellular and extracel-
lular recordings suggest that at least some of these effects
are due to direct actions on dopamine neurons (Clark et
al., 1985a; Steinfels et al., 1989).
The effects PP onto these cells during intracellular and extracel-
lar recordings suggest that at least some of these effects
e due to direct actions on dopamine neurons (Clark et
, 1985a; Steinfels et al., 1989).
The effects of BMY 1

Iular recordings suggest that at least some of these effects
are due to direct actions on dopamine neurons (Clark et
al., 1985a; Steinfels et al., 1989).
The effects of BMY 14802 and rimcazole on midbrain
dopamine neurons are due to direct actions on dopamine neurons (Clark et al., 1985a; Steinfels et al., 1989).
The effects of BMY 14802 and rimcazole on midbrain
dopamine neurons are considerably more difficult to
interpret because these co al., 1985a; Steinfels et al., 1989).
The effects of BMY 14802 and rimcazole on midbrain
dopamine neurons are considerably more difficult to
interpret because these compounds are nonspecific and
because many different recep The effects of BMY 14802 and rimcazole on midbrain
dopamine neurons are considerably more difficult to
interpret because these compounds are nonspecific and
because many different receptor types are found in the
A9 and A1 interpret because these compounds are nonspecific and because many different receptor types are found in the A9 and A10 region of the brain. In contrast to the inhibitory effects of DTG, $(+)$ -pentazocine, and $(+)$ -3-PPP, interpret because these compounds are nonspecific and
because many different receptor types are found in the
A9 and A10 region of the brain. In contrast to the
inhibitory effects of DTG, $(+)$ -pentazocine, and $(+)$ -3-
PPP, because many different receptor types are found in the A9 and A10 region of the brain. In contrast to the inhibitory effects of DTG, (+)-pentazocine, and (+)-3-PPP, intravenous application of the BMY 14802 increases the fi A9 and A10 region of the brain. In contrast to the
inhibitory effects of DTG, $(+)$ -pentazocine, and $(+)$ -3-
PPP, intravenous application of the BMY 14802 in-
creases the firing rate of A9 dopamine neurons (Steinfels
and T inhibitory effects of DTG, (+)-pentazocine, and (+)-3-
PPP, intravenous application of the BMY 14802 in-
creases the firing rate of A9 dopamine neurons (Steinfels
and Tam, 1988). Furthermore, BMY 14802 reversed the
inhibit PPP, intravenous application of the BMY 14802 in-
creases the firing rate of A9 dopamine neurons (Steinfels
and Tam, 1988). Furthermore, BMY 14802 reversed the
inhibition produced by (+)-3-PPP (Steinfels and Tam,
1988), al and Tam, 1988). Furthermore, BMY 14802 reversed the inhibition produced by $(+)$ -3-PPP (Steinfels and Tam, 1988), although the effects of BMY 14802 do not appear and Tam, 1988). Furthermore, BMY 14802 reversed the
inhibition produced by $(+)$ -3-PPP (Steinfels and Tam,
1988), although the effects of BMY 14802 do not appear
to result from a direct interaction with dopamine recep-
tor inhibition produced by $(+)$ -3-PPP (Steinfels and Tam 1988), although the effects of BMY 14802 do not appear to result from a direct interaction with dopamine receptors (Wachtel and White, 1988). Whether the effects of BMY 1988), although the effector result from a direct in
tors (Wachtel and White
BMY 14802 are due to a
ever, remains unresolved
Although the effects result from a direct interaction with dopamine receptors (Wachtel and White, 1988). Whether the effects of MY 14802 are due to actions at sigma receptors, hower, remains unresolved.
Although the effects of rimcazole, anoth

tors (Wachtel and White, 1988). Whether the effects of BMY 14802 are due to actions at sigma receptors, how-
ever, remains unresolved.
Although the effects of rimcazole, another atypical
antipsychotic with affinity for sig BMY 14802 are due to actions at sigma receptors, how-
ever, remains unresolved.
Although the effects of rimcazole, another atypical
antipsychotic with affinity for sigma receptors, have been
tested by a number of laborator

FIG. 15. Inhibition of firing of a red nucleus neuron by iontophoretic application of the sigma ligand DTG. A, Action potentials of a rubral
neuron before, during, and immediately after an application of DTG. B, Expanded r FIG. 15. Inhibition of firing of a red nucleus neuron by iontophoretic application of the sigma ligand DTG. A, Action potentials of a rubral neuron before, during, and immediately after an application of DTG. B, Expanded r

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to interpret. Acute and chronic administration of rim-
cazole preferentially alters the spontaneous firing rate of walker B
to interpret. Acute and chronic administration of rim-
cazole preferentially alters the spontaneous firing rate of
A10 over A9 cells (Piontek and Wang, 1986). However, WALKE
to interpret. Acute and chronic administration of rim-
cazole preferentially alters the spontaneous firing rate of
A10 over A9 cells (Piontek and Wang, 1986). However,
intravenous administration of rimcazole has no c to interpret. Acute and chronic administration of ricazole preferentially alters the spontaneous firing rate A10 over A9 cells (Piontek and Wang, 1986). However intravenous administration of rimcazole has no consistent eff to interpret. Acute and chronic administration of rim-
cazole preferentially alters the spontaneous firing rate of
A10 over A9 cells (Piontek and Wang, 1986). However,
intravenous administration of rimcazole has no consist cazole preferentially alters the spontaneous firing rate of A10 over A9 cells (Piontek and Wang, 1986). However, intravenous administration of rimcazole has no consistent effects on the firing rate of A9 dopamine neurons a A10 over A9 cells (Piontek and Wang, 1986). However,
intravenous administration of rimcazole has no consist-
ent effects on the firing rate of A9 dopamine neurons
and fails to alter apomorphine-induced inhibitions
(Piontek intravenous administration of rimcazole has no consistent effects on the firing rate of A9 dopamine neurons and fails to alter apomorphine-induced inhibitions (Piontek and Wang, 1986; Steinfels and Tam, 1988). The compoun ent effects on the firing rate of A9 dopamine neurons
and fails to alter apomorphine-induced inhibitions
(Piontek and Wang, 1986; Steinfels and Tam, 1988). The
compound has also been reported to antagonize the ef-
fects of and fails to alter apomorphine-induced inhibitions (Piontek and Wang, 1986; Steinfels and Tam, 1988). The compound has also been reported to antagonize the effects of $(+)$ -SKF 10,047 on A10 neurons, but careful examinatio (Piontek and Wang, 1986; Steinfels and Tam, 1988). The compound has also been reported to antagonize the effects of $(+)$ -SKF 10,047 on A10 neurons, but careful examination of the dose-response curves suggests that rimcazo compound has also been reported to antagonize the effects of (+)-SKF 10,047 on A10 neurons, but careful examination of the dose-response curves suggests that rimcazole is a partial agonist/antagonist (Ceci et al., 1988). T fects of $(+)$ -SKF 10,047 on A10 neurons, but careful
examination of the dose-response curves suggests that
rimcazole is a partial agonist/antagonist (Ceci et al.,
1988). Taken together with the relatively weak affinity
of examination of the dose-response curves suggests that
rimeazole is a partial agonist/antagonist (Ceci et al.,
1988). Taken together with the relatively weak affinity
of rimeazole for sigma receptors, it is difficult at thi Although more studies are needed before the electro-

been mediated through sigma receptors.
Although more studies are needed before the electro-
physiological effects described above can be attributed to of rimcazole for sigma receptors, it is difficult at this
time to evaluate which of the observed effects may have
been mediated through sigma receptors.
Although more studies are needed before the electro-
physiological e time to evaluate which of the observed effects may have
been mediated through sigma receptors.
Although more studies are needed before the electro-
physiological effects described above can be attributed to
actions at sigm been mediated through sigma receptors.

Although more studies are needed before the electro-

physiological effects described above can be attributed to

actions at sigma receptors, two general trends occur: (a)

local a Although more studies are needed before the electro-
physiological effects described above can be attributed to
actions at sigma receptors, two general trends occur: (a)
hocal application of sigma ligands predominantly i physiological effects described above can be attributed to
actions at sigma receptors, two general trends occur: (*a*)
local application of sigma ligands predominantly inhibits
the firing of spontaneously active neurons a actions at sigma receptors, two general trends occurriocal application of sigma ligands predominantly inhite firing of spontaneously active neurons and (*b* vitro studies sometimes reveal inactivation of potass conductance local application of sigma ligands predominantly inhibits
the firing of spontaneously active neurons and (b) in
vitro studies sometimes reveal inactivation of potassium
conductances. These trends pose an apparent contrad the firing of spontaneously active neurons and (b) in vitro studies sometimes reveal inactivation of potassium conductances. These trends pose an apparent contradiction because inactivation of potassium conductances woul vitro studies sometimes reveal inactivation of potassium conductances. These trends pose an apparent contradiction because inactivation of potassium conductances $\frac{D}{D}$ would result in cellular excitation, not cellular conductances. These trends pose an apparent contradic-
tion because inactivation of potassium conductances
would result in cellular excitation, not cellular inhibition.
It appears that the differences between these sets o tion because inactivation of potassium conductances DCh would result in cellular excitation, not cellular inhibition. (adaint appears that the differences between these sets of findings coincides with whether the data were would result in cellular excitation, not cellular inhibition. (ad
It appears that the differences between these sets of
findings coincides with whether the data were obtained
from in vivo or in vitro preparations. The alte It appears that the differences between these sets of
findings coincides with whether the data were obtained
from in vivo or in vitro preparations. The alterations in
potassium conductances are observed in vitro, where the findings coincides with whether the data were obtained
from in vivo or in vitro preparations. The alterations in
potassium conductances are observed in vitro, where the
ability of sigma ligands to modulate ongoing actions from in vivo or in vitro preparations. The alterations in
potassium conductances are observed in vitro, where the
ability of sigma ligands to modulate ongoing actions of
classical neurotransmitters is minimized. By contra potassium conductances are observed in vitro, where the ability of sigma ligands to modulate ongoing actions o
classical neurotransmitters is minimized. By contrast
the in vivo inhibitions occur in preparations that show
t ability of sigma ligands to modulate ongoing actions classical neurotransmitters is minimized. By contra the in vivo inhibitions occur in preparations that she tonic activity from active excitatory inputs. Conceivable sigm classical neurotransmitters is minimized. By contrast,
the in vivo inhibitions occur in preparations that show
tonic activity from active excitatory inputs. Conceivably,
sigma ligands negatively modulate excitatory neuro-
 the in vivo inhibitions occur in preparations that show
tonic activity from active excitatory inputs. Conceivably
sigma ligands negatively modulate excitatory neuro
transmitters, in the same manner seen biochemicall
with c tonic activity from active excitatory inputs. Conceivably,
sigma ligands negatively modulate excitatory neuro-
transmitters, in the same manner seen biochemically
with cholinergic ligands. If so, further studies using modsigma ligands negatively modulate excitatory neuro-
transmitters, in the same manner seen biochemically
with cholinergic ligands. If so, further studies using mod-
eling approaches coupled with extracellular recording
and transmitters, in the same manner seen biochemically
with cholinergic ligands. If so, further studies using mod-
eling approaches coupled with extracellular recording
and intracellular studies of interactions between sigma
 E. E. *Peripheral Intracellular studies of interactions***
E. Peripheral Nervous System Actions
E. Peripheral Nervous System Actions
***1. Sigma actions on the guinea pig ill 1. Sigma actions on the guinea pig ileum.* In what is the grade pig ileum. In stage of interactions on the guinea pig ileum. In what is thaps the most clearly defined sigma action on periphend.

igands and excitatory neurotransmitters may be fruit
E. Peripheral Nervous System Actions
1. Sigma actions on the guinea pig ileum. In what
perhaps the most clearly defined sigma action on perip
eral tissues, Campbell et a E. Peripheral Nervous System Actions
1. Sigma actions on the guinea pig ileum. In what is
perhaps the most clearly defined sigma action on periph-
eral tissues, Campbell et al. (1989) showed that sigma
ligands block electr E. Peripheral Nervous System Actions
1. Sigma actions on the guinea pig ileum. In what is
perhaps the most clearly defined sigma action on periph-
eral tissues, Campbell et al. (1989) showed that sigma
ligands block electr 1. Sigma actions on the guinea pig ileum. In what if perhaps the most clearly defined sigma action on peripheral tissues, Campbell et al. (1989) showed that sigmaligands block electrically or $5HT$ -induced contraction of perhaps the most clearly defined sigma action on peripheral tissues, Campbell et al. (1989) showed that sigma
ligands block electrically or 5HT-induced contractions gui
of the isolated guinea pig ileum/myenteric plexus pre eral tissues, Campbell et al. (1989) showed that sigma
ligands block electrically or 5HT-induced contractions
of the isolated guinea pig ileum/myenteric plexus prep-
aration. As shown in figs. 16 and 17, these effects were ligands block electrically or 5HT-induced contractions gof the isolated guinea pig ileum/myenteric plexus preparation. As shown in figs. 16 and 17, these effects were concentration dependent, highly correlated with sigmab of the isolated guinea pig ileum/myenteric plexus pre
aration. As shown in figs. 16 and 17, these effects we
concentration dependent, highly correlated with sign
binding affinity, and appeared to be due to inhibition
the s aration. As shown in figs. 16 and 17, these effects were concentration dependent, highly correlated with sigma-
binding affinity, and appeared to be due to inhibition of
the stimulated release of acetylcholine from the pre concentration dependent, highly correlated with sigma-
binding affinity, and appeared to be due to inhibition of
the stimulated release of acetylcholine from the prepa-
nation. Many compounds from several different chemica binding affinity, and appeared to be due to inhibition of
the stimulated release of acetylcholine from the prepa-
ration. Many compounds from several different chemical
classes were tested in this assay and a series of ver the stimulated release of acetylcholine from the preparation. Many compounds from several different chemical classes were tested in this assay and a series of very strong correlations between sigma binding and efficacy wit ration. Many compounds from several different chemical relasses were tested in this assay and a series of very till strong correlations between sigma binding and efficacy in within chemical classes were found. However, se classes were tested in this assay and a series of very the strong correlations between sigma binding and efficacy in within chemical classes were found. However, several clompounds were well off the regression line, includ strong correlations between sigma binding and efficacy is
within chemical classes were found. However, several compounds were well off the regression line, including r
(+)- and (-)-3-PPP and chlorpromazine. As a result, t within chemical classes were found. However, several compounds were well off the regression line, including $(+)$ - and $(-)$ -3-PPP and chlorpromazine. As a result, the roverall correlation using least squares linear regress

guineary guineary guineary guineary guineary electrically evoked
**guinea pig brain using [²H]DTG) and potency in inhibiting electrically
evoked** contractions of the guinea pig ileum. A high correlation bet **evolutions.** Log IC ₅₀ In μ FIG. 16. Correlation between sigma-binding potency (measured in guinea pig brain using [²H]DTG) and potency in inhibiting electrically evoked contractions of the guinea pig ileum. A high **FIG. 16. Correlation between sigma-binding potency (measured in guinea pig brain using [³H]DTG) and potency in inhibiting electrically evoked contractions of the guinea pig ileum. A high correlation between sigma-bindin** FIG. 16. Correlation between sigma-binding potency (measured in guinea pig brain using [²H]DTG) and potency in inhibiting electrically evoked contractions of the guinea pig ileum. A high correlation between sigma-binding guinea pig brain using [³H]DTG) and potency in inhibiting elect
evoked contractions of the guinea pig ileum. A high correlation be
sigma-binding affinity and potency in this bioassay is found wi
exception of (+)- and (-) evoked contractions of the guinea pig ileum. A high correlation between sigma-binding affinity and potency in this bioassay is found with the exception of (+)- and (-)-3-PPP and chlorpromazine. Abbreviation +pent, (+)-pent sigma-binding affinity and potency in this bioassay is found exception of $(+)$ - and $(-)$ -3-PPP and chlorpromazine. Abbr
+pent, $(+)$ -pentazocine; DXG, N,N-di(2,6-methiphenyl)g
DChG, N,N'-(dicyclohexyl)guanidine; AdChG, 5,N-

evoked twitch

(Log iC₈₀ in am)

FIG. 17. Correlation between sigma-binding potency (measured in

guinea pig brain using [³H]DTG) and potency in inhibiting serotonin-

evoked contractions of the guinea pig ileum. As FIG. 17. Correlation between sigma-binding potency (measured in guinea pig brain using [³H]DTG) and potency in inhibiting serotoninevoked contractions of the guinea pig ileum. As with the electrically evoked twitch, inh FIG. 17. Correlation between sigma-binding potency (measured in guinea pig brain using [⁹H]DTG) and potency in inhibiting serotoninevoked contractions of the guinea pig ileum. As with the electrically evoked twitch, inhi guinea pig brain using $[^1]$ I)D'
evoked contractions of the g
evoked twitch, inhibitory pot
with sigma-binding potency.
from Campbell et al., 1989. evoked contractions of the guinea pig ileum. As with the electrically evoked twitch, inhibitory potency in the bioassay is highly correlated with sigma-binding potency. Abbreviations: Hal, haloperidol. Data from Campbell e

evoked twitch, inhibitory potency in the bioassay is nighty correlated
with sigma-binding potency. Abbreviations: Hal, haloperidol. Data
from Campbell et al., 1989.
0.37). However, the correlation value from a Spearman
ran from Campbell et al., 1989.

0.37). However, the correlation value from a Spearman

rank correlation, which is less affected by extremes in

the distribution of data, was close to 0.7. Not surpris-

ingly, if the outliers 0.37). However, the correlation value from a Spearman rank correlation, which is less affected by extremes in the distribution of data, was close to 0.7. Not surprisingly, if the outliers are omitted the correlation is ve 0.37). However, the correlation value from a Spearman rank correlation, which is less affected by extremes in the distribution of data, was close to 0.7. Not surprisingly, if the outliers are omitted the correlation is ve rank correlation, which is less affected by extremes in the distribution of data, was close to 0.7. Not surprisingly, if the outliers are omitted the correlation is very close to unity. These data thus provide support for the distribution of data, was close to 0.7. Not surprisingly, if the outliers are omitted the correlation is very close to unity. These data thus provide support for the notion that sigma receptors modulate cholinergic neu ingly, if the outliers are omitted the correlation is very close to unity. These data thus provide support for the notion that sigma receptors modulate cholinergic neurotransmission in the guinea pig ileum. The weak action close to unity. These data thus provide support for the notion that sigma receptors modulate cholinergic neu-
rotransmission in the guinea pig ileum. The weak actions
of (+)-3-PPP in this system are difficult to explain bu

REVIEW

PHARMACOLOGI

of PPI turnover (Bowen et al., 1990b), and in the production of postural changes following rubral microinjections (Matsumoto et al., 1990).
2. Sigma actions on other peripheral tissues. In a separate study, Campbell et al duction of postural changes following rubral microinjec-
tions (Matsumoto et al., 1990).
2. Sigma actions on other peripheral tissues. In a sep-
lungted study, Campbell et al. (1987) reported that (+)-3-
PPP potentiates el tions (Matsumoto et al., 1990).
2. Sigma actions on other peripheral tissues. In a
arate study, Campbell et al. (1987) reported that (-
PPP potentiates electrically induced contractions o
mouse vas deferens by enhancing re 2. Sigma actions on other peripheral tissues. In a separate study, Campbell et al. (1987) reported that $(+)$ -3-
PPP potentiates electrically induced contractions of the
mouse vas deferens by enhancing release of norepinep arate study, Campbell et al. (1987) reported that $(+)$ -3-
PPP potentiates electrically induced contractions of the
mouse vas deferens by enhancing release of norepineph-
reference from the preparation. Kennedy and Hende PPP potentiates electrically induced contractions of the rich mouse vas deferens by enhancing release of norepinephriecties of the preparation. Kennedy and Henderson nuc (1989b) observed a similar potentiation but only in mouse vas deferens by enhancing release of norepinephrine from the preparation. Kennedy and Henderson (1989b) observed a similar potentiation but only in the presence of sulpiride which was needed to block an inhibitory e rine from the preparation. Kennedy and Henderson
(1989b) observed a similar potentiation but only in the
presence of sulpiride which was needed to block an
inhibitory effect of $(+)$ -3-PPP alone. Other sigma ligand
that ha (1989b) observed a similar potentiation but only in the presence of sulpiride which was needed to block an inhibitory effect of $(+)$ -3-PPP alone. Other sigma ligands that had this effect included $(+)$ -SKF 10,047 and halop presence of sulpiride which was needed to block an inhibitory effect of $(+)$ -3-PPP alone. Other sigma ligands that had this effect included $(+)$ -SKF 10,047 and haloperidol. However, DTG produced only inhibitory effects, a inhibitory effect of $(+)$ -3-PPP alone. Other sigma ligands the that had this effect included $(+)$ -SKF 10,047 and halomorperidol. However, DTG produced only inhibitory effects, cen and these required high doses. Kennedy an that had this effect included (+)-SKF 10,047 and halo-
peridol. However, DTG produced only inhibitory effects,
and these required high doses. Kennedy and Henderson
r(1989b) noted that, although these effects may reflect a
 peridol. However, DTG produce
and these required high doses. 1
(1989b) noted that, although the
sigma action, the surprising lack
questions about the mechanism
A site showing the typical d these required high doses. Kennedy and Henderson ma
989b) noted that, although these effects may reflect a ph
ma action, the surprising lack of action of DTG raises
stions about the mechanism. (1990;
A site showing the t

(1989b) noted that, although these effects may reflect a
sigma action, the surprising lack of action of DTG raises
questions about the mechanism.
A site showing the typical sigma-binding profile is
found in the guinea pig sigma action, the surprising lack of action of DTG raises
questions about the mechanism.
A site showing the typical sigma-binding profile is
found in the guinea pig vas deferens (Su and Wu, 1990;
Vaupel and Su, 1987). In t questions about the mechanism. (19

A site showing the typical sigma-binding profile is frequined in the guinea pig vas deferens (Su and Wu, 1990; cetaple

Vaupel and Su, 1987). In this tissue, certain sigma ligands everte A site showing the typical sigma-binding profile is from found in the guinea pig vas deferens (Su and Wu, 1990; certain sigma ligands evolutional Su, 1987). In this tissue, certain sigma ligands evolution protentiate elec found in the guinea pig vas deferens (Su and Wu, 1990; Vaupel and Su, 1987). In this tissue, certain sigma ligands potentiate electrically stimulated contractions much as they do in the rat. However, the stereoselectivity potentiate electrically stimulated contractions much as they do in the rat. However, the stereoselectivity is the reverse of that seen in binding assays, i.e., $(-)$ -isomers of the opiates are more potent than $(+)$ -isomers they do in the rat. However, the stereoselectivity is inverse of that seen in binding assays, i.e., $(-)$ -isom of the opiates are more potent than $(+)$ -isomers. Thesembles the low affinity binding site discussed by Hewell reverse of that seen in binding assays, i.e., $(-)$ -isomers of the opiates are more potent than $(+)$ -isomers. This resembles the low affinity binding site discussed by He lewell and Bowen (1990) and the electrophysiologi of the opiates are more potent than $(+)$ -isomers. This Hesembles the low affinity binding site discussed by Hellewell and Bowen (1990) and the electrophysiological treffects found in NCB20 cells, which also show this prop resembles the low aff
lewell and Bowen (1
effects found in NCB
erty. However, it is
found in this tissue.
In summary, it app well and Bowen (1990) and the electrophysiological the electrophysiological the electrophysiological that is found in NCB20 cells, which also show this prop-
ty. However, it is the reverse of the binding profile that is i

effects found in NCB20 cells, which also show this property. However, it is the reverse of the binding profile
found in this tissue.
In summary, it appears that sigma receptors mediate
the inhibition of electrically and 5H erty. However, it is the reverse of the binding profile
found in this tissue.
In summary, it appears that sigma receptors mediate
the inhibition of electrically and 5HT-stimulated con-
tractions of the guinea pig ileum. In found in this tissue.
In summary, it appears that sigma receptors mediate
the inhibition of electrically and 5HT-stimulated con-
tractions of the guinea pig ileum. In other peripheral
tissues, some sigma ligands have effec In summary, it appears that sigma receptors mediate
the inhibition of electrically and 5HT-stimulated con-
tractions of the guinea pig ileum. In other peripheral
tissues, some sigma ligands have effects, but the actions
a tractions of the guinea pig ileum. In other peripheral tissues, some sigma ligands have effects, but the actions are not entirely consistent with actions at the high affinity site described by Tam (1983; 1984) and Su (1982 tractions of the guinea pig ileum. In other peripheral
tissues, some sigma ligands have effects, but the actions
are not entirely consistent with actions at the high
affinity site described by Tam (1983; 1984) and Su (1982 tissues, some sigma ligands have effects, but the actions
are not entirely consistent with actions at the high
affinity site described by Tam (1983; 1984) and Su (1982).
It is clear from the binding data described above t are not entirely consistent with actions at the high

affinity site described by Tam $(1983; 1984)$ and Su (1982) .

It is clear from the binding data described above that

more than one sigma-binding site exists, and it affinity site described by Tam (1983; 1984) and Su (1982).
It is clear from the binding data described above that
more than one sigma-binding site exists, and it may be
that these peripheral tissue preparations will provi It is clear from the binding data descreed the subtypes of the receptor.

that these peripheral tissue preparation

means to understand the physiological

ligands at the subtypes of the receptor.
 $F.$ Role of Sigma Recep *F.* that these peripheral tissue preparations will provide the means to understand the physiological actions of sigma ligands at the subtypes of the receptor.
F. Role of Sigma Receptors in the Central Nervous

System

glucose utilization of ligands that bind to sigma receptors F. Role of Sigma Receptors in the Central Nervous
System
1. Glucose utilization. In a single study the effects on
glucose utilization of ligands that bind to sigma receptors
were examined. Puppa and London (1989) investiga m and the effects on all the single study the effects on all plucose utilization of ligands that bind to sigma receptors were examined. Puppa and London (1989) investigated single pregional glucose utilization following in 1. Glucose utilization. In a single study the effects on glucose utilization of ligands that bind to sigma receptors were examined. Puppa and London (1989) investigated regional glucose utilization following injection of glucose utilization of ligands that bind to sigma receptors
were examined. Puppa and London (1989) investigated
regional glucose utilization following injection of a single
dose of (+)-pentazocine, BMY 14802, and rimcazole were examined. Puppa and London (1989) investigated surface regional glucose utilization following injection of a single year dose of $(+)$ -pentazocine, BMY 14802, and rimcazole. state extensive pharmacological characteriz regional glucose utilization following injection of a single year dose of (+)-pentazocine, BMY 14802, and rimcazole. studies Extensive pharmacological characterization of the effects provade above. Nevertheless, the provad dose of (+)-pentazocine, BMY 14802, and rimcazole. studies were not conducted with enough compounds to Extensive pharmacological characterization of the effects produce the correlations needed to provide a reasonable are Extensive pharmacological characterization of the effects
are lacking, and the latter two of these ligands have
certain limitations discussed above. Nevertheless, the
marked overlap between anatomical distribution of the
c are lacking, and the latter two of these ligands have contain limitations discussed above. Nevertheless, the pinarked overlap between anatomical distribution of the (1 changes and the distribution of sigma receptors suppor certain limitations discussed above. Nevertheless, the
marked overlap between anatomical distribution of the
changes and the distribution of sigma receptors supports
the investigators' conclusion that occupation of sigma
r marked overlap between anatomical distribution of the (increases and the distribution of sigma receptors upports between the investigators' conclusion that occupation of sigma henceptors leads to changes in glucose utiliz changes and the distribution of sigma receptors supports bre
the investigators' conclusion that occupation of sigma have
receptors leads to changes in glucose utilization. Fur-
thermore, the observation that $(+)$ -pentazoc

EPTORS 387
tendency for neuroleptic like compounds to possess
greater potency than (+)-opiates in rats. Significant algreater of the compounds to possess
tendency for neuroleptic like compounds to possess
greater potency than (+)-opiates in rats. Significant al-
terations in glucose utilization were observed in cerebel-EPTORS
tendency for neuroleptic like compounds to poss
greater potency than (+)-opiates in rats. Significant
terations in glucose utilization were observed in cereb
lum, hippocampus, paraventricular hypothalamic tendency for neuroleptic like compounds to possess
greater potency than (+)-opiates in rats. Significant al-
terations in glucose utilization were observed in cerebel-
lum, hippocampus, paraventricular hypothalamic nu-
cle tendency for neuroleptic like compounds to posse
greater potency than $(+)$ -opiates in rats. Significant at
terations in glucose utilization were observed in cereb
lum, hippocampus, paraventricular hypothalamic n
cleus, som greater potency than $(+)$ -opiates in rats. Significant alterations in glucose utilization were observed in cerebel-
lum, hippocampus, paraventricular hypothalamic nucleus, some cranial nerve nuclei, and several other sigma terations in glucose utilization were observed in cerebel-
lum, hippocampus, paraventricular hypothalamic nucleus, some cranial nerve nuclei, and several other sigma-
rich areas. However, certain areas that are rich in sig lum, hippocampus, paraventricular hypothalamic nucleus, some cranial nerve nuclei, and several other sigmarich areas. However, certain areas that are rich in sigma receptors, such as the oculomotor nucleus, supraoptic nucl cleus, some cranial nerve nuclei, and several other sigmarich areas. However, certain areas that are rich in sigma
receptors, such as the oculomotor nucleus, supraoptic
nucleus, and locus coeruleus, did not exhibit signifi rich areas. However, certain areas that are rich in sigma receptors, such as the oculomotor nucleus, supraoptic nucleus, and locus coeruleus, did not exhibit significant changes in glucose utilization. Although more work i receptors, such as the oculomotor nucleus, supraoptic
nucleus, and locus coeruleus, did not exhibit significant
changes in glucose utilization. Although more work is
needed to firmly establish a role of sigma receptors in
 changes in glucose utilization. Although more work is
needed to firmly establish a role of sigma receptors in
these effects, the findings are important because they
imply a physiological function for sigma receptors in the changes in glucose utilization. Although more work is
needed to firmly establish a role of sigma receptors in
these effects, the findings are important because they
imply a physiological function for sigma receptors in the meeded to firmly establish a role of sigma receptors in these effects, the findings are important because they imply a physiological function for sigma receptors in the central nervous system and point to anatomical loci t these effects, the findings are important because the imply a physiological function for sigma receptors in the central nervous system and point to anatomical loci the may be good candidates for future investigations of th ply a physiological function for sigma receptors in the
ntral nervous system and point to anatomical loci that
ay be good candidates for future investigations of the
ysiological and behavioral effects of sigma ligands.
2.

Vaupel and Su, 1987). In this tissue, certain sigma ligands ever, these animals failed to generalize to $(-)$ -butaclamol potentiate electrically stimulated contractions much as or to haloperidol, both of which bind potentl *1. Glucose utilization*. In a single study the effects on and antagonists.
 1. Glucose utilization. In a single study the effects on and antagonists.
 1. Glucose utilization. In a single study the effects on and antag central nervous system and point to anatomical loci that
may be good candidates for future investigations of the
physiological and behavioral effects of sigma ligands.
2. Sigma ligands as discriminative stimuli. Holtzman
 may be good candidates for future investigations of the physiological and behavioral effects of sigma ligands.
2. Sigma ligands as discriminative stimuli. Holtzman (1989) found that animals trained to discriminate DTG fro physiological and behavioral effects of sigma ligands.
2. Sigma ligands as discriminative stimuli. Holtzma
(1989) found that animals trained to discriminate DT
from saline, generalized to a variety of ligands [includin
cer 2. Sigma ligands as discriminative stimuli. Holtzma
(1989) found that animals trained to discriminate DT
from saline, generalized to a variety of ligands [includii
certain (+)- and (-)-opiates and PCP-like drugs]. Ho
ever (1989) found that animals trained to discriminate DTG
from saline, generalized to a variety of ligands [including
certain (+)- and (-)-opiates and PCP-like drugs]. How-
ever, these animals failed to generalize to (-)-buta from saline, generalized to a variety of ligands [inclu certain $(+)$ - and $(-)$ -opiates and PCP-like drugs]. Hever, these animals failed to generalize to $(-)$ -butacle or to haloperidol, both of which bind potently to si re certain $(+)$ - and $(-)$ -opiates and PCP-like drugs]. How-
ever, these animals failed to generalize to $(-)$ -butaclamol
or to haloperidol, both of which bind potently to sigma
receptors. Steinfels et al. (1988) found that $(+$ ever, these animals failed to generalize to $(-)$ -butaclamol
or to haloperidol, both of which bind potently to sigma
receptors. Steinfels et al. (1988) found that $(+)$ -penta-
zocine-trained animals generalized $(+)$ -SKF 10, or to haloperidol, both of which bind potently to sigma
receptors. Steinfels et al. (1988) found that (+)-penta-
zocine-trained animals generalized (+)-SKF 10,047.
However, they also generalized to PCP, although the
effect receptors. Steinfels et al. (1988) found that $(+)$ -penta-
zocine-trained animals generalized $(+)$ -SKF 10,047.
However, they also generalized to PCP, although the
effect was incomplete. Balster (1989) found that animals
 physiological and behavioral effects of sigma ligands.

2. Sigma ligands as discriminative stimuli. Holtzman

(1989) found that animals trained to discriminate DTG

from saline, generalized to a variety of ligands [includi However, they also generalized to PCP, although the
effect was incomplete. Balster (1989) found that animals
trained to discriminate (+)-SKF 10,047 from saline gen-
eralize well to PCP-related compounds but not at all to
t effect was incomplete. Balster (1989) found that animals
trained to discriminate (+)-SKF 10,047 from saline gen-
eralize well to PCP-related compounds but not at all to
the sigma compounds DTG, (+)-ketocyclazocine, (--)-
b the sigma compounds DTG, $(+)$ -ketocyclazocine, $(-)$ -
butaclamol, and haloperidol. This finding was recently
replicated by Singh et al. (1990). It is perhaps not sur-
prising that the pattern of results from these studies eralize well to PCP-related compounds but not at all to
the sigma compounds DTG, $(+)$ -ketocyclazocine, $(-)$ -
butaclamol, and haloperidol. This finding was recently
replicated by Singh et al. (1990). It is perhaps not surthe sigma compounds DTG, $(+)$ -ketocyclazocine, $(-)$ -butaclamol, and haloperidol. This finding was recently replicated by Singh et al. (1990). It is perhaps not surprising that the pattern of results from these studies is butaclamol, and haloperidol. This finding was recently
replicated by Singh et al. (1990). It is perhaps not sur-
prising that the pattern of results from these studies is
not particularly clear, because in every case it wa replicated by Singh et al. (1990). It is perhaps not surprising that the pattern of results from these studies is
not particularly clear, because in every case it was necessary to use drugs that bind to several different t prising that the pattern of results from these studies is
not particularly clear, because in every case it was nec-
essary to use drugs that bind to several different types
of receptors. Thus, the failure of haloperidol t not particularly clear, because in every case it was necessary to use drugs that bind to several different types of receptors. Thus, the failure of haloperidol to generalize to (+)-pentazocine is not surprising, because it essary to use drugs that bind to several different types
of receptors. Thus, the failure of haloperidol to generalize
to (+)-pentazocine is not surprising, because it binds to
certain classes of dopamine, adrenergic, and s of receptors. Thus, the failure of haloperidol to generalize
to $(+)$ -pentazocine is not surprising, because it binds to
certain classes of dopamine, adrenergic, and serotonergic
receptors in addition to sigma receptors (S to $(+)$ -pentazocine is not surprising, because it binds to certain classes of dopamine, adrenergic, and serotonergic receptors in addition to sigma receptors (Seeman, 1981). Likewise, $(+)$ -SKF 10,047, which potently binds certain classes of dopamine, adrenergic, and serotonergic
receptors in addition to sigma receptors (Seeman, 1981).
Likewise, (+)-SKF 10,047, which potently binds to PCP
receptors should not be expected to display a particu receptors in addition to sigma receptors (Seeman, 1981).
Likewise, (+)-SKF 10,047, which potently binds to PCP
receptors should not be expected to display a particularly
sigma-like profile. It appears that definite conclus Likewise, (+)-SKF 10,047, which potently binds to PCP
receptors should not be expected to display a particularly
sigma-like profile. It appears that definite conclusions
regarding the stimulus properties of the sigma recep receptors shoule
sigma-like prof
regarding the s
may require the
and antagonists
3. Open field pma-like profile. It appears that definite conclusions garding the stimulus properties of the sigma receptor ay require the development of more selective agonists of antagonists.
3. Open field behavior. Several attempts to

regarding the stimulus properties of the sigma receptor
may require the development of more selective agonists
and antagonists.
3. Open field behavior. Several attempts to identify
sigma-mediated behaviors have been publis may require the development of more selective agonists
and antagonists.
3. Open field behavior. Several attempts to identify
sigma-mediated behaviors have been published in recent
years (Contreras et al, 1988b; Iwamoto 198 and antagonists.

3. Open field behavior. Several attempts to identify

sigma-mediated behaviors have been published in recent

years (Contreras et al, 1988b; Iwamoto 1989). These

studies were not conducted with enough co 3. Open field behavior. Several attempts to identify sigma-mediated behaviors have been published in recent years (Contreras et al, 1988b; Iwamoto 1989). These studies were not conducted with enough compounds to produce th sigma-mediated behaviors have been published in recent
years (Contreras et al, 1988b; Iwamoto 1989). These
studies were not conducted with enough compounds to
produce the correlations needed to provide a reasonable
connect years (Contreras et al. 1988b; Iwamoto 1989). These
studies were not conducted with enough compounds to
produce the correlations needed to provide a reasonable
connection to the sigma receptor. However, they did
produce s produce the correlations needed to provide a reasonable produce the correlations needed to provide a reasonable
connection to the sigma receptor. However, they did
produce some interesting findings. Contreras et al.
(1988b) reported that DTG ($ED_{50} = 55$ nmol, intracere-
brove connection to the sigma receptor. However, they did
produce some interesting findings. Contreras et al.
(1988b) reported that DTG ($ED_{50} = 55$ nmol, intracere-
broventricularly) produced a pattern of stereotyped be-
havio produce some interesting findings. Contreras et a
(1988b) reported that DTG ($ED_{50} = 55$ nmol, intracer-
broventricularly) produced a pattern of stereotyped ba
havior and ataxia that was indistinguishable from tha
produce (1988b) reported that DTG ($ED_{50} = 55$ nmol, intracere-
broventricularly) produced a pattern of stereotyped be-
havior and ataxia that was indistinguishable from that
produced by PCP and MK-801, a drug that binds selec-
t broventricularly) produced a pattern of stereotyped behavior and ataxia that was indistinguishable from that produced by PCP and MK-801, a drug that binds selectively to the PCP/NMDA receptor complex. Because these behavio

988

PCP receptor, it is tempting to conclude that DTG tant if

produced some effects through the PCP site. However, mover walket
PCP receptor, it is tempting to conclude that DTG
produced some effects through the PCP site. However,
these results are more difficult to interpret because DTG WALKER ET AL

PCP receptor, it is tempting to conclude that DTG tant if

produced some effects through the PCP site. However, moves

these results are more difficult to interpret because DTG sigma

was the most potent of t PCP receptor, it is tempting to conclude that DTG tarefroduced some effects through the PCP site. However, mothese results are more difficult to interpret because DTG signos the most potent of the three drugs, although the PCP receptor, it is tempting to conclude that D'
produced some effects through the PCP site. Howev
these results are more difficult to interpret because D'
was the most potent of the three drugs, although
weakest at the PC produced some effects through the PCP site. However,
these results are more difficult to interpret because DTG
was the most potent of the three drugs, although the
weakest at the PCP site. Together with the drug discrim-
i weakest at the PCP site. Together with the drug discrim-

through distinct PCP and sigma sites. More work is tor
needed to clarify the nature of these effects. 198
Iwamoto (1989) hypothesized a "sigma syndrome" that The
occurs following sensitization of animals by five daily tio needed to clarify the nature of these effects. 198
Iwamoto (1989) hypothesized a "sigma syndrome" that Theocurs following sensitization of animals by five daily tion
systemic injections of the opiate $(-)$ -SKF 10,047. An t Iwamoto (1989) hypothesized a "sigma syndrome" that occurs following sensitization of animals by five daily systemic injections of the opiate $(-)$ -SKF 10,047. An injection of $(+)$ -butaclamol in these animals results in a occurs following sensitization of animals by five daystemic injections of the opiate $(-)$ -SKF 10,047.
injection of $(+)$ -butaclamol in these animals results in marked increase in locomotor activation, sideways α cling, systemic injections of the opiate $(-)$ -SKF 10,047. An injection of $(+)$ -butaclamol in these animals results in a marked increase in locomotor activation, sideways circling, and backward walking. These effects are antagoni injection of $(+)$ -butaclamol in these animals results in a
marked increase in locomotor activation, sideways cir-
cling, and backward walking. These effects are antago-
nized by compounds with sigma affinity, hypothesized marked increase in locomotor activation, sideways ci
cling, and backward walking. These effects are antag
nized by compounds with sigma affinity, hypothesize
by Iwamoto to be sigma antagonists (rimcazole, $(+/-$ BMY 14802, a cling, and backward walking. These effects are antagonized by compounds with sigma affinity, hypothesized by Iwamoto to be sigma antagonists (rimcazole, $(+/-)$ -BMY 14802, and haloperidol) but not sulpiride, a dopamine D_2 nized by compounds with sigma affinity, hypothesize
by Iwamoto to be sigma antagonists (rimcazole, $(+/-$ BMY 14802, and haloperidol) but not sulpiride, a dopa
mine D_2 antagonist lacking activity at the other recepto:
hav by Iwamoto to be sigma antagonists (rimcazole, $(+/-)$ -BMY 14802, and haloperidol) but not sulpiride, a dopamine D_2 antagonist lacking activity at the other receptors having affinity for haloperidol. A more detailed phar BMY 14802, and haloperidol) but not sulpiride, a dopa-
mine D_2 antagonist lacking activity at the other receptors
having affinity for haloperidol. A more detailed phar-
macological analysis of this phenomen should reve mine D_2 antagonist lacking activity at the other receptors
having affinity for haloperidol. A more detailed phar-
macological analysis of this phenomen should reveal
whether, in fact, the sigma system becomes hyperacti macological analysis of this phenomen should reveal

macological analysis of this phenomen should reveal in whether, in fact, the sigma system becomes hyperactive of i in $(-)$ -SKF 10,047-treated animals.
Anatomical studies revealed high levels of sigma bind-
ing in the P whether, in fact, the sigma system becomes hyperactive
in $(-)$ -SKF 10,047-treated animals.
Anatomical studies revealed high levels of sigma bind-
ing in the PAG (Gundlach et al., 1986; McLean and
Weber, 1988), an area inv in $(-)$ -SKF 10,047-treated animals.

Anatomical studies revealed high levels of sigma bind-

ing in the PAG (Gundlach et al., 1986; McLean and

Weber, 1988), an area involved in defensive behaviors.

One function of the c Anatomical studies revealed high levels of sigma binding in the PAG (Gundlach et al., 1986; McLean and Weber, 1988), an area involved in defensive behaviors.
One function of the circuitry in the PAG is to regulate startle ing in the PAG (Gundlach et al., 1986; McLean and al.
Weber, 1988), an area involved in defensive behaviors. Si
One function of the circuitry in the PAG is to regulate
startle responses to strong acoustic stimuli (Davis, 1 Weber, 1988), an area involved in defensive behaviors.
One function of the circuitry in the PAG is to regulate
startle responses to strong acoustic stimuli (Davis, 1989),
presumably through its connections to the nucleus o One function of the circuitry in the PAG is to regula
startle responses to strong acoustic stimuli (Davis, 1989
presumably through its connections to the nucleus of t
lateral lemniscus (part of the primary acoustic circuit startle responses to strong acoustic stimu
presumably through its connections to the
lateral lemniscus (part of the primary ac
Davis et al., 1982). Recent data suggest ti
tors are part of this modulatory circuit.
The role esumably through its connections to the nucleus of the teral lemniscus (part of the primary acoustic circuit
avis et al., 1982). Recent data suggest that sigma rece
rs are part of this modulatory circuit.
The role of sigma lateral lemniscus (part of the primary acoustic circuitry;
Davis et al., 1982). Recent data suggest that sigma recep-
tors are part of this modulatory circuit.
The role of sigma receptors in this circuit was inves-
tigated

Davis et al., 1982). Recent data suggest that sigma recep-
tors are part of this modulatory circuit.
The role of sigma receptors in this circuit was inves-
tigated by presenting powerful acoustic stimuli (115 db,
3840 Hz) tors are part of this modulatory circuit.
The role of sigma receptors in this circuit was in
tigated by presenting powerful acoustic stimuli (118
3840 Hz) to rats and quantifying the resulting st
response. Microinjections The role of sigma receptors in this circuit was inves-
tigated by presenting powerful acoustic stimuli (115 db, ilari
3840 Hz) to rats and quantifying the resulting startle or in
response. Microinjections of both DTG and tigated by presenting powerful acoustic stimuli $(115 \text{ d} 3840 \text{ Hz})$ to rats and quantifying the resulting star
response. Microinjections of both DTG and $(+)$ -pent
zocine into the PAG markedly amplified responses
these t 3840 Hz) to rats and quantifying the resulting startle response. Microinjections of both DTG and $(+)$ -penta-
zocine into the PAG markedly amplified responses to
these tone bursts (Jones and Walker, unpublished obser-
vati response. Microinjections of both DTG and (+)-penta-
zocine into the PAG markedly amplified responses to
these tone bursts (Jones and Walker, unpublished obser-
vations). Clearly, more work is necessary to establish
whethe zocine into the PAG markedly amplified responses to
these tone bursts (Jones and Walker, unpublished observations). Clearly, more work is necessary to establish
whether these responses are mediated by sigma receptors,
beca these tone bursts (Jones and Walker, unpublished observations). Clearly, more work is necessary to establish whether these responses are mediated by sigma receptors, because only two compounds have been tested. If an unequ vations). Clearly, more work is necessary to establish whether these responses are mediated by sigma receptors, because only two compounds have been tested. If an unequivocal role of sigma receptors can be established in t whether these responses are mediated by sigma receptors,
because only two compounds have been tested. If an
unequivocal role of sigma receptors can be established in
this paradigm, it would suggest that sigma receptors pla because only two compounds have been tested. If an unequivocal role of sigma receptors can be established in this paradigm, it would suggest that sigma receptors play a role in defensive behaviors. In addition to startle, unequivocal role of sigma receptors can be established in
this paradigm, it would suggest that sigma receptors play
a role in defensive behaviors. In addition to startle, the
PAG is involved in a number of behaviors relate this paradigm, it would suggest that sigma receptors play
a role in defensive behaviors. In addition to startle, the
PAG is involved in a number of behaviors related to
acoustic startle, including pain, fear, escape behavi a role in defensive behaviors. In addition to startle, the PAG is involved in a number of behaviors related to acoustic startle, including pain, fear, escape behavior, freezing behavior, and defensive behavior (Liebman et PAG is involved in a number of behaviors related to
acoustic startle, including pain, fear, escape behavior,
freezing behavior, and defensive behavior (Liebman et
al., 1970; Jacquet and Lajtha, 1974; Jacquet et al., 1977;
 acoustic startle, including pain, fear, escape behavior,
freezing behavior, and defensive behavior (Liebman et
al., 1970; Jacquet and Lajtha, 1974; Jacquet et al., 1977;
Edwards and Adams, 1974)—behaviors that share the
pr al., 1970; Jacquet and Lajtha, 1974; Jacquet et al., 1977; Edwards and Adams, 1974)—behaviors that share the property of being responses to threat. Hence, although microinjections of sigma ligands into the PAG do not appea Edwards and Adams, 1974)—behaviors that share the
property of being responses to threat. Hence, although
microinjections of sigma ligands into the PAG do not
appear to alter pain sensitivity (Matsumoto and Walker,
unpublis Edwards and Adams, 1974)—behaviors that share the
property of being responses to threat. Hence, although
microinjections of sigma ligands into the PAG do not
appear to alter pain sensitivity (Matsumoto and Walker,
unpubli property of being responses to threat. Hence, although
microinjections of sigma ligands into the PAG do not
appear to alter pain sensitivity (Matsumoto and Walker,
unpublished data), more work may establish a role in
defen responses. 4. appear to alter pain sensitivity (Matsumoto and Walke unpublished data), more work may establish a role is
defensive behavior evidenced by the modulation of startles
ponses.
4. Role of sigma receptors in posture and mov

was the most potent of the three drugs, although the intimately linked to movement: the cerebellum, red nu-
weakest at the PCP site. Together with the drug discrim-cleus, superior colliculus, spinal ventral horn, and vario through distinct PCP and sigma sites. More work is tor oculomotor, trochlear, and abducens; Gundlach et al., needed to clarify the nature of these effects.

Iwamoto (1989) hypothesized a "sigma syndrome" that The locus co ET AL.
tant functions of sigma receptors in the regulation of
movement and posture. The highest concentrations of ET AL.
tant functions of sigma receptors in the regulation of
movement and posture. The highest concentrations of
sigma receptors in the brain occur in areas that are ET AL.
tant functions of sigma receptors in the regulation of
movement and posture. The highest concentrations of
sigma receptors in the brain occur in areas that are
intimately linked to movement: the cerebellum, red nutant functions of sigma receptors in the regulation of movement and posture. The highest concentrations of sigma receptors in the brain occur in areas that are intimately linked to movement: the cerebellum, red nu-cleus, s tant functions of sigma receptors in the regulation of movement and posture. The highest concentrations of sigma receptors in the brain occur in areas that are intimately linked to movement: the cerebellum, red nucleus, su movement and posture. The highest concentrations of sigma receptors in the brain occur in areas that are sigma receptors in the brain occur in areas that are
intimately linked to movement: the cerebellum, red nu-
cleus, superior colliculus, spinal ventral horn, and various
cranial nerve nuclei (facial, hypoglossal, trigeminal 1986; Largent et al., 1984; McLean and Weber, 1988). cranial nerve nuclei (facial, hypoglossal, trigeminal m
tor oculomotor, trochlear, and abducens; Gundlach et a
1986; Largent et al., 1984; McLean and Weber, 1988
The locus coeruleus, which influences cerebellar fun
tion, i tor oculomotor, trochlear, and abducens; Gundlach et al., 1986; Largent et al., 1984; McLean and Weber, 1988).
The locus coeruleus, which influences cerebellar function, is one of the most heavily labeled hindbrain structu 1986; Largent et al., 1984; McLean and Weber, 1988).
The locus coeruleus, which influences cerebellar func-
tion, is one of the most heavily labeled hindbrain struc-
tures (Gundlach et al., 1986; McLean and Weber, 1988).
L The locus coeruleus, which influences cerebellar function, is one of the most heavily labeled hindbrain structures (Gundlach et al., 1986; McLean and Weber, 1988). Lower levels of sigma binding occur in the substantia nigr tion, is one of the most heavily labeled hindbrain structures (Gundlach et al., 1986; McLean and Weber, 1988).
Lower levels of sigma binding occur in the substantia
nigra and striatum (Graybiel et al., 1989; Gundlach et
al tures (Gundlach et al., 1986; McLean and Weber, 1988).
Lower levels of sigma binding occur in the substantia
nigra and striatum (Graybiel et al., 1989; Gundlach et
al., 1986). It follows from this distribution that sigma
r nigra and striatum (Graybiel et al., 1989; Gundlach et al., 1986). It follows from this distribution that sigma
receptors would influence the motor system, a notion
supported by physiological studies.
a. MOTOR ACTIONS OF al., 1986). It follows from this distribution that sigma
receptors would influence the motor system, a notion
supported by physiological studies.
a. MOTOR ACTIONS OF SIGMA LIGANDS IN THE RED
NUCLEUS. The red nucleus has pr

receptors would influence the motor system, a notion supported by physiological studies.

a. MOTOR ACTIONS OF SIGMA LIGANDS IN THE RED

NUCLEUS. The red nucleus has proven to be a fruitful

site for investigating the poten supported by physiological studies.

a. MOTOR ACTIONS OF SIGMA LIGANDS IN THE RED

NUCLEUS. The red nucleus has proven to be a fruitful

site for investigating the potential role of sigma receptors

in motor control, becau a. MOTOR ACTIONS OF SIGMA LIGANDS IN THE RI
NUCLEUS. The red nucleus has proven to be a fruit
site for investigating the potential role of sigma recepto
in motor control, because it contains high concentratio
of sigma rece NUCLEUS. The red nucleus has proven to be a fruitful site for investigating the potential role of sigma receptors in motor control, because it contains high concentrations of sigma receptors but very low densities of othe site for investigating the potential role of sigma receptors
in motor control, because it contains high concentrations
of sigma receptors but very low densities of other recep-
tors that have affinity for some sigma ligan in motor control, because it contains high concentrations
of sigma receptors but very low densities of other recep-
tors that have affinity for some sigma ligands (dopamine,
opiate, PCP, 5HT, or α -adrenergic receptors; of sigma receptors but very low densities of other re
tors that have affinity for some sigma ligands (dopan
opiate, PCP, 5HT, or α -adrenergic receptors; Boyso
al., 1986; Pazos and Palacios, 1985; Quirion et al., 1
Sirc tors that have affinity for some sigma ligands (dopamine, opiate, PCP, 5HT, or α -adrenergic receptors; Boyson et al., 1986; Pazos and Palacios, 1985; Quirion et al., 1981; Sircar and Zukin, 1988). As shown in fig. 18, opiate, PCP, 5HT, or α -adrenergic receptors; Boyson e al., 1986; Pazos and Palacios, 1985; Quirion et al., 1981
Sircar and Zukin, 1988). As shown in fig. 18, microinjections of a variety of sigma ligands in the red nucl al., 1986; Pazos and Palacios, 1985; Quirion et al., 1981; Sircar and Zukin, 1988). As shown in fig. 18, microinjections of a variety of sigma ligands in the red nucleus, including (+)-SKF10,047, (+)-pentazocine, BD614, de Sircar and Zukin, 1988). As shown in fig. 18, microinjections of a variety of sigma ligands in the red nucleus, including $(+)$ -SKF10,047, $(+)$ -pentazocine, BD614, dextrallorphan, DTG, and haloperidol, resulted in quantifi tions of a variety of sigma ligands in the red nucleus,
including $(+)$ -SKF10,047, $(+)$ -pentazocine, BD614, dex-
trallorphan, DTG, and haloperidol, resulted in quantifi-
able dystonia (torticollis) in rats, whereas non-sig trallorphan, DTG, and haloperidol, resulted in quantifi
able dystonia (torticollis) in rats, whereas non-sigma
controls, such as (+)-nordihydrocodeinone [a structura
homolog of (+)-opiate sigma ligands with low affinity fo able dystonia (torticollis) in rats, whereas non-sigma
controls, such as $(+)$ -nordihydrocodeinone [a structural
homolog of $(+)$ -opiate sigma ligands with low affinity for
sigma receptors] did not (Matsumoto et al., 1990). controls, such as $(+)$ -nordihydrocodeinone [a structural
homolog of $(+)$ -opiate sigma ligands with low affinity for
sigma receptors] did not (Matsumoto et al., 1990). Sim-
ilarly, a series of ligands for other receptors t homolog of $(+)$ -opiate sigma ligands with low affinity for
sigma receptors] did not (Matsumoto et al., 1990). Sim-
ilarly, a series of ligands for other receptors that are weak
or inactive at sigma receptors failed to pro

infection: *top left.* **18. Appearance of a rat at various times following microinjection of DTG (and other sigma ligands) in the red nucleus. Times after injection:** *top left***, 1 min;** *top right***, 5 min;** *bottom lef* FIG. 18. Appearance of a rat at various times following microinjection of DTG (and other sigma ligands) in the red nucleus. Times after injection: *top left*, 1 min; *top right*, 5 min; *bottom left*, 15 min; *bottom right* injection: top left, 1 min; top right, 5 min; bottom left, 15 min; bottom right, 30 min. The eye ipsilateral to the injections site faces upward; the limbs are affected as well especially in the later periods. The effect

sigma RECEP
the dopamine D_2 antagonist (-)-sulpiride, the $5HT_{1a}$ signagonist 8-hydroxydipropylaminotetralin, PCP, and the you sig MA RECEF
the dopamine D₂ antagonist (-)-sulpiride, the 5HT_{1a} sig
agonist 8-hydroxydipropylaminotetralin, PCP, and the you
atypical antipsychotic clozapine (Matsumoto et al., 1990; alt siGMA REC
the dopamine D_2 antagonist $(-)$ -sulpiride, the $5HT_{1a}$
agonist 8-hydroxydipropylaminotetralin, PCP, and the
atypical antipsychotic clozapine (Matsumoto et al., 1990;
Walker et al., 1988). the dopamine D₂ ant
agonist 8-hydroxydipi
atypical antipsychotic
Walker et al., 1988).
As illustrated in fig. e dopamine D_2 antagonist (-)-sulpiride, the $5HT_{1a}$ signist 8-hydroxydipropylaminotetralin, PCP, and the yopical antipsychotic clozapine (Matsumoto et al., 1990; all alker et al., 1988). in the interval in fig. 19, si

agonist 8-hydroxydipropylaminotetralin, PCP, and the
atypical antipsychotic clozapine (Matsumoto et al., 1990;
Walker et al., 1988).
As illustrated in fig. 19, sigma receptor-binding affinity
(defined by [³H]DTG binding atypical antipsychotic clozapine (Matsumoto et al., 1990; alwalker et al., 1988).
Walker et al., 1988).
As illustrated in fig. 19, sigma receptor-binding affinity guidefined by $[^{3}H]DTG$ binding in rat brain) correlated t Walker et al., 1988).

As illustrated in fig. 19, sigma receptor-binding affinity

(defined by [³H]DTG binding in rat brain) correlated

highly with potency in this behavioral assay, for those

compounds that had suffic As illustrated in fig. 19, sigma receptor-binding affinity g
(defined by [³H]DTG binding in rat brain) correlated thighly with potency in this behavioral assay, for those the
compounds that had sufficient activity to de (defined by $[{}^{3}H]DTG$ binding in rat brain) correlated thighly with potency in this behavioral assay, for those the compounds that had sufficient activity to derive an ED₅₀. yo This highly significant correlation ($r =$ highly with potency in this behavioral assay, for those tompounds that had sufficient activity to derive an ED₅₀.
This highly significant correlation $(r = 0.94)$ suggested ethat sigma receptors mediate the dystonic actio compounds that had sufficient activity to derive an EI
This highly significant correlation $(r = 0.94)$ sugges
that sigma receptors mediate the dystonic actions
these ligands in the red nucleus. The only compou
with high bi This highly significant correlation $(r = 0.94)$ suggested ethat sigma receptors mediate the dystonic actions of these ligands in the red nucleus. The only compound is with high binding affinity that failed to produce consi that sigma receptors mediate the dystonic actions of these ligands in the red nucleus. The only compound in with high binding affinity that failed to produce consistbent effects in this system was $(+)\text{-}3\text{-PPP}$, a compoun these ligands in the red nucleus. The only compound
with high binding affinity that failed to produce consist-
ent effects in this system was $(+)$ -3-PPP, a compound
that also lacked efficacy in other assays in which high
 with high binding affinity that failed to produce consist-
ent effects in this system was $(+)$ -3-PPP, a compound va
that also lacked efficacy in other assays in which high
formulations were found between sigma binding and ent effects in this system was (+)-3-PPP, a compound v
that also lacked efficacy in other assays in which high
froorrelations were found between sigma binding and po-
itency, i.e., the guinea pig ileum and PPI turnover (Bo that also lacked efficacy in other assays in which high forcerelations were found between sigma binding and po-
tency, i.e., the guinea pig ileum and PPI turnover (Bowen m
et al., 1990b; Campbell et al., 1989). These findi tency, i.e., the guinea pig ileum and PPI turnover (Bowen
et al., 1990b; Campbell et al., 1989). These findings thus
support the biological relevance of sigma-binding sites
and suggest the same mode of action at the recept et al., 1990b; Campbell et al., 1989). These findings thus
support the biological relevance of sigma-binding sites
and suggest the same mode of action at the receptor for
the compounds tested. These data are also consisten support the biological relevance of sigma-binding sites
and suggest the same mode of action at the receptor for
the compounds tested. These data are also consistent
with sigma actions in the guinea pig ileum and PPI
turnov and suggest the same mode of action at the receptor f
the compounds tested. These data are also consister
with sigma actions in the guinea pig ileum and Pl
turnover where haloperidol, DTG, and the (+)-opiat
all had similar e compounds tested. These data are also consistent
th sigma actions in the guinea pig ileum and PPI
rnover where haloperidol, DTG, and the (+)-opiates
had similar actions, presumably acting as agonists.
Further support for

with sigma actions in the guinea pig ileum and PPI sensitive turnover where haloperidol, DTG, and the $(+)$ -opiates stages.
all had similar actions, presumably acting as agonists. It are Further support for the notion that turnover where haloperidol, DTG, and the $(+)$ -opiates
all had similar actions, presumably acting as agonists.
Further support for the notion that sigma receptors
mediate the effects observed in these experiments stem
from all had similar actions, presumably acting as agonists.
Further support for the notion that sigma receptors numediate the effects observed in these experiments stem is
from developmental studies of this phenomenon. Sigma-
 Further support for the notion that sigma receptors
mediate the effects observed in these experiments stem
from developmental studies of this phenomenon. Sigma-
binding parameters were determined in young adult rats
(2-3 m mediate the effects observed in these experiments stem
from developmental studies of this phenomenon. Sigma-
binding parameters were determined in young adult rats
(2-3 months old) and middle-aged rats (5-6 months old). la binding parameters were determined in young adult rats $(2-3$ months old) and middle-aged rats $(5-6$ months old).
Scatchard analyses revealed that the density and affinity of receptors labeled with $[^{3}H]DTG$ was markedl binding parameters were determined in young adult rats mediate (2-3 months old) and middle-aged rats (5-6 months old). larly su
Scatchard analyses revealed that the density and affinity neurons
of receptors labeled with (2–3 months old) and middle-aged rats (5–6 months old). larly
Scatchard analyses revealed that the density and affinity neu
of receptors labeled with $[^{3}H]DTG$ was markedly greater sien
in the young adult rats (Matsumoto

SIGMA RECEPTORS 389
e $5HT_{1a}$ sigma ligands was observed. Compared to older animals,
and the voung adult rats showed an approximately 300% greater EPTORS
sigma ligands was observed. Compared to older animals,
young adult rats showed an approximately 300% greater
alteration in head angle following microinjection of DTG 389
sigma ligands was observed. Compared to older animals,
young adult rats showed an approximately 300% greater
alteration in head angle following microinjection of DTG
into the red nucleus and, again, an approximately 30 sigma ligands was observed. Compared to older animals,
young adult rats showed an approximately 300% greater
alteration in head angle following microinjection of DTG
into the red nucleus and, again, an approximately 300%
g sigma ligands was observed. Compared to older animals,
young adult rats showed an approximately 300% greater
alteration in head angle following microinjection of DTG
into the red nucleus and, again, an approximately 300%
g young adult rats showed an approximately 300% greater
alteration in head angle following microinjection of DTG
into the red nucleus and, again, an approximately 300%
greater circling response following microinjection into
 alteration in head angle following microinjection of DTG
into the red nucleus and, again, an approximately 300%
greater circling response following microinjection into
the substantia nigra (Matsumoto et al., 1989a). Hence, into the red nucleus and, again, an approximately 300%
greater circling response following microinjection into
the substantia nigra (Matsumoto et al., 1989a). Hence
the greater number and affinity of sigma receptors in
you greater circling response following micr
the substantia nigra (Matsumoto et al.,
the greater number and affinity of sigm
younger rats is consistent with the greate
effects of sigma ligands in these animals.
These age-relat the substantia nigra (Matsumoto et al., 1989a). Hence, the greater number and affinity of sigma receptors in younger rats is consistent with the greater physiological effects of sigma ligands in these animals. These age-re

correlations were found between sigma binding and po-
tency, i.e., the guinea pig ileum and PPI turnover (Bowen
micronipections of DTG in littermates resulted in a cor-
et al., 1990b; Campbell et al., 1989). These finding the greater number and affinity of sigma receptors in
younger rats is consistent with the greater physiological
effects of sigma ligands in these animals.
These age-related differences were further examined
in younger rats younger rats is consistent with the greater physiological
effects of sigma ligands in these animals.
These age-related differences were further examined
in younger rats by Hemstreet et al. (1990). Male rats
between the age effects of sigma ligands in these animals.
These age-related differences were further examined
in younger rats by Hemstreet et al. (1990). Male rats
between the ages of 30 and 90 days showed marked
variations in sigma bind These age-related differences were further examined
in younger rats by Hemstreet et al. (1990). Male rats
between the ages of 30 and 90 days showed marked
variations in sigma binding characterized by a U-shaped
function wi in younger rats by Hemstreet et al. (1990). Male rats
between the ages of 30 and 90 days showed marked
variations in sigma binding characterized by a U-shaped
function with a nadir at approximately 75 days. As shown
in fig between the ages of 30 and 90 days showed marked
variations in sigma binding characterized by a U-shaped
function with a nadir at approximately 75 days. As shown
in fig. 20, a similar pattern of responsiveness to rubral
mi variations in sigma binding characterized by a U-shaped
function with a nadir at approximately 75 days. As shown
in fig. 20, a similar pattern of responsiveness to rubral
microinjections of DTG in littermates resulted in a function with a nadir at approximately 75 days. As shown
in fig. 20, a similar pattern of responsiveness to rubral
microinjections of DTG in littermates resulted in a cor-
relation of 0.87 between sigma binding at various in fig. 20, a similar pattern of responsiveness to rubral microinjections of DTG in littermates resulted in a correlation of 0.87 between sigma binding at various ages and the potency of DTG in producing dystonia. Thus, th microinjections of DTG in littermates resulted in a correlation of 0.87 between sigma binding at various ages and the potency of DTG in producing dystonia. Thus, the extent of dystonia correlated not only with the potency relation of 0.87 between sigma binding at various age and the potency of DTG in producing dystonia. Thut the extent of dystonia correlated not only with the potency of the drug for sigma receptors but also with the sensiti stages. Extent of dystonia correlated not only with the po-
ncy of the drug for sigma receptors but also with the
nsitivity of the receptors at different developmental
ges.
It appears that the drugs microinjected into the red
cleu tency of the drug for sigma receptors but also with the sensitivity of the receptors at different developmental stages.
It appears that the drugs microinjected into the red nucleus had direct effects on this structure, bec

sensitivity of the receptors at different developmental
stages.
It appears that the drugs microinjected into the red
nucleus had direct effects on this structure, because
iontophoretic application of sigma ligands inhibits stages.
It appears that the drugs microinjected into the r
nucleus had direct effects on this structure, becau
iontophoretic application of sigma-ligands inhibits the
cells. The alterations in posture produced by the sigm
 It appears that the drugs microinjected into the red
nucleus had direct effects on this structure, because
iontophoretic application of sigma ligands inhibits these
cells. The alterations in posture produced by the sigma-
 nucleus had direct effects on this structure, because
iontophoretic application of sigma ligands inhibits these
cells. The alterations in posture produced by the sigma-
mediated inhibition of rubral neurons are not particu iontophoretic application of sigma ligands inhibits thes
cells. The alterations in posture produced by the sigma
mediated inhibition of rubral neurons are not particu
larly surprising because other means of inhibiting rubr cells. The alterations in posture produced by the sigma-
mediated inhibition of rubral neurons are not particu-
larly surprising because other means of inhibiting rubral
neurons also cause postural changes. For example, tr

 $(+)$ -PENT З DEX SKF 10.047 **BD614** Log **Ki** [HJDTG (rat) 'OTG Log ED50 Dystonia (nmol)
Log ED50 Dystonia (nmol)
Ween potency in displacing (*HII) 0
1.0 0.2 0.4 0.6 0.8 1.0
1.0 Log ED50 Dystonia (nmol)
FIG. 19. Relationship between potency in displacing [³H]DTG from
brain membranes and ED_{so} in producing torticollis following rubral FIG. 0.2 0.4 0.6 0.8 1.0
 **FIG. 19. Relationship between potency in displacing [³H]DTG from

rat brain membranes and ED_{so} in producing torticollis following rubral

microinjections. The significant correlation** $(r = 0.94)$ **be** 0.2 0.4 0.6 0.8
Log ED50 Dystonia (nmol) 1.0 Log EU50 UySiONa (NTOI)
Fig. 19. Relationship between potency in displacing [³H]DTG from
rat brain membranes and ED_{so} in producing torticollis following rubral
microinjections. The significant correlation ($r = 0.94$) b

microinjections. The significant
affinity and potency in this te
mediate the actions of these c
(+)-pentazocine; DEX, dextral
from Matsumoto et al., 1990.

rat brain membranes and ED_{so} in producing torticollis following rubral
microinjections. The significant correlation $(r = 0.94)$ between binding
affinity and potency in this test suggests that sigma receptors may
mediate **branch from rats of various ages and the degree of torticollis produced**
branes from rats of various ages and the degree of torticollis produced
by a microinjection of DTG in the red nucleus. Higher levels of sigma **by a microinjection of DTG in the red nucleus. Higher levels of sigma**
branes from rats of various ages and the degree of torticollis produced
by a microinjection of DTG in the red nucleus. Higher levels of sigma
binding **biound (motong)**
FIG. 20. Relationship between specifically bound [³H]DTG mem-
branes from rats of various ages and the degree of torticollis produced
by a microinjection of DTG in the red nucleus. Higher levels of sigm **produced** by a microinjection of DTG in the red nucleus. Higher levels of sigma
binding at various ages correlated highly with efficacy of DTG in
producing the behavioral effect; $r = 0.87$. Data from Hemstreet et al.,
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Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

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the inhibitory γ -aminobutyric acid mimetic muscimol the night (Matsumoto and Walker, unpublished observations), and mine ((Matsumoto and Walker, unpublished observations), and mine (Goldstein et al., 1989).
a similar although long-lasting change in head posture BMY 14802 was also found to decrease dopamine walker F
the inhibitory γ -aminobutyric acid mimetic muscimol
(Matsumoto and Walker, unpublished observations), and
a similar although long-lasting change in head posture
was induced in primates with rubral lesions (Bat the inhibitory γ -aminobutyric acid mimetic muscimol
(Matsumoto and Walker, unpublished observations), and
a similar although long-lasting change in head posture
was induced in primates with rubral lesions (Battista et the inhibitory γ -aminobutyric acid mimetic muscimol (Matsumoto and Walker, unpublished observations), and a similar although long-lasting change in head posture was induced in primates with rubral lesions (Battista et (Matsumoto and Walker, unpublished observations), and min
a similar although long-lasting change in head posture B
was induced in primates with rubral lesions (Battista et leve
al., 1976; Carpenter, 1956). These findings i a similar although long-lasting change in head posture
was induced in primates with rubral lesions (Battista et
al., 1976; Carpenter, 1956). These findings indicate that
inhibition of the red nucleus, either permanently (b was induced in primates with rubral lesions (Battista et al., 1976; Carpenter, 1956). These findings indicate that inhibition of the red nucleus, either permanently (by lesion) or temporarily (by microinjecting inhibitory al., 1976; Carpenter, 1956). These findings indicate that moves inhibition of the red nucleus, either permanently (by 19 lesion) or temporarily (by microinjecting inhibitory substances), leads to changes in the motor syste inhibition of the red nucleus, either permanently (by lesion) or temporarily (by microinjecting inhibitory substances), leads to changes in the motor system. In fact, experiments dating back to the time of Sherrington have stances), leads to changes in the motor system. In fact, experiments dating back to the time of Sherrington have suggested that an important function of the red nucleus is the maintenance of muscle tone (Massion et al., 19 experiments dating back to the time of Sherrington have
suggested that an important function of the red nucleus
is the maintenance of muscle tone (Massion et al., 1967;
Ingram et al., 1934).
Sigma receptors on neurons in t periments dating back to the time of Sherrington have
ggested that an important function of the red nucleus
the maintenance of muscle tone (Massion et al., 1967;
gram et al., 1934).
Sigma receptors on neurons in the magnoc

suggested that an important function of the red nucleus re
is the maintenance of muscle tone (Massion et al., 1967;
Ingram et al., 1934).
Sigma receptors on neurons in the magnocellular division of the red nucleus appear is the maintenance of muscle tone (Massion et al., 1967;

Ingram et al., 1934).

Sigma receptors on neurons in the magnocellular division of the red nucleus appear to mediate the effects of

sigma drugs on posture. This ar Ingram et al., 1934).

Sigma receptors on neurons in the magnocellular di-

vision of the red nucleus appear to mediate the effects of

sigma drugs on posture. This area receives its major

input from the nucleus interpos Sigma receptors on neurons in the magnocellular division of the red nucleus appear to mediate the effects of sigma drugs on posture. This area receives its major input from the nucleus interpositus of the cerebellum (Dekke sigma drugs on posture. This area receives its major input from the nucleus interpositus of the cerebellum (Dekker, 1981; Massion, 1967). It affects movement through the efferent projection of the rubrospinal tract to the sigma drugs on posture. This area receives its major
input from the nucleus interpositus of the cerebellum
(Dekker, 1981; Massion, 1967). It affects movement
through the efferent projection of the rubrospinal tract
to the input from the nucleus interpositus of the cerebellum
(Dekker, 1981; Massion, 1967). It affects movement
through the efferent projection of the rubrospinal tract
to the intermediate levels of the spinal cord, the nucleus
i (Donaer, 1991, Massion, 1997). It directs increased
through the efferent projection of the rubrospinal tract
to the intermediate levels of the spinal cord, the nucleus
interpositus, and the lateral reticular nucleus (Brown to the intermediate levels of the spinal cord, the nucleus interpositus, and the lateral reticular nucleus (Brown, 1974; Flumerfelt and Hrycyshyn, 1985; Massion, 1967; Flumerfelt and Hrycyshyn, 1985; Massion, 1967; Flumer 1974; Flumerfelt and Hrycyshyn, 1985; Massion, 1967;

Robinson et al., 1987). Although current investigators

have stressed the role of the red nucleus in the regulation

of distal and proximal musculature (Ghez, 1975; Gi of distal and proximal musculature (Ghez, 1975; Gibson
et al., 1985a,b; Kennedy, 1987; McCurdy et al., 1987), it
also influences axial structures, e.g., the neck muscles,
also influences axial structures, e.g., the neck mu Robinson et al., 1987). Although current investigators have stressed the role of the red nucleus in the regulation of distal and proximal musculature (Ghez, 1975; Gibson et al., 1985a,b; Kennedy, 1987; McCurdy et al., 1987 have stressed the role of the red nucleus in the regulation
of distal and proximal musculature (Ghez, 1975; Gibson
et al., 1985a,b; Kennedy, 1987; McCurdy et al., 1987), it
also influences axial structures, e.g., the neck of distal and proximal musculature (Ghez, 1975; G:
et al., 1985a,b; Kennedy, 1987; McCurdy et al., 198
also influences axial structures, e.g., the neck mu
through rubrospinal projections to the cervical
(Huisman et al., 19 et al., 1985a,b; Kennedy, 1987; McCurdy et al., 1987), it
also influences axial structures, e.g., the neck muscles,
through rubrospinal projections to the cervical cord
(Huisman et al., 1981). The anatomical, electrophysi also influences axial structures, e.g., the neck muscles, through rubrospinal projections to the cervical cord (Huisman et al., 1981). The anatomical, electrophysiological, and behavioral evidence thus suggest that sigma r through rubrospinal project
(Huisman et al., 1981). The
logical, and behavioral evider
receptors in the red nucleus
that regulates muscle tone.
b. MOTOR ACTIONS OF SIG pical, and behavioral evidence thus suggest that sigm
ceptors in the red nucleus function as part of a circui
at regulates muscle tone.
b. MOTOR ACTIONS OF SIGMA LIGANDS IN THE SUE
ANTIA NIGRA. This presence of sigma recep

logical, and behavioral evidence thus suggest that sigma
receptors in the red nucleus function as part of a circuit
that regulates muscle tone.
b. MOTOR ACTIONS OF SIGMA LIGANDS IN THE SUB-
STANTIA NIGRA. This presence of receptors in the red nucleus function as part of a circuit
that regulates muscle tone.
b. MOTOR ACTIONS OF SIGMA LIGANDS IN THE SUB-
sTANTIA NIGRA. This presence of sigma receptors in the
substantia nigra also suggests th that regulates muscle tone.

b. MOTOR ACTIONS OF SIGMA LIGANDS IN THE SUB-

STANTIA NIGRA. This presence of sigma receptors in the

substantia nigra also suggests their role in voluntary

movement. This possibility has bee b. MOTOR ACTIONS OF SIGMA LIGANDS IN THE SUB-

STANTIA NIGRA. This presence of sigma receptors in the

substantia nigra also suggests their role in voluntary

movement. This possibility has been confirmed in be-

havioral STANTIA NIGRA. This presence of sigma receptors in the substantia nigra also suggests their role in voluntary movement. This possibility has been confirmed in behavioral experiments, which showed that sigma ligands act in substantia nigra also suggests their role in voluntary
movement. This possibility has been confirmed in be-
havioral experiments, which showed that sigma ligands
act in the nigra to increase motor activity (Goldstein et
a movement. This possibility has been confirmed in behavioral experiments, which showed that sigma ligands act in the nigra to increase motor activity (Goldstein et al., 1989). Nigral microinjections of $(+)$ -pentazocine and havioral experiments, which showed that sigma ligand
act in the nigra to increase motor activity (Goldstein e
al., 1989). Nigral microinjections of (+)-pentazocine and
DTG induced significant contralateral circling, yet th act in the nigra to increase motor activity (Goldstein et

al., 1989). Nigral microinjections of $(+)$ -pentazocine and

DTG induced significant contralateral circling, yet this

effect did not occur in animals with 6-hydro al., 1989). Nigral microinjections of $(+)$ -pentazocine and
DTG induced significant contralateral circling, yet this
effect did not occur in animals with 6-hydroxydopamine
lesions of ascending dopamine tracts (Goldstein et DTG induced significant contralateral circling, yet the effect did not occur in animals with 6-hydroxydopamine lesions of ascending dopamine tracts (Goldstein et al 1989). It thus appeared that the circling behavior we med mine. mediated mainly by sigma-stimulated release of dopa-
mine.
c. DOPAMINE-RELEASING ACTION OF SIGMA LIGANDS.
Biochemical data also suggest that sigma ligands induce

1989). It thus appeared that the circling behavior was
mediated mainly by sigma-stimulated release of dopa-
mine.
c. DOPAMINE-RELEASING ACTION OF SIGMA LIGANDS. H
Biochemical data also suggest that sigma ligands induce
th mediated mainly by sigma-stimulated release of dopa-
mine.
c. DOPAMINE-RELEASING ACTION OF SIGMA LIGANDS.
Biochemical data also suggest that sigma ligands induce
the release of dopamine from central neurons. Berkowitz
(197 mine.

c. DOPAMINE-RELEASING ACTION OF SIGMA LIGANDS.

Biochemical data also suggest that sigma ligands induce

the release of dopamine from central neurons. Berkowitz

(1974) found that (+)-pentazocine decreases brain le c. DOPAMINE-RELEASING ACTION OF SIGMA LIGANDS.
Biochemical data also suggest that sigma ligands induce
the release of dopamine from central neurons. Berkowitz
(1974) found that (+)-pentazocine decreases brain levels
of do Biochemical data also suggest that sigma ligands induce
the release of dopamine from central neurons. Berkowitz
(1974) found that (+)-pentazocine decreases brain levels
of dopamine in animals treated with the dopamine syn (1974) found that $(+)$ -pentazocine decreases brain levels
of dopamine in animals treated with the dopamine syn-
thesis inhibitor α -methyl-tyrosine. Because this effect
cannot be attributed to decreased synthesis, a dop (1974) found that $(+)$ -pentazocine decreases brain levels
of dopamine in animals treated with the dopamine syn-
thesis inhibitor α -methyl-tyrosine. Because this effect
cannot be attributed to decreased synthesis, a dop of dopamine in animals treated with the dopamine s;
thesis inhibitor α -methyl-tyrosine. Because this eff
cannot be attributed to decreased synthesis, a dopami
releasing action appears likely. This interpretation
ceives thesis inhibitor α -methyl-tyrosine. Because this effect
cannot be attributed to decreased synthesis, a dopamine-
releasing action appears likely. This interpretation re-
ceives support from the finding that unilateral cannot be attributed to decreased synthesis, a dopamine-
releasing action appears likely. This interpretation re-
ceives support from the finding that unilateral microin-
diections of $(+)$ -pentazocine in the substantia ni

ET AL.
the nigrostriatal dopamine system with 6-hydroxy
mine (Goldstein et al., 1989). ET AL.
the nigrostriatal dopamine sys
mine (Goldstein et al., 1989).
BMY 14802 was also foun

AL.

e nigrostriatal dopamine system with 6-hydroxydopa-

ine (Goldstein et al., 1989).

BMY 14802 was also found to decrease dopamine

vels in rats and to increase the levels of the dopamine the nigrostriatal dopamine system with 6-hydroxydopa-
mine (Goldstein et al., 1989).
BMY 14802 was also found to decrease dopamine
levels in rats and to increase the levels of the dopamine
metabolite 3,4 dihydroxyphenylace the nigrostriatal dopamine system with 6-hydroxydopa-
mine (Goldstein et al., 1989).
BMY 14802 was also found to decrease dopamine
levels in rats and to increase the levels of the dopamine
metabolite 3,4 dihydroxyphenylace mine (Goldstein et al., 1989).

BMY 14802 was also found to decrease dopamine

levels in rats and to increase the levels of the dopamine

metabolite 3,4 dihydroxyphenylacedic acid (Taylor et al.,

1990). These findings sug BMY 14802 was also found to decrease dopamine
levels in rats and to increase the levels of the dopamine
metabolite 3,4 dihydroxyphenylacedic acid (Taylor et al.,
1990). These findings suggest that it caused the release
of metabolite 3,4 dihydroxyphenylacedic acid (Taylor et al., 1990). These findings suggest that it caused the release of dopamine, although an alteration in synthesis cannot be ruled out from these observations.
(+)-3-PPP nea etabolite 3,4 dihydroxyphenylacedic acid (Taylor et al., 90). These findings suggest that it caused the release dopamine, although an alteration in synthesis cannot ruled out from these observations.
(+)-3-PPP nearly doub

1990). These findings suggest that it caused the release
of dopamine, although an alteration in synthesis cannot
be ruled out from these observations.
 $(+)-3$ -PPP nearly doubled the rate of spontaneous
release of $[^{3}H]$ do of dopamine, although an alteration in synthesis cannot
be ruled out from these observations.
(+)-3-PPP nearly doubled the rate of spontaneous
release of [³H]dopamine from preloaded striatal slices
(Arbilla and Langer, 1 be ruled out from these observations.

(+)-3-PPP nearly doubled the rate of spontaneou

release of [³H]dopamine from preloaded striatal slice

(Arbilla and Langer, 1984). In contrast, it slightly re

duced the release of (+)-3-PPP nearly doubled the rate of spontaneous
release of [³H]dopamine from preloaded striatal slices
(Arbilla and Langer, 1984). In contrast, it slightly re-
duced the release of dopamine induced by electrical stim-
 (Arbilla and Langer, 1984). In contrast, it slightly re-
duced the release of dopamine induced by electrical stim-
ulation (Arbilla and Langer, 1984). These findings were
originally interpreted as reflecting a dopamine aut (Arbilla and Langer, 1984). In contrast, it slightly re-
duced the release of dopamine induced by electrical stim-
ulation (Arbilla and Langer, 1984). These findings were
originally interpreted as reflecting a dopamine au duced the release of dopamine induced by electrical stimulation (Arbilla and Langer, 1984). These findings were originally interpreted as reflecting a dopamine autoreceptor agonist action of $(+)$ -3-PPP. However, because $(+$ ulation (Arbilla and Langer, 1984). These findings were
originally interpreted as reflecting a dopamine autore-
ceptor agonist action of (+)-3-PPP. However, because
(+)-3-PPP is approximately 150 times more potent at
sigma originally interpreted as reflecting a dopamine autore-
ceptor agonist action of $(+)$ -3-PPP. However, because
 $(+)$ -3-PPP is approximately 150 times more potent at
sigma receptors than at dopamine receptors, a sigma
action (+)-3-PPP is approximately 150 times more potent at sigma receptors than at dopamine receptors, a sigma action in these assays is certainly possible. Some support for this notion stems from the weak effects of $(-)$ -sulpir (+)-3-PPP is approximately 150 times more potent at sigma receptors than at dopamine receptors, a sigma action in these assays is certainly possible. Some support for this notion stems from the weak effects of $(-)$ -sulpir sigma receptors than at dopamine receptors, a sigm
action in these assays is certainly possible. Some suppor
for this notion stems from the weak effects of $(-)$
sulpiride in this experiment, because this compound is
poten tion in these assays is certainly possible. Some support
 $\mathbf r$ this notion stems from the weak effects of $(-)$ -

lpiride in this experiment, because this compound is a

tent dopamine D_2 antagonist lacking sigma activ

for this notion stems from the weak effects of $(-)$ -
sulpiride in this experiment, because this compound is a
potent dopamine D_2 antagonist lacking sigma activity.
In the striatal slice preparation described above, it sulpiride in this experiment, because this compound is a potent dopamine D_2 antagonist lacking sigma activity.
In the striatal slice preparation described above, it has been found that the spontaneous release of dopami potent dopamine D_2 antagonist lacking sigma activity.
In the striatal slice preparation described above, it has
been found that the spontaneous release of dopamine is
reduced by the presence of tetrodotoxin or the abse In the striatal slice preparation described above, it has
been found that the spontaneous release of dopamine is
reduced by the presence of tetrodotoxin or the absence
of calcium (Dismukes and Mulder, 1977; Giorguieff et
a been found that the spontaneous release of dopamine is
reduced by the presence of tetrodotoxin or the absence
of calcium (Dismukes and Mulder, 1977; Giorguieff et
al., 1977). These findings were surprising because they
sug of calcium (Dismukes and Mulder, 1977; Giorguieff et al., 1977). These findings were surprising because they suggest an action potential-stimulated release in a preparation free of external stimulation (Starke, 1978). This al., 1977). These findings were surprising because they suggest an action potential-stimulated release in a preparation free of external stimulation (Starke, 1978). This, together with the inhibitory electrophysiological e suggest an action potential-stimulated release in a preparation free of external stimulation (Starke, 1978). This, together with the inhibitory electrophysiological effects of sigma compounds and the inhibition of electric aration free of external stimulation (Starke,
together with the inhibitory electrophysiolof
of sigma compounds and the inhibition of
evoked dopamine release by $(+)$ -3-PPP,
questions about the basis for these effects.
d. T gether with the inhibitory electrophysiological effects
sigma compounds and the inhibition of electrically
oked dopamine release by (+)-3-PPP, raises many
estions about the basis for these effects.
d. THE (+)-3-PPP ENIGMA.

of sigma compounds and the inhibition of electrically
evoked dopamine release by $(+)$ -3-PPP, raises many
questions about the basis for these effects.
d. THE $(+)$ -3-PPP ENIGMA. The effects discussed
above typify the confus evoked dopamine release by $(+)$ -3-PPP, raises many
questions about the basis for these effects.
d. THE $(+)$ -3-PPP ENIGMA. The effects discussed
above typify the confusing effects of $(+)$ -3-PPP. Apart
from its behavior in questions about the basis for these effects.

d. THE $(+)$ -3-PPP ENIGMA. The effects discuss

above typify the confusing effects of $(+)$ -3-PPP. Ap

from its behavior in binding assays, the effects of $(+)$

PPP relative to d. THE $(+)$ -3-PPP ENIGMA. The effects discussed
above typify the confusing effects of $(+)$ -3-PPP. Apart
from its behavior in binding assays, the effects of $(+)$ -3-
PPP relative to the sigma receptor may be best charac-
te above typify the confusing effects of $(+)$ -3-PPP. Apart
from its behavior in binding assays, the effects of $(+)$ -3-
PPP relative to the sigma receptor may be best charac-
terized as mysterious. In all three assay systems from its behavior in binding assays, the effects of $(+)$ -3-
PPP relative to the sigma receptor may be best charac-
terized as mysterious. In all three assay systems dis-
cussed above in which binding affinity of a series PPP relative to the sigma receptor may be best characterized as mysterious. In all three assay systems discussed above in which binding affinity of a series of ligands correlates well with assay potency (PPI turnover, guin terized as mysterious. In all three assay systems discussed above in which binding affinity of a series of ligands correlates well with assay potency (PPI turnover, guinea pig ileum, and rubral dystonia), (+)-3-PPP has sho cussed above in which binding affinity of a series of
ligands correlates well with assay potency (PPI turnover,
guinea pig ileum, and rubral dystonia), (+)-3-PPP has
shown neither clear agonist nor antagonist actions. This guinea pig ileum, and rubral dystonia), $(+)$ -3-PPP has
shown neither clear agonist nor antagonist actions. This
is a serious problem in view of the high sigma-binding
affinity of $(+)$ -3-PPP and cannot be ignored.
It is po ceptor agoma action of $(+)$ -3-PPP. However, because
eliginal action in these assays is certainly possible. Some support
sigma receptors than at dopamine receptors, a sigma
action in these assays is certainly possible. Som

is a serious problem in view of the high sigma-binding
affinity of $(+)$ -3-PPP and cannot be ignored.
It is possible that the sigma actions of $(+)$ -3-PPP are
masked by its actions at other receptors. Developed by
Hjorth an affinity of $(+)$ -3-PPP and cannot be ignored.
It is possible that the sigma actions of $(+)$ -3-PPP are
masked by its actions at other receptors. Developed by
Hjorth and coworkers, $(+)$ -3-PPP was originally thought
to be a It is possible that the sigma actions of $(+)$ -3-PPP are
masked by its actions at other receptors. Developed by
Hjorth and coworkers, $(+)$ -3-PPP was originally thought
to be a dopamine autoreceptor agonist (reviewed by Cla masked by its actions at other receptors. Developed by
Hjorth and coworkers, $(+).3$ -PPP was originally thought
to be a dopamine autoreceptor agonist (reviewed by Clark
et al., 1985b). $(+).3$ -PPP produced marked suppression
o Hjorth and coworkers, $(+)$ -3-PPP was originally thought
to be a dopamine autoreceptor agonist (reviewed by Clark
et al., 1985b). $(+)$ -3-PPP produced marked suppression
of locomotor activity, an effect that was blocked by
 to be a dopamine autoreceptor agonist (reviewed by Clie
et al., 1985b). (+)-3-PPP produced marked suppress
of locomotor activity, an effect that was blocked
pretreatment with haloperidol. Because the binding
agonists to do et al., 1985b). (+)-3-PPP produced marked suppression
of locomotor activity, an effect that was blocked by
pretreatment with haloperidol. Because the binding of
agonists to dopamine autoreceptors inhibits dopami-
nergic tr of locomotor activity, an effect that was blocked by
pretreatment with haloperidol. Because the binding of
agonists to dopamine autoreceptors inhibits dopami-
nergic transmission, resulting in profound effects on
motor fun pretreatment with haloperidol. Because the binding of agonists to dopamine autoreceptors inhibits dopaminergic transmission, resulting in profound effects on motor function, the inhibition of locomotor activity produced by agonists to dopamine autoreceptors inhibits dopami-
nergic transmission, resulting in profound effects on
motor function, the inhibition of locomotor activity pro-
duced by $(+)$ -3-PPP, along with its various other in vivo nergic transmission, resulting in profound effects on
motor function, the inhibition of locomotor activity pro-
duced by (+)-3-PPP, along with its various other in vive
effects, was thought to result from an agonist action

sIGMA RECE
binding studies with $[{}^{3}H](+)$ -3-PPP showed its marked cantinity for sigma receptors and its relatively low binding m sigma RECE
binding studies with $[{}^{3}H](+)$ -3-PPP showed its marked cantinity for sigma receptors and its relatively low binding m
affinity for dopamine receptors (IC₆₀ against $[{}^{3}H]$ dopa-ne sigm
binding studies with $[{}^3H](+)$ -3-PPP showed its mariaffinity for sigma receptors and its relatively low bind
affinity for dopamine receptors (IC₅₀ against $[{}^3H]$ do
mine in rat striatal membranes = 5 μ M, cf. Se binding studies with $[{}^3H](+)-3$ -PPP showed its marked
affinity for sigma receptors and its relatively low binding
affinity for dopamine receptors (IC₅₀ against $[{}^3H]$ dopa-
mine in rat striatal membranes = 5 μ M, cf binding studies with $[{}^{3}H](+)-3$ -PPP showed its marked
affinity for sigma receptors and its relatively low binding
affinity for dopamine receptors (IC₆₀ against $[{}^{3}H]$ dopa-
mine in rat striatal membranes = 5 μ M, 1987). finity for dopamine receptors $(IC_{50}$ against $[^{3}H]$ dopanine in rat striatal membranes = 5μ M, cf. Seeman, 1981;
 ${}_{50}$ against $[^{3}H]$ spiperone = 1.7 μ M, Wikstrom et al., in

87).

In spite of the relatively p

mine in rat striatal membranes = 5 μ M, cf. Seeman, 1981;
IC₅₀ against [³H]spiperone = 1.7 μ M, Wikstrom et al.,
1987).
In spite of the relatively poor affinity of (+)-3-PPP for
³H]dopamine-binding sites in vitr IC₅₀ against [³H]spiperone = 1.7 μ M, Wikstrom et al., 1987).

In spite of the relatively poor affinity of (+)-3-PPP for

[³H]dopamine-binding sites in vitro, Clark et al. (1985b)

have maintained that (+)-3-PPP d 1987).

In spite of the relatively poor affinity of $(+)$ -3-PP

[³H]dopamine-binding sites in vitro, Clark et al. (19

have maintained that $(+)$ -3-PPP does act at dopa

autoreceptors, and certain behavioral and electrop
 In spite of the relatively poor affinity of $(+)$ -3-PPP for mal m
[³H]dopamine-binding sites in vitro, Clark et al. (1985b) can be
have maintained that $(+)$ -3-PPP does act at dopamine tarily r
autoreceptors, and certain [³H]dopamine-binding sites in vitro, Clark et al. (1985b) chave maintained that $(+)$ -3-PPP does act at dopamine tautoreceptors, and certain behavioral and electrophysi-
alogical effects of this compound support this cla have maintained that $(+)$ -3-PPP does act at dopamine tare autoreceptors, and certain behavioral and electrophysiological effects of this compound support this claim bec (Clark et al., 1985a; Essman and Woods, 1988). Altho autoreceptors, and certain behavioral and electrophysiological effects of this compound support this claim b
(Clark et al., 1985a; Essman and Woods, 1988). Although dits affinity for dopamine receptors is low, there may be ological effects of this compound support this claim becomes contorted, an affliction leading to premature (Clark et al., 1985a; Essman and Woods, 1988). Although death). The vast majority of dystonias are idiopathic its (Clark et al., 1985a; Essman and Woods, 1988). Although
its affinity for dopamine receptors is low, there may be
sufficient binding for some dopaminergic activity. This
idea receives some support from the instances when t its affinity for dopamine receptors is low, there may be
sufficient binding for some dopaminergic activity. This
idea receives some support from the instances when the
itications of $(+)$ -3-PPP have been antagonized by sul sufficient binding for some dopaminergic activity. This
idea receives some support from the instances when the
actions of $(+)$ -3-PPP have been antagonized by sulpiride,
a dopamine D_2 antagonist that lacks activity at s idea receives some support from the instances when the actions of $(+)$ -3-PPP have been antagonized by sulpiride, a dopamine D_2 antagonist that lacks activity at sigma receptors (cf. Clark et al., 1985b). Actions throug actions of $(+)$ -3-PPP have been antagonized by sulpirica dopamine D_2 antagonist that lacks activity at signer receptors (cf. Clark et al., 1985b). Actions through other receptors have also been suggested. For example, receptors (cf. Clark et al., 1985b). Actions through other
receptors have also been suggested. For example, $(+)$ -3-
PPP has also been found to inhibit phospholipid break-
down through the α_1 -adrenergic receptor and th carinic receptor (Fowler and Thorell, 1987).

Because a number of reports have brought the speci-
ficity of $(+)$ -3-PPP to question, its failures to produce PPP has also been found to inhibit phospholipid break-
down through the α_1 -adrenergic receptor and the mus-
carinic receptor (Fowler and Thorell, 1987).
Because a number of reports have brought the speci-
ficity of (+ down through the α_1 -adrenergic receptor and the mus-
carinic receptor (Fowler and Thorell, 1987). tor
Because a number of reports have brought the speci-
ficity of $(+)$ -3-PPP to question, its failures to produce
the e carinic receptor (Fowler and Thorell, 1987). tonically to be consider the specificity of $(+)$ -3-PPP to question, its failures to produce occupate the expected actions in sigma biological assays must be or vinterpreted wit Because a number of reports have brought the specificity of $(+)$ -3-PPP to question, its failures to produce octor of the expected actions in sigma biological assays must be or interpreted with caution. And certainly, thes ficity of $(+)$ -3-PPP to question, its failures to produce
the expected actions in sigma biological assays must be
interpreted with caution. And certainly, these failures in
themselves do not negate the data suggesting tha the expected actions in sigma biological assays must be ontertainty, these failures in an intermselves do not negate the data suggesting that the $\frac{1}{10}$ for sigma receptor is biologically relevant. At the same time, i interpreted with caution. And certainly, these failures in and
themselves do not negate the data suggesting that the
sigma receptor is biologically relevant. At the same time,
it must be recognized that understanding the themselves do not negate the data suggesting that the sigma receptor is biologically relevant. At the same tin
it must be recognized that understanding the nature
the biological effects of sigma receptor occupation
(+)-3-P sigma receptor is biologically relevant. At the same time,
it must be recognized that understanding the nature of
the biological effects of sigma receptor occupation by
 $(+)$ -3-PPP is necessary if we are to gain a full und $(+)$ -3-PPP is necessary if we are to gain a full under-Following is necessary if we are to gain a full under
anding of the sigma receptor.
VI. Clinical Implications and Possibilities
Following the discovery that sigma receptors bind anti-
ychotic drugs came the expected intere

standing of the sigma receptor.

VI. Clinical Implications and Possibilities

Following the discovery that sigma receptors bind ant

psychotic drugs came the expected interest in the poss

ble clinical significance of sigm VI. Clinical Implications and Possibilities
Following the discovery that sigma receptors bind ant
psychotic drugs came the expected interest in the poss-
ble clinical significance of sigma ligands. Here the ques-
tion of w VI. Clinical Implications and Possibilities

Following the discovery that sigma receptors bind anti-

psychotic drugs came the expected interest in the possi-

ble clinical significance of sigma ligands. Here the ques-

ac Following the discovery that sigma receptors bind anti-
psychotic drugs came the expected interest in the possi-
ble clinical significance of sigma ligands. Here the ques-
tion of which effects of antipsychotic drugs may b psychotic drugs came the expected interest in the possible clinical significance of sigma ligands. Here the question of which effects of antipsychotic drugs may be mediated by sigma receptors becomes the central focus.
The be clinical significance of sigma ligands. Here the question of which effects of antipsychotic drugs may be mediated by sigma receptors becomes the central focus.
The high concentration of sigma receptors in the motor side mediated by sigma receptors becomes the central for
The high concentration of sigma receptors in the more
system immediately raised the issue of the motor seffects of antipsychotic drugs. Simultaneously, the are
psychotic The high concentration of sigma receptors in the motor
system immediately raised the issue of the motor side
effects of antipsychotic drugs. Simultaneously, the anti-
psychotic activity of sigma-active drugs such as halop system immediately raised the issue of the motor side
effects of antipsychotic drugs. Simultaneously, the anti-
psychotic activity of sigma-active drugs such as haloper-
idol, coupled with the sigma-activity of rimcazole effects of antipsychotic drugs. Simultaneously, the anti-
psychotic activity of sigma-active drugs such as haloper-
idol, coupled with the sigma-activity of rimcazole (a
putative antipsychotic), raised the important questi psychotic activity of sigma-active drugs such as haloperidol, coupled with the sigma-activity of rimcazole (a structure antipsychotic), raised the important question of the possibility of novel sigma-binding antipsychotic idol, coupled with the sigma-activity of rimcazole (a putative antipsychotic), raised the important question of between the possibility of novel sigma-binding antipsychotic with drugs. Unfortunately, however, few human dat putative antipsychotic), raised the in
the possibility of novel sigma-bin
drugs. Unfortunately, however, fev
available, so the following discussion
on animal models of these disorders.
A Sigma Peasators and Mousmant F *A.* Sigma Pointing antipsychotic drugs. Unfortunately, however, few human data are available, so the following discussion is necessarily based on animal models of these disorders.
A. Sigma Receptors and Movement Disorders

on animal models of these disorders.

A. Sigma Receptors and Movement Disorders in Man

Before discussing the evidence for a role of sigma

receptors in movement disorders, brief descriptions of due

the clinical features A. Sigma Receptors and Movement Disorders in Man
Before discussing the evidence for a role of sigma
receptors in movement disorders, brief descriptions of c
the clinical features of the relevant diseases are presented
alon A. Sigma Receptors and Movement Disorders in Man
Before discussing the evidence for a role of sigma
receptors in movement disorders, brief descriptions of
the clinical features of the relevant diseases are presented
along Before discussing the evidence for a role of sigma
receptors in movement disorders, brief descriptions of
the clinical features of the relevant diseases are presented
along with current models of the pathophysiology
though receptors in movement disorders, brief descriptions of
the clinical features of the relevant diseases are presented
along with current models of the pathophysiology
thought to underlie these states. Although connections
be

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can be established, this discussion is limited to the two

most prominent candidates: dystonia and tardive dyski-EPTORS
can be established, this discussion is limited to the ty
most prominent candidates: dystonia and tardive dysl
nesia. nesia. ¹ be established, this discussion is limited to the two
 1. Background. a. DYSTONIA. Dystonias are disorders
 1. Background. a. DYSTONIA. Dystonias are disorders

volving sustained, involuntary muscle contractions

can be established, this discussion is limited to the two most prominent candidates: dystonia and tardive dyskinesia.

1. Background. a. DYSTONIA. Dystonias are disorders involving sustained, involuntary muscle contraction most prominent candidates: dystonia and tardive dyskinesia.

1. Background. a. DYSTONIA. Dystonias are disorders

involving sustained, involuntary muscle contractions

that result in abnormal posture and interfere with nor nesia.

1. Background. a. DYSTONIA. Dystonias are disorders

involving sustained, involuntary muscle contractions

that result in abnormal posture and interfere with nor-

mal motor function (Jankovic and Fahn, 1988). They 1. Background. a. DYSTONIA. Dystonias are disord
involving sustained, involuntary muscle contractic
that result in abnormal posture and interfere with n
mal motor function (Jankovic and Fahn, 1988). The
can be focal, as in involving sustained, involuntary muscle contraction
that result in abnormal posture and interfere with nor
mal motor function (Jankovic and Fahn, 1988). They
can be focal, as in torticollis (in which the neck involun
taril that result in abnormal posture and interfere with normal motor function (Jankovic and Fahn, 1988). They can be focal, as in torticollis (in which the neck involuntarily rotates), or they can be progressive and generalized mal motor function (Jankovic and Fahn, 1988). They
can be focal, as in torticollis (in which the neck involun-
tarily rotates), or they can be progressive and generalized,
as in torsion dystonia (in which the whole body sl can be focal, as in torticollis (in which the neck involuntarily rotates), or they can be progressive and generalized, as in torsion dystonia (in which the whole body slowly becomes contorted, an affliction leading to prem tarily rotates), or they can be progressive and generalized,
as in torsion dystonia (in which the whole body slowly
becomes contorted, an affliction leading to premature
death). The vast majority of dystonias are idiopathi as in torsion dystonia (in which the whole body sk
becomes contorted, an affliction leading to prema
death). The vast majority of dystonias are idiopa
(Marsden 1982). Because autopsy and neuroima,
studies fail to reveal a becomes contorted, an affliction leading to premat
death). The vast majority of dystonias are idiopat
(Marsden 1982). Because autopsy and neuroimag
studies fail to reveal a consistent anatomical abnorm
ity, most investigat death). The vast majority of dystomas are idiopathic
(Marsden 1982). Because autopsy and neuroimaging
studies fail to reveal a consistent anatomical abnormal-
ity, most investigators assume that the primary dysfunc-
tion i studies fail to reveal a consistent anatomical abnormality, most investigators assume that the primary dysfunction is neurochemical. Torsion dystonia is familial, and recent findings showing the location of the defective g ity, most investigators assume that the primary dysfuntion is neurochemical. Torsion dystonia is familial, an recent findings showing the location of the defective geoffer hope for a better understanding of its biologic ba on is neurochemical. Torsion dystonia is familial, and
cent findings showing the location of the defective gene
fer hope for a better understanding of its biological
sis (Ozelius et al., 1989; Muller and Kupke, 1990).
The

recent findings showing the location of the defective gene
offer hope for a better understanding of its biological
basis (Ozelius et al., 1989; Muller and Kupke, 1990).
The most common symptomatic dystonias result from
the offer hope for a better understanding of its biological
basis (Ozelius et al., 1989; Muller and Kupke, 1990).
The most common symptomatic dystonias result from
the administration of neuroleptics, either as acute dys-
tonic ity, most investigators assume that the primary dystina-
tion is neurochemical. Torsion dystonia is familial, and
recent findings showing the location of the defective gene
offer hope for a better understanding of its bio The most common symptomatic dystonias result from
the administration of neuroleptics, either as acute dys-
tonic reactions or tardive dystonia (Burke et al., 1982;
Roos and Bruyn, 1988). Acute dystonic reactions tend to
oc the administration of neuroleptics, either as acute dystonic reactions or tardive dystonia (Burke et al., 1982; Roos and Bruyn, 1988). Acute dystonic reactions tend to occur primarily in young men and usually develop days tonic reactions or tardive dystonia (Burke et al., 1982;
Roos and Bruyn, 1988). Acute dystonic reactions tend to
occur primarily in young men and usually develop days
or weeks after initiation of neuroleptic therapy (Roos
 Roos and Bruyn, 1988). Acute dystonic reactions tend to occur primarily in young men and usually develop days or weeks after initiation of neuroleptic therapy (Roos and Buruma, 1984). These are temporary but dramatic focal occur primarily in young men and usually develop days
or weeks after initiation of neuroleptic therapy (Roos
and Buruma, 1984). These are temporary but dramatic
focal dystonic reactions, usually involving profound tor-
tic or weeks after initiation of neuroleptic therapy (Roos
and Buruma, 1984). These are temporary but dramatic
focal dystonic reactions, usually involving profound tor-
ticollis and an otherwise rare ocular dystonia known as
o and Burdina, 1984). These are temporary but dramatic focal dystonic reactions, usually involving profound tor-
ticollis and an otherwise rare ocular dystonia known as
oculogyric crisis, in which the eyes show extreme and
p decomis and an otherwise rate octual dystomia known as
oculogyric crisis, in which the eyes show extreme and
persistent ocular deviation (Jankovic and Fahn, 1988;
Roos and Bruyn, 1988; Roos and Buruma, 1984). Tardive
dysto persistent ocular deviation (Jankovic and Fahn, 1988;
Roos and Bruyn, 1988; Roos and Buruma, 1984). Tardive
dystonia occurs following chronic treatment (months to
years) of neuroleptics; as with tardive dyskinesia, symp-
t Roos and Bruyn, 1988; Roos and Buruma, 1984). Tardive
dystonia occurs following chronic treatment (months to
years) of neuroleptics; as with tardive dyskinesia, symp-
toms often begin after withdrawal of the drug (Burke et dystoma occurs following emoint treatment (molitis to
years) of neuroleptics; as with tardive dyskinesia, symp-
toms often begin after withdrawal of the drug (Burke et
al., 1982). Although less severe than acute dystonic r toms often begin after withdrawal of the drug (Burke et al., 1982). Although less severe than acute dystonic reactions, tardive dystonia frequently is permanent and difficult to treat. al., 1982). Although less severe than acute dystonic re-
actions, tardive dystonia frequently is permanent and
difficult to treat.
Because the blockade of dopamine receptors was pre-
viously the only known function of neur

available, so the following discussion is necessarily based of dystonia are not accompanied by anatomical or neu-
on animal models of these disorders.
A. Sigma Receptors and Movement Disorders in Man
Before discussing the Because the blockade of dopamine receptors was preactions, tardive dystonia frequently is permanent and
difficult to treat.
Because the blockade of dopamine receptors was pre-
viously the only known function of neuroleptics, and
because anecdotal cases suggested a connect difficult to treat.

Because the blockade of dopamine receptors was previously the only known function of neuroleptics, and

because anecdotal cases suggested a connection to the

basal ganglia, the cause of dystonia has b Because the blockade of dopamine receptors was previously the only known function of neuroleptics, and because anecdotal cases suggested a connection to the basal ganglia, the cause of dystonia has been assumed to involve viously the only known function of neuroleptics, and
because anecdotal cases suggested a connection to the
basal ganglia, the cause of dystonia has been assumed to
involve lesions of the nigrostriatal pathway or a related
 because anecuotal cases suggested a connection to the
basal ganglia, the cause of dystonia has been assumed to
involve lesions of the nigrostriatal pathway or a related
structure, such as the pallidum. However, there have
 involve lesions of the nigrostriatal pathway or a related
structure, such as the pallidum. However, there have
been few findings to support this idea. Most patients
with lesions in the basal ganglia show no evidence of
dys structure, such as the pallidum. However, there have
been few findings to support this idea. Most patients
with lesions in the basal ganglia show no evidence of
dystonia (Roos and Bruyn, 1988). Conversely, most cases
of dy been few findings to support this idea. Most patients
with lesions in the basal ganglia show no evidence of
dystonia (Roos and Bruyn, 1988). Conversely, most cases
of dystonia are not accompanied by anatomical or neu-
roch with lesions in the basal ganglia show no evidence of dystonia (Roos and Bruyn, 1988). Conversely, most cases of dystonia are not accompanied by anatomical or neurochemical changes within the basal ganglia. In fact, a numb dystonia (Roos and Bruyn, 1988). Conversely, most cases
of dystonia are not accompanied by anatomical or neu-
rochemical changes within the basal ganglia. In fact, a
number of cases have been associated with lesions in the of dystonia are not accompanied by anatomical or ne
rochemical changes within the basal ganglia. In fact,
number of cases have been associated with lesions in t
brainstem (Gibb et al., 1988; Jankovic and Patel, 198
Jankovi rochemical changes within the basal ganglia. In fact, a
number of cases have been associated with lesions in the
brainstem (Gibb et al., 1988; Jankovic and Patel, 1983;
Jankovic and Ford, 1983; Lang and Sharpe, 1984; Leennumber of cases have been associated with lesions in the brainstem (Gibb et al., 1988; Jankovic and Patel, 1983; Jankovic and Ford, 1983; Lang and Sharpe, 1984; Leenders et al., 1986; Day et al., 1986). For example, the as brainstem (Gibb et al., 1988; Jankovic and Patel, 1983; Jankovic and Ford, 1983; Lang and Sharpe, 1984; Leenders et al., 1986; Day et al., 1986). For example, the association of rubral lesions with dystonia in man has been Jankovic and Ford, 1983; Lang and Sharpe, 1984; Leen-
ders et al., 1986; Day et al., 1986). For example, the
association of rubral lesions with dystonia in man has
been recognized (Castaigne et al., 1981; Jankovic et al.,
 ders et al., 1986; Day et al., 1986). For example, the association of rubral lesions with dystonia in man has been recognized (Castaigne et al., 1981; Jankovic et al., 1987; Smith, 1975), and in macaques, rubral lesions ar

Section 1956). The cerebellum, which is intimately a
Carpenter, 1956). The cerebellum, which is intimately a
linked to the red nucleus anatomically, has also been WALKER ET
Carpenter, 1956). The cerebellum, which is intimately sio
linked to the red nucleus anatomically, has also been clu
implicated in human dystonia (Fletcher et al., 1988). tra WALKE
Carpenter, 1956). The cerebellum, which is intimately
linked to the red nucleus anatomically, has also been
implicated in human dystonia (Fletcher et al., 1988).
Similarly, in rats, lesions of the locus coeruleus, a Carpenter, 1956). The cerebellum, which is intimate linked to the red nucleus anatomically, has also been implicated in human dystonia (Fletcher et al., 1988)
Similarly, in rats, lesions of the locus coeruleus, a structure Carpenter, 1956). The cerebellum, which is intimately slinked to the red nucleus anatomically, has also been implicated in human dystonia (Fletcher et al., 1988). the Similarly, in rats, lesions of the locus coeruleus, a s linked to the red nucleus anatomically, has also been clumplicated in human dystonia (Fletcher et al., 1988). transilarly, in rats, lesions of the locus coeruleus, a struc-
Similarly, in rats, lesions of the locus coeruleu implicated in human dystonia (Fletcher et al., 1988).
Similarly, in rats, lesions of the locus coeruleus, a structure that exerts significant modulatory influences over
the cerebellum, also produce dystonia. The brainstem Similarly, in rats, lesions of the locus coeruleus, a struc-
ture that exerts significant modulatory influences over
the cerebellum, also produce dystonia. The brainstem is in t
again implicated in the hereditary mutant mo ture that exerts significant modulatory influences over pose
the cerebellum, also produce dystonia. The brainstem is in
again implicated in the hereditary mutant mouse model ma
of dystonia (Stanley et al., 1983), which is brainstem. ain implicated in the hereditary mutant mouse model
dystonia (Stanley et al., 1983), which is also known to
associated with lesions within the cerebellum and
ainstem.
b. TARDIVE DYSKINESIA. Tardive dyskinesia is a syn-
ome

be associated with lesions within the cerebellum and
brainstem.
b. TARDIVE DYSKINESIA. Tardive dyskinesia is a syn-
drome that follows chronic use (usually months or years)
of neuroleptics, involving choreiform movements, michtem. model is a syn-

michtem of the face, model is a syn-

drome that follows chronic use (usually months or years) stre

of neuroleptics, involving choreiform movements, pre-

dominantly of the face, mouth, and tongu b. TARDIVE DYSKINESIA. Tardive dyskinesia is a syndrome that follows chronic use (usually months or years
of neuroleptics, involving choreiform movements, predominantly of the face, mouth, and tongue (Tolosa an
Alom, 1988; drome that follows chronic use (usually months or years) structof neuroleptics, involving choreiform movements, pre-
dominantly of the face, mouth, and tongue (Tolosa and B
Alom, 1988; Tanner, 1986). Symptoms occur after w of neuroleptics, involving choreiform movements, pre-
dominantly of the face, mouth, and tongue (Tolosa and
Alom, 1988; Tanner, 1986). Symptoms occur after with-
of
drawal of the neuroleptic and can be ameliorated by op
re Alom, 1988; Tanner, 1986). Symptoms occur after with-
drawal of the neuroleptic and can be ameliorated by
replacement of the drug, although this merely masks the
from human dystonia in having identifiable lesions
symptoms Alom, 1988; Tanner, 1986). Symptoms occur after with-
drawal of the neuroleptic and can be ameliorated by
replacement of the drug, although this merely masks the
symptoms of the disorder. In contrast to acute dystonic
reac drawal of the neuroleptic and can be ameliorated by complacement of the drug, although this merely masks the faymptoms of the disorder. In contrast to acute dystonic (reactions, tardive dyskinesia is most common in older h replacement of the drug, although this merely symptoms of the disorder. In contrast to accreactions, tardive dyskinesia is most comm
women (Kane et al., 1988). Like tardive dysto
to be permanent, and it is difficult to tre mptoms of the disorder. In contrast to acute dystonic (Stanle
actions, tardive dyskinesia is most common in older have a
omen (Kane et al., 1988). Like tardive dystonia, it tends anatom
be permanent, and it is difficult to

women (Kane et al., 1988). Like tardive dystonia, it tends
to be permanent, and it is difficult to treat.
Tardive dyskinesia is commonly thought to result from
the up-regulation of dopamine receptors known to be
caused by to be permanent, and it is difficult to treat. The dynamic of the up-regulation of dopamine receptors known to be an caused by neuroleptic drugs. This is thought to enhance tide effects of physiological dopamine secretion, Tardive dyskinesia is commonly thought to result from
the up-regulation of dopamine receptors known to b
caused by neuroleptic drugs. This is thought to enhance
the effects of physiological dopamine secretion, leadin
to hy caused by neuroleptic drugs. This is thought to enhance
the effects of physiological dopamine secretion, leading
to hyperkinesias after the neuroleptics are discontinued.
Although it provides a simple explanation for the e caused by neuroleptic drugs. This is thought to enhance
the effects of physiological dopamine secretion, leading
to hyperkinesias after the neuroleptics are discontinued.
Although it provides a simple explanation for the e the effects of physiological dopamine secretion, leading to hyperkinesias after the neuroleptics are discontinued.
Although it provides a simple explanation for the emergence of dyskinesias, this model has never found conv though it provides a simple explanation for the emer-
nce of dyskinesias, this model has never found con-
site
ncing proof, despite many attempts to establish its
lidity.
Gerlach (1985) pointed out some failures to support

vincing proof, despite many attempts to establish its
validity.
Gerlach (1985) pointed out some failures to support a
dopaminergic model, including the following: (*a*) no sig-
nificant differences in dopamine D_1 or D vincing proof, despite many attempts to establish its
validity. \cos
Gerlach (1985) pointed out some failures to support a stite
dopaminergic model, including the following: (a) no sig-
bonificant differences in dopamine validity.

Gerlach (1985) pointed out some failures to support a

dopaminergic model, including the following: (a) no significant differences in dopamine D_1 or D_2 receptors have

been found in the postmortem brains Gerlach (1985) pointed out some failures to support a st
dopaminergic model, including the following: (a) no sig-
nificant differences in dopamine D_1 or D_2 receptors have ((
been found in the postmortem brains of dopaminergic model, including the following: (a) no significant differences in dopamine D_1 or D_2 receptors have been found in the postmortem brains of schizophrenics with tardive dyskinesia, compared to a similarly mificant differences in dopamine D_1 or D_2 receptors have
been found in the postmortem brains of schizophrenics
with tardive dyskinesia, compared to a similarly treated
group that did not develop the disorder (Cross been found in the postmortem brains of schizophrenics
with tardive dyskinesia, compared to a similarly treated
group that did not develop the disorder (Cross et al.,
1985); (b) in endocrinological studies, patients with ta with tardive dyskinesia, compared to a similarly treated group that did not develop the disorder (Cross et al., 1985); (*b*) in endocrinological studies, patients with tardive dyskinesia show a decrease, rather than the pr group that did not develop the disorder (Cross et 1985); (*b*) in endocrinological studies, patients with dive dyskinesia show a decrease, rather than the dicted increase, in sensitivity to dopaminergic drugs tigi et al., 1985); (b) in endocrinological studies, patients with tar-
dive dyskinesia show a decrease, rather than the pre-
dicted increase, in sensitivity to dopaminergic drugs (Et-
tigi et al., 1976; Tamminga et al., 1977); (c) Pa dicted increase, in sensitivity to dopaminergic drugs (Ettigi et al., 1976; Tamminga et al., 1977); (c) Parkinsonism, which involves the loss of nigrostriatal dopamine neurons, and tardive dyskinesia sometimes occur simultigi et al., 1976; Tamminga et al., 1977); *(c)* Parkinson-ogenesis of idiopathic dystonia. This model of dystonia
ism, which involves the loss of nigrostriatal dopamine is attractive because it offers a potential means o tigi et al., 1976; Tamminga et al., 1977); (c) Parkinson-
ism, which involves the loss of nigrostriatal dopamine is
neurons, and tardive dyskinesia sometimes occur simul-
taneously in the same patient (Tanner, 1986); (d) ism, which involves the loss of nigrostriatal dopamineurons, and tardive dyskinesia sometimes occur simulaneously in the same patient (Tanner, 1986); *(d)* DOPA has minimal or no effect on the severity of tardidyskinesia (neurons, and tardive dyskinesia sometimes occur simul-
taneously in the same patient (Tanner, 1986); (*d*) *l*-tor:
DOPA has minimal or no effect on the severity of tardive paties
dyskinesia (Gerlach and Casey, 1983); (*e* taneously in the same patient (Tanner, 1986); (d) *l*-DOPA has minimal or no effect on the severity of tardive dyskinesia (Gerlach and Casey, 1983); (e) some neuroleptics that cause tardive dyskinesia do not appear to c DOPA has minimal or no effect on the severity of tar
dyskinesia (Gerlach and Casey, 1983); (e) some ne
leptics that cause tardive dyskinesia do not appear
cause dopamine hypersensitivity (Christensen et
1981); and (f) the dyskinesia (Gerlach and Casey, 1983); (e) some neuro-
leptics that cause tardive dyskinesia do not appear to
cause dopamine hypersensitivity (Christensen et al.,
1981); and (f) the time course of dopamine hypersensi-
tivit leptics that cause tardive dyskinesia do not appear to dyst cause dopamine hypersensitivity (Christensen et al., b. 1981); and (*f*) the time course of dopamine hypersensi-DYS is tivity in animals treated with neuroleptics cause dopamine hypersensitivity (Christensen et al., 1981); and (f) the time course of dopamine hypersensitivity in animals treated with neuroleptics does not correlate with the time course of tardive dyskinesia in patie 1981); and (f) the time course of dopamine hypersensitivity in animals treated with neuroleptics does not correlate with the time course of tardive dyskinesia in patients (Christensen, 1981). Although these findings coul tivity in animals treated with neuroleptics does not correlate with the time course of tardive dyskinesia in rotations. (Christensen, 1981). Although these findings si could be debated on an individual basis, taken as a gr relate with the t
patients (Christer
could be debated of
they raise serious
tardive dyskinesia.
2. Role of sigma IDIO Could be debated on an individual basis, taken as a group,

I hey raise serious doubts about the dopamine theory of

Indive dyskinesia.

2. Role of sigma receptors. a. SIGMA RECEPTORS AND

IDIOPATHIC DYSTONIA. The abs

be associated with lesions within the cerebellum and profound motor effects induced when sigma ligands are
brainstem.
b. TARDIVE DYSKINESIA. Tardive dyskinesia is a syn-
drome that follows chronic use (usually months or ye **ET AL.**
sions in idiopathic dystonia leads naturally to the con-
clusion that it is caused by neurotransmitter or neuro-ET AL.
sions in idiopathic dystonia leads naturally to the co
clusion that it is caused by neurotransmitter or neuro-
transmitter receptor imbalances. The presence of t ET AL.
sions in idiopathic dystonia leads naturally to the con-
clusion that it is caused by neurotransmitter or neuro-
transmitter receptor imbalances. The presence of the
sigma receptor in structures that control movemen sions in idiopathic dystonia leads naturally to the conclusion that it is caused by neurotransmitter or neuro-
transmitter receptor imbalances. The presence of the
sigma receptor in structures that control movement and
pos sions in idiopathic dystonia leads naturally to the conclusion that it is caused by neurotransmitter or neuro-
transmitter receptor imbalances. The presence of the
sigma receptor in structures that control movement and
pos clusion that it is caused by neurotransmitter or neuro-
transmitter receptor imbalances. The presence of the
sigma receptor in structures that control movement and
posture (particularly in the red nucleus, a site implicate transmitter receptor imbalances. The presence of the
sigma receptor in structures that control movement and
posture (particularly in the red nucleus, a site implicated
in the pathogenesis of dystonia in both animals and
ma sigma receptor in structures that control movement and
posture (particularly in the red nucleus, a site implicated
in the pathogenesis of dystonia in both animals and
man) provides indirect evidence for a link between sigm posture (particularly in the red nucleus, a site implicated
in the pathogenesis of dystonia in both animals and
man) provides indirect evidence for a link between sigma
receptors and dystonia. Supporting data stem from the in the pathogenesis of dystonia in both animals and
man) provides indirect evidence for a link between sigma
receptors and dystonia. Supporting data stem from the
profound motor effects induced when sigma ligands are
micro man) provides indirect evidence for a link between sigma
receptors and dystonia. Supporting data stem from the
profound motor effects induced when sigma ligands are
microinjected into the red nucleus of animals. The dys-
t profound motor effects induced when sigma ligands are tor that could account for this idiopathic condition.

women (Kane et al., 1988). Like tardive dystonia, it tends anatomical lesions; yet, these animals develop lethal
to be permanent, and it is difficult to treat. dystonia. To further test the sigma hypothesis of idi-
Tardive Both the mutant mouse and the rubral lesion model tonia provoked by these drugs provides among the first structure-function relationships of an endogenous receptor that could account for this idiopathic condition.
Both the mutant mouse and the rubral lesion model of dysto structure-function relationships of an endogenous receptor that could account for this idiopathic condition.
Both the mutant mouse and the rubral lesion model
of dystonia are compatible with a sigma theory of idi-
opathic for that could account for this idiopathic condition.
Both the mutant mouse and the rubral lesion model
of dystonia are compatible with a sigma theory of idi-
opathic dystonia. However, both preparations deviate
from human Both the mutant mouse and the rubral lesion model
of dystonia are compatible with a sigma theory of idi-
opathic dystonia. However, both preparations deviate
from human dystonia in having identifiable lesions
(Stanley et a opathic dystonia. However, both preparations deviate opathic dystonia. However, both preparations deviate
from human dystonia in having identifiable lesions
(Stanley et al., 1983). In contrast, Lorden et al. (1988)
have a strain of rats that are free of any identifiable
anat from human dystonia in having identifiable lesions (Stanley et al., 1983). In contrast, Lorden et al. (1988) have a strain of rats that are free of any identifiable anatomical lesions; yet, these animals develop lethal dys (Stanley et al., 1983). In contrast, Lorden et al. (1988)
have a strain of rats that are free of any identifiable
anatomical lesions; yet, these animals develop lethal
dystonia. To further test the sigma hypothesis of idianatomical lesions; yet, these animals develop lethal of dystonia are compatible with a sigma theory of idi-
opathic dystonia. However, both preparations deviate
from human dystonia in having identifiable lesions
(Stanley et al., 1983). In contrast, Lorden et al. (1988)
abav dystonia. To further test the sigma hypothesis of idi-
opathic dystonia, the brains of these dystonic rats were
analyzed for the concentration and binding characteris-
tics of sigma receptors. This study revealed a 500%
de opathic dystonia, the brains of these dystonic rats were
analyzed for the concentration and binding characteritics of sigma receptors. This study revealed a 500%
decrease in the affinity of sigma receptors (labeled wite
[[] tics of sigma receptors. This study revealed a 500% decrease in the affinity of sigma receptors (labeled with $[^{3}H]DTG$) in dystonic rats compared with their unaffected littermates and a 200% increase in the number sites was also found (Bowen et al., i988b). crease in the affinity of sigma receptors (labeled with
H]DTG) in dystonic rats compared with their unaf-
ted littermates and a 200% increase in the number of
ces was also found (Bowen et al., 1988b).
Previous studies had

[³H]DTG) in dystonic rats compared with their unaffected littermates and a 200% increase in the number of sites was also found (Bowen et al., 1988b).
Previous studies had revealed markedly abnormal glucose utilization i fected littermates and a 200% increase in the number
sites was also found (Bowen et al., 1988b).
Previous studies had revealed markedly abnormal gl
cose utilization in dystonic rats, including brainste
structures (Brown an sites was also found (Bowen et al., 1988b).
Previous studies had revealed markedly abnormal glu-
cose utilization in dystonic rats, including brainstem
structures (Brown and Lorden, 1989); glutamate decar-
boxylase utiliza Previous studies had revealed markedly abnormal glu-
cose utilization in dystonic rats, including brainstem
structures (Brown and Lorden, 1989); glutamate decar-
boxylase utilization in the cerebellum is also abnormal
(Olt cose utilization in dystonic rats, including brainstem
structures (Brown and Lorden, 1989); glutamate decar-
boxylase utilization in the cerebellum is also abnormal
(Oltmans et al., 1988). Yet extensive investigations of
t structures (Brown and Lorden, 1989); glutamate decarboxylase utilization in the cerebellum is also abnormal (Oltmans et al., 1988). Yet extensive investigations of these rats have shown no abnormalities in dopamine, acetyl boxylase utilization in the cerebellum is also abnorm
(Oltmans et al., 1988). Yet extensive investigations
these rats have shown no abnormalities in dopamin
acetylcholine, serotonin, or adrenergic receptors (Lord
et al., 1 (Oltmans et al., 1988). Yet extensive investigations of these rats have shown no abnormalities in dopamine, acetylcholine, serotonin, or adrenergic receptors (Lorden et al., 1988). To date, the marked change in sigma recep these rats have shown no abnormalities in dopamine, acetylcholine, serotonin, or adrenergic receptors (Lorden et al., 1988). To date, the marked change in sigma receptors is one of the most profound alterations observed in acetylcholine, serotonin, or adrenergic receptors (Lorde
et al., 1988). To date, the marked change in sigma receptors is one of the most profound alterations observed i
these animals and, taken together with other data, su et al., 1988). To date, the marked change in sigma receptors is one of the most profound alterations observed in these animals and, taken together with other data, suggests that sigma receptors may be involved in the patho tors is one of the most profound alterations observed i
these animals and, taken together with other data, sugests that sigma receptors may be involved in the path
ogenesis of idiopathic dystonia. This model of dystoni
is gests that sigma receptors may be involved in the path-
ogenesis of idiopathic dystonia. This model of dystonia gests that sigma receptors may be involved in the path-
ogenesis of idiopathic dystonia. This model of dystonia
is attractive because it offers a potential means of phar-
macotherapeutic intervention. Analysis of sigma rec ogenesis of idiopathic dystonia. This model of dystonia
is attractive because it offers a potential means of phar-
macotherapeutic intervention. Analysis of sigma recep-
tor affinity and number in postmortem brains of dyst is attractive because it offers a potential means of phar-
macotherapeutic intervention. Analysis of sigma recep-
tor affinity and number in postmortem brains of dystonic
patients is of critical importance. Unfortunately, macotherapeutic intervention. An
tor affinity and number in postmo
patients is of critical importance
few brains from patients who su
dystonia are available for study.
b. SIGMA RECEPTORS AND N

patients (Christensen, 1981). Although these findings sigma receptors in the oculomotor, abducens, and troch-
could be debated on an individual basis, taken as a group, lear nuclei, all subserving eye movements, provides a patients is of critical importance. Unfortunately, very
few brains from patients who suffered from idiopathic
dystonia are available for study.
b. SIGMA RECEPTORS AND NEUROLEPTIC INDUCED
DYSTONIAS. The discovery of potent net few brains from patients who suffered from idiopathic
dystonia are available for study.
b. SIGMA RECEPTORS AND NEUROLEPTIC INDUCED
DYSTONIAS. The discovery of potent sigma binding by
neuroleptics suggests a novel patho dystonia are available for study.

b. SIGMA RECEPTORS AND NEUROLEPTIC INDUCED

DYSTONIAS. The discovery of potent sigma binding by

neuroleptics suggests a novel pathogenetic basis for neu-

roleptic induced dystonia. The b. SIGMA RECEPTORS AND NEUROLEPTIC INDUCED
DYSTONIAS. The discovery of potent sigma binding by
neuroleptics suggests a novel pathogenetic basis for neu-DYSTONIAS. The discovery of potent sigma binding by
neuroleptics suggests a novel pathogenetic basis for neu-
roleptic induced dystonia. The high concentration of
sigma receptors in the oculomotor, abducens, and troch-
lea neuroleptics suggests a novel pathogenetic basis for neuroleptic induced dystonia. The high concentration of sigma receptors in the oculomotor, abducens, and trochlear nuclei, all subserving eye movements, provides a putat roleptic induced dystonia. The high concentration of sigma receptors in the oculomotor, abducens, and trochlear nuclei, all subserving eye movements, provides a putative anatomical substrate for the oculogyric crises seen sigma receptors in the oculomotor, abducens, and trochlear nuclei, all subserving eye movements, provides a putative anatomical substrate for the oculogyric crises seen in acute dystonic reactions. Furthermore, the tortico lear nuclei, all subserving eye movements, provides a
putative anatomical substrate for the oculogyric crises
seen in acute dystonic reactions. Furthermore, the tor-
ticollis in rats caused by intrarubral microinjection of

PHARMACOLOGICAL REVIEWS

SIGMA RECEPTORS
receptors mediate neuroleptic induced dystonic move- dopamir ments.

SIGMA I
Ceptors mediate neuroleptic induced dystonic move-
The differences between the typical and atypical neu-
leptic drugs also support a sigma hypothesis of neuroreceptors mediate neuroleptic induced dystonic movements.
The differences between the typical and atypical neuroleptic drugs also support a sigma hypothesis of neuro-
leptic induced movement disorders. Typical neurolept receptors mediate neuroleptic induced dystonic move-
ments.
The differences between the typical and atypical neuroleptic drugs also support a sigma hypothesis of neuro-
leptic induced movement disorders. Typical neurolepti ments.
The differences between the typical and atypical neuroleptic drugs also support a sigma hypothesis of neuroleptic
leptic induced movement disorders. Typical neuroleptic
are the traditional antipsychotic drugs that c The differences between the typical and atypical neu-
roleptic drugs also support a sigma hypothesis of neuro-
leptic induced movement disorders. Typical neuroleptics
none the traditional antipsychotic drugs that cause cat roleptic drugs also support a sigma hypothesis of neuroleptic induced movement disorders. Typical neuroleptics
are the traditional antipsychotic drugs that cause cata-
lepsy in rats and movement disorders in humans. Two
dr leptic induced movement disorders. Typical neuroleptics D
are the traditional antipsychotic drugs that cause cata-
lepsy in rats and movement disorders in humans. Two
drugs (clozapine and sulpiride) have been found to exer are the traditional antipsychotic drugs that cause cata-
lepsy in rats and movement disorders in humans. Two (Bodrugs (clozapine and sulpiride) have been found to exert ind
significant antipsychotic effects in humans with lepsy in rats and movement disorders in humans. Two
drugs (clozapine and sulpiride) have been found to exert
significant antipsychotic effects in humans with little or
no liability for producing motor dysfunctions (Miller significant antipsychotic effects in humans with little or
no liability for producing motor dysfunctions (Miller and
Jankovic, 1990; Achiron et al., 1990; Gerlach et al., 1974;
Matz et al., 1974; Lindstrom et al., 1988; Fr significant antipsychotic effects in humans with little or
no liability for producing motor dysfunctions (Miller and
Jankovic, 1990; Achiron et al., 1990; Gerlach et al., 1974;
Matz et al., 1974; Lindstrom et al., 1988; Fr no liability for producing motor dysfunctions (Miller and ve
Jankovic, 1990; Achiron et al., 1990; Gerlach et al., 1974; re
Matz et al., 1974; Lindstrom et al., 1988; Friedman et al., an
1987). These drugs have become know Jankovic, 1990; Achiron et al., 1990; Geriach et al., 1974; recently Matz et al., 1974; Lindstrom et al., 1988; Friedman et al., and 1987). These drugs have become known as the atypical was antipsychotics. More recently, s 1987). These drugs have become known as the atypical was antipsychotics. More recently, some investigators have modesignated other novel drugs as atypical because they do vernot produce catalepsy in rats. Unfortunately, ho antipsychotics. More recently, some investigators have m
designated other novel drugs as atypical because they do
not produce catalepsy in rats. Unfortunately, however, po
because the connection between catalepsy in rats a designated other novel drugs as atypical because they d
not produce catalepsy in rats. Unfortunately, however
because the connection between catalepsy in rats an
movement disorders in humans is largely a matter c
conjectur not produce catalepsy in rats. Unfortunately, however, percent because the connection between catalepsy in rats and hunder movement disorders in humans is largely a matter of weight conjecture, and because clinical data ar compounds. by ement disorders in humans is largely a matter of njecture, and because clinical data are lacking, judgent should be reserved on the classification of these mpounds.
Nevertheless, clozapine and sulpiride, the only atypic

conjecture, and because clinical data are lacking, judg-
ment should be reserved on the classification of these
compounds.
Nevertheless, clozapine and sulpiride, the only atypical
Fantipsychotic drugs for which there is a compounds.
Nevertheless, clozapine and sulpiride, the only atypical
antipsychotic drugs for which there is a solid base of
human data, bind with reasonable affinities to dopamine
receptors but poorly to sigma receptors (Li Nevertheless, clozapine and sulpiride, the only atypical
antipsychotic drugs for which there is a solid base of
human data, bind with reasonable affinities to dopamine
receptors but poorly to sigma receptors (Lindstrom, 19 antipsychotic drugs for which there is a solid base of cluman data, bind with reasonable affinities to dopamine
receptors but poorly to sigma receptors (Lindstrom, 1988; for
Friedman et al., 1987, Rupniak et al., 1984). Th human data, bind with
receptors but poorly t
Friedman et al., 1987,
that sigma binding
movement disorders.
Reserpine, a drug ceptors but poorly to sigma receptors (Lindstrom, 1988; fiedman et al., 1987, Rupniak et al., 1984). This suggests that sigma binding is important in the production of represent disorders.
Reserpine, a drug that depletes d

Friedman et al., 1987, Rupniak et al., 1984). This suggests
that sigma binding is important in the production of
movement disorders.
Reserpine, a drug that depletes dopamine and exerts
Parkinsonian and mild antipsychotic e that sigma binding is important in the production of mumovement disorders. lite
movement disorders. Reserpine, a drug that depletes dopamine and exerts sug
Parkinsonian and mild antipsychotic effects, also shows hal
no evi movement disorders.

Reserpine, a drug that depletes dopamine and exerts

Parkinsonian and mild antipsychotic effects, also shows

mo evidence of acute or tardive dystonia (Tarsy and

Baldessarini, 1976). Only those antips Reserpine, a drug that depletes dopamine and exert
Parkinsonian and mild antipsychotic effects, also show
no evidence of acute or tardive dystonia (Tarsy and
Baldessarini, 1976). Only those antipsychotic drugs tha
show hig Parkinsonian and mild antipsychotic effects, also show
no evidence of acute or tardive dystonia (Tarsy and
Baldessarini, 1976). Only those antipsychotic drugs tha
show high or moderate sigma-binding affinity are asso
ciate no evidence of acute or tardive dystonia (Tarsy and und
Baldessarini, 1976). Only those antipsychotic drugs that trop
show high or moderate sigma-binding affinity are asso-
ciated with the development of dystonic reactions Baldessarini, 1976). Only those antipsychotic drugs the
show high or moderate sigma-binding affinity are asseciated with the development of dystonic reactions; ant
psychotic drugs specific for dopamine receptors show r
suc

ciated with the development of dystonic reactions; anti-
peychotic drugs specific for dopamine receptors show no
such behavior.
c. SIGMA RECEPTORS AND TARDIVE DYSKINESIA. Sev-
eral lines of indirect evidence raise the poss psychotic drugs specific for dopamine receptors show no
such behavior. pe
c. SIGMA RECEPTORS AND TARDIVE DYSKINESIA. Sev-
heral lines of indirect evidence raise the possibility that
in the sigma receptors are involved in t per
c. SIGMA RECEPTORS AND TARDIVE DYSKINESIA. Sev-
eral lines of indirect evidence raise the possibility that
in
sigma receptors are involved in tardive dyskinesia. The
stingh concentration of sigma receptors in the facia eral lines of indirect evidence raise the possibility that
sigma receptors are involved in tardive dyskinesia. The
high concentration of sigma receptors in the facial and
hypoglossal nuclei would provide an anatomical basi eral lines of indirect evidence raise the possibility that
sigma receptors are involved in tardive dyskinesia. The
high concentration of sigma receptors in the facial and
hypoglossal nuclei would provide an anatomical basi sigma receptors are involved in tardive dyskinesia. The
high concentration of sigma receptors in the facial and
hypoglossal nuclei would provide an anatomical basis for
the tendency of tardive dyskinesia to involve oral-bu high concentration of sigma receptors in the facial and hypoglossal nuclei would provide an anatomical basis f
the tendency of tardive dyskinesia to involve oral-bucc
and lingual movements. Neither clozapine nor sulpirid
e hypoglossal nuclei would provide an anatomical basis for
the tendency of tardive dyskinesia to involve oral-buccal
and lingual movements. Neither clozapine nor sulpiride,
each of which binds to dopamine but not to sigma re the tendency of tardive dyskinesia to involve oral-buccal any
and lingual movements. Neither clozapine nor sulpiride, (do
each of which binds to dopamine but not to sigma recep-
tors, is commonly associated with tardive d and lingual movements. Neither clozapine nor sulpiride, (deach of which binds to dopamine but not to sigma receptors, is commonly associated with tardive dyskinesia un (Lindstrom 1988; Friedman et al., 1987; Jenner and ga each of which binds to dopamine but not to sigma receptors, is commonly associated with tardive dyskinesia (Lindstrom 1988; Friedman et al., 1987; Jenner and Marsden, 1979; Rupniak et al., 1984). It must be noted that the tors, is commonly associated with tardive dyskines
(Lindstrom 1988; Friedman et al., 1987; Jenner an
Marsden, 1979; Rupniak et al., 1984). It must be not
that the study of tardive dyskinesia has been problemat
from the out (Lindstrom 1988; Friedman et al., 1987; Jenner and
Marsden, 1979; Rupniak et al., 1984). It must be noted
that the study of tardive dyskinesia has been problematic
from the outset, because it is difficult to induce dyski-
 Marsden, 1979; Rupniak et al., 1984). It must be noted
that the study of tardive dyskinesia has been problematic
from the outset, because it is difficult to induce dyski-
nesias in animals, even with typical neuroleptics t that the study of tardive dyskinesia has been problematic
from the outset, because it is difficult to induce dyski-
nesias in animals, even with typical neuroleptics that
commonly produce the effect in humans. The motor
re from the outset, because it is difficult to induce dyski-for mixtures of selective compounds [e.g., sulpiride plus
nesias in animals, even with typical neuroleptics that $(+)$ -pentazocine] to produce movement disorders in nesias in animals, even with typical neuroleptics that (commonly produce the effect in humans. The motor neffects of sigma ligands in the substantia nigra (Goldstein vet al., 1989) suggest a possible physiological basis fo commonly produce the effect in humans. The motor materies of sigma ligands in the substantia nigra (Goldstein value of al., 1989) suggest a possible physiological basis for dyskinesias in humans and further suggest a possi effects of sigma ligands in the substantia nigra (Goldstein valued al., 1989) suggest a possible physiological basis for Adyskinesias in humans and further suggest a possible tem role of sigma receptors in Parkinson's synd

EPTORS
dopamine receptors are responsible for other neuroleptic
induced movement disorders remains an important ave-EPTORS
dopamine receptors are responsible for other neuroleptic
induced movement disorders remains an important ave-
nue for further study. EPTORS
dopamine receptors are
induced movement dise
nue for further study.
d. METABOLISM OF 1 induced movement disorders remains an important ave-
nue for further study.
d. METABOLISM OF HALOPERIDOL TO SIGMA-ACTIVE/

dopamine receptors are responsible for other neuroleptic
induced movement disorders remains an important ave-
nue for further study.
d. METABOLISM OF HALOPERIDOL TO SIGMA-ACTIVE/
DOPAMINE-INACTIVE METABOLITES. Haloperidol induced movement disorders remains an important ave-
nue for further study.
d. METABOLISM OF HALOPERIDOL TO SIGMA-ACTIVE/
DOPAMINE-INACTIVE METABOLITES. Haloperidol has
about equal affinity for sigma and dopamine receptors nue for further study.

d. METABOLISM OF HALOPERIDOL TO SIGMA-ACTIVE/

DOPAMINE-INACTIVE METABOLITES. Haloperidol has

about equal affinity for sigma and dopamine receptors

(Bowen et al., 1990a). However, this compound ma d. METABOLISM OF HALOPERIDOL TO SIGMA-ACTIVE/
DOPAMINE-INACTIVE METABOLITES. Haloperidol has
about equal affinity for sigma and dopamine receptors
(Bowen et al., 1990a). However, this compound may
induce greater and more p about equal affinity for sigma and dopamine receptors (Bowen et al., 1990a). However, this compound may induce greater and more prolonged actions through sigma receptors, because it produces metabolites that are still very about equal affinity for sigma and dopamine receptors (Bowen et al., 1990a). However, this compound may induce greater and more prolonged actions through sigma receptors, because it produces metabolites that are still very (Bowen et al., 1990a). However, this compound may
induce greater and more prolonged actions through sigma
receptors, because it produces metabolites that are still
very active at sigma receptors but weak at dopamine
recep induce greater and more prolonged actions through sigma
receptors, because it produces metabolites that are still
very active at sigma receptors but weak at dopamine
receptors. Studies in which the binding of haloperidol
 receptors, because it produces metabolites that are still
very active at sigma receptors but weak at dopamine
receptors. Studies in which the binding of haloperidol
and its metabolites to dopamine D_2 and sigma receptor very active at sigma receptors but weak at dopamine receptors. Studies in which the binding of haloperidol and its metabolites to dopamine D_2 and sigma receptors was compared revealed that reduced haloperidol has only receptors. Studies in which the binding of haloperide and its metabolites to dopamine D_2 and sigma receptor was compared revealed that reduced haloperidol has only moderate affinity for dopamine D_2 receptors but is and its metabolites to dopamine D_2 and sigma receptors
was compared revealed that reduced haloperidol has only
moderate affinity for dopamine D_2 receptors but is still
very potent at sigma receptors. Because reduced was compared revealed that reduced haloperidol has only moderate affinity for dopamine D_2 receptors but is still very potent at sigma receptors. Because reduced haloperidol accumulates in the brains of chronically trea very potent at sigma receptors. Because reduced halo-
peridol accumulates in the brains of chronically treated
humans (Korpi et al., 1984), it is likely that sigma activity
would eventually become dominant.
The relatively ry potent at sigma receptors. Because reduced
ridol accumulates in the brains of chronically t
mans (Korpi et al., 1984), it is likely that sigma a
vuld eventually become dominant.
The relatively slow accumulation of sigma

compounds. Corresponds to the time course of actions of this drug.
Nevertheless, clozapine and sulpiride, the only atypical For example, certain motor disorders and the antipsy-
antipsychotic drugs for which there is a sol peridol accumulates in the brains of chronically treated
humans (Korpi et al., 1984), it is likely that sigma activity
would eventually become dominant.
The relatively slow accumulation of sigma-active/do-
pamine-inactive humans (Korpi et al., 1984), it is likely that sigma activity
would eventually become dominant.
The relatively slow accumulation of sigma-active/do-
pamine-inactive metabolites of haloperidol in humans
corresponds to the t would eventually become dominant.
The relatively slow accumulation of sigma-active/
pamine-inactive metabolites of haloperidol in hum
corresponds to the time course of actions of this different
For example, certain motor d The relatively slow accumulation of sigma-active/do-
pamine-inactive metabolites of haloperidol in humans
corresponds to the time course of actions of this drug.
For example, certain motor disorders and the antipsy-
chotic pamine-inactive metabolites of haloperidol in humans corresponds to the time course of actions of this drug.
For example, certain motor disorders and the antipsy-
chotic actions of haloperidol do not occur immediately
afte corresponds to the time course of actions of this drug.
For example, certain motor disorders and the antipsy-
chotic actions of haloperidol do not occur immediately
after drug administration. Although many explanations
for For example, certain motor disorders and the antipsy
chotic actions of haloperidol do not occur immediatel
after drug administration. Although many explanation
for this phenomenon could be offered, it is conceivable
that t chotic actions of haloperidol do not occur immediate after drug administration. Although many explanation for this phenomenon could be offered, it is conceive that the delay results from the time required to acculate suffi after drug administration. Although many explanations
for this phenomenon could be offered, it is conceivable
that the delay results from the time required to accu-
mulate sufficient plasma levels of sigma-active metabol-
 mulate sufficient plasma levels of sigma-active metabolites. The presence of sigma-active metabolites further suggests that individual differences in the metabolism of haloperidol to sigma-active or inactive metabolites ma that the delay results from the time required to accumulate sufficient plasma levels of sigma-active metabolites. The presence of sigma-active metabolites further suggests that individual differences in the metabolism of h mulate sufficient plasma levels of sigma-active metalites. The presence of sigma-active metabolites furtlesuggests that individual differences in the metabolism haloperidol to sigma-active or inactive metabolites munderlie lites. The presence of sigm
suggests that individual diff
haloperidol to sigma-active
underlie some of the variat
tropic effects of haloperidol
A serious question for th ggests that individual differences in the metabolism of
loperidol to sigma-active or inactive metabolites may
derlie some of the variation in the motor or psycho-
ppic effects of haloperidol.
A serious question for the sig

haloperidol to sigma-active or inactive metabolites may
underlie some of the variation in the motor or psycho-
tropic effects of haloperidol.
A serious question for the sigma hypothesis of motor
disorders is why sigma-act underlie some of the variation in the motor or psycho-
tropic effects of haloperidol.
A serious question for the sigma hypothesis of motor
disorders is why sigma-active compounds used clinically,
e.g., DM and (+)-pentazoci tropic effects of haloperidol.

A serious question for the sigma hypothesis of motor

disorders is why sigma-active compounds used clinically,

e.g., DM and (+)-pentazocine [found in Talwin, $(+/-)$ -

pentazocine], have not A serious question for the sigma hypothesis of motor
disorders is why sigma-active compounds used clinically,
e.g., DM and $(+)$ -pentazocine [found in Talwin, $(+/-)$ -
pentazocine], have not caused movement disorders in
huma disorders is why sigma-active compounds used clinically,
e.g., DM and (+)-pentazocine [found in Talwin, (+/-)-
pentazocine], have not caused movement disorders in
humans. Conceivably, more than one receptor is involved
in e.g., DM and (+)-pentazocine [found in Talwin, (+/-)-
pentazocine], have not caused movement disorders in
humans. Conceivably, more than one receptor is involved
in neuroleptic induced dystonias so that simultaneous
stimul pentazocine], have not caused movement disorders in
humans. Conceivably, more than one receptor is involved
in neuroleptic induced dystonias so that simultaneous
stimulation and/or blockade of both dopamine and sigma
recep humans. Conceivably, more than one receptor is involved
in neuroleptic induced dystonias so that simultaneous
stimulation and/or blockade of both dopamine and sigma
receptors might be necessary for their induction. This
se stimulation and/or blockade of both dopamine and sigma
receptors might be necessary for their induction. This
seems plausible because none of the selective ligands for
any of the receptors that typically bind neuroleptics
 stimulation and/or blockade of both dopamine and sigma
receptors might be necessary for their induction. This
seems plausible because none of the selective ligands for
any of the receptors that typically bind neuroleptics
 receptors might be necessary for their induction. Thesems plausible because none of the selective ligands fany of the receptors that typically bind neuroleptic (dopamine, adrenergic, serotonergic, sigma) are prove to cause seems plausible because none of the selective ligands for
any of the receptors that typically bind neuroleptics
(dopamine, adrenergic, serotonergic, sigma) are proven
to cause movement disorders on their own. Furthermore, any of the receptors that typically bind neuroleptics (dopamine, adrenergic, serotonergic, sigma) are proven to cause movement disorders on their own. Furthermore, under certain conditions, synergies do occur among ligand (dopamine, adrenergic, serotonergic, sigma) are proven
to cause movement disorders on their own. Furthermore,
under certain conditions, synergies do occur among li-
gands for different receptors (e.g., dopamine $D_1 + D_2$ to cause movement disorders on their own. Furthermore,
under certain conditions, synergies do occur among li-
gands for different receptors (e.g., dopamine $D_1 + D_2$ or
 $D_1 + 5HT_{1a}$; Dall'Olio et al., 1989; Gessa et al., under certain conditions, synergies do occur among ii-
gands for different receptors (e.g., dopamine $D_1 + D_2$ or
 $D_1 + 5HT_{1a}$; Dall'Olio et al., 1989; Gessa et al., 1985;
Molloy and Waddington, 1985). Studies of the pro D_1 + 5HT_{1a}; Dall'Olio et al., 1989; Gessa et al., 1985;
Molloy and Waddington, 1985). Studies of the propensity
for mixtures of selective compounds [e.g., sulpiride plus
(+)-pentazocine] to produce movement disorders valuable. $(+)$ -pentazocine] to produce movement disorders in pri-
mates, compared to the individual substances, would be
valuable.
Another plausible explanation for the failure of sys-

(+)-pentazocine] to produce movement disorders in pri-
mates, compared to the individual substances, would be
valuable.
Another plausible explanation for the failure of sys-
temic administration of (+)-pentazocine and DM mates, compared to the individual substances, would be
valuable.
Another plausible explanation for the failure of sys-
temic administration of (+)-pentazocine and DM to pro-
duce movement disorders is based on the multipli valuable.
Another plausible explanation for the failure of systemic administration of (+)-pentazocine and DM to produce movement disorders is based on the multiplicity of sigma-binding sites in the brain. It is possible th

those drugs that bind to the UV-susceptible (neuroleptic) wal
those drugs that bind to the UV-susceptible (neurolepti
site or the PC12-like subtype [sigma-2, which is inse
sitive to (+)-opiates] produce movement disorders. T WALKER ET
those drugs that bind to the UV-susceptible (neuroleptic) has
site or the PC12-like subtype [sigma-2, which is insen-
sitive to (+)-opiates] produce movement disorders. The of
marked difference in the actions of those drugs that bind to the UV-susceptible (neurolept
site or the PC12-like subtype [sigma-2, which is inse
sitive to (+)-opiates] produce movement disorders. T
marked difference in the actions of chronically administered those drugs that bind to the UV-susceptible (neuroleptic)
site or the PC12-like subtype [sigma-2, which is insen-
sitive to $(+)$ -opiates] produce movement disorders. The
marked difference in the actions of chronically adm site or the PC12-like subtype [sigma-2, which is insen-
sitive to $(+)$ -opiates] produce movement disorders. The of r
marked difference in the actions of chronically admin-rece
istered haloperidol on the neuroleptic versus sitive to $(+)$ -opiates] produce movement disorders. The one marked difference in the actions of chronically administered haloperidol on the neuroleptic versus $(+)$ -opiate resites (fig. 12) and the reduced efficacy of $(+)$ view. istered haloperidol on the neuroleptic versus $(+)$ -opiate
sites (fig. 12) and the reduced efficacy of $(+)$ -opiates in
producing dystonia in rats provide some support for this
view.
In summary, multiple lines of indirect e

sites (fig. 12) and the reduced efficacy of $(+)$ -opiates in it
producing dystonia in rats provide some support for this ps
view.
In summary, multiple lines of indirect evidence sup-
port the hypothesis that sigma receptor producing dystonia in rats provide some support for this
view.
In summary, multiple lines of indirect evidence sup-
port the hypothesis that sigma receptors mediate some
of the motor effects of antipsychotic drugs. These i view.
In summary, multiple lines of indirect evidence support the hypothesis that sigma receptors mediate some
of the motor effects of antipsychotic drugs. These include
the anatomical distribution of sigma receptors, the In summary, multiple lines of indirect evidence support the hypothesis that sigma receptors mediate some bind of the motor effects of antipsychotic drugs. These include it he anatomical distribution of sigma receptors, the port the hypothesis that sigma receptors mediate some biddenconfects of antipsychotic drugs. These include it the anatomical distribution of sigma receptors, the motor Heffects of sigma ligands in rats, altered sigma bindi of the motor effects of antipsychotic drugs. These
the anatomical distribution of sigma receptors, the
effects of sigma-ligands in rats, altered sigma-bin
mutant dystonic rats, the dopamine-releasing ac
sigma-ligands, and the anatomical distribution of sigma receptors, the motor Heffects of sigma ligands in rats, altered sigma binding in chutant dystonic rats, the dopamine-releasing action of tusigma ligands, and the formation of sigma-acti effects of sigma ligands in rats, altered sigma binding in chomoutant dystonic rats, the dopamine-releasing action of tula
sigma ligands, and the formation of sigma-active/dopa-active-inactive metabolites of haloperidol. H mutant dystonic rats, the dopamine-releasing action of sigma ligands, and the formation of sigma-active/dopamine-inactive metabolites of haloperidol. However, these data are indirect, and clinically used sigma ligands do n sigma ligands, and the formation of sigma-active/dopa-
mine-inactive metabolites of haloperidol. However, these
data are indirect, and clinically used sigma ligands do
not produce movement disorders, raising questions abou mine-inactive metabolites of haloperidol. However, these
data are indirect, and clinically used sigma ligands do
not produce movement disorders, raising questions about
the nature of this relationship. Further investigatio data are indirect, and clinically used sigma ligands do
not produce movement disorders, raising questions about
the nature of this relationship. Further investigation will
be required to establish a role of sigma receptors not produce movement disorders, raising questions about
the nature of this relationship. Further investigation will
be required to establish a role of sigma receptors in motor
disorders. In particular, sigma binding and ha the nature of this relationship. Further investigation will the required to establish a role of sigma receptors in motor disorders. In particular, sigma binding and haloperidol metabolism in the brains of patients treated be required to establish a role of sigma receptors in motor
disorders. In particular, sigma binding and haloperidol
metabolism in the brains of patients treated with neu-
roleptics should be studied. Studies of the motor e disorders. In particular, sigma binding and haloperidol Base
metabolism in the brains of patients treated with neu-
movem
roleptics should be studied. Studies of the motor effects that B
of sigma-inactive antipsychotics (e metabolism in the brains of patients treated with neu-
roleptics should be studied. Studies of the motor effects the
of sigma-inactive antipsychotics (e.g., sulpiride) are bee
needed. Finally, studies of the motor effects roleptics should be studied. Sof sigma-inactive antipsychereded. Finally, studies of antipsychotic drugs with signals BMY 14802) are needed.
As BMY 14802) are needed.
3. Sigma receptors and psy algona-inactive antipsychotics (e.g., sulpiride) are be-
 3. *Sigma receptors and psychosis.* For many years, the and
 3. Sigma receptors and psychosis. For many years, the are

minant theory of the biological basis of

needed. Finally, studies of the motor effects of new
antipsychotic drugs with significant sigma affinity (such
as BMY 14802) are needed.
3. Sigma receptors and psychosis. For many years, the
dominant theory of the biologic antipsychotic drugs with significant sigma affinity (suce as BMY 14802) are needed.
3. Sigma receptors and psychosis. For many years, the dominant theory of the biological basis of schizophrenic has been the dopamine theor as BMY 14802) are needed.
3. Sigma receptors and psychosis. For many years, the
dominant theory of the biological basis of schizophrenia
has been the dopamine theory, which asserts that dopa-
mine hyperactivity (broadly d 3. Sigma receptors and psychosis. For many years, the
dominant theory of the biological basis of schizophrenia
has been the dopamine theory, which asserts that dopa-
mine hyperactivity (broadly defined) is the underlying
 dominant theory of the biological basis of schizophrenia
has been the dopamine theory, which asserts that dopa-
mine hyperactivity (broadly defined) is the underlying
cause of the disorder (Snyder et al., 1974; Losonczy et has been the dopamine theory, which asserts that dopa-
mine hyperactivity (broadly defined) is the underlying
cause of the disorder (Snyder et al., 1974; Losonczy et 5
al., 1987). Although recent data have offered consider mine hyperactivity (broadly defined) is the underlying escause of the disorder (Snyder et al., 1974; Losonczy et 5H al., 1987). Although recent data have offered considerable mapport for this notion, certain aspects of the cause of the disorder (Snyder et al., 1974; Losonczy
al., 1987). Although recent data have offered considers
support for this notion, certain aspects of the dise
cannot be accounted for by dopamine dysfunction.
"more recen al., 1987). Although recent data have offered considers support for this notion, certain aspects of the dise
cannot be accounted for by dopamine dysfunction. T
more recently discovered common property of neurol
tic drugs (support for this notion, certain aspects of the dise
cannot be accounted for by dopamine dysfunction. T
more recently discovered common property of neurol
tic drugs (binding to sigma receptors) raises the possi
ity that si cannot be accounted for by dopamine dysfunction. The seemore recently discovered common property of neuroleptic drugs (binding to sigma receptors) raises the possibil-
ity that sigma interactions mediate some of the antips more recently discovered common property of neurole
tic drugs (binding to sigma receptors) raises the possib
ity that sigma interactions mediate some of the antips
chotic effects of neuroleptics. The distribution of sign
r tic drugs (binding to sigma receptors) r
ity that sigma interactions mediate sore
chotic effects of neuroleptics. The dist
receptors in limbic areas known to be i
tion and emotion supports this view.
The development of rim It that sigma interactions mediate some of the antipsy-
otic effects of neuroleptics. The distribution of sigma
the deptors in limbic areas known to be involved in cogni-
on and emotion supports this view.
The development

receptors in limbic areas known to be involved in cognition and emotion supports this view.
The development of rimcazole (BW234U) has provided
some experimental support for a role of sigma receptors
in schizophrenia. Behav receptors in limbic areas known to be involved in cogni-
tion and emotion supports this view.
The development of rimcazole (BW234U) has provided
risome experimental support for a role of sigma receptors
in schizophrenia. B tion and emotion supports this view.
The development of rimcazole (BW234U) has provide
some experimental support for a role of sigma receptor
in schizophrenia. Behavioral studies in rats suggeste
that this drug may possess The development of rimcazole (BW234U) has provided
some experimental support for a role of sigma receptors
in schizophrenia. Behavioral studies in rats suggested
that this drug may possess antipsychotic efficacy inde-
pend some experimental support for a role of sigma receptors
in schizophrenia. Behavioral studies in rats suggested
that this drug may possess antipsychotic efficacy inde-
pendent of classic anti-dopaminergic effects (Ferris et in schizophrenia. Behavioral studies in rats suggested late this drug may possess antipsychotic efficacy independent of classic anti-dopaminergic effects (Ferris et al., 1986), and in preliminary clinical trials, some evid that this drug may possess antipsychotic efficacy independent of classic anti-dopaminergic effects (Ferris et al., 1986), and in preliminary clinical trials, some evidence of antipsychotic efficacy was found (Chouinard and pendent of classic anti-dopaminergic effects (Ferris et al., 1986), and in preliminary clinical trials, some evidence of antipsychotic efficacy was found (Chouinard and Annable, 1984; Davidson et al., 1982; Ferris et al., al., 1986), and in preliminary clinical trials, some evi-
dence of antipsychotic efficacy was found (Chouinard
and Annable, 1984; Davidson et al., 1982; Ferris et al.,
1982). However, it should be noted that the clinical
s dence of antipsychotic efficacy was found (Chouinard
and Annable, 1984; Davidson et al., 1982; Ferris et al.,
1982). However, it should be noted that the clinical
studies were not double-blind and that no effect on global
 1982). However, it should be noted that the clinical studies were not double-blind and that no effect on global improvement was noted in at least one open-label trial (Davidson et al., 1985). studies were not double-blind and that no effect on glob
improvement was noted in at least one open-label tr
(Davidson et al., 1985).
The behavioral effects of rimcazole have been attri
uted to sigma receptors. However, th

The behavioral effects of rimcazole have been attributed to sigma receptors. However, the activity of rimcaimprovement was noted in at least one open-label trial (
(Davidson et al., 1985).
The behavioral effects of rimcazole have been attrib-
uted to sigma receptors. However, the activity of rimca-
zole at sigma receptors is ap

ET AL.
haloperidol and 50% that of propranolol (Ferris et al.,
1986), a drug with minimal cognitive effects. The affinity ET AL.
haloperidol and 50% that of propranolol (Ferris et al.,
1986), a drug with minimal cognitive effects. The affinity
of rimcazole for certain other central nervous system ET AL.
haloperidol and 50% that of propranolol (Ferris et al.,
1986), a drug with minimal cognitive effects. The affinity
of rimcazole for certain other central nervous system
receptors casts further doubt upon the role of receptor and 50% that of propranolol (Ferris et al., 1986), a drug with minimal cognitive effects. The affinity of rimcazole for certain other central nervous system receptors casts further doubt upon the role of sigma rec haloperidol and 50% that of propranolol (Ferris et al., 1986), a drug with minimal cognitive effects. The affinity of rimcazole for certain other central nervous system receptors casts further doubt upon the role of sigma 1986), a drug with minimal cognitive effects. The affinity
of rimcazole for certain other central nervous system
receptors casts further doubt upon the role of sigma
receptors in its actions (cf. Ferris et al., 1986). Alth of rimcazole for certain other central nervous system
receptors casts further doubt upon the role of sigma
receptors in its actions (cf. Ferris et al., 1986). Although
it is tempting to infer a role for sigma receptors in
 receptors in its actions (cf. Ferris et al., 1986). Although
it is tempting to infer a role for sigma receptors in
psychosis from these data, they must be considered no
more than preliminary at this time.
The potential ant it is tempting to infer a role for sigma receptors in
psychosis from these data, they must be considered no
more than preliminary at this time.
The potential antipsychotic agent BMY 14802 also
binds to sigma receptors (Tay

it is tempting to infer a role for sigma receptors in
psychosis from these data, they must be considered no
more than preliminary at this time.
The potential antipsychotic agent BMY 14802 also
binds to sigma receptors (Tay psychosis from these data, they must be considered no
more than preliminary at this time.
The potential antipsychotic agent BMY 14802 also
binds to sigma receptors (Taylor and Dekleva, 1987), and
it has a greater affinity more than preliminary at this time.
The potential antipsychotic agent BMY 14802 also
binds to sigma receptors (Taylor and Dekleva, 1987), and
it has a greater affinity for the site than rimcazole.
However, this compound ha The potential antipsychotic agent BMY 14802 also
binds to sigma receptors (Taylor and Dekleva, 1987), and
it has a greater affinity for the site than rimcazole.
However, this compound has never been tested on psy-
chotic p binds to sigma receptors (Taylor and Dekleva, 1987), and
it has a greater affinity for the site than rimcazole.
However, this compound has never been tested on psy-
chotic patients; its antipsychotic actions have been posit has a greater affinity for the site than rimcazole
However, this compound has never been tested on psy
chotic patients; its antipsychotic actions have been pos
tulated based on animal models of antipsychotic drug
action However, this compound has never been tested on psy-
chotic patients; its antipsychotic actions have been pos-
tulated based on animal models of antipsychotic drug
action (Matthews et al., 1986). In particular, this com-
p chotic patients; its antipsychotic actions have been pos-
tulated based on animal models of antipsychotic drug
action (Matthews et al., 1986). In particular, this com-
pound was found to reduce the avoidance behavior more
 tulated based on animal models of antipsychotic drug
action (Matthews et al., 1986). In particular, this com-
pound was found to reduce the avoidance behavior more
effectively than escape behavior in rats (Taylor et al.,
1 action (Matthews et al., 1986). In particular, this compound was found to reduce the avoidance behavior more effectively than escape behavior in rats (Taylor et al., 1990). Because many antipsychotics have this effect (Wor pound was found to reduce the avoidance behavior more
effectively than escape behavior in rats (Taylor et al.,
1990). Because many antipsychotics have this effect
(Worms et al., 1983), these data were taken as evidence
for fectively than escape behavior in rats (Taylor et al., 90). Because many antipsychotics have this effect Vorms et al., 1983), these data were taken as evidence r a selective antipsychotic action.
Based on current models of

1990). Because many antipsychotics have this effect (Worms et al., 1983), these data were taken as evidence for a selective antipsychotic action.

Based on current models of antipsychotic drug-induced movement disorders, T action (Matthews et al., 1986). In particular, this compound was found to reduce the avoidance behavior more effectively than escape behavior in rats (Taylor et al., 1990). Because many antipsychotics have this effect for for a selective antipsychotic action.
Based on current models of antipsychotic drug-induced
movement disorders, Taylor and Dekleva (1988) argued
that BMY 14802 will not cause motor effects in man
because it lacks activity Based on current models of antipsychotic drug-in
movement disorders, Taylor and Dekleva (1988) a
that BMY 14802 will not cause motor effects in
because it lacks activity at dopamine D_2 receptors
to induce catalepsy in movement disorders, Taylor and Dekleva (1988) argued
that BMY 14802 will not cause motor effects in man
because it lacks activity at dopamine D_2 receptors, fails
to induce catalepsy in rats, and reverses trifluperazine that BMY 14802 will not cause motor effects in man
because it lacks activity at dopamine D_2 receptors, fails
to induce catalepsy in rats, and reverses trifluperazine-
induced catalepsy. Although these findings are inde because it lacks activity at dopamine D_2 receptors, fails
to induce catalepsy in rats, and reverses trifluperazine-
induced catalepsy. Although these findings are indeed
encouraging, it must be noted that motor dysfunc to induce catalepsy in rats, and reverses trifluperazion
induced catalepsy. Although these findings are indencouraging, it must be noted that motor dysfunction
are produced by all sigma-active antipsychotic drugs
which the induced catalepsy. Although these findings are indeed
encouraging, it must be noted that motor dysfunctions
are produced by all sigma-active antipsychotic drugs for
which there is significant clinical experience. Further-
 encouraging, it must be noted that motor dysfunctions
are produced by all sigma-active antipsychotic drugs for
which there is significant clinical experience. Further-
more, the reliability of these animal models is not we are produced by all sigma-active antipsychotic drugs for which there is significant clinical experience. Furthermore, the reliability of these animal models is not well established, and the high affinity of BMY 14802 for 5 which there is significant clinical experience. Furthenore, the reliability of these animal models is not westablished, and the high affinity of BMY 14802 is $5HT_{1a}$ receptors raises questions about the mechanism mediati more, the reliability of these animal models is not well
established, and the high affinity of BMY 14802 for
5HT_{1a} receptors raises questions about the mechanism(s)
mediating its effects. This is problematic for the inh established, and the high affinity of BMY 14803
5HT_{1a} receptors raises questions about the mechanis
mediating its effects. This is problematic for the in
tion of trifluoperazine-induced catalepsy, because
selective $5HT_{$ $5HT_{1a}$ receptors raises questions about the mechanism(s)
mediating its effects. This is problematic for the inhibi-
tion of trifluoperazine-induced catalepsy, because the
selective $5HT_{1a}$ agonist 8-hydroxydipropylamin mediating its effects. This is problematic for the inhibition of trifluoperazine-induced catalepsy, because the selective $5HT_{1a}$ agonist 8-hydroxydipropylaminotetralin produces the same effect (McMillen et al., 1989). 5 tion of trifluoperazine-induced catalepsy, because the selective $5HT_{1a}$ agonist 8-hydroxydipropylaminotetralin produces the same effect (McMillen et al., 1989). $5HT_{1a}$ receptors also bind certain neuroleptics (Pedigo selective 5HT_{1a} agonist 8-hydroxydipropylaminotetralin
produces the same effect (McMillen et al., 1989). 5HT_{1a}
receptors also bind certain neuroleptics (Pedigo et al.,
1975; Wander et al., 1987) raising the possibility drugs. ceptors also bind certain neuroleptics (Pedigo et al., 75; Wander et al., 1987) raising the possibility that
is site may mediate certain effects of antipsychotic
ugs.
Despite the somewhat suggestive findings provided by
nc

1975; Wander et al., 1987) raising the possibility that
this site may mediate certain effects of antipsychotic
drugs.
Despite the somewhat suggestive findings provided by
rimcazole and BMY 14802, there are substantive line this site may mediate certain effects of antipsychotic drugs.

Despite the somewhat suggestive findings provided by

rimcazole and BMY 14802, there are substantive lines of

evidence that argue against a relationship betwe drugs.

Despite the somewhat suggestive findings provide

rimcazole and BMY 14802, there are substantive line

evidence that argue against a relationship between si

binding and antipsychotic efficacy. Although dopam

bind Despite the somewhat suggestive findings provided by
rimcazole and BMY 14802, there are substantive lines of
evidence that argue against a relationship between sigma
binding and antipsychotic efficacy. Although dopamine-
b rimcazole and BMY 14802, there are substantive lines of
evidence that argue against a relationship between sigma
binding and antipsychotic efficacy. Although dopamine-
binding properties of neuroleptics correlate closely w evidence that argue against a relationship between sigma
binding and antipsychotic efficacy. Although dopamine-
binding properties of neuroleptics correlate closely with
their antipsychotic effectiveness (Peroutka and Snyd binding and antipsychotic efficacy. Although dopamine-
binding properties of neuroleptics correlate closely with
their antipsychotic effectiveness (Peroutka and Snyder,
1980), no such correlation with sigma binding has bee binding properties of neuroleptics correlate closely with
their antipsychotic effectiveness (Peroutka and Snyder,
1980), no such correlation with sigma binding has been
found (see fig. 21 for comparison). Furthermore, drug their antipsychotic effectiveness (Peroutka and Snydu 1980), no such correlation with sigma binding has be
found (see fig. 21 for comparison). Furthermore, dru
such as clozapine and sulpiride show extremely po
binding to s 1980), no such correlation with sigma binding has been
found (see fig. 21 for comparison). Furthermore, drugs
such as clozapine and sulpiride show extremely poor
binding to sigma receptors yet bind to dopamine recep-
tors Cook, 1984). ch as clozapine and sulpiride show extremely poor
nding to sigma receptors yet bind to dopamine recep-
rs and have substantial antipsychotic effects (Tam and
ok, 1984).
Another blow to the sigma receptor hypothesis of
hizo

binding to sigma receptors yet bind to dopamine receptors and have substantial antipsychotic effects (Tam and Cook, 1984).
Cook, 1984). Another blow to the sigma receptor hypothesis of schizophrenia came from recent insigh tors and have substantial antipsychotic effects (Tam and Cook, 1984).

Another blow to the sigma receptor hypothesis of schizophrenia came from recent insights suggesting that

sigma receptors do not mediate the psychotomi Cook, 1984).

Another blow to the sigma receptor hypothesis of

schizophrenia came from recent insights suggesting that

sigma receptors do not mediate the psychotomimetic

actions of prototypic sigma ligands (Musacchio, 1

PHARMACOLOGICAL REVIEWS

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Avg Clinical Dose for Controlling Schizophrenia

(mg/day)

FIG. 21. Correlation between doses of neuroleptics required to control schizophrenia and binding potency at sigma $(left)$ and dopamine (rig

binding data from Seema FIG. 21. Correlation between dosen
binding data from Seeman (1981).
binding data from Seeman (1981). FIG. 21. Correlation between does of neuroleptics required to control secoptors. A strong relationship is found for dopamine but not sigma rechinding data from Seeman (1981).
This is problematic because theories of the und chizophrenia and binding potency at sigma $(left)$ and dopamine (rigceptors. Sigma-binding data from Tam and Cook (1984); dopamine strongly suggest that $(+)$ -opiates do not exert psychomimetic actions through the sigma recept

FIG. 21. Correlation between does of metrologics required to contract
proceptors. A strong relationship is found for dopamine but not signal
binding data from Seeman (1981).
This is problematic because theories of the unde binding data from Seeman (1981).
This is problematic because theories of the underlying
basis of psychosis inevitably rest upon psychotomimetic
or antipsychotic properties of prototypic ligands. For
example, the dopamine t This is problematic because theories of the underlying stress
basis of psychosis inevitably rest upon psychotomimetic tor
or antipsychotic properties of prototypic ligands. For the
example, the dopamine theory of schizophr basis of psychosis inevitably rest upon psychotomimetic
or antipsychotic properties of prototypic ligands. For
example, the dopamine theory of schizophrenia is
founded on amphetamine psychosis and the antipsy-
chotic activ basis of psychosis inevitably rest upon psychotomimetic
or antipsychotic properties of prototypic ligands. For
example, the dopamine theory of schizophrenia is
founded on amphetamine psychosis and the antipsy-
chotic activ or antipsychotic properties of prototypic ligands. For example, the dopamine theory of schizophrenia is founded on amphetamine psychosis and the antipsychotic activity and dopamine-antagonist action of neuroleptics (Snyder example, the dopamine theory of schizophrenifounded on amphetamine psychosis and the ant
chotic activity and dopamine-antagonist action of
roleptics (Snyder et al., 1974). Similarly, other the
rely on the psychotomimetic e founded on amphetamine psychosis and the antipsy-
chotic activity and dopamine-antagonist action of neu-
roleptics (Snyder et al., 1974). Similarly, other theories
rely on the psychotomimetic effects of phenylethyl-
amines chotic activity and dopamine-antagonist action of neu-

roleptics (Snyder et al., 1974). Similarly, other theories not

rely on the psychotomimetic effects of phenylethyl- Two

namines and PCP (Domino and Luby, 1973, Bower roleptics (Snyder et al., 1974). Similarly, other theories rely on the psychotomimetic effects of phenylethyl-
namines and PCP (Domino and Luby, 1973, Bowers, I
1987). Likewise, the psychotomimetic effects of SKF t
10,047, rely on the psychotomimetic effects of phenylethyl-

The painties and PCP (Domino and Luby, 1973, Bowers, P(

1987). Likewise, the psychotomimetic effects of SKF

10,047, together with the sigma actions of this compound ps amines and PCP (Domino and Luby, 1973, Bowers, PC
1987). Likewise, the psychotomimetic effects of SKF typ
10,047, together with the sigma actions of this compound psy
and the binding of neuroleptics to sigma receptors, wer 1987). Likewise, the psychotomimetic ef 10,047, together with the sigma actions of the antion of the binding of neuroleptics to sigma retaken to suggest a possible etiology of sching mechanism for antipsychotic drug action and the binding of neuroleptics to sigma receptors, were 1973).

taken to suggest a possible etiology of schizophrenia and The role of sigma receptors in psychosis remains am-

mechanism for antipsychotic drug action.

Al

and the binding of neuroleptics to sigma receptors, were
taken to suggest a possible etiology of schizophrenia and
mechanism for antipsychotic drug action. bi
Although the psychotomimetic actions of SKF 10,047 si
provided taken to suggest a possible etiology of schizophrenia and
mechanism for antipsychotic drug action. bi
Although the psychotomimetic actions of SKF 10,047 si
provided a logical basis for assuming a role of sigma bi
receptors mechanism for antipsychotic drug action.
Although the psychotomimetic actions of SKF 10,047
provided a logical basis for assuming a role of sigma
receptors in psychosis, a reevaluation of the data has
shown that it is ext Although the psychotomimetic actions of SKF 10,04
provided a logical basis for assuming a role of sigm-
receptors in psychosis, a reevaluation of the data ha
shown that it is extremely unlikely that sigma receptor
mediate provided a logical basis for assuming a role of sigma
receptors in psychosis, a reevaluation of the data has
shown that it is extremely unlikely that sigma receptors
mediate the psychotomimetic effects of $(+)$ -opiates.
Fo receptors in psychosis, a reevaluation of the data has
shown that it is extremely unlikely that sigma receptors
mediate the psychotomimetic effects of $(+)$ -opiates.
Foremost among these is the lack of psychotomimetic
actio shown that it is extremely unlikely that sigma receptors
mediate the psychotomimetic effects of $(+)$ -opiates.
Foremost among these is the lack of psychotomimetic
actions of the potent and selective sigma ligand $(+)$ -
pent mediate the psychotomimetic effects of $(+)$ -opiates. Is
Foremost among these is the lack of psychotomimetic e
actions of the potent and selective sigma ligand $(+)$ - h
pentazocine (Bellville and Forrest, 1967; Forrest et a Foremost among these is the lack of psychotomim
actions of the potent and selective sigma-ligand (
pentazocine (Bellville and Forrest, 1967; Forrest et
1969). Although the psychotomimetic effects of race
pentazocine have b actions of the potent and selective sigma ligand (+)-
pentazocine (Bellville and Forrest, 1967; Forrest et al.,
1969). Although the psychotomimetic effects of racemic
pentazocine have been cited as evidence for sigma-me-
d pentazocine (Bellville and Forrest, 1967; Forrest et al., 1969). Although the psychotomimetic effects of racemic pentazocine have been cited as evidence for sigma-mediated psychotomimetic symptoms in humans, this effect is 1969). Although the psychotomimetic effects of racemic
pentazocine have been cited as evidence for sigma-me-
diated psychotomimetic symptoms in humans, this effect
is reversed by naloxone (cf. Martin, 1984), demonstrating
 pentazocine have been cited as evidence for sigma-me-
diated psychotomimetic symptoms in humans, this effect the
is reversed by naloxone (cf. Martin, 1984), demonstrating m
mediation by opiate receptors, not sigma receptor has been widely used in humans for its antitussive propmediation by opiate receptors, not sigma receptors. Parties, the allel logic applies to studies of DM. This compound has psychothy relatively high affinity for sigma receptors (table 1) and the has been widely used in huma allel logic applies to studies of DM. This compound has relatively high affinity for sigma receptors (table 1) and has been widely used in humans for its antitussive properties, yet it does not have psychotomimetic effects

tomizophiema and binding potency at sigma (e_i) , and departure (r_i) , coeptors. Sigma-binding data from Tam and Cook (1984); dopamine-
strongly suggest that (+)-opiates do not exert psycho-
tomimetic actions through the si the conclusions do not exert psychotomimetic actions through the sigma receptor. However, these conclusions do not preclude antipsychotic actions of neuroleptics through the sigma-2 site, which has low strongly suggest that $(+)$ -opiates do not exert psycho-
tomimetic actions through the sigma-receptor. However,
these conclusions do not preclude antipsychotic actions
of neuroleptics through the sigma-2 site, which has lo strongly suggest that
tomimetic actions thro
these conclusions do n
of neuroleptics through
affinity for (+)-opiates
If the psychotomime mimetic actions through the sigma receptor. However,
ese conclusions do not preclude antipsychotic actions
neuroleptics through the sigma-2 site, which has low
finity for $(+)$ -opiates.
If the psychotomimetic effects of $(+$

these conclusions do not preclude antipsychotic actions
of neuroleptics through the sigma-2 site, which has low
affinity for $(+)$ -opiates.
If the psychotomimetic effects of $(+)$ -SKF 10,047 are
not sigma mediated, then wha of neuroleptics through the sigma-2 site, which has low
affinity for $(+)$ -opiates.
If the psychotomimetic effects of $(+)$ -SKF 10,047 are
not sigma mediated, then what is their biological basis?
Two logical possibilities a affinity for $(+)$ -opiates.
If the psychotomimetic effects of $(+)$ -SKF 10,047 are
not sigma mediated, then what is their biological basis?
Two logical possibilities are kappa-opiate receptors and
PCP receptors because $(+/-)$ If the psychotomimetic effects of $(+)$ -SKF 10,047 are
not sigma mediated, then what is their biological basis?
Two logical possibilities are kappa-opiate receptors and
PCP receptors because $(+/-)$ -SKF 10,047 binds to both
 Two logical possibilities are kappa-opiate receptors and PCP receptors because $(+/-)$ -SKF 10,047 binds to both types of receptors and both sites apparently mediate 1973). CP receptors because $(+/-)$ -SKF 10,047 binds to both
pes of receptors and both sites apparently mediate
ychotomimesis (Pfeiffer et al., 1986; Domino and Luby,
73).
The role of sigma receptors in psychosis remains am-
guous

is reversed by naloxone (cf. Martin, 1984), demonstrating metic effects of $(+)$ -opiates in humans. What is clear is
mediation by opiate receptors, not sigma receptors. Par-
allel logic applies to studies of DM. This compo types of receptors and both sites apparently mediate
psychotomimesis (Pfeiffer et al., 1986; Domino and Luby,
1973).
The role of sigma receptors in psychosis remains am-
biguous. On the positive side, the evidence shows t psychotomimesis (Pfeiffer et al., 1986; Domino and Luby, 1973).
1973).
The role of sigma receptors in psychosis remains am-
biguous. On the positive side, the evidence shows that
sigma receptors (*a*) are concentrated in l 1973).
The role of sigma receptors in psychosis remains ambiguous. On the positive side, the evidence shows that
sigma receptors (a) are concentrated in limbic areas, (b)
bind haloperidol and other neuroleptics with hig The role of sigma receptors in psychosis remains am-
biguous. On the positive side, the evidence shows that
sigma receptors (a) are concentrated in limbic areas, (b)
bind haloperidol and other neuroleptics with high or
 biguous. On the positive side, the evidence shows that
sigma receptors (a) are concentrated in limbic areas, (b)
bind haloperidol and other neuroleptics with high or
moderate affinity, and (c) bind certain novel potent bind haloperidol and other neuroleptics with high or moderate affinity, and (c) bind certain novel potential antipsychotics that are predicted from animal models to lack significant motor effects. On the negative side, t bind haloperidol and other neuroleptics with high or moderate affinity, and (c) bind certain novel potential
antipsychotics that are predicted from animal models to
lack significant motor effects. On the negative side, t moderate animity, and (c) bind certain nover potential
antipsychotics that are predicted from animal models to
lack significant motor effects. On the negative side, the
evidence shows that sigma receptors (a) are found in
 lack significant motor effects. On the negative side, the evidence shows that sigma receptors (a) are found in highest concentration in motor systems, not limbic areas; (b) bind rimcazole only weakly; (c) are of questi evidence shows that sigma receptors (a) are found in
highest concentration in motor systems, not limbic areas;
 (b) bind rimcazole only weakly; (c) are of questionable
significance in the actions of BMY 14802, because t highest concentration in motor systems, not limbic a (b) bind rimcazole only weakly; (c) are of question significance in the actions of BMY 14802, because compound binds to $5HT_{1a}$ receptors and has not tested in humans; (b) bind rimcazole only weakly; (c) are of questionable significance in the actions of BMY 14802, because the compound binds to 5HT_{1a} receptors and has not been tested in humans; and (d) do not mediate psychotomimetic e significance in the actions of BMY 14802, because the compound binds to $5HT_{1a}$ receptors and has not been tested in humans; and (d) do not mediate psychotomimetic effects of $(+)$ -opiates in humans. What is clear is tha compound binds to 5HT_{1a} receptors and has not been
tested in humans; and (d) do not mediate psychotomi-
metic effects of $(+)$ -opiates in humans. What is clear is
that the establishment of a role of sigma receptors in
p tested in humans; and (d) do not mediate psychotomi-
metic effects of $(+)$ -opiates in humans. What is clear is
that the establishment of a role of sigma receptors in
psychosis could have profound implications both for dr metic effects of (+)-opiates in humans. What is clear is
that the establishment of a role of sigma receptors in
psychosis could have profound implications both for drug
therapy and the prognosis of those afflicted with the that the establishment of a role of sigma receptors in psychosis could have profound implications both for dru
therapy and the prognosis of those afflicted with the
disease (Snyder and Largeut, 1989; Sonders et al. 1988
Th psychosis could have profound implications behavior of the prognosis of those afflicted
isease (Snyder and Largeut, 1989; Sonders of
Therefore, this question deserves to receive
ment before definite conclusions are drawn.

A. Pharmacological Evidence for Biologically Relevant Sigma Receptors

Sigma Receptors
In addition to the accumulating evidence for an endog-
enous ligand for sigma receptors, there is now consider-
able pharmacological data supporting its biological rele-A. Pharmacological Evidence for Biologically Relevant
Sigma Receptors
In addition to the accumulating evidence for an ence
enous ligand for sigma receptors, there is now consider-
able pharmacological data supporting its b A. Framacological Eculence for Biologically Relevant
Sigma Receptors
In addition to the accumulating evidence for an endog-
enous ligand for sigma receptors, there is now consider-
able pharmacological data supporting its In addition to the accumulating evidence for an endo
enous ligand for sigma receptors, there is now conside
able pharmacological data supporting its biological rel
vance. The strongest support is found in the high corr
la In addition to the accumulating evidence for an endog-
enous ligand for sigma-receptors, there is now consider-
able pharmacological data supporting its biological rele-
ing
vance. The strongest support is found in the hi enous ligand for sigma receptors, there is now consider-
able pharmacological data supporting its biological rele-
vance. The strongest support is found in the high corre-
lations (≥ 0.70) between sigma-binding affinit able pharmacological data supporting its biological relevance. The strongest support is found in the high correlations (≥ 0.70) between sigma-binding affinity and potency in at least four biological assay systems: (a) vance. The strongest support is found in the high corre-
lations (≥ 0.70) between sigma-binding affinity and for
potency in at least four biological assay systems: (a) PPI to
turnover (Bowen et al., 1988a; 1990b), (b) lations (≥ 0.70) between sigma-binding affinity and potency in at least four biological assay systems: (*a*) PPI turnover (Bowen et al., 1988a; 1990b), (*b*) stimulated guinea pig ileum (Campbell et al., 1989), (*c*) b potency in at least four biological assay systems: (*a*) turnover (Bowen et al., 1988a; 1990b), (*b*) stimulguinea pig ileum (Campbell et al., 1989), (*c*) blocitonic K⁺ currents in NCB-20 cells in culture (Bell et 1988) turnover (Bowen et al., 1988a; 1990b), (b) stimulated (C
guinea pig ileum (Campbell et al., 1989), (c) block of 19
tonic K⁺ currents in NCB-20 cells in culture (Bell et al., e_{X}
1988), and (d) torticollis induced guinea pig ileum (Campbell et al., 1989), (c) block of 19
tonic K⁺ currents in NCB-20 cells in culture (Bell et al., ex
1988), and (d) torticollis induced by rubral microinjec-
tions of sigma ligands (Matsumoto et al. 1988), and (d) torticollis induced by rubral microin
tions of sigma ligands (Matsumoto et al., 1990).
compounds used in all of these assays cover a b
range of chemical classes and include the most selec
and potent compou tions of sigma ligands (Matsumoto et al., 1990).
compounds used in all of these assays cover a larange of chemical classes and include the most selend potent compounds discussed above [e.g., $(+)$ -p
zocine, BD614, DTG, $(+)$ mpounds used in all of these assays cover a broad potent compounds discussed above [e.g., $(+)$ -pentational potent compounds discussed above [e.g., $(+)$ -pentatione, BD614, DTG, $(+)$ -SKF 10,047, haloperidol]. These function range of chemical classes and include the most selective
and potent compounds discussed above $[e.g., (+)-$ penta-
zocine, BD614, DTG, $(+)$ -SKF 10,047, haloperidol].
These functional assays appear to represent the activ-
ities o

and potent compounds discussed above [e.g., $(+)$ -penta-
zocine, BD614, DTG, $(+)$ -SKF 10,047, haloperidol].
These functional assays appear to represent the activ-
ities of different subtypes of the sigma receptor. Hellewel zocine, BD614, DTG, $(+)$ -SKF 10,047, haloperidol]. These functional assays appear to represent the activities of different subtypes of the sigma receptor. Hellewell and Bowen's sigma-1 site (1990), the site that follows These functional assays appear to represent the activities of different subtypes of the sigma receptor. Hellewell and Bowen's sigma-1 site (1990), the site that follows $B.A$ the binding profile established initially by Su ities of different subtypes of the sigma receptor. Hellewell
and Bowen's sigma-1 site (1990), the site that follows
the binding profile established initially by Su (1982) and
Tam (1983), appears to mediate the effects obse and Bowen's sigma-1 site (1990), the site that follows the binding profile established initially by Su (1982) and Tam (1983), appears to mediate the effects observed in the guinea pig ileum and in the PPI assay because (+ the binding profile established initially by Su (1982) and Populations of Sigma Receptors

Tam (1983), appears to mediate the effects observed in Current evidence suggests that all sigma ligands tested

the guinea pig ile the guinea pig ileum and in the PPI assay because $(+)$ -

opiates were more potent than $(-)$ -isomers and drugs sy
followed the binding profile shown by $[^{3}H]DTG$ and th
 $[^{3}H](+)$ -3-PPP in guinea pig brain.
Considerable evidence now suggests the existence and ag
functional sign followed the binding profile shown by $[^{3}H]DTG$ and the $[^{3}H](+)-3-PPP$ in guinea pig brain. It considerable evidence now suggests the existence and a functional significance of a second sigma site, termed stagma-2 by Hell [³H](+)-3-PPP in guinea pig brain.
Considerable evidence now suggests the existence and
functional significance of a second sigma site, termed
sigma-2 by Hellewell and Bowen (1990) and in this
review. (-)-Opiates are m Considerable evidence now suggests the existence and
functional significance of a second sigma site, termed
sigma-2 by Hellewell and Bowen (1990) and in this
review. $(-)$ -Opiates are more potent than $(+)$ -opiates a
this s functional significance of a second sigma site, termed stagma-2 by Hellewell and Bowen (1990) and in this tyreview. (-)-Opiates are more potent than (+)-opiates at acthis site, although its binding profile is clearly nonsigma-2 by Hellewell and Bowen (1990) and in t
review. (-)-Opiates are more potent than (+)-opiates
this site, although its binding profile is clearly no
opiate. Several laboratories have now encountered t
site in several review. $(-)$ -Opiates are more potent than $(+)$ -opiates at act
this site, although its binding profile is clearly non-
stra
opiate. Several laboratories have now encountered this 1484
site in several tissues: (a) Bowen and this site, although its binding profile is clearly non-
opiate. Several laboratories have now encountered this 148
site in several tissues: (*a*) Bowen and coworkers (Hellew-
e.gl and Bowen, 1990; Helewell et al., 1990) d opiate. Several laboratories have now encountered this 148
site in several tissues: (a) Bowen and coworkers (Hellew-
ell and Bowen, 1990; Helewell et al., 1990) describe it in lige
PC12 cells and rat liver, (b) Itzhak's gr ell and Bowen, 1990; Helewell et al., 1990) describe it in ligands. For example, DTG, haloperidol, $(+)$ -SKF 10,047,
PC12 cells and rat liver, (b) Itzhak's group has seen it in $(+)$ -pentazocine, and dextrallorphan all have ell and Bowen, 1990; Helewell et al., 1990) describe it in light PC12 cells and rat liver, (b) Itzhak's group has seen it in $(+657 \text{ black mouse brain}$ (Kassim et al., 1990), and (c) Wu effet al. (1990) have also discovered this s PC12 cells and rat liver, (b) Itzhak's group has seen it in $(+57 \text{ black mouse brain}$ (Kassim et al., 1990), and (c) Wu effect al. (1990) have also discovered this site in NCB-20 (Morells using Scatchard analysis and curve fitting. Th C57 black mouse brain (Kassim et al., 1990), and (c) Wu et al. (1990) have also discovered this site in NCB-20 cells using Scatchard analysis and curve fitting. The potency of a series of drugs for this site correlates h et al. (1990) have also discovered this site in NCB-20 (1) cells using Scatchard analysis and curve fitting. The icorrelates of a series of drugs for this site correlates highly V(0.96) with their potency in inhibiting a cells using Scatchard analysis and curve fitting. The ion potency of a series of drugs for this site correlates highly W. (0.96) with their potency in inhibiting a tonic K^+ conductance in these cells. Another report potency of a series of drugs for this site correlates highly W
(0.96) with their potency in inhibiting a tonic K^+ con-
ductance in these cells. Another report from studies of an
guinea pig brain (Reid et al., 1988) sho (0.96) with
ductance in
guinea pig dentancterist
not tested.
To date, ductance in these cells. Another report from studies of guinea pig brain (Reid et al., 1988) shows some of the characteristics of this site, although stereoisomers were not tested.
To date, the demonstrations of high corre

guinea pig brain (Reid et al., 1988) shows some of the characteristics of this site, although stereoisomers were not tested.
To date, the demonstrations of high correlations be tween sigma binding and potency in the rubral characteristics of this site, although stereoisomers we
not tested.
To date, the demonstrations of high correlations b
tween sigma binding and potency in the rubral/torticol
assay have not used stereoisomers. However, the reduced to the demonstrations of high correlations be-
vation sigma binding and potency in the rubral/torticollis SF
assay have not used stereoisomers. However, the obser-
vation that (+)-opiates are substantially less pot To date, the demonstrations of high correlations t tween sigma binding and potency in the rubral/torticol assay have not used stereoisomers. However, the observation that $(+)$ -opiates are substantially less potent the D tween sigma binding and potency in the rubral/torticc
assay have not used stereoisomers. However, the obvation that (+)-opiates are substantially less potent t
DTG or haloperidol would suggest actions at the sign
2 site. F assay have not used stereoisomers.
vation that (+)-opiates are substant
DTG or haloperidol would suggest 2
2 site. Further investigation of the
mers are needed to establish this.
The regulation of sigma receptor tion that $(+)$ -opiates are substantially less potent the Grand Correlation of the sigmatic. Further investigation of the actions of stereoisties are needed to establish this.
The regulation of sigma receptors by chronic a DTG or haloperidol would suggest actions at the sigma-
2 site. Further investigation of the actions of stereoiso-
mers are needed to establish this. et
The regulation of sigma receptors by chronic admin-
thistration of sig

2 site. Further investigation of the actions of stereoiso-
mers are needed to establish this. The regulation of sigma receptors by chronic admin-
interation of sigma drugs adds further support to the of the
notion that thi mers are needed to establish this. The regulation of sigma receptors by chronic admin-
The regulation of sigma receptors by chronic admin-
istration of sigma drugs adds further support to the of the presumed agonists.
noti

ET AL.
was altered by chronic administration of haloperidol
(Bremer et al., 1989; Itzhak and Alerhand, 1989; Mat-ET AL.
was altered by chronic administration of haloperide
(Bremer et al., 1989; Itzhak and Alerhand, 1989; Mat
sumoto et al., 1989b). It seems implausible that chroni ET AL.
was altered by chronic administration of haloperidol
(Bremer et al., 1989; Itzhak and Alerhand, 1989; Mat-
sumoto et al., 1989b). It seems implausible that chronic
administration of sigma ligands would alter the exp was altered by chronic administration of haloperi
(Bremer et al., 1989; Itzhak and Alerhand, 1989; M
sumoto et al., 1989b). It seems implausible that chrono
administration of sigma ligands would alter the expresion or affi was altered by cliftonic administration of haloperic
(Bremer et al., 1989; Itzhak and Alerhand, 1989; Ma
sumoto et al., 1989b). It seems implausible that chror
administration of sigma ligands would alter the expre
sion or

gunea pig neum (Campbell et al., 1989), (c) block of 1989). Demonstrations by other laboratories of brain tonic K⁺ currents in NCB-20 cells in culture (Bell et al., extracts with sigma activity add further support to th sumoto et al., 1989b). It seems implausible that chronology administration of sigma ligands would alter the expression or affinity of an inactive acceptor.
The demonstration of occupancy of sigma sites following focal elec administration of sigma ligands would alter the expression or affinity of an inactive acceptor.
The demonstration of occupancy of sigma sites following focal electrical stimulation or potassium- or veratridine-induced depo sion or affinity of an inactive acceptor.
The demonstration of occupancy of sigma sites following focal electrical stimulation or potassium- or veration-induced depolarization provides powerful eviden
for an endogenous neu The demonstration of occupancy of sigma sites following focal electrical stimulation or potassium- or veratridine-induced depolarization provides powerful evidence for an endogenous neurotransmitter for the sigma receptor ing focal electrical stimulation or potassium- or veratri-
dine-induced depolarization provides powerful evidence
for an endogenous neurotransmitter for the sigma recep-
tor and strengthens the case for its biological sign dine-induced depolarization provides powerful evidence
for an endogenous neurotransmitter for the sigma recep-
tor and strengthens the case for its biological significance
(Connors and Chavkin, 1990; Neumaier and Chavkin,
 tor and strengthens the case for its biological significance
(Connors and Chavkin, 1990; Neumaier and Chavkin, tor and strengthens the case for its biological significance (Connors and Chavkin, 1990; Neumaier and Chavkin, 1989). Demonstrations by other laboratories of brain extracts with sigma activity add further support to this n (Connors and Chavkin, 1990; Neumaier and Chavkin, 1989). Demonstrations by other laboratories of brain extracts with sigma activity add further support to this notion (Contreras et al., 1987a; Sonders et al., 1986; Su et a 1989). Demonstrations by other laboratories of brain extracts with sigma activity add further support to this notion (Contreras et al., 1987a; Sonders et al., 1986; Su et al., 1986; Su and Vaupel, 1988). Therefore, based o extracts with sigma activity add further support to this notion (Contreras et al., 1987a; Sonders et al., 1986; Su et al., 1986; Su and Vaupel, 1988). Therefore, based on the demonstrations that biological changes follow s notion (Contreras et al., 1987a; Sonders et al., 1986; Su et al., 1986; Su and Vaupel, 1988). Therefore, based on the demonstrations that biological changes follow sigma binding, that the site is regulated by administratio et al., 1986; Su and Vaupel, 1988). Therefore, based the demonstrations that biological changes follow signalized by administration sigma-active ligands, and that an endogenous ligand exists, we conclude that the sigma-bin the demonstration
binding, that the
sigma-active ligs
exists, we conclu
ically significant
R. Agonist Action *B. B. Agonist Actions of Sigma Ligarids, and that an endogenous ligand(s)* exists, we conclude that the sigma-binding site is biologically significant.
B. Agonist Actions of *Sigma Ligands, at Least at Some* Populatio *Populations of Sigma Receptors*
Populations of Sigma Ligan
Populations of Sigma Receptors
Populations of Sigma Receptors
Current evidence suggests that a

opiates were more potent than $(-)$ -isomers and drugs systems and act as agonists. This view contrasts with
followed the binding profile shown by [³H]DTG and the assertions of those investigators (e.g., Deutsch et al.,
Ally significant.

Agonist Actions of Sigma Ligands, at Least at Some

poulations of Sigma Receptors

Current evidence suggests that all sigma ligands tested

cept (+)-3-PPP have similar effects in physiological B. Agonist Actions of Sigma Ligands, at Least at Some
Populations of Sigma Receptors
Current evidence suggests that all sigma ligands tested
except $(+)$ -3-PPP have similar effects in physiologica
systems and act as agonis B. Agonist Actions of Sigma Ligands, at Least at Some
Populations of Sigma Receptors
Current evidence suggests that all sigma ligands tested
except $(+)$ -3-PPP have similar effects in physiological
systems and act as agoni Fopulations of Sigma Receptors
Current evidence suggests that all sigma ligands tested
except $(+)$ -3-PPP have similar effects in physiological
systems and act as agonists. This view contrasts with
the assertions of those Current evidence suggests that all sigma ligands tested
except $(+)$ -3-PPP have similar effects in physiological
systems and act as agonists. This view contrasts with
the assertions of those investigators (e.g., Deutsch et except $(+)$ -3-PPP have similar effects in physiological
systems and act as agonists. This view contrasts with
the assertions of those investigators (e.g., Deutsch et al.,
1988) who have stated or implied that $(+)$ -opiates systems and act as agonists. This view contrasts with
the assertions of those investigators (e.g., Deutsch et al.,
1988) who have stated or implied that (+)-opiates are
agonists at the sigma receptor, whereas haloperidol a the assertions of those investigators (e.g., Deutsch et al., 1988) who have stated or implied that (+)-opiates are agonists at the sigma receptor, whereas haloperidol and structurally related neuroleptic like compounds (su 1988) who have stated or implied that $(+)$ -opiates agonists at the sigma receptor, whereas haloperidol a structurally related neuroleptic like compounds (such typical neuroleptics, DTG, rimcazole, and BMY 1488 act as anta agonists at the sigma receptor, whereas haloperidol and
structurally related neuroleptic like compounds (such as
typical neuroleptics, DTG, rimcazole, and BMY 14802)
act as antagonists. The physiological evidence demon-
s typical neuroleptics, DTG, rimcazole, and BMY 14802) act as antagonists. The physiological evidence demonstrates that the actions of haloperidol, rimcazole, BMY 14802, and compounds with a similar binding profile (e.g., D typical neuroleptics, DTG, rimcazole, and BMY 14802)
act as antagonists. The physiological evidence demon-
strates that the actions of haloperidol, rimcazole, BMY
14802, and compounds with a similar binding profile
(e.g., act as antagonists. The physiological evidence demonstrates that the actions of haloperidol, rimcazole, BMY 14802, and compounds with a similar binding profile (e.g., DTG) are similar to those of the $(+)$ -opiate sigma lig strates that the actions of haloperidol, rimcazole, BMY
14802, and compounds with a similar binding profile
(e.g., DTG) are similar to those of the (+)-opiate sigma
ligands. For example, DTG, haloperidol, (+)-SKF 10,047,
((e.g., DTG) are similar to those of the $(+)$ -opiate sigma
ligands. For example, DTG, haloperidol, $(+)$ -SKF 10,047,
 $(+)$ -pentazocine, and dextrallorphan all have the same
effect on posture following intrarubral microinject ligands. For example, DTG, haloperidol, (+)-SKF 10,047,
(+)-pentazocine, and dextrallorphan all have the same
effect on posture following intrarubral microinjections
(Matsumoto et al., 1990; Walker et al., 1988). Using
ion (+)-pentazocine, and dextrallorphan all have the same

effect on posture following intrarubral microinjections

(Matsumoto et al., 1990; Walker et al., 1988). Using

iontophoretic application in the rat, Matsumoto and

Wa effect on posture following intrarubral microinjections (Matsumoto et al., 1990; Walker et al., 1988). Using iontophoretic application in the rat, Matsumoto and Walker (1988a,b) found that (+)-pentazocine and DTG both inhi (Matsumoto et al., 1990; Walker et al., 1988). Usin
iontophoretic application in the rat, Matsumoto an
Walker (1988a,b) found that (+)-pentazocine and DTG
both inhibit the firing rate of red nucleus neurons. Bowe
and colle iontophoretic application in the rat, Matsumoto and
Walker (1988a,b) found that (+)-pentazocine and DTG
both inhibit the firing rate of red nucleus neurons. Bowen
and colleagues (1988a; 1990b) showed that DTG, halo-
perido Walker (1988a,b) found that (+)-pentazocine and DTG
both inhibit the firing rate of red nucleus neurons. Bowen
and colleagues (1988a; 1990b) showed that DTG, halo-
peridol, fluphenazine, (+)-pentazocine, and several other
 both inhibit the firing rate of red nucleus neurons. Bot and colleagues (1988a; 1990b) showed that DTG, hiperidol, fluphenazine, (+)-pentazocine, and several ot sigma ligands all inhibit carbachol-stimulated (and of tremor and colleagues (1988a; 1990b) showed that DTG, halo-
peridol, fluphenazine, (+)-pentazocine, and several other
sigma ligands all inhibit carbachol-stimulated (and oxo-
tremorine-M-stimulated) PPI turnover in rat synapto-
n peridol, fluphenazine, (+)-pentazocine, and several other
sigma ligands all inhibit carbachol-stimulated (and oxo-
tremorine-M-stimulated) PPI turnover in rat synapto-
neurosomes. In a recent study similar actions of (+)-
 sigma ligands all inhibit carbachol-stimulated (and oxo-
tremorine-M-stimulated) PPI turnover in rat synapto-
neurosomes. In a recent study similar actions of (+)-
SKF 10,047, (+)-pentazocine, DTG, rimcazole, and BMY
14802 tremorine-M-stimulated) PPI turnover in rat synapto-
neurosomes. In a recent study similar actions of (+)-
SKF 10,047, (+)-pentazocine, DTG, rimcazole, and BMY
14802 on muscle contractions in the guinea pig ileum
(Campbell neurosomes. In a recent study similar actions of (+)-
SKF 10,047, (+)-pentazocine, DTG, rimcazole, and BMY
14802 on muscle contractions in the guinea pig ileum
(Campbell et al., 1989) were also demonstrated. Thus,
although SKF 10,047, (+)-pentazocine, DTG, rimcazole, and BMY
14802 on muscle contractions in the guinea pig ileum
(Campbell et al., 1989) were also demonstrated. Thus,
although a few reports discuss the possibility of sigma
antago 14802 on muscle contractions in the guinea pig ileum (Campbell et al., 1989) were also demonstrated. Thus, although a few reports discuss the possibility of sigma antagonist actions of certain compounds (e.g., Deutsch et a (Campbell et al., 1989) were also demonstrated. Thus,
although a few reports discuss the possibility of sigma
antagonist actions of certain compounds (e.g., Deutsch
et al., 1988; Ferris et al., 1986), most studies show tha although a few reports di
antagonist actions of cert
et al., 1988; Ferris et al.,
these substances produce of
the presumed agonists.
Stronger evidence fave tagonist actions of certain compounds (e.g., Deutsch
al., 1988; Ferris et al., 1986), most studies show that
ese substances produce effects that are similar to those
the presumed agonists.
Stronger evidence favoring agonis et al., 1988; Ferris et al., 1986), most studies show that
these substances produce effects that are similar to those
of the presumed agonists.
Stronger evidence favoring agonist actions of the
known sigma ligands stems fr

PHARMACOLOGICAL REVIEWS

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SIGMA F
sigma receptors by chronic administration of haloperidol
in mice (Itzhak and Alerhand, 1989) and rats (Bremer et sigma receptors by chronic administration of haloperidol
in mice (Itzhak and Alerhand, 1989) and rats (Bremer et
al., 1989; Matsumoto et al., 1989b). Although there are SIGMA RECEP
sigma receptors by chronic administration of haloperidol aff
in mice (Itzhak and Alerhand, 1989) and rats (Bremer et mi
al., 1989; Matsumoto et al., 1989b). Although there are
instances in which antagonists ar sigma receptors by chronic administration of haloperid
in mice (Itzhak and Alerhand, 1989) and rats (Bremer
al., 1989; Matsumoto et al., 1989b). Although there a
instances in which antagonists are suspected of dow
regulati sigma receptors by chronic administration of haloperidol
in mice (Itzhak and Alerhand, 1989) and rats (Bremer et
al., 1989; Matsumoto et al., 1989b). Although there are
instances in which antagonists are suspected of down in mice (Itzhak and Alerhand, 1989) and rats (Bremer et mindel, 1989). Although there are instances in which antagonists are suspected of down-regulation of a receptor, the weight of the evidence supports the view that do al., 1989; Matsumoto et al., 1989b). Although there are instances in which antagonists are suspected of down-
regulation of a receptor, the weight of the evidence asupports the view that down-regulation accompanies the
ac regulation of a receptor, the weight of the evidence
supports the view that down-regulation accompanies the
actions of agonist drugs (cf. Seeman, 1981). Thus, the
down-regulation of sigma receptors by haloperidol sugregulation of a receptor, the weight of the evidence aupports the view that down-regulation accompanies the actions of agonist drugs (cf. Seeman, 1981). Thus, the sidown-regulation of sigma receptors by haloperidol suggest supports the view that down-regulation accompanies the actions of agonist drugs (cf. Seeman, 1981). Thus, the down-regulation of sigma receptors by haloperidol suggests an agonist action at the sigma receptors. These obser actions of agonist drugs (cf. Seeman, 1981). Thus, the
down-regulation of sigma receptors by haloperidol sug-
gests an agonist action at the sigma receptors. These
observations, together with studies establishing similar
p gests an agonist action at the sigma receptors. These
observations, together with studies establishing similar
physiological actions of sigma compounds, imply that all
the known active sigma ligands are agonists.
C. Neurom *C. Neuromodulatory Actions of Sigma Compounds, imply*
C. Neuromodulatory Actions of Sigma Ligands
C. Neuromodulatory Actions of Sigma Ligands
From the findings discussed in this review, Music discussed in the findings discussed in this review, we may characterize in the findings discussed in this review, we may characterized points of Sigma Ligands
From the findings discussed in this review, we may charac

the known active sigma ligands are agonists. The conclude that sigma ligands are signal in this review, we may characterized that sigma ligands act primarily as yes neuromodulators. We use this term in the manner pro-C. Neuromodulatory Actions of Sigma Ligands
From the findings discussed in this review, we may
tentatively conclude that sigma ligands act primarily as
neuromodulators. We use this term in the manner pro-
posed originally C. *Neuromoauatory Actions of Sigma Liganas*
From the findings discussed in this review, we may
tentatively conclude that sigma ligands act primarily as
neuromodulators. We use this term in the manner pro-
posed originally tentatively conclude that sigma ligands act primarily as
neuromodulators. We use this term in the manner pro-
posed originally by Barker et al. (1978) to describe sub-
stances that act by altering the activity of another t tentatively conclude that sigma ligands act primarily as y
neuromodulators. We use this term in the manner pro-
posed originally by Barker et al. (1978) to describe sub-
tistances that act by altering the activity of anoth neuromodulators. We use this term in the manner pro-
posed originally by Barker et al. (1978) to describe sub-
stances that act by altering the activity of another trans-
mitter rather than by a direct action of their own. posed originally by Barker et al. (1978) to describe sub-
stances that act by altering the activity of another trans-
mitter rather than by a direct action of their own. This stappears to be a rather common process in the stances that act by altering the activity of another trans-
mitter rather than by a direct action of their own. This stappears to be a rather common process in the nervous is
system and it appears likely that many of the a mitter rather than by a direct action of their own. This suppears to be a rather common process in the nervous is system and it appears likely that many of the actions of esigma ligands are neuromodulatory in nature. In e appears to be a rather common process in the nervous is
system and it appears likely that many of the actions of en
sigma ligands are neuromodulatory in nature. In each of the
functional assays that appear to be sigma med system and it appears likely that many of the actions of sigma ligands are neuromodulatory in nature. In each of the functional assays that appear to be sigma mediate other transmitters appear to be involved: alteration of the functional assays that appear to be sigma mediated
other transmitters appear to be involved: alteration of
acetylcholine actions, 5HT actions, and electrically stim-
ulated tissues. The in vivo effects occur in systems other transmitters appear to be involved: alteration of acetylcholine actions, 5HT actions, and electrically stimulated tissues. The in vivo effects occur in systems in which ample opportunity exists for neuromodulation, i acetylcholine actions, 5HT actions, and electrically stim-
ulated tissues. The in vivo effects occur in systems in
which ample opportunity exists for neuromodulation, i.e.,
in "spontaneously" active systems such as the red ulated tissues. The in vivo effects occur in systems in wou which ample opportunity exists for neuromodulation, i.e., sion in "spontaneously" active systems such as the red nu-
cleus, cerebellum, and substantia nigra. By c which ample opportunity exists for neuromodulation, i.e., sion "spontaneously" active systems such as the red nu-
cleus, cerebellum, and substantia nigra. By contrast, clear sigma actions have been difficult to identify in cleus, cerebellum, and substantia nigra. By contrast, clear sigma actions have been difficult to identify in preparations that are free of external stimulation, such as in brain slice preparations treated with tetrodotoxin cleus, cerebellum, and substantia nigra. By contrast clear sigma actions have been difficult to identify in preparations that are free of external stimulation, such as in brain slice preparations treated with tetrodotoxin clear sigma actions have been difficult to identify in
preparations that are free of external stimulation, such
as in brain slice preparations treated with tetrodotoxin.
These observations encourage further studies of the preparations that a
as in brain slice pre
These observations
ity of sigma ligands
roactive substances *D. Clinical Implications* The investigants to modify the actions of other neu-
active substances.
Clinical Implications
The investigation into the clinical applicability of de
ma ligands is still in its infancy. One important ques-

roactive substances.

D. Clinical Implications

The investigation into the clinical applicability

sigma ligands is still in its infancy. One important ques-

tion is whether the motor effects of sigma ligands is cellum contains the motor sells. The investigation into the clinical applicability of dem
sigma ligands is still in its infancy. One important ques-
tion is whether the motor effects of sigma ligands in inve
animals reflec D. Canteal Impucations
The investigation into the clinical applicability of
sigma ligands is still in its infancy. One important ques-
tion is whether the motor effects of sigma ligands in
animals reflect processes that un The investigation into the clinical applicability of sigma ligands is still in its infancy. One important question is whether the motor effects of sigma ligands in animals reflect processes that underlie certain motodistur sigma ligands is still in its infancy. One important question is whether the motor effects of sigma ligands in animals reflect processes that underlie certain motor disturbances in acute or chronic antipsychotic drug thera tion is whether the motor effects of sigma ligands in in
animals reflect processes that underlie certain motor pl
disturbances in acute or chronic antipsychotic drug ther-
apy. Beyond these considerations is the possibilit animals reflect processes that underlie certain modisturbances in acute or chronic antipsychotic drug the possibility the apy. Beyond these considerations is the possibility the these drugs might have efficacy in the treat disturbances in acute or chronic antipsychotic drug the apy. Beyond these considerations is the possibility these drugs might have efficacy in the treatment certain motor disorders. In particular, motor distances in which apy. Beyond these considerations is the possibility that these drugs might have efficacy in the treatment of carectain motor disorders. In particular, motor disturbonices in which antipsychotics are used, such as Hunting-i these drugs might have efficacy in the treatment of
certain motor disorders. In particular, motor disturb-
ances in which antipsychotics are used, such as Hunting-
ton's chorea, dystonia, and Tourette's syndrome, are
candi certain motor disorders. In particular, motor disturb-
ances in which antipsychotics are used, such as Hunting-
ton's chorea, dystonia, and Tourette's syndrome, are fu
candidates. The presence of sigma receptors in the sub ances in which antipsychotics are used, such as Hunting-
ton's chorea, dystonia, and Tourette's syndrome, are
candidates. The presence of sigma receptors in the sub-
stantia nigra raises the possibility of the use of sigma ton's chorea, dystonia, and Tourette's syndrome, are candidates. The presence of sigma receptors in the substantia nigra raises the possibility of the use of sigma ligands in treating Parkinson's disease. Clinical trials m candidates. The presence of sigma receptors in the substantia nigra raises the possibility of the use of sigmiligands in treating Parkinson's disease. Clinical trial may not carry great liability, considering the apparenex stantia nigra raises the possibility of
ligands in treating Parkinson's disem
may not carry great liability, conside
excellent safety margin found in co
pounds [e.g., (+)-pentazocine, DM].
The other clear direction discuss rands in treating Parkinson's disease. Clinical trials I
ay not carry great liability, considering the apparent
cellent safety margin found in certain sigma com-
unds [e.g., (+)-pentazocine, DM].
The other clear direction may not carry great liability, considering the apparent excellent safety margin found in certain sigma compounds [e.g., (+)-pentazocine, DM].
The other clear direction discussed was the possibility of antipsychotic actions

excellent safety margin found in certain sigma com-
pounds [e.g., $(+)$ -pentazocine, DM].
The other clear direction discussed was the possibility
of antipsychotic actions of these compounds. The fact
that certain antidepre

affinity also raises the possibility that affective disorders **EPTORS** 397
affinity also raises the possibility that affective disorders
might be amenable to therapy with antipsychotic drugs.
 E Future Directions in the Pharmacology of Sigma ³⁹⁷
affinity also raises the possibility that affective disorders
might be amenable to therapy with antipsychotic drugs.
E. Future Directions in the Pharmacology of Sigma
Receptors

Receptors

sigma ligands are neuromodulatory in nature. In each of the possibility of developing an antagonist quite unlikely.
the functional assays that appear to be sigma mediated Conversely, the development of an antagonist would ight be amenable to therapy with antipsychotic drugs.
Future Directions in the Pharmacology of Sigma
ceptors
Many questions about the nature and function of the
gma receptor loom before us. Among the most pressing E. Future Directions in the Pharmacology of Sigma
Receptors
Many questions about the nature and function of the
sigma receptor loom before us. Among the most pressing
present needs are (a) the development of a sigma rece $E.$ Future Directions in the Pharmacology of Sigma
Receptors
Many questions about the nature and function of the
sigma receptor loom before us. Among the most pressing
present needs are (a) the development of a sigma rec Receptors
Many questions about the nature and function of the
sigma receptor loom before us. Among the most pressing
present needs are (a) the development of a sigma receptor
antagonist, (b) the identification of the endog Many questions about the nature and function of the sigma receptor loom before us. Among the most pressing present needs are (a) the development of a sigma receptor antagonist, (b) the identification of the endogenous l sigma receptor loom before us. Among the most pressing
present needs are (a) the development of a sigma receptor
antagonist, (b) the identification of the endogenous li-
gand(s) for the sigma-receptor, and (c) identifi present needs are (a) the development of a sigma receptor
antagonist, (b) the identification of the endogenous li-
gand(s) for the sigma receptor, and (c) identification of
the sequence of the sigma-binding protein. At gand(s) for the sigma receptor, and (c) identification of the sequence of the sigma-binding protein. At present, only a few assays have been studied in enough detail to make a reasonable connection between efficacy and gand(s) for the sigma receptor, and (c) identification of
the sequence of the sigma-binding protein. At present,
only a few assays have been studied in enough detail to
make a reasonable connection between efficacy and
s the sequence of the sigma-binding protein. At present only a few assays have been studied in enough detail t make a reasonable connection between efficacy and sigma binding. For each of these, it was necessary t characteri omly a rew assays have been studied in enough detail to make a reasonable connection between efficacy and sigma binding. For each of these, it was necessary to characterize many drugs and carry out correlational analyses t characterize many drugs and carry out correlational anal-
yeas to establish the connection to sigma receptors. In
addition to the tediousness of this approach, correla-
tional analyses are weak because they cannot establi characterize many drugs and carry out correlational anal-
yses to establish the connection to sigma receptors. In
addition to the tediousness of this approach, correla-
tional analyses are weak because they cannot establis yses to establish the connection to sigma receptors. In addition to the tediousness of this approach, correlational analyses are weak because they cannot establish a causal link. The main risk in this line of investigation addition to the tediousness of this approach, correlational analyses are weak because they cannot establish a causal link. The main risk in this line of investigation stems from the possibility that the sigma site may be a tional analyses are weak because they cannot establish a causal link. The main risk in this line of investigation stems from the possibility that the sigma site may be an ion channel site (such as the PCP site) or some oth causal link. The main risk in this line of investigation stems from the possibility that the sigma site may be an ion channel site (such as the PCP site) or some other entity rather than a neurotransmitter receptor, making stems from the possibility that the sigma site may be an
ion channel site (such as the PCP site) or some other
entity rather than a neurotransmitter receptor, making
the possibility of developing an antagonist quite unlike ion channel site (such as the PCP site) or some other
entity rather than a neurotransmitter receptor, making
the possibility of developing an antagonist quite unlikely.
Conversely, the development of an antagonist would ad entity rather than a neurotransmitter receptor, making
the possibility of developing an antagonist quite unlikely.
Conversely, the development of an antagonist would add
to the data supporting the biological relevance of t the possibility of developing an antagonist quite unlikel
Conversely, the development of an antagonist would acto
to the data supporting the biological relevance of the
sigma site. It is clear, therefore, that a sigma anta Conversely, the development of an antagonist would ad
to the data supporting the biological relevance of th
sigma site. It is clear, therefore, that a sigma antagonis
would overcome several problems, increasing the preci-
 to the data supporting
sigma site. It is clear, t
would overcome severation and hastening the
tion of sigma receptors
The identification of

The identification of the putative endogenous sigma would overcome several problems, increasing the preci-
sion and hastening the progress of research on the func-
tion of sigma receptors.
The identification of the putative endogenous sigma
ligand(s) is another major hurdle is ion and hastening the progress of research on the function of sigma receptors.

The identification of the putative endogenous sigma

ligand(s) is another major hurdle. Until this question is

resolved, we cannot be comp tion of sigma receptors.
The identification of the putative endogenous sigma
ligand(s) is another major hurdle. Until this question is
resolved, we cannot be completely secure in referring to
sigma-binding sites as recepto The identification of the putative endogenous sigma
ligand(s) is another major hurdle. Until this question is
resolved, we cannot be completely secure in referring to
sigma-binding sites as receptors. A similar logic appli ligand(s) is another major hurdle. Until this question is
resolved, we cannot be completely secure in referring to
sigma-binding sites as receptors. A similar logic applies
to the purification and sequencing of the sigma-b resolved, we cannot be completely secure in referring to
sigma-binding sites as receptors. A similar logic applies
to the purification and sequencing of the sigma-binding
protein, because by comparison to homologous struct to the purification and sequencing of the sigma-binding
protein, because by comparison to homologous structures
this may demonstrate beyond any reasonable doubt the
cellular function of this site. In this article, we have
 protein, because by comparison to homologous structure
this may demonstrate beyond any reasonable doubt th
cellular function of this site. In this article, we have
freely used the term sigma receptor based on severn
demons cellular function of this site. In this article, we have freely used the term sigma receptor based on several demonstrations pointing to its biological activity. However, it must be observed that sigma receptors cannot be cellular function of this site. In this article, we have freely used the term sigma receptor based on several demonstrations pointing to its biological activity. However, it must be observed that sigma receptors cannot be pharmacological) context until these problems are solved. These problems are solved. These questions notwithstanding, this review of the literature demonstrates that in recent years signifiever, it must be observed that sigma receptors cannot
investigated in their true neurobiological (rather th
pharmacological) context until these problems a
solved. These questions notwithstanding, this review
the literatur investigated in their true neurobiological (rather than
pharmacological) context until these problems are
solved. These questions notwithstanding, this review of
the literature demonstrates that in recent years signifi-
ca solved. These questions notwithstanding, this review of the literature demonstrates that in recent years significant advances have taken place in virtually every aspect of the sigma receptor research including medicinal ch solved. These questions notwithstanding, this review of
the literature demonstrates that in recent years signifi-
cant advances have taken place in virtually every aspect
of the sigma receptor research including medicinal

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Donohoe, Susan Huff, Keith A. Trujillo, John T. Williams, an *leen box of the correlates.*
 leen M. Acknowledgments. The authors are deeply grateful for the critical commentary and editorial assistance provided by Huda Akil, Eileen M. Donohoe, Susan Huff, Keith A. Trujillo, John T commentary and editorial assistance provided by Huda Akil, Eileen M.
Donohoe, Susan Huff, Keith A. Trujillo, John T. Williams, and Kathleen D. Walker. We thank Janice Viticonte for her help and patience
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