Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

## Copyright C 1988 by The American Society for Pharmacology and Experimental Therapeutics<br>Copyright C 1988 by The American Society for Pharmacology and Experimental Therapeutics<br>Dopamine Release in Vivo from Nigrostriatal,<br>M MCOLOGICAL REVIEWS<br>
MCOLOGICAL REVIEWS<br>
And Dopamine Release in Vivo from Nigrostriatal,<br>
Mesolimbic, and Mesocortical Neurons: Utility of 3-<br>
Methoxytyramine Measurements **Methoxytyramine Measurements**<br>
PAUL L. WOOD and C. ANTHONY ALTAR

*CNS Dsseoses Research, G. D. Searle & Co., Monsanto Company-AA4A, St. Louis, Missouri 63198 (P. L. W.), and Pharmacologka! Sciences,*







## **I. Introduction**

RESEARCH over the last decade has dramatically advanced our understanding of how drugs modify synaptic I. Introduction<br>RESEARCH over the last decade has dramatically advanced our understanding of how drugs modify synaptic<br>function. This knowledge encompasses a wide range of **Function**<br>**Function**<br>**RESEARCH** over the last decade has dramatically advanced our understanding of how drugs modify synaptic<br>function. This knowledge encompasses a wide range of<br>mechanisms involved in the production, rel EXEARCH over the last decade has dramatically advanced our understanding of how drugs modify synaptic (function. This knowledge encompasses a wide range of artimechanisms involved in the production, release, and postsynapt RESEARCH over the last decade has dramatically advanced our understanding of how drugs modify synaptic function. This knowledge encompasses a wide range of art mechanisms involved in the production, release, and postsynapt vanced our understanding of how drugs modify synaptic<br>function. This knowledge encompasses a wide range of<br>mechanisms involved in the production, release, and<br>postsynaptic coupling of received chemical signals. It is<br>the function. This knowledge encompasses a wide range of mechanisms involved in the production, release, and postsynaptic coupling of received chemical signals. It is the purpose of this review to integrate data from a number mechanisms involved in the production, release, and<br>postsynaptic coupling of received chemical signals. It is<br>the purpose of this review to integrate data from a<br>number of biochemical approaches which are relevant to<br>evalu postsynaptic coupling of received chemical signals. It is<br>the purpose of this review to integrate data from a<br>number of biochemical approaches which are relevant to<br>evaluating the concept that 3-methoxytyramine (3-MT)<br>is a the purpose of this review to integrate data from a<br>number of biochemical approaches which are relevant to<br>evaluating the concept that 3-methoxytyramine (3-MT)<br>is a metabolite of dopamine (DA) that is formed after<br>DA rele number of biochemical approaches which<br>evaluating the concept that 3-methoxyty;<br>is a metabolite of dopamine (DA) that i<br>DA release and is therefore a biochemic:<br>release (for abbreviations, see table 1).<br>Detailed studies of aluating the concept that 3-methoxytyramine  $(3-MT)$ <br>a metabolite of dopamine  $(DA)$  that is formed after<br>A release and is therefore a biochemical index of  $DA$ <br>lease (for abbreviations, see table 1).<br>Detailed studies of neu

is a metabolite of dopamine (DA) that is formed after<br>
DA release and is therefore a biochemical index of DA<br>
release (for abbreviations, see table 1).<br>
Detailed studies of neurotransmitter synthesis and<br>
postsynaptic rec DA release and is therefore a biochemical index of DA<br>release (for abbreviations, see table 1).<br>Detailed studies of neurotransmitter synthesis and<br>postsynaptic receptor function have been made possible<br>with the introductio release (for abbreviations, see table 1).<br>Detailed studies of neurotransmitter synthesis and<br>postsynaptic receptor function have been made possible<br>with the introduction of molecular approaches to neu-<br>roscience research. Detailed studies of neurotransmitter synthesis an postsynaptic receptor function have been made possible with the introduction of molecular approaches to neuroscience research. However, the intervening process neurotransmi postsynaptic receptor function have been made possible<br>with the introduction of molecular approaches to neu-<br>roscience research. However, the intervening process,<br>neurotransmitter release, is still the most difficult procwith the introduction of molecular approaches to neu-<br>roscience research. However, the intervening process,<br>neurotransmitter release, is still the most difficult proc-<br>ess to study, requiring in vivo procedures with which roscience research. However, the intervening process, the meurotransmitter release, is still the most difficult proc-<br>ess to study, requiring in vivo procedures with which<br>tonic actions of afferent fiber systems to chemic neurotransmitter release, is still the most difficult process to study, requiring in vivo procedures with which which tonic actions of afferent fiber systems to chemically endefined pathways can be monitored. Such in vivo ess to study, requiring in vivo procedures with which<br>tonic actions of afferent fiber systems to chemically<br>endefined pathways can be monitored. Such in vivo release<br>studies require sensitive analytical methods and, in man tonic actions of afferent fiber systems to chemically<br>defined pathways can be monitored. Such in vivo release<br>studies require sensitive analytical methods and, in many<br>dicases, complex surgical procedures are needed. In th defined pathways can be monitored. Such in vivo release studies require sensitive analytical methods and, in man cases, complex surgical procedures are needed. In the specific case of DA release, a number of approaches hav studies require sensitive analytical methods and, in many cases, complex surgical procedures are needed. In the specific case of DA release, a number of approaches have been extensively investigated, all of which use DA ov ses, complex surgical procedures are needed. In the ecific case of DA release, a number of approaches have en extensively investigated, all of which use DA over-<br>www as an index of DA release (see ref. 122 for review).<br>(a)

specific case of DA release, a number of approaches have<br>been extensively investigated, all of which use DA over-<br>flow as an index of DA release (see ref. 122 for review).<br>(a) With the *push-pull perfusion technique* (26, been extensively investigated, all of which use DA over-<br>flow as an index of DA release (see ref. 122 for review).<br>(a) With the *push-pull perfusion technique* (26, 126),<br>the push-pull cannula consists of two concentric t flow as an index of DA release (see ref. 122 for review).<br>
(a) With the *push-pull perfusion technique* (26, 126),<br>
the push-pull cannula consists of two concentric tubes<br>
which are stereotaxically inserted into a defined (a) With the *push-pull perfusion technique* (26, 126), the push-pull cannula consists of two concentric tubes which are stereotaxically inserted into a defined brain region. A perfusion fluid is pumped into this local br the push-pull cannula consists of two concentric tubes<br>which are stereotaxically inserted into a defined brain<br>region. A perfusion fluid is pumped into this local brain<br>region via the inner tube ("push") and the perfusate<br> which are stereotaxically inserted into a defined brain to j<br>region. A perfusion fluid is pumped into this local brain par<br>region via the inner tube ("push") and the perfusate foll<br>collected from the outer tube ("pull"). region. A perfusion fluid is pumped into this local brain<br>region via the inner tube ("push") and the perfusate<br>collected from the outer tube ("pull"). This approach,<br>however, suffers from the major problem of local and<br>var region via the inner tube ("push") and the perfusate follected from the outer tube ("pull"). This approach, however, suffers from the major problem of local and variable tissue damage at the tip of the cannula (122) and h collected from the outer tube ("pull"). This approach,<br>however, suffers from the major problem of local and A.<br>variable tissue damage at the tip of the cannula (122)<br>and has therefore been used to a greater extent in spec however, suffers from the major problem of local and <br>variable tissue damage at the tip of the cannula (122)<br>and has therefore been used to a greater extent in species<br>larger than the rat where larger brain regions can be variable tissue damage at the tip of the cannula (122)<br>and has therefore been used to a greater extent in species<br>larger than the rat where larger brain regions can be<br>perfused. Although never proven, this presumably limit and has ther<br>larger than<br>perfused. Alt<br>local tissue d<br>in the rat.<br>(b) With

perfused. Although never proven, this presumably limits local tissue damage compared to the use of this technique in the rat.<br>
(b) With the *cup technique*  $(26)$ , a brain region of interest is exposed and covered with a cup compared to the use of this technique<br>in the rat.<br>(b) With the *cup technique* (26), a brain region<br>interest is exposed and covered with a small plexigla<br>cup containing a perfusion fluid. The leakage of tran<br>mitters i in the rat.<br>
(b) With the *cup technique* (26), a brain region of to interest is exposed and covered with a small plexiglass cap containing a perfusion fluid. The leakage of transtinies into this fluid bathing the surface (b) With the *cup technique* (26), a brain region of interest is exposed and covered with a small plexiglass cup containing a perfusion fluid. The leakage of transmitters into this fluid bathing the surface of the area un interest is exposed and covered with a small plexiglass cause cup containing a perfusion fluid. The leakage of trans-<br>time mitters into this fluid bathing the surface of the areas two<br>under study is then monitored. This te cup containing a perfusion fluid. The leakage of transmitters into this fluid bathing the surface of the are under study is then monitored. This technique require radical surgery to remove overlying cortical areas the stri

tum, and has mainly been used in species larger than the rat.<br>
(c) With the ventricular perfusion technique  $(146)$ , rat.

m, and has mainly been used in species larger than the the *c* (c) With the *ventricular perfusion technique* (146), is ificial cerebrospinal fluid is perfused into the lateral tum, and has mainly been used in species larger than the rat.<br>
(c) With the *ventricular perfusion technique* (146), artificial cerebrospinal fluid is perfused into the lateral ventricle and collected from the cisterna mag tum, and has mainly been used in species larger than the rat.<br>
(c) With the *ventricular perfusion technique* (146) artificial cerebrospinal fluid is perfused into the latera<br>
ventricle and collected from the cisterna magn rat.<br>
(c) With the *ventricular perfusion technique* (146),<br>
artificial cerebrospinal fluid is perfused into the lateral<br>
ventricle and collected from the cisterna magna; how-<br>
ever, the site of origin of released neurotra (c) With the *ventricular perfusion*<br>artificial cerebrospinal fluid is perfuse<br>ventricle and collected from the ciste<br>ever, the site of origin of released neu<br>their metabolites can only be inferred.<br>(d) With in vivo volta ventricle and collected from the cisterna magna; how-<br>ever, the site of origin of released neurotransmitters or<br>their metabolites can only be inferred.<br>(d) With *in vivo voltammetry* (111), the oxidation of<br>locally release

ventricle and collected from the cisterna magna; how-<br>ever, the site of origin of released neurotransmitters or<br>their metabolites can only be inferred.<br>(d) With *in vivo voltammetry* (111), the oxidation of<br>locally releas ever, the site of origin of released neurotransmitters or<br>their metabolites can only be inferred.<br>(d) With in vivo voltammetry (111), the oxidation of<br>locally released catecholamines is monitored with a<br>graphite electrode. their metabolites can only be inferred.<br>
(d) With *in vivo voltammetry* (111), the oxidation of<br>
locally released catecholamines is monitored with a<br>
graphite electrode. In vivo voltammetry is unique in that<br>
it offers a r (d) With in vivo voltammetry  $(111)$ , the oxidation of locally released catecholamines is monitored with graphite electrode. In vivo voltammetry is unique in this it offers a real-time analysis of neurotransmitter release locally released catecholamines is monitored with<br>graphite electrode. In vivo voltammetry is unique in the<br>it offers a real-time analysis of neurotransmitter releas<br>However, the identity of the monitored electrochemic<br>sign graphite electrode. In vivo voltammetry is unique in<br>it offers a real-time analysis of neurotransmitter re<br>However, the identity of the monitored electroche<br>signal can only be inferred from general electroche<br>responses mea offers a real-time analysis of neurotransmitter release.<br>
bwever, the identity of the monitored electrochemical<br>
grad can only be inferred from general electrochemical<br>
gronses measured in vitro and is never absolute.<br>
(e)

However, the identity of the monitored electrochemical<br>signal can only be inferred from general electrochemical<br>responses measured in vitro and is never absolute.<br> $(e)$  With *intracerebral dialysis*  $(200, 215)$ , the use o signal can only be inferred from general electrochemical<br>responses measured in vitro and is never absolute.<br> $(e)$  With *intracerebral dialysis*  $(200, 215)$ , the use of a<br>selectively permeable dialysis membrane is involved responses measured in vitro and is never absolute.<br>
(e) With *intracerebral dialysis* (200, 215), the use of a<br>
selectively permeable dialysis membrane is involved, and<br>
therefore this technique is not susceptible to the d (e) With *intracerebral dialysis* (200, 215), the use of selectively permeable dialysis membrane is involved, at therefore this technique is not susceptible to the degrof local tissue damage observed with push-pull perfus selectively permeable dialysis membrane is involved, a<br>therefore this technique is not susceptible to the deg<br>of local tissue damage observed with push-pull perfusi<br>while allowing direct confirmation of the dialyzed end<br>en therefore this technique is not susceptible to the degree<br>of local tissue damage observed with push-pull perfusion,<br>while allowing direct confirmation of the dialyzed endog-<br>enous compounds. This method is limited by the r of local tissue damage observed with push-pull perfusion,<br>while allowing direct confirmation of the dialyzed endog-<br>enous compounds. This method is limited by the require-<br>ment of surgery, by the growth of a glial coating while allowing direct confirmation of the dialyzed endogenous compounds. This method is limited by the requirement of surgery, by the growth of a glial coating on the dialysis membrane, by the collection periods of 10 to 2 enous compounds. This method is limited by the req<br>ment of surgery, by the growth of a glial coating or<br>dialysis membrane, by the collection periods of 10 t<br>min, and by the sensitive analytical methods which<br>required to mo ment of surgery, by the growth of a glidialysis membrane, by the collection po<br>min, and by the sensitive analytical m<br>required to monitor the very low leve<br>mitter which diffuse into the dialysate.

## **II.** Methodology

quired to monitor the very low levels of neurotrans-<br>itter which diffuse into the dialysate.<br>II. Methodology<br>Since the steady-state levels of 3-MT are in the fmol<br>pmol per mg protein range, the measurement of this mitter which diffuse into the dialysate.<br>
II. Methodology<br>
Since the steady-state levels of 3-MT are in the fmol<br>
to pmol per mg protein range, the measurement of this<br>
parameter of DA release awaited the development of th II. Methodology<br>Since the steady-state levels of 3-MT are in the fmol<br>to pmol per mg protein range, the measurement of this<br>parameter of DA release awaited the development of the<br>following key methodological advances. following Since the steady-state levels of 3-MT<br>to pmol per mg protein range, the mea<br>parameter of DA release awaited the de<br>following key methodological advances. *A.* **A.** *A.* **A.** *A. A.**A.**Microwave**Tissue**Fixation***<br>***A.**Microwave**Tissue**Fixation***<br>***A. Microwave**Tissue**Fixation***<br>***After decapitation***, there is a** 

**EXECUTE:** Interest than the rat where larger brain regions can be<br> **EXECU 2.1.1.6)** to form 3-MT (42). This<br>
perfused. Although never proven, this presumably limits<br>
local tissue damage compared to the use of this techniq A. Microwave Tissue Fixation<br>After decapitation, there is a postmortem release of DA which is rapidly methylated by catechol-o-methyl-A. Microwave Tissue Fixation<br>After decapitation, there is a postmortem release of<br>DA which is rapidly methylated by catechol-o-methyl-<br>transferase (COMT; EC 2.1.1.6) to form 3-MT (42). This<br>postmortem accumulation has been A. *Mucrowave 1 issue Fixtation*<br>
After decapitation, there is a postmortem release of<br>
DA which is rapidly methylated by catechol-o-methyl-<br>
transferase (COMT; EC 2.1.1.6) to form 3-MT (42). This<br>
postmortem accumulation After decapitation, there is a postmortem release of<br>DA which is rapidly methylated by catechol-o-methyl-<br>transferase (COMT; EC 2.1.1.6) to form 3-MT (42). This<br>postmortem accumulation has been shown to be biphasic<br>with a DA which is rapidly methylated by catechol-o-methyl-<br>transferase (COMT; EC 2.1.1.6) to form 3-MT (42). This<br>postmortem accumulation has been shown to be biphasic<br>with an initial exponential phase followed by a linear<br>phas transferase (COMT; EC 2.1.1.6) to form 3-MT (42). This<br>postmortem accumulation has been shown to be biphasic<br>with an initial exponential phase followed by a linear<br>phase that continues for up to 2 h in the rat (42) and up postmortem accumulation has been shown to be biphasic<br>with an initial exponential phase followed by a linear<br>phase that continues for up to 2 h in the rat (42) and up<br>to 60 h, independent of age (1 to 84 yr), in human<br>caud with an initial exponential phase followed by a linear<br>phase that continues for up to 2 h in the rat  $(42)$  and up<br>to 60 h, independent of age  $(1 \text{ to } 84 \text{ yr})$ , in human<br>caudate-putamen  $(43, 168)$ . The biphasic curve fo phase that continues for up to 2 h in the rat (42) and up<br>to 60 h, independent of age (1 to 84 yr), in human<br>caudate-putamen (43, 168). The biphasic curve for early<br>time points in the rat (42) is presumably the result of<br>t to 60 h, independent of age  $(1$  to 84 yr), in human caudate-putamen  $(43, 168)$ . The biphasic curve for early time points in the rat  $(42)$  is presumably the result of two processes. At early times following death, there caudate-putamen (43, 168). The biphasic curve for early<br>time points in the rat (42) is presumably the result of<br>two processes. At early times following death, there is an<br>initial rapid release of DA which has been determin time points in the rat (42) is presumably the result of two processes. At early times following death, there is an initial rapid release of DA which has been determined with push-pull perfusion studies (26) and brain dialy

PHARMACOLOGICAL REVIEWS

## 3-MT MEASUREMENTS AND DA RELEASE *IN VIVO* FROM NEURONS <sup>165</sup>

# TABLE 1 *Explanation of ternu*





TTX Tetrodotoxin<br>U-50488H *trans-3*,4-Dichloro-N-methyl-N-[2-(1-pyrn<br>matic postmortem increase in 3-MT that results from a (20'<br>loss of monoamine oxidase (MAO) activity (MAO is an than<br>oxygen-dependent enzyme) and continue U-50488H Frans-3,4-Dichloro-N-methyl-N-<br>matic postmortem increase in 3-MT that results from<br>loss of monoamine oxidase (MAO) activity (MAO is a<br>oxygen-dependent enzyme) and continued COMT activ-<br>ity (168) which metabolicall matic postmortem increase in 3-MT that results from a (207 loss of monoamine oxidase (MAO) activity (MAO is an than oxygen-dependent enzyme) and continued COMT activ-<br>ity (168) which metabolically traps the released DA in matic postmortem increase in 3-MT that results from a (207<br>loss of monoamine oxidase (MAO) activity (MAO is an<br>oxygen-dependent enzyme) and continued COMT activ-<br>and<br>tity (168) which metabolically traps the released DA in<br> loss of monoamine oxidase (MAO) activity (MAO is an thoxygen-dependent enzyme) and continued COMT activity (168) which metabolically traps the released DA in nthe form of 3-MT (fig. 1). These biphasic surges in 3 postmort oxygen-dependent enzyme) and continued COMT activ-<br>ity (168) which metabolically traps the released DA in atte technique of in situ freezing in liquid nitrogen yields<br>the form of 3-MT (fig. 1). These biphasic surges in 3ity (168) which metabolically traps the released DA in<br>the form of 3-MT (fig. 1). These biphasic surges in<br>postmortem DA release emphasize the requirement for<br>rapid (i.e., ms) inactivation of COMT, which has only<br>been ach the form of  $3-MT$  (fig. 1). These biphasic surges in rapid (i.e., ms) inactivation of COMT, which has only

than sacrifice by freeze-blowing, since it is more rapid<br>(207). Microwave irradiation is also more convenient<br>than sacrifice by freeze-blowing, since it is more rapid<br>and allows microdissection of brain regions. The alter-Formally revendexy possesses and allows microdissection of brain regions. The alternate technique of in situ freezing in liquid nitrogen yield (207). Microwave irradiation is also more convenient<br>than sacrifice by freeze-blowing, since it is more rapid<br>and allows microdissection of brain regions. The alter-<br>nate technique of in situ freezing in liquid nitrogen yi (207). Microwave irradiation is also more convenient<br>than sacrifice by freeze-blowing, since it is more rapid<br>and allows microdissection of brain regions. The alter-<br>nate technique of in situ freezing in liquid nitrogen yi and allows microdissection of brain regions. The alternate technique of in situ freezing in liquid nitrogen yields MT levels which are intermediate between those ob-<br>ined by decapitation and microwave fixation (63).<br>Micropunch Methods<br>Micropunch techniques (136) allow discrete brain re-<br>pns to be microdissected from 250- to 1000-µm-thi

tained by decapitation and microwave fixation (63).<br>B. Micropunch Methods<br>Micropunch techniques (136) allow discrete brain re-<br>gions to be microdissected from 250- to 1000- $\mu$ m-thick

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

Downloaded from pharmrev.aspetjournals.org at Thammasart University on December 8, 2012

**a**spet



**DOPAMINE METABOLISM**

AD., aldehyde dehydrogenase (EC 1.2.1.3); *COMT,* catechol-O-meth- yltransferase (EC 2.1.1.6); *MAO,* **monoamine oxidase** (EC 1.4.3.4). FIG. 1. Metabolic routes for the degradation of DA in the CNS.<br>A.D., aldehyde dehydrogenase (EC 1.2.1.3); COMT, catechol-O-meth-<br>pltransferase (EC 2.1.1.6); MAO, monoamine oxidase (EC 1.4.3.4).<br>brain sections and have grea

**HVA**

ric. 1. Metabolic routes for the degradation of DA in the CNS.<br>A.D., aldehyde dehydrogenase (EC 1.2.1.3); COMT, catechol-O-meth-<br>yltransferase (EC 2.1.1.6); MAO, monoamine oxidase (EC 1.4.3.4).<br>brain sections and have gre resolution of neurochemical measurements of DA and its<br>metabolites (207).<br>C. Neuroanatomical Methods **Example 15 and have greatly<br><b>Fresolution of neurochemical methodites** (207).<br>*C. Neuroanatomical Methods*<br>Tyrosine hydroxylase immu

Tyrosine hydroxylase immunohistochemistry (117, 120), in situ hybridization of tyrosine hydroxylase mRNA (30), dopamine receptor binding (196), dopamine fluometabolites (207). 166)<br>
C. Neuroanatomical Methods<br>
Tyrosine hydroxylase immunohistochemistry (117, the n<br>
120), in situ hybridization of tyrosine hydroxylase mRNA zyme<br>
(30), dopamine receptor binding (196), dopamine flu C. Neuroanatomical Methods<br>
Tyrosine hydroxylase immunohistochemistry (117<br>
120), in situ hybridization of tyrosine hydroxylase mRNA<br>
(30), dopamine receptor binding (196), dopamine fluo-<br>
rescence microscopy (85, 118), qu by<br>Tyrosine hydroxylase immunohistochemistry (117, the<br>120), in situ hybridization of tyrosine hydroxylase mRNA zyn<br>(30), dopamine receptor binding (196), dopamine fluo-<br>rescence microscopy (85, 118), quantitative D-1 and Tyrosine hydroxylase immunohistochemistry (11<br>120), in situ hybridization of tyrosine hydroxylase mRN<br>(30), dopamine receptor binding (196), dopamine flu<br>rescence microscopy (85, 118), quantitative D-1 and D<br>receptor autor 120), in situ hybridization of tyrosine hydroxylase mRNA (30), dopamine receptor binding (196), dopamine fluorescence microscopy (85, 118), quantitative D-1 and D-2 (receptor autoradiography (9, 10), and fiber tracing met (30), dopamine receptor binding (196), dopamine fluorescence microscopy (85, 118), quantitative D-1 and D-2 receptor autoradiography (9, 10), and fiber tracing methods (178) have all been used to localize dopamine cell bod receptor autoradiography  $(9, 10)$ , and fiber tracing methods  $(178)$  have all been used to localize dopamine cell body and terminal areas in the brain. This data base is useful in the definition of brain regions to be mi useful in the definition of brain regions to be micro-

The first studies of drug effects on 3-MT dynamics dissected for neurochemical studies.<br>
D. Analytical Methods<br>
The first studies of drug effects on 3-MT dynamics<br>
utilized fluorescence spectroscopy. With this technique,<br>
baseline levels of 3-MT had to be elevated (99, 101 D. Analytical Methods<br>The first studies of drug effects on 3-MT dynamics<br>utilized fluorescence spectroscopy. With this technique,<br>baseline levels of 3-MT had to be elevated (99, 101) by<br>inhibition of 3-MT metabolism with m D. Analytical methods<br>
The first studies of drug effects on 3-MT dynamics<br>
utilized fluorescence spectroscopy. With this technique,<br>
baseline levels of 3-MT had to be elevated (99, 101) by<br>
inhibition of 3-MT metabolism w The first studies of drug effects on 3-MT dynamics<br>utilized fluorescence spectroscopy. With this technique,<br>baseline levels of 3-MT had to be elevated (99, 101) by<br>inhibition of 3-MT metabolism with monoamine oxidase<br>inhib utilized fluorescence spectroscopy. With this technique,<br>baseline levels of 3-MT had to be elevated (99, 101) by<br>inhibition of 3-MT metabolism with monoamine oxidase<br>inhibitors. Subsequently, several laboratories developed baseline levels of 3-MT had to be elevated (99, 101) by<br>inhibition of 3-MT metabolism with monoamine oxidase<br>inhibitors. Subsequently, several laboratories developed<br>a gas chromatography-mass fragmentographic (GC-MF)<br>assay inhibition of 3-MT metabolism with monoamine oxidase<br>inhibitors. Subsequently, several laboratories developed<br>a gas chromatography-mass fragmentographic (GC-MF)<br>assay using electron impact ionization (68, 105, 191, 225)<br>wh inhibitors. Subsequently, several laboratories developed<br>a gas chromatography-mass fragmentographic (GC-MF<br>assay using electron impact ionization (68, 105, 191, 225<br>which could detect striatal steady-state levels of 3-MT<br>i a gas chromatography-mass fragmentographic (GC-MF) assay using electron impact ionization (68, 105, 191, 225) which could detect striatal steady-state levels of 3-MT in animals sacrificed by focused microwave irradiation. negative chemical ionization conditions, which increased<br>by 42-fold the sensitivity of 3-MT measurements (63,<br>metabolism of DA. Intraneuronally, DA free in the cytosol is accessible which could detect striatal steady-state levels of 3-MT<br>in animals sacrificed by focused microwave irradiation.<br>This GC-MF assay was further improved by the use of<br>negative chemical ionization conditions, which increased<br>b in animals sacrificed by focused microwave irradia<br>This GC-MF assay was further improved by the u<br>negative chemical ionization conditions, which incre<br>by 42-fold the sensitivity of 3-MT measurements<br>206). Subsequently, hig This GC-MF assay was further improved by the use of<br>negative chemical ionization conditions, which increased<br>by 42-fold the sensitivity of 3-MT measurements (63,<br> $206$ ). Subsequently, high-pressure liquid chromatogra-<br>phy negative chemical ionization conditions, which increased<br>by 42-fold the sensitivity of 3-MT measurements (63,<br>206). Subsequently, high-pressure liquid chromatogra-<br>phy methods were established (145, 201) which could<br>measur by 42-fold the sensitivity of 3-MT measurements (63, meta<br>206). Subsequently, high-pressure liquid chromatogra-<br>phy methods were established (145, 201) which could from<br>measure striatal and olfactory tubercle 3-MT levels 206). Subsequently, high-pressure liquid chromatog<br>phy methods were established (145, 201) which counneasure striatal and olfactory tubercle 3-MT levels b<br>not cortical 3-MT (201). For the measurements of 3-N<br>in less densel phy methods were established (145, 201) which could<br>measure striatal and olfactory tubercle 3-MT levels but<br>not cortical 3-MT (201). For the measurements of 3-MT<br>in less densely innervated brain regions, such as neocor-<br>ti measure striatal and olfactory tubercle 3-MT levels but<br>not cortical 3-MT (201). For the measurements of 3-MT<br>in less densely innervated brain regions, such as neocor-<br>tical areas innervated by mesocortical dopaminerigic

Native of ALTAR<br>Were required (213). These refinements involved the<br>inclusion of a simple organic solvent extraction of do-INCOTTAR<br>
inclusion of a simple organic solvent extraction of do-<br>
pamine and 3-MT from acidic tissue extracts to reduce parameter and 3-MT from acidic tissue extraction of do-<br>pamine and 3-MT from acidic tissue extracts to reduce<br>background noise (213). were required  $(213)$ . The inclusion of a simple organine and  $3-MT$  from a background noise  $(213)$ . **Pamine and 3-MT from acidic tissue extracts to reduce background noise (213).**<br> **III. Biochemistry**<br> *A. 3-MT Steady-State Levels*<br> *I. Sources of 3-MT.* As summarized in figs. 1 and 2,

## III. **Biochemistry**

zyme immunohistochemistry  $(98)$ . These findings, and<br>studies of DA metabolite dynamics, have led to the<br>conclusions that DOPAC is an accurate index of intra-<br>DA Nerve Synaptic Postsynaptic conclusions that DOPAC is an accurate index of intra-*III.* Biochemistry<br>*1. Sources of 3-MT.* As summarized in figs. 1 and 2,<br>4 in dopaminergic nerve endings can be metabolized **III. Biochemistry**<br> **A. 3-MT Steady-State Levels**<br> **DA in dopaminergic nerve endings can be metabolized**<br> **DA in dopaminergic nerve endings can be metabolized**<br> **intraneuronally** (50, 108, 157, 199) by MAO to generate A. 3-MT Steady-State Levels<br>1. Sources of 3-MT. As summarized in figs. 1 and 2,<br>DA in dopaminergic nerve endings can be metabolized<br>intraneuronally (50, 108, 157, 199) by MAO to generate<br>dihydroxyphenylacetic acid (DOPAC). different actions of 3-MT. As summarized in figs. 1 and 2,<br>1. Sources of 3-MT. As summarized in figs. 1 and 2,<br>DA in dopaminergic nerve endings can be metabolized<br>intraneuronally (50, 108, 157, 199) by MAO to generate<br>dihy 1. Sources of 3-MT. As summarized in figs. 1 and 2,<br>DA in dopaminergic nerve endings can be metabolized<br>intraneuronally (50, 108, 157, 199) by MAO to generate<br>dihydroxyphenylacetic acid (DOPAC). This MAO pool<br>in the dopam intraneuronally (50, 108, 157, 199) by MAO to generate<br>
dihydroxyphenylaete caid (DOPAC). This MAO pool<br>
in the dopamine<br>rgic nerve endings of the rat striatum<br>
has been shown with 6-hydroxydopamine lesions to be<br>
monoami intraneuronally (50, 108, 157, 199) by MAO to generate<br>dihydroxyphenylacetic acid (DOPAC). This MAO pool<br>in the dopaminergic nerve endings of the rat striatum<br>has been shown with 6-hydroxydopamine lesions to be<br>monoamine o dihydroxyphenylacetic acid (DOPAC). This MAO po<br>in the dopaminergic nerve endings of the rat striatu<br>has been shown with 6-hydroxydopamine lesions to l<br>monoamine oxidase (type A) (MAO-A) (55, 123) and v<br>brain dialysis expe in the dopaminergic nerve endings of the rat striatum<br>has been shown with 6-hydroxydopamine lesions to be<br>monoamine oxidase (type A) (MAO-A) (55, 123) and via<br>brain dialysis experiments with selective MAO-A inhib-<br>itors (1 has been shown with 6-hydroxydopamine lesions to b<br>monoamine oxidase (type A) (MAO-A) (55, 123) and vi<br>brain dialysis experiments with selective MAO-A inhil<br>itors (100). In contrast, DA released into the synapt<br>cleft is in monoamine oxidase (type A) (MAO-A) (55, 123) and via<br>brain dialysis experiments with selective MAO-A inhib-<br>itors (100). In contrast, DA released into the synaptic<br>cleft is inactivated both by DA reuptake into the dopa-<br>mi brain dialysis experiments with selective MAO-A inhibitors (100). In contrast, DA released into the synaptic cleft is inactivated both by DA reuptake into the dopa-<br>minergic nerve ending and by methylation involving membra itors (100). In contrast, DA released into the synaptic<br>cleft is inactivated both by DA reuptake into the dopa-<br>minergic nerve ending and by methylation involving<br>membrane-bound COMT on postsynaptic neuronal ele-<br>ments (96 cleft is inactivated both by DA reuptake into the dopa<br>minergic nerve ending and by methylation involving<br>membrane-bound COMT on postsynaptic neuronal ele<br>ments (96, 98). Released DA is also taken up by glia (81<br>138) and p minergic nerve ending and by methylation involving<br>membrane-bound COMT on postsynaptic neuronal ele-<br>ments (96, 98). Released DA is also taken up by glia (81,<br>138) and possibly by local neurons. Within these com-<br>partments membrane-bound COMT on postsynaptic neuronal elements (96, 98). Released DA is also taken up by glia (81, 138) and possibly by local neurons. Within these compartments, DA is oxidized by MAO to form DOPAC (2, 55, 163, 175) 138) and possibly by local neurons. Within these compartments, DA is oxidized by MAO to form DOPAC (2, 55, 163, 175) and methylated by soluble COMT (96, 155, 166) to form 3-MT. Importantly, the dopaminergic nerve endings t 138) and possibly by local neurons. Within these compartments, DA is oxidized by MAO to form DOPAC (2, 55, 163, 175) and methylated by soluble COMT (96, 155, 166) to form 3-MT. Importantly, the dopaminergic nerve endings t partments, DA is oxidized by MAO to form DOPAC (2, 55, 163, 175) and methylated by soluble COMT (96, 155, 166) to form 3-MT. Importantly, the dopaminergic nerve endings themselves are devoid of COMT as determined by electr 55, 163, 175) and methylated by soluble COMT (96, 155, 166) to form 3-MT. Importantly, the dopaminergic nerve endings themselves are devoid of COMT as determined by electrolytic (96, 123) and chemical (2, 183) lesions of t 166) to form 3-MT. Importantly, the dopaminergic nerve<br>endings themselves are devoid of COMT as determined<br>by electrolytic (96, 123) and chemical (2, 183) lesions of<br>the nigrostriatal pathway and by observations with en-<br>z endings themselves are devoid of COMT as determined<br>by electrolytic (96, 123) and chemical (2, 183) lesions of<br>the nigrostriatal pathway and by observations with en-<br>zyme immunohistochemistry (98). These findings, and<br>stud by electrolytic (96, 123) and chemical (2, 183) lesions the nigrostriatal pathway and by observations with express immunohistochemistry (98). These findings, an studies of DA metabolite dynamics, have led to the conclusion



FIG. 2. Simplified working model of the neuronal and extraneuronal FIG. 2. Simplified working model of the neuronal and extraneuronal<br>metabolism of DA. Intraneuronally, DA free in the cytosol is accessible<br>to MAO and can be oxidized to form DOPAC which in turn can efflux<br>from the nerve en FIG. 2. Simplified working model of the neuronal and extraneuro<br>metabolism of DA. Intraneuronally, DA free in the cytosol is accessi<br>to MAO and can be oxidized to form DOPAC which in turn can eff<br>from the nerve ending to b n to immediate warming models in the cytosol is accessible<br>to MAO and can be oxidized to form DOPAC which in turn can efflux<br>from the nerve ending to be methylated to form the secondary metab-<br>olite HVA in both surrounding common or our manufactured in the manufacture of the domestic the domestic from the nerve ending to be methylated to form the secondary metabolite HVA in both surrounding glia and postsynaptic neurons. In the cleft, reupta from the nerve ending to be methylated to form the secondary metabolite HVA in both surrounding glia and postsynaptic neurons. In the cleft, reuptake of DA into the dopaminergic nerve ending, methylation by membrane-bound **form HVA.**

 $3-MT$  MEASUREMENTS AND DA RELEAS<br>neuronal DA metabolism (157, 199, 207) and that  $3-MT$ <br>is an index of DA release (207, 215), Homovanillic acid  $3-MT$  MEASUREMENTS AND DA RELEA<br>neuronal DA metabolism (157, 199, 207) and that  $3-MT$ <br>is an index of DA release (207, 215), Homovanillic acid<br>(HVA) is a secondary metabolite of both DOPAC and  $3-$ <sup>3-</sup>MT MEASUREMENTS AND DA RELI<br>neuronal DA metabolism (157, 199, 207) and that 3-MT<br>is an index of DA release (207, 215), Homovanillic acid<br>(HVA) is a secondary metabolite of both DOPAC *and* 3-<br>MT and is therefore of lim meuronal DA metabolism (157, 199, 207) and that 3-MT<br>is an index of DA release (207, 215), Homovanillic acid<br>(HVA) is a secondary metabolite of both DOPAC and 3-<br>MT and is therefore of limited utility in defining the<br>effec neuronal DA metabolism (157, 199, 207) and that 3-MT<br>is an index of DA release (207, 215), Homovanillic acid<br>(HVA) is a secondary metabolite of both DOPAC *and* 3-<br>MT and is therefore of limited utility in defining the<br>eff is an index of DA release (207<br>(HVA) is a secondary metaboli<br>MT and is therefore of limite<br>ffects of experimental manip<br>lease or metabolism (fig. 1).<br>In the case of 3-MT, levels IVA) is a secondary metabolite of both DOPAC and 3-<br>T and is therefore of limited utility in defining the<br>fects of experimental manipulations on dopamine re-<br>see or metabolism (fig. 1).<br>In the case of 3-MT, levels of this

MT and is therefore of limited utility in defining the effects of experimental manipulations on dopamine release or metabolism (fig. 1).<br>In the case of 3-MT, levels of this metabolite will be influenced by two different c effects of experimental manipulations on dopamine release or metabolism (fig. 1).<br>In the case of 3-MT, levels of this metabolite will b<br>influenced by two different compartments which contain<br>COMT: the synaptic cleft and gl lease or metabolism (fig. 1).<br>In the case of 3-MT, levels of this metabolite will be<br>influenced by two different compartments which contain<br>COMT: the synaptic cleft and glia (96, 155). Importantly,<br>the generation of 3-MT i In the case of 3-MT, levels of this metabolite will be<br>influenced by two different compartments which contain<br>COMT: the synaptic cleft and glia (96, 155). Importantly,<br>the generation of 3-MT in *either* compartment require influenced by two different compartments which contain<br>COMT: the synaptic cleft and glia (96, 155). Importantly<br>the generation of 3-MT in *either* compartment require<br>prior DA release and therefore can serve as an index o<br> COMT: the synaptic cleft and glia (96, 155). Importantly,<br>the generation of 3-MT in *either* compartment requires<br>prior DA release and therefore can serve as an index of<br>DA release. Thus, 3-MT is a relative, not a direct, the generation of 3-MT in *either* compartment requires<br>prior DA release and therefore can serve as an index of<br>DA release. Thus, 3-MT is a relative, not a direct, mea-<br>sure of DA release. The very rapid (5 to 10 min) chan prior DA release and therefore can serve as an index of DA release. Thus, 3-MT is a relative, not a direct, measure of DA release. The very rapid (5 to 10 min) changes in 3-MT following modifications of DA release (reviewe DA release. Thus, 3-MT is a relative, not a direct, m<br>sure of DA release. The very rapid (5 to 10 min) chan<br>in 3-MT following modifications of DA release (reviev<br>below) demonstrate the temporally close coupling<br>tween DA re sure of DA release. The very rapid<br>in 3-MT following modifications<br>below) demonstrate the temporative and 3-MT form<br>aptic compartments (215, 216).<br>2. Regional levels of 3-MT in ti 3-MT following modifications of DA release (reviewedow) demonstrate the temporally close coupling be<br>**2. Phonometrical A regional 3-MT** formation in these postsyntic compartments (215, 216).<br>2. *Regional levels of 3-MT*

below) demonstrate the temporally close coupling be-<br>tween DA release and 3-MT formation in these postsyn-<br>aptic compartments (215, 216).<br>2. Regional levels of 3-MT in the rat. A regional com-<br>parison of the steady-state l tween DA release and 3-MT formation in these postsyn-<br>aptic compartments  $(215, 216)$ .<br>2. Regional levels of 3-MT in the rat. A regional com-<br>parison of the steady-state levels of 3-MT in rat brain is<br>presented in table 2 aptic compartments  $(215, 216)$ .<br>
2. Regional levels of  $3-MT$  in the rat. A regional comparison of the steady-state levels of  $3-MT$  in rat brain is<br>
presented in table 2. The distribution of  $3-MT$  levels<br>
correlates well 2. Regional levels of  $3-MT$  in the rat. A regional comparison of the steady-state levels of  $3-MT$  in rat brain is presented in table 2. The distribution of  $3-MT$  level correlates well with the associated regional levels o parison of the steady-state levels of  $3-MT$  in rat brain is<br>presented in table 2. The distribution of  $3-MT$  levels<br>correlates well with the associated regional levels of DA<br>(6). An excellent agreement is obtained from nin presented in table 2. The distribution of 3-MT levels correlates well with the associated regional levels of DA (6). An excellent agreement is obtained from nine laboratories for absolute steady-state concentrations of striated 3-MT in microwave fixed tissues. The only except (6). An excellent agreement is obtained from nine laboratories for absolute steady-state concentrations of striated 3-MT in microwave fixed tissues. The only exception is found in a report  $(190)$  in which case basal 3-MT ratories for absolute steady-state concentrations of stria-<br>tal 3-MT in microwave fixed tissues. The only exception<br>is found in a report (190) in which case basal 3-MT levels<br>were in the typical range of concentrations rep tal 3-MT in microwave fixed tissues. The only<br>is found in a report  $(190)$  in which case basal 3-<br>were in the typical range of concentrations re<br>animals killed by decapitation  $(68)$ . Clearly,<br>suffered from inadequate mic found in a report (190) in which case basal 3-MT levels<br> *3.* Becies differences differences in 3-MT levels. Clearly, this study<br> *3. Species differences in 3-MT levels.* Of the four species<br>
which 3-MT has been measured f

were in the typical range of concentrations reported for<br>animals killed by decapitation (68). Clearly, this study<br>suffered from inadequate microwave fixation.<br>3. Species differences in 3-MT levels. Of the four species<br>in w animals killed by decapitation  $(68)$ . Clearly, this study<br>suffered from inadequate microwave fixation.<br>3. Species differences in  $3$ -MT levels. Of the four species<br>in which  $3$ -MT has been measured following microwave<br>ir suffered from inadequate microwave fixation.<br>
3. Species differences in  $3$ -MT levels. Of the four species<br>
in which  $3$ -MT has been measured following microwave<br>
irradiation, steady-state  $3$ -MT levels in the mouse, gerb 3. Species differences in  $3$ -MT levels. Of the four specin which  $3$ -MT has been measured following microws irradiation, steady-state  $3$ -MT levels in the mouse, ger and hamster striatum are all significantly greater the in which 3-MT has been measured following microwave<br>irradiation, steady-state 3-MT levels in the mouse, gerbil,<br>and hamster striatum are all significantly greater than<br>those observed in the rat (table 3; ref. 207). In a co irradiation, steady-state 3-MT levels in the mouse, gerbil,<br>and hamster striatum are all significantly greater than<br>those observed in the rat (table 3; ref. 207). In a compar-<br>ison of the kinetics of 3-MT in the rat and mo and hamster striatum are all significantly greater than<br>those observed in the rat (table 3; ref. 207). In a compar-<br>ison of the kinetics of 3-MT in the rat and mouse (216),<br>the fractional rate constant (the proportion of t those observed in the rat (table 3; ref. 207). In a comparison of the kinetics of 3-MT in the rat and mouse (216), the fractional rate constant (the proportion of the 3-MT pool that is metabolized per unit time) was deter ison of the kinetics of 3-MT in the rat and mouse (216),<br>the fractional rate constant (the proportion of the 3-MT<br>pool that is metabolized per unit time) was determined<br>after pargyline treatment. The fractional rate consta the fractional rate constant (the proportion of the 3-MT<br>pool that is metabolized per unit time) was determined<br>after pargyline treatment. The fractional rate constant<br>was 3 times greater in rat striatum and 6 times greate pool that is metabolized per unit time) was determined<br>after pargyline treatment. The fractional rate constant<br>was 3 times greater in rat striatum and 6 times greater<br>in rat striatal dialysates than in the mouse. These da after pargyline treatment. The fractional rate constant was 3 times greater in rat striatum and 6 times greater in rat striatal dialysates than in the mouse. These data suggest either that a greater proportion of released was 3 times greater in rat striatum and 6 times greater<br>in rat striatal dialysates than in the mouse. These data<br>suggest either that a greater proportion of released DA<br>in the rat striatum is methylated to form 3-MT or th rat striatal dialysates than in the mouse. These data agrest either that a greater proportion of released DA<br>the rat striatum is methylated to form 3-MT or that<br>e clearance of 3-MT differs in these two species.<br>4.  $3-MT$  *c* 

suggest either that a greater proportion of released DA<br>in the rat striatum is methylated to form 3-MT or that<br>the clearance of 3-MT differs in these two species.<br>4. 3-MT conjugation. Virtually all 3-MT is in the free<br>(no in the rat striatum is methylated to form 3-MT or that<br>the clearance of 3-MT differs in these two species.<br>4.  $3-MT$  conjugation. Virtually all 3-MT is in the free<br>(nonconjugated) form in both the rat (198) and mouse<br>(63) 4. 3-MT conjugation. Virtually all 3-MT is in the free<br>(nonconjugated) form in both the rat (198) and mouse<br>(63) striatum. However, in the cerebrospinal fluid (CSF)<br>of the squirrel monkey, dog, and human, 3-MT exists<br>main (nonconjugated) form in both the rat  $(198)$  and mouse  $(63)$  striatum. However, in the cerebrospinal fluid  $(CSF)$  of the squirrel monkey, dog, and human, 3-MT exists mainly in the conjugated form  $(63)$ . Both the human an (63) striatum. However, in the cerebrospinal fluid (CSF)<br>of the squirrel monkey, dog, and human, 3-MT exists<br>mainly in the conjugated form (63). Both the human and<br>squirrel monkey CSF contains approximately 1.2 pmol/<br>ml o of the squirrel monkey, dog, and human, 3-MT exists CO<br>mainly in the conjugated form (63). Both the human and<br>squirrel monkey CSF contains approximately 1.2 pmol/<br>ml of free 3-MT and 12 pmol/ml of conjugated 3-MT. It<br>from mainly in the conjugated form  $(63)$ . Both the human and squirrel monkey CSF contains approximately 1.2 pmol/ $\mu$  ml of free 3-MT and 12 pmol/ $\mu$ l of conjugated 3-MT. It from the reat brain but is further metabolized to squirrel monkey CSF contains approximately 1.2 pmol/<br>ml of free 3-MT and 12 pmol/ml of conjugated 3-MT. It<br>has been suggested that 3-MT is not cleared from the<br>rat brain but is further metabolized to HVA, since brain<br>3-MT ml of free 3-MT and 12 pmol/ml of conjugated 3-MT. It<br>has been suggested that 3-MT is not cleared from the<br>rat brain but is further metabolized to HVA, since brain<br>3-MT levels are stable for more than 3 h after inhibition<br> has been suggested that 3-MT is not cleared from the rat brain but is further metabolized to HVA, since brain 3-MT levels are stable for more than 3 h after inhibition of DA synthesis with alpha-methylparatyrosine (AMPT) i **B. 3-MT levels are stable for more than 3-MT levels are stable for more than 4-ME of DA synthesis with alpha-methyly in combination with monoamine of B. 3-Methoxytyramine Dynamics** 1. Enzyme inhibition. a. 3-MT ACC DA synthesis with alpha-methylparatyrosine (AMPT)<br>combination with monoamine oxidase inhibition (79).<br>3-*Methoxytyramine Dynamics*<br>1. *Enzyme inhibition*. a. 3-MT ACCUMULATION. In most<br>ain regions, the steady-state levels

TABLE 2 *Regional dopamine and 3-MT levels and 3-MTfractionoi rate constants for microwave-irradiated rat brain*

Region	Dopamine (pmol/mg protein)	$3-MT$	3-MT, $k(hr^{-1})$	Ref.
Striatum	670	2.9		77
		2.3		68
		1.5		78
		2.3		58
		2.4		47
		1.5		121
	642	1.4		225
	607	1.9	36.4	191
	497	1.1		145
	649	1.9		224
	588	1.8		211
	511	1.2	18.1	202
	520	2.0	17.7	203
	660	2.0	12.9	212
	590	2.5		128
	633	1.9		217
	388	2.2	8.9	160
	664	2.2	17.3	213
	597	2.8		94
	416	1.9		8
	456	2.7		6
	937	8.4		190
Nucleus accum- bens	429	2.4	$10.4*$	94
Olfactory tubule		1.7	8†	202
	485	1.7		6
	485	1.7	6.6	214
Prefrontal cortex	18	0.11	9.1	213
Cingulate cortex	11	0.11	15.5	213
	15	0.16		6
Hypothalamus	36	0.26		6
Entorhinal cortex	21	0.40		6
Hippocampus	15	0.25		6

\* Unpublished observations.

<sup>t</sup> Estimate based on one accumulation point after pargyline.

4. 3-MT conjugation. Virtually all 3-MT is in the free<br>(nonconjugated) form in both the rat (198) and mouse<br>(63) striatum. However, in the cerebrospinal fluid (CSF) monitoring the decline in 3-MT after treatment with the<br> in combination with monoamine oxidase inhibition (79). accumulation in the rat nucleus accumbens after inhibition  $B$ . 3-Methoxytyramine Dynamics<br>B. 3-Methoxytyramine Dynamics<br>I. Enzyme inhibition. a. 3-MT ACCUMULATION. I Hippocampus 15 0.25 6<br>
\* Unpublished observations.<br>
† Estimate based on one accumulation point after pargyline.<br>
than 1% of the DA steady-state levels (table 2). However,<br>
when the dynamics of this pool are examined either When the dynamics of this pool are examined either by<br>than 1% of the DA steady-state levels (table 2). However,<br>when the dynamics of this pool are examined either by<br>monitoring the decline in 3-MT after treatment with the monitoring the decline in 3-MT after pargyline.<br>than 1% of the DA steady-state levels (table 2). However,<br>when the dynamics of this pool are examined either by<br>monitoring the decline in 3-MT after treatment with the<br>COMT i than 1% of the DA steady-state levels (table 2). However,<br>when the dynamics of this pool are examined either by<br>monitoring the decline in 3-MT after treatment with the<br>COMT inhibitor, tropolone (191, 201), or by monitoring than 1% of the DA steady-state levels (table 2). However,<br>when the dynamics of this pool are examined either by<br>monitoring the decline in 3-MT after treatment with the<br>COMT inhibitor, tropolone (191, 201), or by monitoring when the dynamics of this pool are examined either by<br>monitoring the decline in 3-MT after treatment with the<br>COMT inhibitor, tropolone (191, 201), or by monitoring<br>the accumulation of 3-MT after inhibition of MAO with<br>pa COMT inhibitor, tropolone (191, 201), or by monitoring<br>the accumulation of 3-MT after inhibition of MAO with<br>pargyline (212, 213), fractional rate constants ranging<br>from 7 to 19 h<sup>-1</sup> are obtained depending upon the brain the accumulation of 3-MT after inhibition of MAO with<br>pargyline (212, 213), fractional rate constants ranging<br>from 7 to 19 h<sup>-1</sup> are obtained depending upon the brain<br>region examined. A high rate constant of 36 was report from 7 to 19  $h^{-1}$  are obtained depending upon the brain region examined. A high rate constant of 36 was reported in one study (191), but this was based on the use of only a zero time group and a group sacrificed after 1 region examined. A high rate constant of 36 was reported treatment with tropolone. In fig. 3, an example of 3-MT in one study (191), but this was based on the use of only<br>a zero time group and a group sacrificed after 1-min<br>treatment with tropolone. In fig. 3, an example of 3-MT<br>accumulation in the rat nucleus accumbens after inhibia zero time group and a group sacrificed after 1-min<br>treatment with tropolone. In fig. 3, an example of 3-MT<br>accumulation in the rat nucleus accumbens after inhibi-<br>tion of MAO with pargyline is presented. A comparison<br>of treatment with tropolone. In fig. 3, an example of 3-MT accumulation in the rat nucleus accumbens after inhibition of MAO with pargyline is presented. A comparison of the dynamics of 3-MT compared to the DA pool and other accumulation in the rat nucleus accumbens after inhibition of MAO with pargyline is presented. A comparison of the dynamics of 3-MT compared to the DA pool and other metabolite pools is presented in table 4. These data ind

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

REVIEW





Pool	<b>Steady state</b> (pmol/mg protein)	k $(h^{-1})$	Turnover rate (pmol/mg protein/h)
DA	$620 \pm 15^*$	0.21	$130 \pm 6$
$3-MT$	$2 \pm 0.1$	12.9	$26 \pm 2$
<b>DOPAC</b>	$68 \pm 3$	2.3	$156 \pm 10$
<b>HVA</b>	$58 \pm 2$	$1.3\,$	$75 \pm 4$
	<b>*</b> Mean $\pm$ SEM $(n = 7 \text{ to } 10)$ .		

HVA  $58 \pm 2$  1.3  $75 \pm 4$ <br>
\* Mean  $\pm$  SEM  $(n = 7 \text{ to } 10)$ .<br>
to DA, DOPAC, or HVA, 3-MT is the most dynamic DA<br>
metabolite with a fractional rate constant of 12.9 h<sup>-1</sup>.<br>
These rapid dynamics of the 3-MT pool are also obs \* Mean  $\pm$  SEM  $(n = 7 \text{ to } 10)$ .<br>
to DA, DOPAC, or HVA, 3-MT is the most dynamic DA<br>
metabolite with a fractional rate constant of 12.9 h<sup>-1</sup>.<br>
These rapid dynamics of the 3-MT pool are also observed<br>
with precursor label sta<br>to DA, DOPAC, or HVA, 3-MT is the most dynamic DA vat<br>metabolite with a fractional rate constant of 12.9 h<sup>-1</sup>. hig<br>These rapid dynamics of the 3-MT pool are also observed face<br>with precursor labeling studies. For exam to DA, DOPAC, or HVA, 3-MT is the most dynamic<br>metabolite with a fractional rate constant of 12.9<br>These rapid dynamics of the 3-MT pool are also obse<br>with precursor labeling studies. For example, after<br>intraventricular (77 metabolite with a fractional rate constant of  $12.9 h^{-1}$ . These rapid dynamics of the 3-MT pool are also observed factorially with precursor labeling studies. For example, after both do intraventricular (77) and intraveno These rapid dynamics of the 3-MT pool are also observed<br>with precursor labeling studies. For example, after both<br>intraventricular (77) and intravenous (185) administra-<br>tion of  $[^3H]$ tyrosine, 3-MT is the DA metabolite wi with precursor labeling studies. For example, aftituded intraventricular (77) and intravenous (185) adm<br>tion of [<sup>3</sup>H] tyrosine, 3-MT is the DA metabolite v<br>highest specific activity, supporting a preferential<br>released DA traventricular (77) and intravenous (185) administration of [<sup>3</sup>H]tyrosine, 3-MT is the DA metabolite with the ghest specific activity, supporting a preferential flux cleased DA through the 3-MT metabolic pool.<br>b. MULTIPLE tion of [<sup>3</sup>H]tyrosine, 3-MT is the DA metabolite with the highest specific activity, supporting a preferential flux of released DA through the 3-MT metabolic pool.<br>b. MULTIPLE DA POOLS. One complication in interpreting DA

highest specific activity, supporting a preferential flux<br>released DA through the 3-MT metabolic pool.<br>b. MULTIPLE DA POOLS. One complication in inte<br>preting DA metabolite changes is the possibility of mu<br>tiple DA pools wh released DA through the 3-MT metabolic pool.<br>b. MULTIPLE DA POOLS. One complication in inter-<br>preting DA metabolite changes is the possibility of mul-<br>tiple DA pools which can be mobilized to support trans-<br>mission. Early

**WOOD AND ALTAR**<br>in resolving the different DA pools available for release<br> $\frac{e^{rC}}{rC}$  (50, 199). However, studies using in vivo voltammetry in (50, 199).<br>
Suppose the different DA pools available for release<br>
(50, 199). However, studies using in vivo voltammetry in<br>
the rat striatum along with electrical stimulation of the In resolving the different DA pools available for release (50, 199). However, studies using in vivo voltammetry in the rat striatum along with electrical stimulation of the medial forebrain bundle (MFB) have indicated that in resolving the different DA pools available for release (50, 199). However, studies using in vivo voltammetry in the rat striatum along with electrical stimulation of the medial forebrain bundle (MFB) have indicated tha in resolving the different DA pools available for release (50, 199). However, studies using in vivo voltammetry in the rat striatum along with electrical stimulation of the medial forebrain bundle (MFB) have indicated tha (50, 199). However, studies using in vivo voltammetry in<br>the rat striatum along with electrical stimulation of the<br>medial forebrain bundle (MFB) have indicated that the<br>rate constant for the releasable DA pool is  $2.76 \text{$ the rat striatum along with electrical stimulation of t<br>medial forebrain bundle (MFB) have indicated that t<br>rate constant for the releasable DA pool is  $2.76 \text{ h}^{-1}$  (13<br>A similar value of 2.5 was obtained for the extrac medial forebrain bundle (MFB) have indicated that the rate constant for the releasable DA pool is  $2.76 h^{-1}$  (130). A similar value of  $2.5$  was obtained for the extracellular DA pool in the rat striatum after treatment w rate constant for the releasable DA pool is  $2.76 h^{-1}$  (130).<br>A similar value of 2.5 was obtained for the extracellular<br>DA pool in the rat striatum after treatment with pargy-<br>line (fig. 4) and monitoring DA release with A similar value of 2.5 was obtained for the extracellular<br>DA pool in the rat striatum after treatment with pargy-<br>line (fig. 4) and monitoring DA release with striatal<br>dialysis (215, 216). These values are approximately 10 DA pool in the rat striatum after treatment with pargy-<br>line (fig. 4) and monitoring DA release with striatal<br>dialysis (215, 216). These values are approximately 10<br>times the values obtained for the turnover of the total<br>D line (fig. 4) and monitoring DA release with striatal dialysis (215, 216). These values are approximately 10 times the values obtained for the turnover of the total DA pool using precursor labels or inhibition of synthesis dialysis (215, 216). These values are approximately 10 times the values obtained for the turnover of the total DA pool using precursor labels or inhibition of synthesis (108, 199). These data suggest that the releasable po times the values obtained for the turnover of the total<br>DA pool using precursor labels or inhibition of synthesis<br>(108, 199). These data suggest that the releasable pool of<br>DA is smaller and more dynamic than the total neu DA pool using precursor labels or inhibition of synthesis (108, 199). These data suggest that the releasable pool of DA is smaller and more dynamic than the total neuronal stores of DA within the striatum (216). Studies o (108, 199). These data suggest that the releasable pool of DA is smaller and more dynamic than the total neuronal stores of DA within the striatum (216). Studies of the dynamics of the recovery of DA release in the striat DA is smaller and more dynamic than the total neuronal<br>stores of DA within the striatum (216). Studies of the<br>dynamics of the recovery of DA release in the striatum<br>after 10-Hz electrical stimulation of the MFB have sug-<br>g stores of DA within the striatum (216). Studies of the<br>dynamics of the recovery of DA release in the striatum<br>after 10-Hz electrical stimulation of the MFB have sug-<br>gested that, acutely (from 0.5 to 2 min), this process<br>i dynamics of the recovery of DA release in the striatum<br>after 10-Hz electrical stimulation of the MFB have sug-<br>gested that, acutely (from 0.5 to 2 min), this process<br>involves DA mobilization from another pool and does<br>not after 10-Hz electrical stimulation of the MFB have suggested that, acutely (from 0.5 to 2 min), this process involves DA mobilization from another pool and does not involve DA synthesis except in the case of continued long gested that, acutely (from 0.5 to 2 min), this process<br>involves DA mobilization from another pool and does<br>not involve DA synthesis except in the case of continued<br>longer term stimulation (129). The roles of multiple<br>vesic involves DA mobilization from another pool and does<br>not involve DA synthesis except in the case of continued<br>longer term stimulation (129). The roles of multiple<br>vesicular and/or cytosolic DA pools remain to be defined.<br>Ho not involve DA synthesis except in the case of continued<br>longer term stimulation (129). The roles of multiple<br>vesicular and/or cytosolic DA pools remain to be defined.<br>However, in the same paradigm, amfonelic acid was<br>sho longer term stimulation (129). The roles of multiple vesicular and/or cytosolic DA pools remain to be defined.<br>However, in the same paradigm, amfonelic acid was shown to mobilize a DA pool after inhibition of DA vesicular and/or cytosolic DA pools remain to be defined.<br>However, in the same paradigm, amfonelic acid was<br>shown to mobilize a DA pool after inhibition of DA<br>synthesis with AMPT (59). These data support the con-<br>cept of m However, in the same paradigm, amfonelic acid was<br>shown to mobilize a DA pool after inhibition of DA<br>synthesis with AMPT (59). These data support the con-<br>cept of multiple vesicular DA pools (77). Reserpine ex-<br>periments shown to mobilize a DA pool after inhibition of synthesis with AMPT (59). These data support the coept of multiple vesicular DA pools (77). Reserpine periments also support the role of a nonvesicular is pool in some drug e cept of multiple vesicular DA pools  $(77)$ . Reserpine experiments also support the role of a nonvesicular DA pool in some drug effects  $(197, 202)$ . This pool contributes to approximately  $20\%$  of the 3-MT steady-state l cept of multiple vesicular DA pools (77). Reserpine experiments also support the role of a nonvesicular DA pool in some drug effects (197, 202). This pool contributes to approximately 20% of the 3-MT steady-state levels ob periments also support the role of a nonvesicular DA<br>pool in some drug effects (197, 202). This pool contrib-<br>utes to approximately 20% of the 3-MT steady-state<br>levels observed in the rat striatum (216) with the re-<br>mainin pool in some drug effects (197, 202). This pool contributes to approximately 20% of the 3-MT steady-state levels observed in the rat striatum (216) with the remaining 80% presumably being derived from vesicular DA pools.<br>

maining 80% presumably being derived from vesicular<br>DA pools.<br>c. 3-MT ACCUMULATION VERSUS STEADY-STATE MEAS-<br>UREMENTS. The accumulation of 3-MT after inhibition<br>of MAO has been used to measure, via 3-MT, the effects<br>of dru DA pools.<br>
c. 3-MT ACCUMULATION VERSUS STEADY-STATE MEAS-<br>
UREMENTS. The accumulation of 3-MT after inhibition<br>
of MAO has been used to measure, via 3-MT, the effects<br>
of drugs on dopamine release. Pargyline (75 to 100 mg/ c. 3-MT ACCUMULATION VERSUS STEADY-STATE MEASUREMENTS. The accumulation of 3-MT after inhibition<br>of MAO has been used to measure, via 3-MT, the effects<br>of drugs on dopamine release. Pargyline (75 to 100 mg/<br>kg i.p.) elevat UREMENTS. The accumulation of 3-MT after inhibition<br>of MAO has been used to measure, via 3-MT, the effec<br>of drugs on dopamine release. Pargyline (75 to 100 m<br>kg i.p.) elevates striatal 3-MT levels by 10- to 18-fo<br>within 20 of MAO has been used to measure, via 3-MT, the effects<br>of drugs on dopamine release. Pargyline  $(75 \text{ to } 100 \text{ mg/m})$ <br>kg i.p.) elevates striatal 3-MT levels by 10- to 18-fold<br>within 20 min to 3 h postinjection  $(102, 160)$  of drugs on dopamine release. Pargyl<br>kg i.p.) elevates striatal 3-MT levels<br>within 20 min to 3 h postinjection (1<br>tates detection of this metabolite norm<br>(1 to 6 pmol/mg of protein) amounts.<br>An important aspect in monitori i. i.p.) elevates striatal 3-MT levels by 10- to 18-fold<br>thin 20 min to 3 h postinjection (102, 160) and facili-<br>tes detection of this metabolite normally found in trace<br>to 6 pmol/mg of protein) amounts.<br>An important aspe

within 20 min to 3 h postinjection (102, 160) and facili-<br>tates detection of this metabolite normally found in trace<br>(1 to 6 pmol/mg of protein) amounts.<br>An important aspect in monitoring 3-MT dynamics<br>after MAO inhibition tates detection of this metabolite normally found in trace<br>(1 to 6 pmol/mg of protein) amounts.<br>An important aspect in monitoring 3-MT dynamics<br>after MAO inhibition with pargyline is the mode of<br>animal sacrifice. Historica (1 to 6 pmol/mg of protein) amounts.<br>
An important aspect in monitoring 3-MT dynam<br>
after MAO inhibition with pargyline is the mode<br>
animal sacrifice. Historically, when methods such<br>
microwave fixation were unavailable t An important aspect in monitoring 3-MT dynamics<br>after MAO inhibition with pargyline is the mode of<br>animal sacrifice. Historically, when methods such as<br>microwave fixation were unavailable to measure steady-<br>state 3-MT leve after MAO inhibition with pargyline is the mode of animal sacrifice. Historically, when methods such as microwave fixation were unavailable to measure steady-<br>state 3-MT levels, baseline values were artificially elevated b animal sacrifice. Historically, when methods such a<br>microwave fixation were unavailable to measure steady<br>state 3-MT levels, baseline values were artificially ele<br>vated by decapitation and drug effects monitored on thi<br>hig microwave fixation were unavailable to measure steady-<br>state 3-MT levels, baseline values were artificially ele-<br>vated by decapitation and drug effects monitored on this<br>higher baseline (99, 101, 102). This approach was sa state 3-MT levels, baseline values were artificially elevated by decapitation and drug effects monitored on this higher baseline (99, 101, 102). This approach was satisfactory in situations where profound drug effects on d vated by decapitation and drug effects monitored on this<br>higher baseline (99, 101, 102). This approach was satis-<br>factory in situations where profound drug effects on<br>dopamine release were studied (table 5). However, other higher baseline (99, 101, 102). This approach was satis-<br>factory in situations where profound drug effects on<br>dopamine release were studied (table 5). However, other<br>effects on steady-state 3-MT levels, such as those ob-<br>t factory in situations where profound drug effects dopamine release were studied (table 5). However, other effects on steady-state 3-MT levels, such as those contained with DA uptake blockers (58), were inconclusion in deca dopamine release were studied (table 5). However, other<br>effects on steady-state 3-MT levels, such as those ob-<br>tained with DA uptake blockers (58), were inconclusive<br>using pargyline-dependent 3-MT accumulation in decap-<br>it effects on steady-state 3-MT levels, such as those obtained with DA uptake blockers (58), were inconclusive using pargyline-dependent 3-MT accumulation in decapitated rats (99). This is likely to have been the result of th tained with DA uptake blockers (58), were inconclusive<br>using pargyline-dependent 3-MT accumulation in decap-<br>itated rats (99). This is likely to have been the result of<br>the rapid postmortem increases in 3-MT which masks<br>su using pargyline-dependent 3-MT accumulation in decaproacht it atted rats (99). This is likely to have been the result the rapid postmortem increases in 3-MT which mask such subtle drug effects (202). Clearly, it is advisab itated rats (99). This is likely to have been the result of the rapid postmortem increases in 3-MT which masks such subtle drug effects (202). Clearly, it is advisable even when monitoring pargyline-dependent 3-MT accumula



PHARMACOLOGI

**a**spet



Hours FIG. 4. Actions of pargyline *(PARG)* on the levels of 3-MT, DA, DOPAC, and HVA collected in rat striatal dialysates. Values are the mean ± SEM for 10-min collection periods of 5 animals (215). **4** Hours<br>
Importantly, the increases in rat striatal 3-MT levels<br>
Importantly, the increases in rat striatal 3-MT levels<br>
sarly preceded the increases in DOPAC and HVA (fig. AC, and HVA collected in rat striatal dialysates. Values are the mean<br>Importantly, the increases in rat striatal 3-MT levels<br>clearly preceded the increases in DOPAC and HVA (fig.<br>5), indicating that changes in DA release a From the individual material changes in the set of the mean changes clearly preceded the increases in DOPAC and HVA (fig. 5), indicating that changes in DA release are detected prior to alterations in intraneuronal synthes Importantly, the increases in rat striatal 3-M?<br>clearly preceded the increases in DOPAC and H<sup>5</sup><br>5), indicating that changes in DA release are d<br>prior to alterations in intraneuronal synthesis/n<br>lism of DA. Of interest, wh Importantly, the increases in rat striatal 3-MT levels<br>clearly preceded the increases in DOPAC and HVA (fig.<br>5), indicating that changes in DA release are detected<br>prior to alterations in intraneuronal synthesis/metabo-<br>li clearly preceded the increases in DOPAC and HVA (fig.<br>5), indicating that changes in DA release are detected<br>prior to alterations in intraneuronal synthesis/metabo-<br>lism of DA. Of interest, when either striatal steady-stat 5), indicating that changes in DA release are detected<br>prior to alterations in intraneuronal synthesis/metabo-<br>lism of DA. Of interest, when either striatal steady-state<br>3-MT levels (219) or DA in striatal dialysates (90) prior to alterations in intraneuronal synthesis/metabolism of DA. Of interest, when either striatal steady-state 3-MT levels (219) or DA in striatal dialysates (90) are monitored after electrical stimulation of the substan lism of DA. Of interest, when either striatal steady-st<br>3-MT levels (219) or DA in striatal dialysates (90)<br>monitored after electrical stimulation of the substar<br>nigra, both parameters increase with stimulation is<br>quencies 3-MT levels (219) or DA in striatal dialysates (90) are<br>monitored after electrical stimulation of the substantia<br>nigra, both parameters increase with stimulation fre-<br>quencies between 2 and 5 Hz and plateau at approxi-<br>ma monitored after electrical stimulation of the substantigra, both parameters increase with stimulation quencies between 2 and 5 Hz and plateau at appromately 20 Hz. At 100 Hz, striatal 3-MT levels begine reverse and decreas

FIG. 4. Actions of pargyline ( $PARG$ ) on the levels of 3-MT, DA,  $\pm$  SEM for 10-min collection periods of 5 animals (215).<br>nating this potential postmortem artifact. However, compared to 3-MT determinations in the brains o FIG. 4. Actions of pargying  $(PANO)$  on the levels of 3- $M1$ , DA, DOFT<br>  $\pm$  SEM for 10-min collection periods of 5 animals (215).<br>
nating this potential postmortem artifact. However, com-<br>
pared to 3-MT determinations in t (15, 185, 16, 16-film conceased periods of o animals (210).<br>
15, 185, 203), the pargyline accumulation technique is pridised<br>
15, 185, 203), the pargyline accumulation technique is pridised<br>
15, 185, 203), the pargyline ac nating this potential postmortem artifact. However, compared to 3-MT determinations in the brains of drug-<br>treated animals killed by focused microwave irradiation<br>(15, 185, 203), the pargyline accumulation technique is<br>dis pared to 3-MT determinations in the brains of drug-<br>treated animals killed by focused microwave irradiation<br>(15, 185, 203), the pargyline accumulation technique is<br>disadvantageous for several reasons. (a) Pargyline pre-<br>tr treated animals killed by focused microwave irradiation 5)<br>
(15, 185, 203), the pargyline accumulation technique is<br>
plisadvantageous for several reasons. (a) Pargyline pre-<br>
listreatment prevents basal measurements of DO (15, 185, 203), the pargyline accumulation technique is<br>disadvantageous for several reasons. ( $a$ ) Pargyline pre-<br>treatment prevents basal measurements of DOPAC,<br>HVA, and dopamine and thereby precludes inferences of<br>dopam disadvantageous for several reasons. (a) Pargyline pre-<br>treatment prevents basal measurements of DOPAC,<br>HVA, and dopamine and thereby precludes inferences of<br>dopamine metabolism based on the acid metabolite lev-<br>els. (b) T treatment prevents basal measurements of DOPAC,<br>HVA, and dopamine and thereby precludes inferences of<br>dopamine metabolism based on the acid metabolite lev-<br>els. (b) The pargyline accumulation technique dampens<br>the magnitud  $HVA$ , and dopamine and thereby precludes inferences of dopamine metabolism based on the acid metabolite levels. (b) The pargyline accumulation technique dampens the magnitude of changes in  $3-MT$  following treatment with a dopamine metabolism based on the acid metabolite lev-<br>els. (b) The pargyline accumulation technique dampens<br>the magnitude of changes in 3-MT following treatment<br>with agents that decrease dopamine neuron impulse con-<br>ductio els. (b) The pargyline accumulation technique damper<br>the magnitude of changes in 3-MT following treatme<br>with agents that decrease dopamine neuron impulse conduction, including gamma-butyrolactone (GBL) or ap<br>morphine (6, 1 the magnitude of changes in 3-MT following treatment<br>with agents that decrease dopamine neuron impulse con-<br>duction, including gamma-butyrolactone (GBL) or apo-<br>morphine (6, 160), and drugs like haloperidol and chlor-<br>prom with agents that decrease dopamine neuron impulse chuction, including gamma-butyrolactone (GBL) or a morphine (6, 160), and drugs like haloperidol and cheromazine, which increase impulse conduction. Fin (c) MAO inhibition duction, including gamma-butyrolactone (GBL) or apo-<br>morphine (6, 160), and drugs like haloperidol and chlor-<br>promazine, which increase impulse conduction. Finally<br>(c) MAO inhibition adds pharmacological and physiolog-<br>ic morphine  $(6, 160)$ , and drugs like haloperidol and chlor-<br>promazine, which increase impulse conduction. Finally<br> $(c)$  MAO inhibition adds pharmacological and physiolog-<br>ical complexities to the experimental design and thu promazine, which i<br>
(c) MAO inhibition<br>
ical complexities t<br>
weakens interpreta<br>
drug under study.<br>
2. Electrical stim *2. MAO* inhibition adds pharmacological and physiolog-<br>
2. Electrical stimulations of the actions on release of the<br>
2. Electrical stimulation. In studies (219) of electrical<br>
2. Electrical stimulation. In studies (219) o ical complexities to the experimental design and thus<br>weakens interpretations of the actions on release of the<br>drug under study.<br>2. Electrical stimulation. In studies (219) of electrical<br>stimulation of the substantia nigra

weakens interpretations of the actions on release of the<br>drug under study.<br>2. Electrical stimulation. In studies (219) of electrical<br>stimulation of the substantia nigra of unanesthetized<br>rats, frequency-dependent increases drug under study.<br>
2. Electrical stimulation. In studies (219) of electrical  $\frac{3. \text{ At}}{3. \text{ At}}$ <br>
stimulation of the substantia nigra of unanesthetized MT lev<br>
rats, frequency-dependent increases in striatal 3-MT, by mic 2. Electrical stimulation. In studies (219) of electrical stimulation of the substantia nigra of unanesthetized rats, frequency-dependent increases in striatal 3-MT, DOPAC, and HVA were observed with no changes in DA stead stimulation of the substantia nigra of unanesthetized rats, frequency-dependent increases in striatal 3-MT, DOPAC, and HVA were observed with no changes in DA steady-state concentrations. Similar data have been obtained wi rats, frequency-dependent increases in striatal 3-MDOPAC, and HVA were observed with no changes in lasteady-state concentrations. Similar data have been cained with ventricular perfusates of the anesthetized in which incre DOPAC, and HVA were observed with no changes in I<br>steady-state concentrations. Similar data have been c<br>tained with ventricular perfusates of the anesthetized of<br>in which increased efflux into the ventricles of radio<br>beled steady-state concentrations. Similar data have been obtained with ventricular perfusates of the anesthetized cat<br>in which increased efflux into the ventricles of radiola-<br>beled DA and 3-MT was observed during nigral stimu-

atal fibers cannot sustain transmission at this high frequency rate. Similarly, in vivo voltammetry studies ha<br>indicated that, with electrical stimulation of the r<br>medial forebrain bundle, DA neurons can follow stim<br>lation quency rate. Similarly, in vivo voltammetry studies ha<br>indicated that, with electrical stimulation of the 1<br>medial forebrain bundle, DA neurons can follow stim<br>lation frequencies between 25 and 50 Hz but that trar<br>mission dicated that, with electrical stimulation of the rat<br>edial forebrain bundle, DA neurons can follow stimu-<br>tion frequencies between 25 and 50 Hz but that trans-<br>ission begins to fail between 100 and 200 Hz (171).<br>3. Attenua medial forebrain bundle, DA neurons can follow stimulation frequencies between 25 and 50 Hz but that transmission begins to fail between 100 and 200 Hz (171).<br>3. Attenuation of DA neuronal impulse flow. Striatal 3-<br>MT lev lation frequencies between 25 and 50 Hz but that transmission begins to fail between 100 and 200 Hz (171).<br>3. Attenuation of DA neuronal impulse flow. Striatal 3-<br>MT levels (102) and the amount of dopamine measured<br>by micr mission begins to fail between 100 and 200 Hz (171).<br>3. Attenuation of DA neuronal impulse flow. Striatal 3-<br>MT levels (102) and the amount of dopamine measured<br>by microdialysis (227) are decreased by cessation of<br>nigrostr 3. Attenuation of DA neuronal impulse flow. Striatal 3-<br>MT levels  $(102)$  and the amount of dopamine measured<br>by microdialysis  $(227)$  are decreased by cessation of<br>nigrostriatal impulse flow following i.p. injections of<br> MT levels (102) and the amount of dopamine measured<br>by microdialysis (227) are decreased by cessation of<br>nigrostriatal impulse flow following i.p. injections of<br>GBL. The suppression of dopamine release by GBL has<br>been subs by microdialysis (227)<br>nigrostriatal impulse 1<br>GBL. The suppression<br>been substantiated by e<br>havioral (14) measures.<br>In contrast, DOPAC<sup>1</sup> grostriatal impulse flow following i.p. injections of<br>BL. The suppression of dopamine release by GBL has<br>en substantiated by electrophysiological (158) and be-<br>vioral (14) measures.<br>In contrast, DOPAC and HVA levels *incre* GBL. The suppression of dopamine release by GBL has<br>been substantiated by electrophysiological (158) and be-<br>havioral (14) measures.<br>In contrast, DOPAC and HVA levels *increase* following<br>cessation of impulse flow (194). T

nigra, both parameters increase with stimulation frequencies between 2 and 5 Hz and plateau at approximately 20 Hz. At 100 Hz, striatal 3-MT levels begin to reverse and decrease (219), indicating that the nigrostriatal fib mately 20 Hz. At 100 Hz, striatal 3-MT levels begin to reverse and decrease (219), indicating that the nigrostriatal fibers cannot sustain transmission at this high frequency rate. Similarly, in vivo voltammetry studies ha mately 20 Hz. At 100 Hz, striatal 3-MT levels begin to<br>reverse and decrease (219), indicating that the nigrostri-<br>atal fibers cannot sustain transmission at this high fre-<br>quency rate. Similarly, in vivo voltammetry studie atal fibers cannot sustain transmission at this high frequency rate. Similarly, in vivo voltammetry studies have indicated that, with electrical stimulation of the rat medial forebrain bundle, DA neurons can follow stimu-<br>

<sup>170</sup> **WOOD AND ALTAR TABLE 5**<br>**Actions of drugs on accumulation of 3-MT after inhibition of MAO** 

Drug	Dose (mg/kg)	Duration (min)	Route	<b>Species</b>	Tissue	3-MT accumulation (% of control)	Ref.
<b>Stimulants</b>							
Amphetamine	3	60	i.v.	<b>Rabbit</b>	<b>Striatum</b>	440	79
Methamphetamine	7	60	i.p.	Mouse	$W.B.*$	216	135
	1	90	i.p.	Rat	<b>W.B.</b>	136	99
	3	90	i.p.	Rat	<b>W.B.</b>	174	99
Cocaine	3	90	i.p.	Rat	<b>W.B.</b>	100	99
	10	90	i.p.	Rat	W.B.	123	99
	30	90	i.p.	Rat	W.B.	225	99
	3	60	i.v.	<b>Rabbit</b>	<b>Striatum</b>	100	79
Desipramine	15	90	i.p.	Rat	W.B.	100	99
	45	90	i.p.	Rat	W.B.	149	99
Imipramine	50	2700	<b>s.c.</b>	Rat	<b>W.B.</b>	100	165
Depressants							
Diazepam	3	90	i.p.	Rat	W.B.	85	99
	10	90	i.p.	Rat	W.B.	87	99
	30	90	i.p.	Rat	W.B.	77	99
Ethanol	2360	90	p.o.	Mouse	W.B.	47	116
<b>GBL</b>	750	30	i.p.	Rat	<b>Striatum</b>	46	101
<b>R-PIA</b>	3	60	i.p.	Rat	Striatum	78	133
Adrenergics							
POB	30	90	i.p.	Rat	W.B.	100	99
Propanolol	30	90	i.p.	Rat	W.B.	100	99
Clonidine	10	90	i.p.	Rat	W.B.	100	99
Dopamine agonists							
Apomorphine	3	90	i.p.	Rat	W.B.	100	99
	10	90	i.p.	Rat	W.B.	73	99
Neuroleptics							
Haloperidol	0.3	90	i.p.	Rat	W.B.	224	99
	$\mathbf{1}$	90	i.p.	Rat	W.B.	289	99
	3	90	i.p.	Rat	<b>W.B.</b>	288	99
	0.5	90	i.p.	Rat	<b>Striatum</b>	385	160
	1	45	i.p.	Rat	<b>Striatum</b>	245	160
<b>CPZ</b>	1	90	i.p.	Rat	<b>W.B.</b>	151	99
	3	90	i.p.	Rat	<b>W.B.</b>	205	99
	10	90	i.p.	Rat	W.B.	311	99
	10	120	i.v.	<b>Rabbit</b>	<b>Striatum</b>	672	79
	10	45	i.p.	Rat	Striatum	160	101
	10	2700	8.C.	Rat	<b>W.B.</b>	235	165
Fluphenazine	1	45	i.p.	Rat	Striatum	190	160
<b>Buspirone</b>	2.5	45	i.p.	Rat	<b>Striatum</b>	195	160
	10	45	i.p.	Rat	Striatum	201	160
Molindone	0.5	45	i.p.	Rat	Striatum	175	160
	2.5	45	i.p.	Rat	Striatum	210	160
Clozapine	10	45	i.p.	Rat	<b>Striatum</b>	164	160
	20	45	i.p.	Rat	Striatum	220	160
<b>SCH 23390</b>	0.25	60	i.p.	Rat	Striatum	100	160
	2.5	60	i.p.	Rat	Striatum	120	160
Rimcazole	20 40	45 45	i.p.	Rat Rat	Striatum Striatum	100 150	160 160
* W.B., whole brain.			i.p.				

PHARMACOLOGICAL REVIEWS

40 45 i.p.<br>
\*W.B., whole brain.<br>
DOPAC in these paradigms cannot be simply explained<br>
by a decrease in autoreceptor feedback on dopaminergic<br>
nerve endings as a result of decreased DA release. This \* W.B., whole brain.<br>DOPAC in these paradigms cannot be simply explained leby a decrease in autoreceptor feedback on dopaminergic in<br>nerve endings as a result of decreased DA release. This F<br>has been clearly demonstrated b has been clearly demonstrated by a decrease in autoreceptor feedback on dopaminergic<br>has been clearly demonstrated by dose-response studies<br>of 1-hydroxy-3-amino-pyrrolidone-2 (HA-966) which de-DOPAC in these paradigms cannot be simply explained<br>by a decrease in autoreceptor feedback on dopaminergic<br>nerve endings as a result of decreased DA release. This<br>has been clearly demonstrated by dose-response studies<br>of 1 by a decrease in autoreceptor feedback on dopaminergic in nerve endings as a result of decreased DA release. This Phas been clearly demonstrated by dose-response studies dof 1-hydroxy-3-amino-pyrrolidone-2 (HA-966) which d nerve endings as a result of decreased DA release. This PAC has been clearly demonstrated by dose-response studies decrease of 1-hydroxy-3-amino-pyrrolidone-2 (HA-966) which decreases nigrostriatal cell firing and DA relea

Rat Striatum 150 160<br>levels) can be decreased to 40% of control with no change<br>in DOPAC levels. However, with increasing doses, DO-<br>PAC levels are increased, in the absence of any further levels) can be decreased to 40% of control with no change<br>in DOPAC levels. However, with increasing doses, DO-<br>PAC levels are increased, in the absence of any further<br>decreases in 3-MT levels. These data argue against a levels) can be decreased to 40% of control with no change<br>in DOPAC levels. However, with increasing doses, DO-<br>PAC levels are increased, in the absence of any further<br>decreases in 3-MT levels. These data argue against a<br>ch levels) can be decreased to 40% of control with no change<br>in DOPAC levels. However, with increasing doses, DO-<br>PAC levels are increased, in the absence of any further<br>decreases in 3-MT levels. These data argue against a<br>ch in DOPAC levels. However, with increasing doses, DO-<br>PAC levels are increased, in the absence of any further<br>decreases in 3-MT levels. These data argue against a<br>change in autoreceptor activity as the cause of the dra-<br>mat PAC levels are increased, in the absence of any further decreases in 3-MT levels. These data argue against a change in autoreceptor activity as the cause of the dramatic increases in DOPAC after interruption of neuronal fi

**a**spet



were unanesthetized. The stimulation consisted of square wave pulses  $(1.5 \text{ ms}, 200 \mu\text{A})$  with alternating 20-s "on" and "off" periods for 20 min  $(219)$ .

(1.5 ms, 200  $\mu$ A) with alternating 20-s "on" and "off" periods for 20<br>min (219).<br>4. *Brain lesions.* a. PARTIAL OR COMPLETE DESTRUC-<br>TION OF DA NEURONS. Degeneration of about 80% of the<br>primate mesotelencephalic dopamin min (219).<br>4. Brain lesions. a. PARTIAL OR COMPLETE DESTRUC<br>TION OF DA NEURONS. Degeneration of about 80% of the<br>primate mesotelencephalic dopamine projection is asso-<br>ciated with the akinesia, rigidity, and tremor of Park 4. Brain lesions. a. PARTIAL OR COMPLETE DESTRITION OF DA NEURONS. Degeneration of about 80% of primate mesotelencephalic dopamine projection is as ciated with the akinesia, rigidity, and tremor of Parkson's disease (25, 8 4. Brain lesions. a. PARTIAL OR COMPLETE DESTR<br>TION OF DA NEURONS. Degeneration of about 80% of<br>primate mesotelencephalic dopamine projection is a<br>ciated with the akinesia, rigidity, and tremor of Parl<br>son's disease (25, 8 TION OF DA NEURONS. Degeneration of about 80% of the primate mesotelencephalic dopamine projection is associated with the akinesia, rigidity, and tremor of Parkinson's disease  $(25, 87, 154)$ . A similar degree of nigrostr primate mesotelencephalic dopamine projection is asso-<br>ciated with the akinesia, rigidity, and tremor of Parkin-<br>son's disease (25, 87, 154). A similar degree of nigrostri-<br>atal degeneration is required for the appearance ciated with the akinesia, rigidity, and tremor of Parkinson's disease (25, 87, 154). A similar degree of nigrostri-<br>atal degeneration is required for the appearance of be-<br>havioral impairments in rodents (124, 151, 162),<br>s son's disease (25, 87, 154). A similar degree of nigrostri<br>atal degeneration is required for the appearance of be<br>havioral impairments in rodents (124, 151, 162)<br>suggesting that as few as 20% of striatal dopamine neu<br>rons atal degeneration is required for the appearance of<br>havioral impairments in rodents (124, 151, 16<br>suggesting that as few as 20% of striatal dopamine n<br>rons can sustain a variety of sensorimotor capabilit<br>However, character havioral impairments in rodents (124, 151, 162),<br>suggesting that as few as 20% of striatal dopamine neurons can sustain a variety of sensorimotor capabilities.<br>However, characterization of the biochemical compensations of suggesting that as few as 20% of striatal dopamine neu-<br>rons can sustain a variety of sensorimotor capabilities.<br>However, characterization of the biochemical compen-<br>sations of these surviving neurons has not resolved<br>whet rons can sustain a variety of sensorimotor capabilities.<br>However, characterization of the biochemical compensations of these surviving neurons has not resolved<br>whether they maintain dopamine release at normal levels<br>or, as However, characterization of the biochemical compensations of these surviving neurons has not resolve whether they maintain dopamine release at normal level or, as proposed by Mortimer and Webster (131), that les than norm sations of these surviving neurons has not resolved<br>whether they maintain dopamine release at normal levels<br>or, as proposed by Mortimer and Webster (131), that less<br>than normal amounts of dopamine release may be suffi-<br>cie whether they maintain dopamine release at normal levels<br>or, as proposed by Mortimer and Webster (131), that less<br>than normal amounts of dopamine release may be suffi-<br>cient for normal behavioral function. Six-fold increase or, as proposed by Mortimer and Webster (131), that less<br>than normal amounts of dopamine release may be suffi-<br>cient for normal behavioral function. Six-fold increases<br>in striatal dopamine release have been measured, eithe than normal amounts of dopamine release may be sufficient for normal behavioral function. Six-fold increases<br>in striatal dopamine release have been measured, either<br>by the in vitro efflux of dopamine (169) or in vivo  $3\text$ cient for normal behavioral function. Six-fold increases<br>in striatal dopamine release have been measured, either<br>by the in vitro efflux of dopamine (169) or in vivo 3-MT<br>levels (12) relative to the dopamine content of ter in striatal dopamine release have been measured, either<br>by the in vitro efflux of dopamine (169) or in vivo 3-MT<br>levels (12) relative to the dopamine content of terminals<br>surviving extensive  $(\geq 80\%)$  denervations. Stria by the in vitro efflux of dopamine  $(169)$  or in vivo 3-MT levels  $(12)$  relative to the dopamine content of terminals surviving extensive  $(\geq 80\%)$  denervations. Striatal do-<br>pamine innervation can be estimated by dopam levels (12) relative to the dopamine content of terminals<br>surviving extensive  $(\geq 80\%)$  denervations. Striatal do-<br>pamine innervation can be estimated by dopamine levels,<br>since they covary with the amount of high-affinit surviving extensive  $(\geq 80\%)$  denervations. Striatal do<br>pamine innervation can be estimated by dopamine levels<br>since they covary with the amount of high-affinity do<br>pamine uptake  $(12, 125, 230)$  and tyrosine hydroxylas<br> pamine innervation can be estimated by dopamine levels,<br>since they covary with the amount of high-affinity do-<br>pamine uptake (12, 125, 230) and tyrosine hydroxylase a<br>(80) over the entire range of dopamine denervation.<br>Th since they covary with the amount of high-affinity do-<br>pamine uptake (12, 125, 230) and tyrosine hydroxylase and  $(80)$  over the entire range of dopamine denervation.<br>Thus, the change in dopamine metabolism or release per pamine uptake (12, 125, 230) and tyrosine hydroxylase (80) over the entire range of dopamine denervation.<br>Thus, the change in dopamine metabolism or release per dopamine nerve terminal can be estimated according to for th

LEASE IN VIVO FROM NEURONS<br>creases in dopamine release from surviving nerve term<br>nals far exceed increases in neuronal dopamine metab 3 AND DA RELEASE IN VIVO FROM NEURONS 171<br>
creases in dopamine release from surviving nerve termi-<br>
3-MT nals far exceed increases in neuronal dopamine metabo-<br>
lism assessed with DOPAC (2-fold) or HVA (3-fold)<br>
increases creases in dopamine release from survey<br>nals far exceed increases in neuronal dism assessed with DOPAC (2-fold)<br>increases relative to dopamine (12).<br>We have also measured the 6-hyd eases in dopamine release from surviving nerve termi-<br>ls far exceed increases in neuronal dopamine metabo-<br>m assessed with DOPAC (2-fold) or HVA (3-fold)<br>creases relative to dopamine (12).<br>We have also measured the 6-hydro

nals far exceed increases in neuronal dopamine metabolism assessed with DOPAC (2-fold) or HVA (3-fold) increases relative to dopamine (12).<br>We have also measured the 6-hydroxydopamine (6-OHDA)-induced depletion of rat stri lism assessed with DOPAC (2-fold) or HVA (3-fold)<br>increases relative to dopamine (12).<br>We have also measured the 6-hydroxydopamine (6-<br>OHDA)-induced depletion of rat striatal 3-MT, DOPAC,<br>HVA, and dopamine to determine the increases relative to dopamine (12).<br>
We have also measured the 6-hydroxydopamine (6-<br>
OHDA)-induced depletion of rat striatal 3-MT, DOPAC,<br>
HVA, and dopamine to determine the extent of changes<br>
in dopamine release and met We have also measured the 6-hydroxydopamine (6-<br>OHDA)-induced depletion of rat striatal 3-MT, DOPAC,<br>HVA, and dopamine to determine the extent of changes<br>in dopamine release and metabolism following less severe<br>dopamine de OHDA)-induced depletion of rat striatal 3-MT, DOPAC,<br>HVA, and dopamine to determine the extent of changes<br>in dopamine release and metabolism following less severe<br>dopamine denervations (11). Unlike DOPAC and HVA,<br>which dec HVA, and dopamine to determine the extent of changes<br>in dopamine release and metabolism following less severe<br>dopamine denervations (11). Unlike DOPAC and HVA,<br>which decrease almost in proportion to the dopamine<br>decreases in dopamine release and metabolism following less severe<br>dopamine denervations (11). Unlike DOPAC and HVA,<br>which decrease almost in proportion to the dopamine<br>decreases when dopamine losses are from 30 to 80%, 3-<br>MT conce



FIG. 6. Extent of striatal dopamine metabolism (*DOPAC*,  $HVA$ ) and release  $(3-MT)$  as a function of dopamine denervation (*Dopamine*).<br>\*,  $P < 0.05$ ; \*\*,  $P < 0.01$  versus 3-MT depletion, Student's t test.  $n = 3$  to 8 per g **dopamine concentrations of** 60% **or less;** 3-MT losses are significant **for** residual dopamine concentrations of 20% or less *(P* **< 0.05,** Stu- **dent's** *<sup>t</sup>* test) (11).

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

equal extent. Importantly, 3-MT, as well as DOPAC and (20<br>HVA, is unmeasureable when dopamine losses are vir- DA WOOD A<br>equal extent. Importantly, 3-MT, as well as DOPAC and<br>HVA, is unmeasureable when dopamine losses are vir-<br>tually complete (98 to 99%). 172<br>equal extent. Importantly, 3-N<br>HVA, is unmeasureable wher<br>tually complete (98 to 99%).<br>The lack of changes in 3 ual extent. Importantly, 3-MT, as well as DOPAC and (200) of<br>VA, is unmeasureable when dopamine losses are vir- DA releally complete (98 to 99%).<br>
c. LES<br>
The lack of changes in 3-MT over the 0 to 80% acid lesi<br>
nervation

equal extent. Importantly, 3-MT, as well as DOPAC and (2<br>HVA, is unmeasureable when dopamine losses are vir-<br>tually complete (98 to 99%).<br>The lack of changes in 3-MT over the 0 to 80% adenervation range is virtually identi HVA, is unmeasureable when dopamine losses are vir-<br>tually complete (98 to 99%).<br>The lack of changes in 3-MT over the 0 to 80% accements by brain dialysis of alt<br>dopamine release measurements by brain dialysis of the the<br> tually complete (98 to 99%). C.<br>The lack of changes in 3-MT over the 0 to 80% acid<br>denervation range is virtually identical to the results of alter<br>dopamine release measurements by brain dialysis of the thes<br>denervated str The lack of changes in 3-MT over the 0 to 80% denervation range is virtually identical to the results dopamine release measurements by brain dialysis of the denervated striatum (156a). The preservation of 3-M levels in ne denervation range is virtually identical to the results of alternation indicates the denervated striatum (156a). The preservation of 3-MT A devels in neostriata depleted by up to 80% of the dopamine innervation indicates dopamine release measurements by brain dialysis of the the denervated striatum (156a). The preservation of 3-MT Alevels in neostriata depleted by up to 80% of the dopamine innervation indicates that dopamine release can b denervated striatum (156a). The preservation of 3-MT A levels in neostriata depleted by up to 80% of the dopa-<br>mine innervation indicates that dopamine release can be efficient maintained at near-normal levels by as few a levels in neostriata depleted by up to 80% of the dopa-<br>mine innervation indicates that dopamine release can be<br>effection maintained at near-normal levels by as few as 20% of back<br>the normal dopamine input. Thus, as shown mine innervation indicates that dopamine release can be<br>maintained at near-normal levels by as few as 20% of<br>the normal dopamine input. Thus, as shown in vitro<br>(169) and in vivo with microdialysis (156a) or 3-MT<br>(refs. 11 maintained at near-normal levels by as few as  $20\%$  of back pathways can be assessed on striatal DA release.<br>the normal dopamine input. Thus, as shown in vitro<br>(169) and in vivo with microdialysis (156a) or 3-MT<br>(refs. 1  $(169)$  and in vivo with microdialysis  $(156a)$  or  $3-MT$ of dopamine nerve terminals can maintain dopamine

(refs. 11 and 12; fig. 6), far fewer than the normal number<br>of dopamine nerve terminals can maintain dopamine<br>release and thus normal behaviors.<br>b. LESIONS OF THE STRIATONIGRAL FEEDBACK PATH-<br>wAYS. Lesions of the crus cere of dopamine nerve terminals can maintain dopamine<br>release and thus normal behaviors.<br>b. LESIONS OF THE STRIATONIGRAL FEEDBACK PATH-<br>WAYS. Lesions of the crus cerebri, which sever most or<br>all of the striatal feedback pathwa release and thus normal behaviors.<br>
b. LESIONS OF THE STRIATONIGRAL FEEDBACK PATH-<br>
wAYS. Lesions of the crus cerebri, which sever most or<br>
all of the striatal feedback pathway to the substantia<br>
migra, result in a 56% inc b. LESIONS OF THE STRIATONIGRAL FEEDBACK PATH-WAYS. Lesions of the crus cerebri, which sever most or all of the striatal feedback pathway to the substantia nigra, result in a 56% increase in striatal 3-MT levels 12 days af WAYS. Lesions of the crus cerebri, which sever most or<br>all of the striatal feedback pathway to the substantia <sup>U</sup><br>nigra, result in a 56% increase in striatal 3-MT levels 12<br> $\frac{1}{2}$ <br>days after the lesion in rats (44). Th all of the striatal feedback pathway to the substantinigra, result in a 56% increase in striatal 3-MT levels 1<br>days after the lesion in rats (44). These augmentation<br>in DA release presumably reflect the loss of the inhibit migra, result in a 56% increase in striatal 3-MT levels 12 mcrease<br>days after the lesion in rats  $(44)$ . These augmentations<br>in DA release presumably reflect the loss of the inhibitory Since de<br>GABAergic feedback loop to days after the lesion in rats (44). These augmentations related decreases of 3-MT in the human basal ganglia.<br>
in DA release presumably reflect the loss of the inhibitory<br>
GABAergic feedback loop to the substantia nigra d in DA release presumably reflect the loss of the inhibitory<br>
GABAergic feedback loop to the substantia nigra dopa-<br>
mine cell bodies. Indeed, this lesion results in a 69%<br>
decrease in the gamma-amino butyric acid (GABA) l GABAergic feedback loop to the substantia nigra dopa-<br>mine cell bodies. Indeed, this lesion results in a 69% m<br>decrease in the gamma-amino butyric acid (GABA) levels<br>of the ipsilateral substantia nigra, supporting the les mine cell bodies. Indeed, this lesion results in a 69% modernease in the gamma-amino butyric acid (GABA) levels reg of the ipsilateral substantia nigra, supporting the lesion age of striatal GABAergic inputs to the nigra. decrease in the gamma-amino butyric acid (GABA) levels<br>of the ipsilateral substantia nigra, supporting the lesion<br>of striatal GABAergic inputs to the nigra. In the case of<br>i.p. in<br>an acute hemitransection where the nigros % of the ipsilateral substantia nigra, supporting the lesion of striatal GABAergic inputs to the nigra. In the case of an acute hemitransection where the nigrostriatal tract is also severed, there is a  $60\%$  decrease in of striatal GABAergic inputs to the nigra. In the case of  $\frac{1}{2}$  an acute hemitransection where the nigrostriatal tract is also severed, there is a 60% decrease in striatal 3-MT levels in the rat (205, 224). This lower an acute hemitransection where the nigrostriatal tract is<br>also severed, there is a 60% decrease in striatal 3-MT<br>levels in the rat (205, 224). This lower 3-MT baseline at<br>2 to 3 h post lesion represents a new steady state also severed, there is a 60% decrease in striatal 3-MT levels in the rat (205, 224). This lower 3-MT baseline at 2 to 3 h post lesion represents a new steady state of increased DA synthesis and decreased DA release (205, 2 levels in the rat  $(205, 224)$ . This lower 3-MT baseline at 2 to 3 h post lesion represents a new steady state of increased DA synthesis and decreased DA release  $(205, 224)$  in the isolated nerve endings, which nonethele increased DA synthesis and decreased DA release (205, 224) in the isolated nerve endings, which nonetheless can be pharmacologically modified with amphetamine (34), opiates (224), and GABAergics (205). In analogy to the ph

224) in the isolated nerve endings, which nonetheless can be pharmacologically modified with amphetamine  $(34)$ , opiates (224), and GABAergics (205). In analogy to the physical lesion induced by acute is the hemitransecti can be pharmacologically modified with ampheta (34), opiates (224), and GABAergics (205).<br>In analogy to the physical lesion induced by a<br>hemitransection, a decrease in impulse conduction of<br>striatonigral tract can also be (34), opiates (224), and GABAergics (205).<br>In analogy to the physical lesion induced by acute<br>hemitransection, a decrease in impulse conduction of the<br>striatonigral tract can also be established pharmacolog-<br>ically with G In analogy to the physical lesion induced by acuted hemitransection, a decrease in impulse conduction of the striatonigral tract can also be established pharmacologically with GBL (71, 90, 101, 184, 209) and HA-966 (3132, hemitransection, a decrease in impulse conduction of the striatonigral tract can also be established pharmacologically with GBL (71, 90, 101, 184, 209) and HA-966 (36, doping 132, 184, 219). In dose-response studies of HA striatonigral tract can also be established pharmacolog-<br>ically with GBL  $(71, 90, 101, 184, 209)$  and HA-966  $(36, 132, 184, 219)$ . In dose-response studies of HA-966, clear-<br>cut decrements in DA release can be monitored ically with GBL  $(71, 90, 101, 184, 209)$  and HA-966  $(36, 132, 184, 219)$ . In dose-response studies of HA-966, clear-<br>cut decrements in DA release can be monitored by in<br>vivo voltammetry  $(132)$ , by decreases in basal  $3$ 132, 184, 219). In dose-response studies of HA-966, clear-<br>cut decrements in DA release can be monitored by in<br>vivo voltammetry (132), by decreases in basal 3-MT<br>levels (219), and by decreases in pargyline-dependent 3-<br>MT cut decrements in DA release can be monitored by in<br>vivo voltammetry (132), by decreases in basal 3-MT<br>levels (219), and by decreases in pargyline-dependent 3-<br>MT accumulation (132). Similarly, GBL also decreases<br>the DA co vivo voltammetry (132), by decreases in basal 3-levels (219), and by decreases in pargyline-dependent MT accumulation (132). Similarly, GBL also decreathe DA collected in striatal dialysates (90), striatedy-state 3-MT leve levels (219), and by decreases in pargyline-dependent 3-MT accumulation (132). Similarly, GBL also decreases<br>the DA collected in striatal dialysates (90), striatal<br>steady-state 3-MT levels (209), and pargyline-dependent<br>3-MT accumulation (132). Similarly, GBL also decreases<br>the DA collected in striatal dialysates (90), striatal<br>steady-state 3-MT levels (209), and pargyline-dependent<br>3-MT accumulation in rat striatum (101). These de-<br>creases the DA collected in striatal dialysates (90), striatal<br>steady-state 3-MT levels (209), and pargyline-dependent<br>3-MT accumulation in rat striatum (101). These de-<br>creases in DA release precede any compensatory in-<br>creases i steady-state 3-MT levels (209), and pargyline-depender<br>3-MT accumulation in rat striatum (101). These decreases in DA release precede any compensatory ir<br>creases in DA synthesis and metabolism (209). Anothe<br>example of phar 3-MT accumulation in rat striatum (101). These de-<br>creases in DA release precede any compensatory in-<br>creases in DA synthesis and metabolism (209). Another Keh<br>example of pharmacological axotomy is with local injec-<br>of I<br> creases in DA release precede any compensatory increases in DA synthesis and metabolism (209). Another example of pharmacological axotomy is with local injections of tetrodotoxin (TTX) into the striatum (223). In this case creases in DA synthesis and metabolism (209). Another Ke<br>example of pharmacological axotomy is with local injec-<br>tions of tetrodotoxin (TTX) into the striatum (223). In D(<br>this case, nigrostriatal as well as all potential example of pharmacological axotomy is with local injections of tetrodotoxin (TTX) into the striatum (223). In<br>this case, nigrostriatal as well as all potential presynaptic<br>afferent inputs are inhibited. Under these condit tions of tetrodotoxin (TTX) into the striatum (223). In DOPA<br>this case, nigrostriatal as well as all potential presynaptic as indi<br>afferent inputs are inhibited. Under these conditions, the shown<br>only DA metabolite change this case, nigrostriatal as well as all potential presynaptic as independent inputs are inhibited. Under these conditions, the shown only DA metabolite changes noted are profound  $(-90\%)$  6) as the decreases in striatal 3afferent inputs are inhibited. Under these conditions, the shown to be inaccurate in many cases (reviewed in table<br>only DA metabolite changes noted are profound  $(\sim 90\%)$  6) as to preclude the use of these parameters for

) ALTAR<br>(200) of the striatum have also demonstrated decreased<br>DA release after local TXX application. ALTAR<br>(200) of the striatum have also demonstrated decreased<br>DA release after local TXX application.<br>c. LESIONS OF INTRINSIC STRIATAL NEURONS. Kainic<br>acid lesions of the striatum have been reported to not

(200) of the striatum have also demonstrated decreased<br>DA release after local TXX application.<br>c. LESIONS OF INTRINSIC STRIATAL NEURONS. Kainic<br>acid lesions of the striatum have been reported to not<br>alter striatal 3-MT lev (200) of the striatum have also demonstrated decreased DA release after local TXX application.<br>
c. LESIONS OF INTRINSIC STRIATAL NEURONS. Kainic<br>
acid lesions of the striatum have been reported to not<br>
alter striatal 3-MT DA release after local TXX application.<br>
c. LESIONS OF INTRINSIC STRIATAL NEURONS. Kainic<br>
acid lesions of the striatum have been reported to not<br>
alter striatal 3-MT levels at 3 days (224) but increase<br>
these levels to 20 c. LESIONS OF INTRINSIC STRIATAL NEURONS. Kainic<br>acid lesions of the striatum have been reported to not<br>alter striatal 3-MT levels at 3 days (224) but increase<br>these levels to 200% of control at 6 days post lesion (44).<br>A acid lesions of the striatum have been reported to not<br>alter striatal 3-MT levels at 3 days (224) but increase<br>these levels to 200% of control at 6 days post lesion (44).<br>A comprehensive time course of this phenomenon re-<br> alter striatal 3-MT levels at 3 days (224) but increase<br>these levels to 200% of control at 6 days post lesion (44)<br>A comprehensive time course of this phenomenon re<br>mains to be defined in one experiment such that the<br>effec A comprehensive time course of this phenomenon remains to be defined in one experiment such that the effects of acute and chronic lesions of striatonigral feed-*C. Compressmess*<br> *C. Effects of acute and chrights of Aging*<br> *C. Effects of Aging*<br>
Dopamine, but not 3-

 $224$  in the isolated nerve endings, which nonetheless<br>can be pharmacologically modified with amphetamine<br>(34), opiates (224), and GABAergics (205).<br>Thus, caudate-putamen 3-MT and the turnover of do-<br>pamine through its re fects of acute and chronic lesions of striatonigral feed-<br>ck pathways can be assessed on striatal DA release.<br>Effects of Aging<br>Dopamine, but not 3-MT, is decreased with age in the<br>sal ganglia of normal humans (43). However back pathways can be assessed on striatal DA release.<br>
C. Effects of Aging<br>
Dopamine, but not 3-MT, is decreased with age in th<br>
basal ganglia of normal humans (43). However, as men-<br>
tioned above, 3-MT levels increase dra C. Effects of Aging<br>Dopamine, but not 3-MT, is decreased with age in the<br>basal ganglia of normal humans (43). However, as men-<br>tioned above, 3-MT levels increase dramatically after<br>death in human caudate-putamen (168) and C. *Effects of Aging*<br>Dopamine, but not 3-MT, is decreased with age in the<br>basal ganglia of normal humans (43). However, as men-<br>tioned above, 3-MT levels increase dramatically after<br>death in human caudate-putamen (168) a Dopamine, but not 3-MT, is decreased with age in the<br>basal ganglia of normal humans (43). However, as men-<br>tioned above, 3-MT levels increase dramatically after<br>death in human caudate-putamen (168) and in rodents<br>(190), wh basal ganglia of normal humans (43). However, as mentioned above, 3-MT levels increase dramatically after<br>death in human caudate-putamen (168) and in rodents<br>(190), when microwave irradiation is not used (102) or<br>used imp tioned above, 3-MT levels increase dramatically after<br>death in human caudate-putamen (168) and in rodents<br>(190), when microwave irradiation is not used (102) or<br>used improperly (190) (section II A). The postmortem<br>increase death in human caudate-putamen (168) and in rodents (190), when microwave irradiation is not used (102) or used improperly (190) (section II A). The postmortem increase in dopamine release could therefore mask age-related (190), when microwave irradiation is not used (102) used improperly (190) (section II A). The postmort increase in dopamine release could therefore mask a related decreases of  $3\text{-}MT$  in the human basal gang Since dopami used improperly (190) (section II A). The postmortem<br>increase in dopamine release could therefore mask age-<br>related decreases of 3-MT in the human basal ganglia.<br>Since dopamine levels are also lower in the caudate-<br>putamen increase in dopamine release could therefore mask age-<br>related decreases of 3-MT in the human basal ganglia.<br>Since dopamine levels are also lower in the caudate-<br>putamen of aged rats (13, 125; see ref. 65 for review), we<br>m related decreases of 3-MT in the human basal ganglia.<br>Since dopamine levels are also lower in the caudate-<br>putamen of aged rats (13, 125; see ref. 65 for review), we<br>measured dopamine, DOPAC, HVA, and 3-MT in this<br>region a Since dopamine levels are also lower in the caudate-<br>putamen of aged rats (13, 125; see ref. 65 for review), we<br>measured dopamine, DOPAC, HVA, and 3-MT in this<br>region and in the olfactory tubercle in aged (28 mo of<br>age) or putamen of aged rats (13, 125; see ref. 65 for review), we<br>measured dopamine, DOPAC, HVA, and 3-MT in this<br>region and in the olfactory tubercle in aged (28 mo of<br>age) or young (4 mo of age) Fischer 344 rats that received<br>i measured dopamine, DOPAC, HVA, and 3-MT in this<br>region and in the olfactory tubercle in aged (28 mo of<br>age) or young (4 mo of age) Fischer 344 rats that received<br>i.p. injections of vehicle or pargyline 10 min before sac-<br>r region and in the olfactory tubercle in aged (28 mo of age) or young (4 mo of age) Fischer 344 rats that received i.p. injections of vehicle or pargyline 10 min before sacrifice by microwave irradiation. Concentrations of age) or young (4 mo of age) Fischer 344 rats that received<br>i.p. injections of vehicle or pargyline 10 min before sac-<br>rifice by microwave irradiation. Concentrations of do-<br>pamine, but neither 3-MT, DOPAC, nor HVA, were<br>de rifice by microwave irradiation. Concentrations of do-<br>pamine, but neither 3-MT, DOPAC, nor HVA, were<br>decreased in the caudate-putamen (table 6). In contrast,<br>each metabolite was lower in the olfactory tubercle of rifice by microwave irradiation. Concentrations of do-<br>pamine, but neither 3-MT, DOPAC, nor HVA, were<br>decreased in the caudate-putamen (table 6). In contrast,<br>each metabolite was lower in the olfactory tubercle of<br>the aged pamine, but neither 3-MT, DOPAC, nor HVA, w<br>decreased in the caudate-putamen (table 6). In contra<br>each metabolite was lower in the olfactory tubercle<br>the aged rats, but the accumulation of 3-MT after p<br>gyline was not, nor decreased in the caudate-putamen (table 6). In contrast, each metabolite was lower in the olfactory tubercle of the aged rats, but the accumulation of 3-MT after pargyline was not, nor was it lower in the caudate-putamen. each metabolite was lower in the olfactory tubercle of<br>the aged rats, but the accumulation of 3-MT after par-<br>gyline was not, nor was it lower in the caudate-putamen.<br>Thus, caudate-putamen 3-MT and the turnover of do-<br>pami the aged rats, but the accumulation of 3-MT after par-<br>gyline was not, nor was it lower in the caudate-putamen.<br>Thus, caudate-putamen 3-MT and the turnover of do-<br>pamine through its releasable pool in either region are<br>not gyline was not, nor was it lower in the caudate-putamen.<br>Thus, caudate-putamen 3-MT and the turnover of do-<br>pamine through its releasable pool in either region are<br>not lower in the aged rat. Possible reasons for the per-<br>s Thus, caudate-putamen 3-MT and the turnover of do-<br>pamine through its releasable pool in either region are<br>not lower in the aged rat. Possible reasons for the per-<br>sistence of 3-MT in brain regions with partial dopamine<br>de pamine through its releasable pool in either reginated to lower in the aged rat. Possible reasons for the usistence of 3-MT in brain regions with partial dopenervations have been made based on the unidopamine lesion model *D. Interpretation* of DA Metabolic Changes<br>*D. Interpretation* of DA Metabolite Changes<br>In general, the use of DA metabolites to int denervations have been made based on the unilateral<br>dopamine lesion model (11) (see section IV D).<br>D. Interpretation of DA Metabolite Changes<br>In general, the use of DA metabolites to interpret the

status of neuronal activity in dopaminergic pathways has D. Interpretation of DA Metabolite Changes<br>
In general, the use of DA metabolites to interpret the<br>
status of neuronal activity in dopaminergic pathways has<br>
been made inappropriately in the literature (reviewed in<br>
refs. D. Interpretation of DA Metabolite Changes<br>In general, the use of DA metabolites to interpret the<br>status of neuronal activity in dopaminergic pathways has<br>been made inappropriately in the literature (reviewed in<br>refs. 50, In general, the use of DA metabolites to interpret the<br>status of neuronal activity in dopaminergic pathways has<br>been made inappropriately in the literature (reviewed in<br>refs. 50, 54, 108, 157, and 199) despite the early st status of neuronal activity in dopaminergic pathways has<br>been made inappropriately in the literature (reviewed in<br>refs. 50, 54, 108, 157, and 199) despite the early studies<br>of Sharman and co-workers, which clearly showed t been made inappropriately in the literature (reviewed<br>refs. 50, 54, 108, 157, and 199) despite the early stud<br>of Sharman and co-workers, which clearly showed th<br>DOPAC is the major intraneuronal (i.e., DA nerve er<br>ing) DA m refs. 50, 54, 108, 157, and 199) despite the early studies<br>of Sharman and co-workers, which clearly showed that<br>DOPAC is the major intraneuronal (i.e., DA nerve end-<br>ing) DA metabolite with HVA being a secondary metab-<br>oli of Sharman and co-workers, which clearly showed that DOPAC is the major intraneuronal (i.e., DA nerve ending) DA metabolite with HVA being a secondary metabolite of this DOPAC pool (157). Similarly, the studies of Kehr (10 DOPAC is the major intraneuronal (i.e., DA nerve end-<br>ing) DA metabolite with HVA being a secondary metab-<br>olite of this DOPAC pool (157). Similarly, the studies of<br>Kehr (101, 102) showed that 3-MT is an accurate index<br>of ing) DA metabolite with HVA being a secondary metab-<br>olite of this DOPAC pool (157). Similarly, the studies of<br>Kehr (101, 102) showed that 3-MT is an accurate index<br>of DA release. Despite these landmark studies, HVA,<br>DOPAC olite of this DOPAC pool (157). Similarly, the studies of Kehr (101, 102) showed that 3-MT is an accurate index of DA release. Despite these landmark studies, HVA, DOPAC, or DOPAC/DA ratios are still often referred to as i Kehr (101, 102) showed that 3-MT is an accurate index<br>of DA release. Despite these landmark studies, HVA,<br>DOPAC, or DOPAC/DA ratios are still often referred to<br>as indices of DA release. This interpretation has been<br>shown t of DA release. Despite these landmark studies, HVA,<br>DOPAC, or DOPAC/DA ratios are still often referred to<br>as indices of DA release. This interpretation has been<br>shown to be inaccurate in many cases (reviewed in table<br>6) as DOPAC, or DOPAC/DA ratios are<br>as indices of DA release. This int<br>shown to be inaccurate in many ca<br>6) as to preclude the use of these per-<br>inferences concerning DA release.<br>Therefore, at this point we will de indices of DA release. This interpretation has been<br>own to be inaccurate in many cases (reviewed in table<br>as to preclude the use of these parameters for making<br>ferences concerning DA release.<br>Therefore, at this point we wi shown to be inaccurate in many cases (reviewed in table 6) as to preclude the use of these parameters for making inferences concerning DA release.<br>Therefore, at this point we will define the assumptions upon which the util

**a**spet



**a**spet

**A RELEASE IN<br>TABLE 6<br>roung and aged rats** 3-MT MEASUREMENTS AND DA RELEASE IN VIVO FROM NEURONS<br>TABLE 6<br>Fischer 344 rats were given injections of either the saline vehicle of young and aged rats  $(n = 9/$ group). Young (4-mo-old) or aged (29-mo-old) male<br>Fischer 344 TABLE 6<br>*i*amine and metabolites in the striatum and olfactory tubercle of young and aged rats (n = 9/group). Young (4-mo-old) or aged (29-mo-old) n<br>Fischer 344 rats were given injections of either the saline vehicle (1 ml



a Mean ± SEM. <sup>t</sup> *<sup>P</sup>* **<sup>&</sup>lt;** 0.05.

II Pargyline singificantly *(P* **< 0.05)** and **consistently altered** 3-MT values compared to those of vehicle-treated, age-matched cohorts.

 $\uparrow P < 0.05$ .<br>  $\uparrow$  Numbers in parentheses, percentage.<br>  $\S P < 0.01$  versus young animals.<br> **Pargyline singificantly**  $(P < 0.05)$  and consistently altered 3-MT values<br>
release is based, and then attempt to validate these a  $\frac{2}{3}P < 0.01$  versus young animals.<br>
Pargyline singificantly  $(P < 0.05)$  and consistently altered 3-M<br>
release is based, and then attempt to validate the<br>
assumptions with studies of the pharmacological mod<br>
lation of D Pargyline singificantly  $(P < 0.05)$  and consistently altere<br>release is based, and then attempt to validate<br>assumptions with studies of the pharmacological<br>lation of DA synthesis, metabolism, and release.<br>In the presence of lease is based, and then attempt to validate the sumptions with studies of the pharmacological motion of DA synthesis, metabolism, and release.<br>In the presence of *unaltered, steady-state concentra-* of *DA*, the following release is based, and then attempt to validate<br>assumptions with studies of the pharmacological is<br>lation of DA synthesis, metabolism, and release.<br>In the presence of *unaltered, steady-state concertions of DA*, the followi

sumptions with studies of the pharmacological modurion of DA synthesis, metabolism, and release.<br>In the presence of *unaltered, steady-state concentras of DA*, the following assumptions are made.<br>(a) Changes in DOPAC level lation of DA synthesis, metabolism, and release.<br>In the presence of *unaltered, steady-state concentra-*<br>tions of DA, the following assumptions are made.<br>(a) Changes in DOPAC levels are an index of intra-<br>neuronal DA synth In the presence of *unaltered, steady-state concentra*-late<br>tions of DA, the following assumptions are made.<br>(a) Changes in DOPAC levels are an index of intra-<br>neuronal DA synthesis/metabolism in the cytoplasmic mea-<br>pool. tions of DA, the following assumptions are made.<br>(a) Changes in DOPAC levels are an index of int<br>neuronal DA synthesis/metabolism in the cytoplasi<br>pool. For example, if DA levels are unchanged afte<br>drug but DOPAC levels ar (a) Changes in DOPAC levels are an index of intra-<br>neuronal DA synthesis/metabolism in the cytoplasmic<br>pool. For example, if DA levels are unchanged after a<br>lism is increased in the DA nerve ending in conjuntion<br>with enha neuronal DA synthesis/metabolism in the cytoplasmingool. For example, if DA levels are unchanged after drug but DOPAC levels are increased, then DA metabolism is increased in the DA nerve ending in conjuntio with enhanced pool. For example, if DA levels are unchanged after a planty of the DA steady state increased, then DA metabomethism is increased in the DA nerve ending in conjuntion of with enhanced DA synthesis which maintains the unaldrug but DOPAC levels are increased, then DA metal<br>lism is increased in the DA nerve ending in conjunti<br>with enhanced DA synthesis which maintains the un<br>tered DA steady-state. This situation exemplifies thomeostatic mecha lism is increased in the DA nerve ending in conjun<br>with enhanced DA synthesis which maintains the u<br>tered DA steady state. This situation exemplifies<br>homeostatic mechanisms which maintain the ste<br>state concentrations of DA *tel* manipulations. red DA steady state. This situation exemplifies the *m* meostatic mechanisms which maintain the steady-<br>metroconcentrations of DA after a variety of experimen-<br>in manipulations.<br>(b) Changes in HVA are secondary to the effl

homeostatic mechanisms which maintain the steady-<br>state concentrations of DA after a variety of experimen-<br>tal manipulations.<br>(b) Changes in HVA are secondary to the efflux of of<br>DOPAC from the nerve ending and/or changes efflux of experimentations of DA after a variety of experimental manipulations.<br>
(b) Changes in HVA are secondary to the efflux of of<br>
DOPAC from the nerve ending and/or changes in the lefflux of this metabolite from the b tal manipulations.<br>
(b) Changes in HVA are secondary to the efflux<br>
DOPAC from the nerve ending and/or changes in<br>
efflux of this metabolite from the brain. Changes in<br>
MT concentrations have never been shown to signicantl (b) Changes in HVA are secondary to the efflux  $\Omega$  DOPAC from the nerve ending and/or changes in the efflux of this metabolite from the brain. Changes in  $\Omega$  MT concentrations have never been shown to significantly alte DOPAC from the nerve ending and/or changes in the<br>efflux of this metabolite from the brain. Changes in 3-<br>MT concentrations have never been shown to signifi-<br>cantly alter HVA concentrations, except following injec-<br>tions o Filim of this metabolite from the brain. Changes in 3-<br> **T** concentrations have never been shown to signifi-<br>
antly alter HVA concentrations, except following injec-<br>
ms of the COMT inhibitor, tropolone (section IV A).<br>
(c MT concentrations have never been shown to significantly alter HVA concentrations, except following injections of the COMT inhibitor, tropolone (section IV A). co (c) Changes in 3-MT levels are indicative of DA release T a

cantly alter HVA concent<br>tions of the COMT inhibi<br>(c) Changes in 3-MT lev<br>and its subsequent methyl<br>surrounding the synapse.<br>This working model is p

(c) Changes in 3-MT levels are indicative of DA release<br>and its subsequent methylation in the cleft and glial cells<br>surrounding the synapse.<br>This working model is presented in fig. 2. A key feature<br>of this conceptual fram and its subsequent methylation in the cleft and glial cells<br>surrounding the synapse.<br>This working model is presented in fig. 2. A key feature<br>of this conceptual framework is that DA, DOPAC, HVA,<br>and 3-MT must be measured i surrounding the synapse. all<br>This working model is presented in fig. 2. A key feature<br>of this conceptual framework is that DA, DOPAC, HVA,<br>and 3-MT must be measured in order to fully evaluate<br>the functional status of dopam This working model is presented in fig. 2. A key feature<br>of this conceptual framework is that DA, DOPAC, HVA,<br>and 3-MT must be measured in order to fully evaluate<br>the functional status of dopaminergic neurons. This is<br>best of this conceptual framework is that DA, DOPAC<br>and 3-MT must be measured in order to fully e<br>the functional status of dopaminergic neurons.<br>best realized by table 7, in which a number of ex<br>present a clear-cut *uncoupling* and 3-MT must be measured in order to fully evaluate olities functional status of dopaminergic neurons. This is chost realized by table 7, in which a number of examples migresent a clear-cut *uncoupling* of DA synthesis/me the functional status of dopaminergic neurons. This is charposet realized by table 7, in which a number of examples minopresent a clear-cut *uncoupling* of DA synthesis/metabo-<br>pomism (DOPAC) and release (3-MT). These exam

(c) Changes in 3-MT levels are indicative of DA release Therefore, in the case of altered DA synthesis rates, and its subsequent methylation in the cleft and glial cells changes in the steady-state levels of DA metabolite and release are *coupled* processes (table 8) and demo<br>and release are *coupled* processes (table 8) and demo<br>strate that false conclusions would be derived if HVA ies compared to those of vehicle-treated, age-matched cohorts.<br>and release are *coupled* processes (table 8) and demonstrate that false conclusions would be derived if HVA or<br>DOPAC were used as indices of DA release and co res compared to those of vehicle-treated, age-matched cohorts.<br>
and release are *coupled* processes (table 8) and demoint strate that false conclusions would be derived if HVA<br>
DOPAC were used as indices of DA release and and release are *coupled* processes (table 8) and demonstrate that false conclusions would be derived if HVA or DOPAC were used as indices of DA release and correlated with behavioral or postsynaptic changes after drug tre and release are *coupled* processes (table 8) and demonstrate that false conclusions would be derived if HVA or DOPAC were used as indices of DA release and correlated with behavioral or postsynaptic changes after drug tre strate that false conclusions would be derived if HVA or<br>DOPAC were used as indices of DA release and corre-<br>lated with behavioral or postsynaptic changes after drug<br>treatment. Therefore, in contrast to studies of choliner DOPAC were used as indices of DA release and corre-<br>lated with behavioral or postsynaptic changes after drug<br>treatment. Therefore, in contrast to studies of cholinergic<br>(221) or amino acid-utilizing (210) pathways, where<br>m lated with behavioral or postsynaptic changes after d<br>treatment. Therefore, in contrast to studies of choline<br>(221) or amino acid-utilizing (210) pathways, wh<br>measurements of transmitter turnover are tightly c<br>pled with tr treatment. Therefore, in contrast to studies of cholinergic (221) or amino acid-utilizing (210) pathways, where measurements of transmitter turnover are tightly coupled with transmitter synthesis and release, measurements (221) or amino acid-utilizing (210) pathways, where<br>measurements of transmitter turnover are tightly cou-<br>pled with transmitter synthesis and release, measure-<br>ments of DA turnover allow only limited interpretations<br>of cha measurements of transmitter turnover are tightly coupled with transmitter synthesis and release, measurements of DA turnover allow only limited interpretations of changes in dopaminergic transmission. There is no logical f pled with transmitter synthesis and release, measurements of DA turnover allow only limited interpretations of changes in dopaminergic transmission. There is no logical framework for the use of such measurements as markers ments of DA turnover allow only limited interpretation<br>of changes in dopaminergic transmission. There is r<br>logical framework for the use of such measurements of<br>markers for DA release. It should thus be clear tha<br>measureme of changes in dopaminergic transmission. There<br>logical framework for the use of such measureme<br>markers for DA release. It should thus be clea<br>measurements of DA turnover utilizing precursor<br>ing (77, 185), measurements of L markers for DA release. It should thus be clear that measurements of DA turnover utilizing precursor labeling  $(77, 185)$ , measurements of L- $(3,4$ -dihydroxyset that the set of DA turnover allow and the decline in DA mathematic (T7, 185), measurement of DA turnover utilizing precursor is and the set of the decline in DA mathematic that false conclusions would be derived if HV measurements of DA turnover utilizing precursor label-<br>ing (77, 185), measurements of L-(3,4-dihydroxy-<br>phenyl)alanine (L-DOPA) accumulation after inhibition<br>of DOPA decarboxylase, or monitoring the decline in DA<br>levels af ing (77, 185), measurements of L-(3,4-dihydroxy-<br>phenyl)alanine (L-DOPA) accumulation after inhibition<br>of DOPA decarboxylase, or monitoring the decline in DA<br>levels after inhibition of tyrosine hydroxylase are only<br>indices of DOPA decarboxylase, or monitoring the decline in DA<br>levels after inhibition of tyrosine hydroxylase are only<br>indices of DA synthesis rates and not release. However,<br>as in cholinergic and amino acidergic pathways, DA<br>neu of DOPA decarboxylase, or monitoring the decline in DA<br>levels after inhibition of tyrosine hydroxylase are only<br>indices of DA synthesis rates and not release. However,<br>as in cholinergic and amino acidergic pathways, DA<br>neu levels after inhibition of tyrosine hydroxylase are only indices of DA synthesis rates and not release. However, as in cholinergic and amino acidergic pathways, DA neurons possess the ability to maintain the steady-state c indices of DA synthesis rates and not release. However, as in cholinergic and amino acidergic pathways, DA neurons possess the ability to maintain the steady-state concentration of DA during changes in neuronal activity. T as in cholinergic and amino acidergic pathways, DA<br>neurons possess the ability to maintain the steady-state<br>concentration of DA during changes in neuronal activity.<br>Therefore, in the case of altered DA synthesis rates,<br>cha neurons possess the ability to maintain the steady-state<br>concentration of DA during changes in neuronal activity.<br>Therefore, in the case of altered DA synthesis rates,<br>changes in the steady-state levels of DA metabolites<br>a concentration of DA during changes in ne<br>Therefore, in the case of altered DA s<br>changes in the steady-state levels of I<br>allow an investigator to determine if st<br>synthetic activity are coupled to release.<br>Caution must be us nerefore, in the case of altered DA synthesis rat<br>anges in the steady-state levels of DA metaboli<br>low an investigator to determine if such changes<br>nthetic activity are coupled to release.<br>Caution must be used in the interp

changes in the steady-state levels of DA metabolites<br>allow an investigator to determine if such changes in<br>synthetic activity are coupled to release.<br>Caution must be used in the interpretation of metab-<br>olite concentration allow an investigator to determine if such changes<br>synthetic activity are coupled to release.<br>Caution must be used in the interpretation of meta<br>olite concentration data when DA steady-state leve<br>change. Indeed, in such ca synthetic activity are coupled to release.<br>Caution must be used in the interpretation of meta<br>olite concentration data when DA steady-state leve<br>change. Indeed, in such cases it is imperative to dete<br>mine the time course a Caution must be used in the interpretation of metab-<br>olite concentration data when DA steady-state levels<br>change. Indeed, in such cases it is imperative to deter-<br>mine the time course and characteristics for the devel-<br>opm olite concentration data when DA steady-state levels<br>change. Indeed, in such cases it is imperative to deter-<br>mine the time course and characteristics for the devel-<br>opment of a new steady-state level of DA. The use of<br>the change. Indeed, in such cases it is imperative to deter-<br>mine the time course and characteristics for the devel-<br>opment of a new steady-state level of DA. The use of<br>these precautions and the aquisition of key indices of D

## <sup>174</sup> **WOOD AND ALTAR**





*<sup>a</sup>* **DA** release as assessed by brain dialysis, voltammetry, or push-pull perfusion.



Examples of pharmacological treatments in which DA metabolism and release are coupled processes



\* **DA release as** assessed by brain dialysis, voltammetry, or push-pull perfusion. <sup>t</sup> **O.T., olfactory tubercule.**

mouse striatum<br>
\* DA release as assessed by brain dialysis, voltammetry, or push-pull pe<br>
t O.T., olfactory tubercule.<br>
utmost importance in the design of studies to evaluate<br>
the more complex roles of polysynaptic circuit \* DA release as assessed by brain dialysis, voltammetry, or push-pull perful  $\dagger$  O.T., olfactory tubercule.<br>utmost importance in the design of studies to evaluate inc<br>the more complex roles of polysynaptic circuits and cr utmost importance in the design of studies to evaluate<br>the more complex roles of polysynaptic circuits and<br>cotransmitters in the regulation of dopaminergic transmission.

## Iv. Pharmacology

transmitters in the regulation of dopaminergic transision.<br>
IV. Pharmacology<br>
In the following discussion of pharmacological modu-<br>
ion of 3-MT levels (table 9), unless otherwise specific mission.<br>
IV. Pharmacology<br>
In the following discussion of pharmacological modu-<br>
lation of 3-MT levels (table 9), unless otherwise specified,<br>
all data are concerned with the rat striatum. In this **all data are concerned with the rat striatum.** In the following discussion of pharmacological modulation of 3-MT levels (table 9), unless otherwise specified, b all data are concerned with the rat striatum. In this secti IV. Pharmacology both<br>In the following discussion of pharmacological modu-<br>lation of 3-MT levels (table 9), unless otherwise specified, bel<br>all data are concerned with the rat striatum. In this<br>section, we will cover spec In the following discussion of pharmacological modu-<br>lation of 3-MT levels (table 9), unless otherwise specified, beh<br>all data are concerned with the rat striatum. In this The<br>section, we will cover species differences wh lation of 3-MT levels (table 9), unless otherwise specified, all data are concerned with the rat striatum. In this section, we will cover species differences whenever they have been encountered. Whenever possible, changes all data are concerned with the rat striatum. In this section, we will cover species differences whenever they have been encountered. Whenever possible, changes in 3-MT levels will be compared with changes in DA collected have been encountered. Whenever possible, changes in

MT levels will be compared with changes in DA col-<br>ted in push-pull perfusates and brain dialysates.<br>Enzyme Inhibitors<br>The tyrosine hydroxylase inhibitor, AMPT, inhibits<br>A synthesis, resulting in rapid decreases in striata lected in push-pull perfusates and brain dialysates.<br>
A. Enzyme Inhibitors<br>
The tyrosine hydroxylase inhibitor, AMPT, inhibits<br>
DA synthesis, resulting in rapid decreases in striatal<br>
steady-state levels of DA, DOPAC, HVA, A. *Enzyme Inhibitors*<br>The tyrosine hydroxylase inhibitor, AMPT, inhibits<br>DA synthesis, resulting in rapid decreases in striatal<br>steady-state levels of DA, DOPAC, HVA, and 3-MT (58).<br>Using trans-striatal dialysis, identica A. Enzyme Innibitors<br>
The tyrosine hydroxylase inhibitor, AMPT, inhibits<br>
DA synthesis, resulting in rapid decreases in striatal str<br>
steady-state levels of DA, DOPAC, HVA, and 3-MT (58). dec<br>
Using trans-striatal dialysis The tyrosine hydroxylase inhibitor, AMPT, inhibits<br>DA synthesis, resulting in rapid decreases in striatal sti<br>steady-state levels of DA, DOPAC, HVA, and 3-MT (58). de<br>Using trans-striatal dialysis, identical actions have b DA synthesis, resulting in rapid decreases in striatal s<br>steady-state levels of DA, DOPAC, HVA, and 3-MT (58). d<br>Using trans-striatal dialysis, identical actions have been<br>observed for DA, DOPAC, and HVA collected in the<br>d steady-state level<br>Using trans-st<br>observed for I<br>dialysates (90)<br>in this study.<br>The monoar Using trans-striatal dialysis, identical actions have been<br>observed for DA, DOPAC, and HVA collected in the<br>dialysates (90); unfortunately 3-MT was not measured<br>in this study.<br>The monoamine oxidase inhibitor (MAOI), pargyl

increases striatal steady-state levels of 3-MT and decreases DOPAC and HVA levels (41, 101, 203, 211, 216). erfusion.<br>increases striatal steady-state levels of 3-MT and de-<br>creases DOPAC and HVA levels (41, 101, 203, 211, 216).<br>Similiarly, striatal dialysates, after pargyline administra-Similiarly, striatal steady-state levels of 3-MT and<br>creases DOPAC and HVA levels (41, 101, 203, 211, 3<br>Similiarly, striatal dialysates, after pargyline admini<br>tion, contain increased DA and 3-MT along with increases striatal steady-state levels of 3-MT and decreases DOPAC and HVA levels (41, 101, 203, 211, 216).<br>Similiarly, striatal dialysates, after pargyline administration, contain increased DA and 3-MT along with decrease increases striatal steady-state levels of 3-MT and decreases DOPAC and HVA levels (41, 101, 203, 211, 216).<br>Similiarly, striatal dialysates, after pargyline administra-<br>tion, contain increased DA and 3-MT along with decrea creases DOPAC and HVA levels (41, 101, 203, 211, 216).<br>Similiarly, striatal dialysates, after pargyline administra-<br>tion, contain increased DA and 3-MT along with de-<br>creased HVA and DOPAC (90, 106, 215; fig. 4). With<br>both Similiarly, striatal dialysates, after pargyline administra-<br>tion, contain increased DA and 3-MT along with de-<br>creased HVA and DOPAC (90, 106, 215; fig. 4). With<br>both the tissue steady-state studies and the brain dialysis tion, contain increased DA and 3-MT along with de-<br>creased HVA and DOPAC (90, 106, 215; fig. 4). With<br>both the tissue steady-state studies and the brain dialysis<br>measurements, the changes in DOPAC and HVA lag<br>behind the ra creased HVA and DOPAC (90, 106, 215; fig. 4). With<br>both the tissue steady-state studies and the brain dialysis<br>measurements, the changes in DOPAC and HVA lag<br>behind the rapid changes in DA release by 15 to 45 min.<br>The MAOboth the tissue steady-state studies and the brain dialysis<br>measurements, the changes in DOPAC and HVA lag<br>behind the rapid changes in DA release by 15 to 45 min.<br>The MAO-A inhibitor, clorgyline, also increases striatal<br>st measurements, the changes in DOPAC and HVA lag<br>behind the rapid changes in DA release by 15 to 45 min.<br>The MAO-A inhibitor, clorgyline, also increases striatal<br>steady-state 3-MT levels (191) and DA collected in stria-<br>tal behind the rapid changes in DA release by 15 to 45 min.<br>The MAO-A inhibitor, clorgyline, also increases striatal<br>steady-state 3-MT levels (191) and DA collected in stria-<br>tal dialysates (100). In contrast, the manoamine ox The MAO-A inhibitor, clorgyline, also increases striatal The MAO-A minimot, clotymic, also increases striatal<br>steady-state 3-MT levels (191) and DA collected in stria-<br>tal dialysates (100). In contrast, the manoamine oxidase<br>(type B) (MAO-B) inhibitor, deprenyl, does not increas els and dialysates (100). In contrast, the manoamine oxidase (type B) (MAO-B) inhibitor, deprenyl, does not increase DA collected in striatal dialysates (100). The reversible MAOI, minaprine (97), also increases striatal 3 A collected in striatal dialysates (100). The reversible<br>AOI, minaprine (97), also increases striatal 3-MT lev-<br>and decreases DOPAC with these actions reversing<br>tween 2 and 3 h (64).<br>The COMT inhibitor, tropolone, rapidly Driverside in Striatal dialystics (100). The reverside MAOI, minaprine (97), also increases striatal 3-MT levels and decreases DOPAC with these actions reversing between 2 and 3 h (64).<br>The COMT inhibitor, tropolone, rapid

between 2 and 3 h (64).<br>The COMT inhibitor, tropolone, rapidly decreases<br>striatal 3-MT levels (191, 201). A parallel but slower decreases DOPAC with these actions reversing<br>between 2 and 3 h (64).<br>The COMT inhibitor, tropolone, rapidly decreases<br>striatal 3-MT levels (191, 201). A parallel but slower<br>decline in HVA levels has also been monitored (20 between 2 and 3 h (64).<br>
The COMT inhibitor, tropolone, rapidly decreases<br>
striatal 3-MT levels (191, 201). A parallel but slower<br>
decline in HVA levels has also been monitored (201),<br>
supporting the more rapid turnover of The COMT inhibitor, tropolone, rapidly decretizated 3-MT levels (191, 201). A parallel but sl decline in HVA levels has also been monitored (supporting the more rapid turnover of 3-MT as asseted and anti-<br>after inhibition after inhibition of monoamine oxidase (212, 213).<br>*B. D-1 Agonists and Antagonists*<br>The initial in vitro studies of Farnebo and Hamberger supporting the more rapid turnover of  $3-MT$  as assessed

(62) and others (115, 173) used apomorphine to show

PHARMACOLOGICAL REVIEWS

## 3-MT MEASUREMENTS AND DA RELEASE *IN VIVO* FROM NEURONS 175<br>TABLE 9 TABLE 9-Continued

**HARM** 

PHARMACOLOGICAL REVIEWS

3-MT MEASUREMENTS AND DA F<br>TABLE 9<br>*Summary table of drug effects on rat striatal DOPAC and 3-MT*<br>*steady-state levels after fixation with microwave irradiation* 





<sup>C</sup> **One** hundred *%,* no statistically significant change.

TABLE 9-Continued

Drug (mg/kg, route)		Time (min)	<b>DOPAC</b>	$3-MT$	Ref.
			(% of control)		
<b>MR 2034</b>	(2, i.p.)	60	100	100	225
	(8, i.p.)	60	100	100	225
	(32, i.p.)	60	100	100	225
Ethylketazocine	(4, i.p.)	60	100	100	225
	(16, i.p.)	60	100	100	225
Trifluadom	(2, i.p.)	60	100	100	207
<b>U-50488H</b>	(8, i.p.)	60	100	100	207
<b>Butorphanol</b>	(2, i.p.)	60	129	100	207
	(16, i.p.)	60	153	100	207
	(64, i.p.)	60	100	100	207
Pentazocine	(32, i.p.)	60	164	100	225
	(64, i.p.)	60	100	100	225
Cyclazocine	(8, i.p.)	60	148	100	225
	(32, i.p.)	60	100	100	225
<b>DADLE</b>	$(0.002, \text{ivt.})\dagger$	60	147	100	225
	$(0.01, \text{ivt.})$	60	176	100	225
	$(0.003, \text{ivt.})$	60	125	100	226
Naloxone	(5, i.p.)	60	100	100	226
Kyotorphan	$(0.8, \text{ivt.})$	60	229	100	148
<b>Muscarinics</b>					
Oxotremorine	(1, i.p.)	60	220	73	201
t ivt., intraventricular.					

 $\begin{array}{llll}\n\text{Oxotremorine} & (1, \text{i.p.}) & 60 & 220 & 73 & 201 & \text{erve} \\
\hline\n\text{t} \text{ivt., intraventricular.} & \text{cho} \\
\text{that dopamine autoreceptors modulate the release of test} \\
\text{dopamine in the striatum.} & \text{The advent of selective D-1} & \text{pro} \\
\text{and D-2 receptor agonists and antagonists allowed the test}\n\end{array}$ thit, intraventricular.<br>
that dopamine autoreceptors modulate the release of test<br>
dopamine in the striatum. The advent of selective D-1 pre<br>
and D-2 receptor agonists and antagonists allowed the<br>
D-2 nature of the autorec that dopamine autoreceptors modulate the release of dopamine in the striatum. The advent of selective D-<br>and D-2 receptor agonists and antagonists allowed th<br>D-2 nature of the autoreceptor to be unequivocally identified. that dopamine autoreceptors modulate the release c<br>dopamine in the striatum. The advent of selective D-<br>and D-2 receptor agonists and antagonists allowed th<br>D-2 nature of the autoreceptor to be unequivocally iden<br>tified. T dopamine in the striatum. The advent of selective D-1 and D-2 receptor agonists and antagonists allowed the D-2 nature of the autoreceptor to be unequivocally identified. Thus, unlike D-2 stimulation, D-1 receptor stimula and D-2 receptor agonists and antagonists allowed t<br>D-2 nature of the autoreceptor to be unequivocally ide<br>tified. Thus, unlike D-2 stimulation, D-1 receptor stin<br>ulation with 2,3,4,5-tetrahydro-1-phenyl-1H-3-benzaz<br>pine-D-2 nature of the autoreceptor to be unequivocally identified. Thus, unlike D-2 stimulation, D-1 receptor stimulation with 2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine-7,8-diol (SKF 38393) fails to decrease the potassium-i ulation with 2,3,4,5-tetrahydro-1-phenyl-1H-3-benzaze-<br>pine-7,8-diol (SKF 38393) fails to decrease the potas-<br>sium-induced (176) or electrical stimulation-induced<br>(114, 174) release of [<sup>3</sup>H]dopamine from neostriatal<br>slic ulation with 2,3,4,5-tetrahydro-1-phenyl-1H-3-benzaze-<br>pine-7,8-diol (SKF 38393) fails to decrease the potas-<br>sium-induced (176) or electrical stimulation-induced ef<br>(114, 174) release of [<sup>3</sup>H]dopamine from neostriatal di pine-7,8-diol (SKF 38393) fails to decrease the potas-<br>sium-induced (176) or electrical stimulation-induced<br>(114, 174) release of [<sup>3</sup>H]dopamine from neostriatal c<br>slices. The ability of D-2 agonists to lower the release o sium-induced (176) or electrical stimulation-induced e:<br>(114, 174) release of [<sup>3</sup>H]dopamine from neostriatal d<br>slices. The ability of D-2 agonists to lower the release of e:<br>[<sup>3</sup>H]dopamine is blocked by D-2, but not D-1, (114, 174) release of [<sup>3</sup>H]dopamine from neostriatal slices. The ability of D-2 agonists to lower the release of [<sup>3</sup>H]dopamine is blocked by D-2, but not D-1, selective antagonists. Similar in vitro findings have been o slices. The ability of D-2 agonists to low<br>[<sup>3</sup>H]dopamine is blocked by D-2, but n<br>antagonists. Similar in vitro findings has<br>for the guinea pig spinal cord (107) an<br>and cingulate cortices (143, 144, 179).<br>Changes in in vi H]dopamine is blocked by D-2, but not D-1, selective datagonists. Similar in vitro findings have been obtained the r the guinea pig spinal cord (107) and rat prefrontal med cingulate cortices (143, 144, 179). Striated 3-M antagonists. Similar in vitro findings have been obtained<br>for the guinea pig spinal cord (107) and rat prefrontal<br>and cingulate cortices (143, 144, 179).<br>Changes in in vivo striatal 3-MT levels following the<br>administration

for the guinea pig spinal cord  $(107)$  and rat prefrontal m<br>and cingulate cortices  $(143, 144, 179)$ .<br>Changes in in vivo striatal 3-MT levels following the wadministration of D-1 or D-2-selective compounds parallel the pa and cingulate cortices (143, 144, 179). strictly strictly the changes in in vivo striatal 3-MT levels following the with administration of D-1 or D-2-selective compounds paranellel the patterns obtained with these in vitro Changes in in vivo striatal 3-MT levels following the with<br>administration of D-1 or D-2-selective compounds par-<br>allel the patterns obtained with these in vitro studies. 3-<br>these MT levels in mouse striatum are increased  $(S)-(+)$ -8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenylallel the patterns obtained with these in vitro studies. 3<br>MT levels in mouse striatum are increased by the D-4<br>antagonists haloperidol and metoclopramide but not by<br>(S)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-<br>1 4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benazepine-7-ol 1H-3-benzazepine-7-ol (SCH 23390) or 7-bromo-2,3, crease, striatal 3-MT but like typical neuroleptics fre-<br>4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benazepine-7-ol quently elevate DOPAC and HVA (15, 78, 218).<br>(SKF 83566) (15 (S)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-<br>1H-3-benzazepine-7-ol (SCH 23390) or 7-bromo-2,3, c<br>4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benazepine-7-ol q<br>(SKF 83566) (15, 33). Similar effects on accumulated 3-<br>MT 1H-3-benzazepine-7-ol (SCH 23390) or 7-bromo-2,3,<br>4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benazepine-7-ol<br>(SKF 83566) (15, 33). Similar effects on accumulated 3-<br>MT levels after pargyline have also been observed for<br>haloper nists  $trans-1,3,4,4\alpha,5,10\beta$ -hexahydro-4-propyl-2H-[1] (SKF 83566) (15, 33). Similar effects on accumulated 3-<br>MT levels after pargyline have also been observed for ure<br>haloperidol and SCH 23390 (160). The partial D-2 ago-<br>mists *trans*-1,3,4,4 $\alpha$ ,5,10 $\beta$ -hexahydro-4-propyl MT levels after pargyline have also been<br>haloperidol and SCH 23390 (160). The pa<br>nists  $trans-1,3,4,4\alpha,5,10\beta$ -hexahydro-4-<br>benzopyrano[3,4-b]pyridin-9-ol (CGS 158<br>full D-2 agonist  $(4\alpha$ -*R-trans*)-4,4 $\alpha$ ,5,6,7,<br>dro-5-*n*haloperidol and SCH 23390 (160). The partial D-2 ago-<br>nists trans-1,3,4,4 $\alpha$ ,5,10 $\beta$ -hexahydro-4-propyl-2H-[1]<br>benzopyrano[3,4-b]pyridin-9-ol (CGS 15855A) and the<br>full D-2 agonist (4 $\alpha$ -R-trans)-4,4 $\alpha$ ,5,6,7,8,8 $\alpha$ ,9 mists  $trans-1,3,4,4\alpha,5,10\beta$ -hexahydro-4-propyl-2H-[1] at<br>benzopyrano[3,4-b]pyridin-9-ol (CGS 15855A) and the afull D-2 agonist  $(4\alpha$ -R-trans)-4,4 $\alpha$ ,5,6,7,8,8 $\alpha$ ,9-octahy- ic<br>dro-5-n-propyl-2H-pyrazolo-3,4- $\gamma$ -guinolin benzopyrano $[3,4-b]$ pyridin-9-ol (CGS 15855A) and the an<br>full D-2 agonist  $(4\alpha \cdot R \cdot trans) - 4, 4\alpha, 5, 6, 7, 8, 8\alpha, 9 - octahy-$ ica<br>dro-5-n-propyl-2H-pyrazolo-3,4- $\gamma$ -guinoline (LY 171555) ch<br>decrease 3-MT, while the D-1 agonist full D-2 agonist  $(4\alpha$ -R-trans)-4,4 $\alpha$ ,5,6,7,8,8 $\alpha$ ,9-octahy-ical<br>dro-5-n-propyl-2H-pyrazolo-3,4- $\gamma$ -guinoline (LY 171555) chlo<br>decrease 3-MT, while the D-1 agonist SKF 38393 does by l<br>not lower 3-MT unless high does dro-5-*n*-propyl-2*H*-pyrazolo-<br>decrease 3-MT, while the D<br>not lower 3-MT unless high<br>used, and even then only sm<br>3-MT are found (4, 6, 33).

WOOD AND ALTAR<br>These in vitro and in vivo studies confirm the D-2<br>nature of the autoreceptor that controls dopamine release NALTAR<br>These in vitro and in vivo studies confirm the D-2<br>nature of the autoreceptor that controls dopamine release<br>and rule out the D-1 receptor in the autoreceptor control ALTAR<br>These in vitro and in vivo studies confirm the D-2<br>nature of the autoreceptor that controls dopamine release<br>and rule out the D-1 receptor in the autoreceptor control<br>of DA release. While this conclusion is consisten These in vitro and in vivo studies confirm the D-2<br>nature of the autoreceptor that controls dopamine release<br>and rule out the D-1 receptor in the autoreceptor control<br>of DA release. While this conclusion is consistent with These in vitro and in vivo studies confirm the D-2<br>nature of the autoreceptor that controls dopamine release<br>and rule out the D-1 receptor in the autoreceptor control<br>of DA release. While this conclusion is consistent with nature of the autoreceptor that controls dopamine release<br>and rule out the D-1 receptor in the autoreceptor control<br>of DA release. While this conclusion is consistent with<br>the absence of D-1 receptors on the terminals and and rule out the D-1 receptor in the autoreceptor control<br>of DA release. While this conclusion is consistent with<br>the absence of D-1 receptors on the terminals and cell<br>bodies of nigrostriatal neurons (9), studies with str of DA release. While this conclusion is consistent with the absence of D-1 receptors on the terminals and cell bodies of nigrostriatal neurons (9), studies with striatal microdialysis present inconsistent results for the D the absence of D-1 receptors on the terminals and cell<br>bodies of nigrostriatal neurons (9), studies with striatal<br>microdialysis present inconsistent results for the D-1<br>receptor control of release. Imperato et al (91) obse bodies of nigrostriatal neurons (9), studies with striat microdialysis present inconsistent results for the D<br>receptor control of release. Imperato et al (91) observe<br>and Zetterstrom et al. (228) failed to observe, increas microdialysis present inconsistent results for the D<br>receptor control of release. Imperato et al (91) observe<br>and Zetterstrom et al. (228) failed to observe, increas<br>in the amount of striatal dopamine recovered into micro<br> receptor control of release. Imperato et al (91) observed, and Zetterstrom et al. (228) failed to observe, increases in the amount of striatal dopamine recovered into microdialysis probes following similar doses of the D-1 and Zetterstrom et al. (228) failed to observe, increases<br>in the amount of striatal dopamine recovered into micro-<br>dialysis probes following similar doses of the D-1 antag-<br>onist, SCH 23390. In contrast, Zetterstrom et al. dialysis probes following similar doses of the D-1 antag-<br>onist, SCH 23390. In contrast, Zetterstrom et al. (228),<br>but not Imperato et al. (91), reported suppressions of<br>dialyzed dopamine following similar doses of the D-1 onist, SCH 23390. In contrast, Zetterstrom et al. (228), but not Imperato et al. (91), reported suppressions of dialyzed dopamine following similar doses of the D-1 agonist SKF 38393. The use of general anesthesia by Zette but not Imperato et al. (91),<br>dialyzed dopamine following<br>agonist SKF 38393. The use<br>Zetterstrom et al. but not Imp<br>for some of these discrepancie<br>C. D-2 Antgonists *C. Deterstrom et al. 1*<br> *C. D-2 Antagonists*<br> *C. D-2 Antagonists*<br>
D-2 receptor antagonists

in the amount of striatal dopamine recovered into micro-<br>dialysis probes following similar doses of the D-1 antag-<br>onist, SCH 23390. In contrast, Zetterstrom et al. (228),<br>but not Imperato et al. (91), reported suppressio tterstrom et al. but not Imperato et al. might account<br>r some of these discrepancies.<br>D-2 Antagonists<br>D-2 receptor antagonists that ameliorate psychosis but<br>thout inducing extrapyramidal side effects are considfor some of these discrepancies.<br>  $C. D-2$  Antagonists<br>  $D-2$  receptor antagonists that ameliorate psychosis but<br>
without inducing extrapyramidal side effects are consid-<br>
ered "atypical" antipsychotics, whereas  $D-2$  anta C. D-2 Antagonists<br>
D-2 receptor antagonists that ameliorate psychosis but<br>
without inducing extrapyramidal side effects are consid-<br>
ered "atypical" antipsychotics, whereas D-2 antagonists<br>
that produce both effects are t  $C. D-2$  Antagonists<br>D-2 receptor antagonists that ameliorate psychosis<br>without inducing extrapyramidal side effects are consered "atypical" antipsychotics, whereas  $D-2$  antagonis<br>that produce both effects are termed "typ D-2 receptor antagonists that ameliorate psychosis but<br>without inducing extrapyramidal side effects are consid-<br>ered "atypical" antipsychotics, whereas D-2 antagonists<br>that produce both effects are termed "typical" antipsy without inducing extrapyramidal side effects are considered "atypical" antipsychotics, whereas D-2 antagonists<br>that produce both effects are termed "typical" antipsy-<br>chotics. Potencies of these drugs in several behavioral ered "atypical" antipsychotics, whereas D-2 antagonists<br>that produce both effects are termed "typical" antipsy-<br>chotics. Potencies of these drugs in several behavioral<br>tests can predict their antipsychotic efficacy and the that produce both effects are termed "typical" antipsy-<br>chotics. Potencies of these drugs in several behavioral<br>tests can predict their antipsychotic efficacy and their<br>propensity to induce extrapyramidal side effects. The chotics. Potencies of these drugs in several behavioral<br>tests can predict their antipsychotic efficacy and their<br>propensity to induce extrapyramidal side effects. These<br>tests are, respectively, inhibition by the drug of ei tests can predict their antipsychotic efficacy and their<br>propensity to induce extrapyramidal side effects. These<br>tests are, respectively, inhibition by the drug of either<br>apomorphine-induced cage-climbing behavior and apopropensity to induce extrapyramidal side effects. These<br>tests are, respectively, inhibition by the drug of either<br>apomorphine-induced cage-climbing behavior and apo-<br>morphine-induced stereotypic behavior  $(52, 70)$ . When<br> tests are, respectively, inhibition by the drug of either apomorphine-induced cage-climbing behavior and apomorphine-induced stereotypic behavior (52, 70). When drug potencies in these tests have been calculated, in vivo n apomorphine-induced cage-climbing behavior and apo-<br>morphine-induced stereotypic behavior (52, 70). When<br>drug potencies in these tests have been calculated, in<br>vivo neurochemical measurements can be made at the<br>effective d morphine-induced stereotypic behavior (52, 70). When drug potencies in these tests have been calculated, vivo neurochemical measurements can be made at the effective dose or at a multiple of the effective dose discern a ne drug potencies in these tests have been calculated,<br>vivo neurochemical measurements can be made at t<br>effective dose or at a multiple of the effective dose<br>discern a neurochemical mechanism that might diffe<br>entiate these tw vivo neurochemical measurements can be made at the<br>effective dose or at a multiple of the effective dose to<br>discern a neurochemical mechanism that might differ-<br>entiate these two groups of drugs. Clozapine and thiori-<br>daz effective dose or at a multiple of the effective dose to<br>discern a neurochemical mechanism that might differ-<br>entiate these two groups of drugs. Clozapine and thiori-<br>dazine have been clearly distinguished in this way from discern a neurochemical mechanism that might differentiate these two groups of drugs. Clozapine and thioridazine have been clearly distinguished in this way from the typical neuroleptics haloperidol, chlorpromazine, and me entiate these two groups of drugs. Clozapine and thiori-<br>dazine have been clearly distinguished in this way from<br>the typical neuroleptics haloperidol, chlorpromazine, and<br>metoclopramide by their diminished capacity to alte dazine have been clearly distinguished in this way from<br>the typical neuroleptics haloperidol, chlorpromazine, and<br>metoclopramide by their diminished capacity to alter<br>striatal dopamine release. This has been demonstrated<br>w the typical neuroleptics haloperidol, chlorpromazine, and<br>metoclopramide by their diminished capacity to alte<br>striatal dopamine release. This has been demonstrate<br>with push-pull cannulae (22), in vivo microdialysis (227)<br>a metoclopramide by their diminished capacity to alt<br>striatal dopamine release. This has been demonstrate<br>with push-pull cannulae (22), in vivo microdialysis (227<br>and in vivo voltammetry (89, 112). Not surprisingl<br>these find striatal dopamine release. This has been demonstrated<br>with push-pull cannulae (22), in vivo microdialysis (227),<br>and in vivo voltammetry (89, 112). Not surprisingly,<br>these findings have been corroborated with 3-MT meas-<br>ur with push-pull cannulae  $(22)$ , in vivo microdialysis  $(227)$ , and in vivo voltammetry (89, 112). Not surprisingly, these findings have been corroborated with 3-MT measurements using gas chromatography-mass spectroscopy (GC-MS) methods (described in section II, A and B). Clozapine and these findings have been corroborated with 3-MT measurements using gas chromatography-mass spectroscopy (GC-MS) methods (described in section II, A and B). Clozapine and thioridazine leave unaltered, or even decrease, stri urements using gas chromatography-mass spectroffic (GC-MS) methods (described in section II, A at Clozapine and thioridazine leave unaltered, or ev crease, striatal 3-MT but like typical neuroleptic quently elevate DOPAC a Clozapine and thioridazine leave unaltered, or even decrease, striatal 3-MT but like typical neuroleptics frequently elevate DOPAC and HVA  $(15, 78, 218)$ .<br>In a more comprehensive study  $(14a)$ , we have meas-

Clozapine and thioridazine leave unaltered, or even<br>crease, striatal 3-MT but like typical neuroleptics is<br>quently elevate DOPAC and HVA (15, 78, 218).<br>In a more comprehensive study (14a), we have me<br>ured 3-MT, DOPAC, HVA, crease, striatal 3-MT but like typical neuroleptics frequently elevate DOPAC and HVA (15, 78, 218).<br>In a more comprehensive study (14a), we have measured 3-MT, DOPAC, HVA, and DA in the caudate-<br>putamen following p.o. admi quently elevate DOPAC and HVA (15, 78, 218).<br>In a more comprehensive study (14a), we have meas-<br>ured 3-MT, DOPAC, HVA, and DA in the caudate-<br>putamen following p.o. administration to mice of ten<br>atypical antipsychotic drug In a more comprehensive study (14a), we have measured 3-MT, DOPAC, HVA, and DA in the caudate-<br>putamen following p.o. administration to mice of ten<br>atypical antipsychotic drugs or candidates and six typical<br>antipsychotics. ured 3-MT, DOPAC, HVA, and DA in the caudate<br>putamen following p.o. administration to mice of ter<br>atypical antipsychotic drugs or candidates and six typica<br>antipsychotics. The first pattern, obtained with the typ<br>ical neur putamen following p.o. administration to mice of ten<br>atypical antipsychotic drugs or candidates and six typical<br>antipsychotics. The first pattern, obtained with the typ-<br>ical neuroleptics (setoperone, perlapine, haloperido atypical antipsychotic drugs or candidates and six typical<br>antipsychotics. The first pattern, obtained with the typ-<br>ical neuroleptics (setoperone, perlapine, haloperidol,<br>chlorpromazine, and metoclopramide), was character MT levels) and even larger increases in dopamine meical neuroleptics (setoperone, perlapine, haloperidol,<br>chlorpromazine, and metoclopramide), was characterized<br>by large (37 to 79%) increases in dopamine release (3-<br>MT levels) and even larger increases in dopamine me-<br>tabo chlorpromazine, and metoclopramide), was characterized<br>by large (37 to 79%) increases in dopamine release (3-<br>MT levels) and even larger increases in dopamine me-<br>tabolism, as measured by DOPAC (97 to 297% increases)<br>and H



PHARMACOLOGICAL REVIEW!

3-MT MEASUREMENTS AND DA RELI<br>
TABLE 10<br>
Actions of classical neuroleptic agents on mouse striatal DOPAC and 3-<br>
MT levels at behaviorally relevant doses. Drugs were injected p.o. at 1<br>
(top row) or 6 (bottom row) times t TABLE 10<br>*(top rop)* or *for classical neuroleptic agents on mouse striatal DOPAC and 3*<br>*(top row)* or 6 *(bottom row)* times the 50% effective dose for the<br>*(top row)* or 6 *(bottom row)* times the 50% effective dose for *i*nduced classical neuroleptic agents on mouse striatal DOPAC and 3-<br>*MT* levels at behaviorally relevant doses. Drugs were injected p.o. at 1<br>(top row) or 6 (bottom row) times the 50% effective dose for the<br>inhibition

at behaviorally relevant doees. Drugs were injected p.o. *a b* or 6 (bottom row) times the 50% effective dose for the of apomorphine-induced climbing. Mice were sacrificed BW 234U was injected i.p. at the 50% effective d min later. BW  $234U$  was injected i.p. at the  $50\%$  effective dose in the



\* Mean for 6 to 8 per group, expressed as the percentage of control<br>lues of the vehicle-injected group.<br> $\dagger P < 0.01$  greater than control.<br> $\dagger P < 0.05$  (Dunnett's test). 12<br> **\*** Mean for 6 to 8 per group, express of the vehicle-injected group<br>  $\uparrow P < 0.01$  greater than control.<br>  $\downarrow P < 0.05$  (Dunnett's test). <sup>\*</sup> Mean for 6 to 8 per group<br>ues of the vehicle-injected g<br>†  $P < 0.01$  greater than cont<br>‡  $P < 0.05$  (Dunnett's test).

values of the vehicle-injected group.<br>  $\uparrow P < 0.01$  greater than control.<br>  $\downarrow P < 0.05$  (Dunnett's test).<br>
Tochemical profile has also been observed in the rat or<br>
mouse striatum following the administration of the typ- $\uparrow P < 0.01$  greater than control.<br>  $\downarrow P < 0.05$  (Dunnett's test).<br>
Frochemical profile has also been observed in the rat or<br>
mouse striatum following the administration of the typ-<br>
cical antipsychotics, chlorpromazine,  $f \sim 0.06$  (bunned s ass).<br>
For the mouse striatum following the administration of the typical antipsychotics, chlorpromazine, haloperidol, meto-<br>
clopramide, perlapine, and to a lesser extent, thioridazine rochemical profile has also been observed in the rat or<br>mouse striatum following the administration of the typ-<br>ical antipsychotics, chlorpromazine, haloperidol, meto-<br>clopramide, perlapine, and to a lesser extent, thiorid rochemical profile has also been observed in the rat or<br>
mouse striatum following the administration of the typ-<br>
ical antipsychotics, chlorpromazine, haloperidol, meto-<br>
clopramide, perlapine, and to a lesser extent, thi ical antipsychotics, chlorpromazine, haloperidol, meto-<br>clopramide, perlapine, and to a lesser extent, thioridazine<br>for striatal dopamine release (3-MT) and metabolism<br> $\frac{1}{3}$ <br>(DOPAC) (15, 78, 218, 220, 227) or metabolis for striatal dopamine release  $(3-MT)$  and metabolism  $(DOPAC)$   $(15, 78, 218, 220, 227)$  or metabolism only  $(37, 38, 172, 192)$ . The one typical neuroleptic that failed to increase dopamine release while markedly elevating for striatal dopamine release  $(3\text{-}MT)$  and metabolism  $(DOPAC)$   $(15, 78, 218, 220, 227)$  or metabolism only  $(37, 38, 172, 192)$ . The one typical neuroleptic that failed to coincrease dopamine release while markedly eleva (DOPAC) (15, 78, 218, 220, 227) or metabolism only (37, 38, 172, 192). The one typical neuroleptic that failed to contrincrease dopamine release while markedly elevating meration tabolism was pimozide. However, pimozide, 38, 172, 192). The one typical neuroleptic that failed to coincrease dopamine release while markedly elevating metabolism was pimozide. However, pimozide, unlike the best other typical neuroleptics tested, is a potent calc increase dopamine release while markedly elevating metabolism was pimozide. However, pimozide, unlike the other typical neuroleptics tested, is a potent calcium channel receptor blocker in the brain (75). This action of pi tabolism was pimozide. However, pimozide, unlike the best other typical neuroleptics tested, is a potent calcium cluster channel receptor blocker in the brain (75). This action sum of pimozide may prevent calcium-dependent channel receptor blocker in the brain  $(75)$ . This action<br>of pimozide may prevent calcium-dependent dopamine<br>release during concomitant  $D-2$  receptor blockade, as<br>described for the calcium channel antagonist nimodipine<br>(142). pimozide may prevent calcium-dependent dopamin<br>lease during concomitant D-2 receptor blockade, a<br>scribed for the calcium channel antagonist nimodipin<br>42).<br>The second pattern, obtained with the atypical com-<br>unds, was chara

release during concomitant D-2 receptor blockade, as to indescribed for the calcium channel antagonist nimodipine not (142).<br>
The second pattern, obtained with the atypical compounds, was characterized by no change or a *d* described for the calcium channel antagonist nimodipine<br>
(142).<br>
The second pattern, obtained with the atypical com-<br>
pounds, was characterized by no change or a *decrease* in<br>
3-MT at either dose (table 11). In only 4 of (142). The second pattern, obtained with the atypical compounds, was characterized by no change or a *decrease* in 3-MT at either dose (table 11). In only 4 of the 24 groups receiving an atypical compound were 3-MT levels The second pattern, obtained with the a<br>pounds, was characterized by no change or<br>3-MT at either dose (table 11). In only 4 of t<br>receiving an atypical compound were 3-M<br>creased. 5-(4-Methyl-1-piperazinyl)imidazo<br>benzothiad pounds, was characterized by no change or a *decrease* in 3-MT at either dose (table 11). In only 4 of the 24 group receiving an atypical compound were 3-MT levels in creased. 5-(4-Methyl-1-piperazinyl)imidazo[2,1-b][1,3,5 cis-5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazincreased. 5-(4-Methyl-1-piperazinyl)imidazo[2,1-b][1,3,5]<br>benzothiadiazepine maleate (CGS 10746B), flumezapine,<br>cis-5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazin-<br>yl)ethyl]indoline (CL 77-328), rimcazole (BW 234U),<br>cloz benzothiadiazepine maleate (CGS 10746B), flumezapine, des<br>cis-5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazin-<br>yl)ethyl]indoline (CL 77-328), rimcazole (BW 234U), ant<br>clozapine, 3-(2-chloro-11H-dibenz[b,e]azepine-11-ylicis-5,6-dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazin-<br>yl)ethyl]indoline (CL 77-328), rimcazole (BW 234U),<br>clozapine, 3-(2-chloro-11H-dibenz[b,e]azepine-11-yli-<br>dene)-N,N-dimethyl-1-propanamine (RMI 81582), and<br>fluperlapin yl)ethyl]indoline (CL 77-328), rimcazole (BW 234U)<br>clozapine, 3-(2-chloro-11*H*-dibenz[*b*,*e*]azepine-11-yli<br>dene)-N,N-dimethyl-1-propanamine (RMI 81582), and<br>fluperlapine did not increase dopamine release and pro<br>duced v clozapine,  $3-(2-\text{chloro}-11)$ -dibenz $[b,e]$ azepine-11-yli-<br>dene)-N,N-dimethyl-1-propanamine (RMI 81582), and<br>fluperlapine did not increase dopamine release and pro-<br>duced variable increases in dopamine metabolism. Mel-<br>perone i dene)-N,N-dimethyl-1-propanamine (RMI 81582), and<br>fluperlapine did not increase dopamine release and pro-<br>duced variable increases in dopamine metabolism. Mel-<br>perone increased dopamine release at one dose while<br>thioridazi fluperlapine did not increase dopamine release and pro-<br>duced variable increases in dopamine metabolism. Mel-<br>perone increased dopamine release at one dose while<br>thioridazine and mesoridazine increased dopamine re-<br>lease a duced variable increases in dopamine metabolism. Mel-<br>perone increased dopamine release at one dose while vir<br>thioridazine and mesoridazine increased dopamine re-<br>lease at relatively high doses but increased dopamine in<br>me perone increased dopamine release at one dose while<br>thioridazine and mesoridazine increased dopamine re-<br>lease at relatively high doses but increased dopamine<br>metabolism at most doses. Importantly, 3-MT levels were<br>lowered thioridazine and mesoridazine increased dopamine re-<br>lease at relatively high doses but increased dopamine in<br>metabolism at most doses. Importantly, 3-MT levels were a<br>lowered or remained unchanged even after doses that li



\* Mean  $\pm$  SEM for 6 to 8 per g<br>ntrol values of the vehicle-inject<br> $\dagger P < 0.05$  less than control (Du<br> $\dagger P < 0.01$  greater than control.<br> $\S P < 0.05$  greater than control.

control values of the vehicle-injected group.<br>  $\dagger P < 0.05$  less than control (Dunnett's test).<br>  $\dagger P < 0.01$  greater than control.<br>
§  $P < 0.05$  greater than control.

control) or HVA (26 to 129% above control). This separation between effects on release and metabolism has been observed for clozapine (218) and CGS 10746B, a ration between effects on release and metabolism has  $\frac{4}{3}P < 0.05$  greater than control.<br>
control) or HVA (26 to 129% above control). This separation between effects on release and metabolism has<br>
been observed for clozapine (218) and CGS 10746B, a<br>
clozapine analog (15, control) or HVA (26 to 129% above control). This separation between effects on release and metabolism has been observed for clozapine (218) and CGS 10746B, a clozapine analog (15, 209). In the case of CGS 10746B, suppress control) or HVA (26 to 129% above control). This a<br>ration between effects on release and metabolism<br>been observed for clozapine (218) and CGS 10746<br>clozapine analog (15, 209). In the case of CGS 107<br>suppressions of 3-MT fo ration between effects on release and metabolism has<br>been observed for clozapine (218) and CGS 10746B, a<br>clozapine analog (15, 209). In the case of CGS 10746B,<br>suppressions of 3-MT following p.o. or i.p. administra-<br>tion o been observed for clozapine (218) and CGS 10746B, a<br>clozapine analog (15, 209). In the case of CGS 10746B,<br>suppressions of 3-MT following p.o. or i.p. administra-<br>tion occur at doses 4- to 6-fold lower than those required<br> clozapine analog (15, 209). In the case of CGS 10746B,<br>suppressions of 3-MT following p.o. or i.p. administra-<br>tion occur at doses 4- to 6-fold lower than those required<br>to increase DOPAC and HVA, which unlike 3-MT were<br>no suppressions of 3-MT following p.o. or i.p. administra-<br>tion occur at doses 4- to 6-fold lower than those required<br>to increase DOPAC and HVA, which unlike 3-MT were<br>not lowered by any dose of CGS 10746B. The changes in<br>3-M tion occur at doses 4- to 6-fold lower than those required<br>to increase DOPAC and HVA, which unlike 3-MT were<br>not lowered by any dose of CGS 10746B. The changes in<br>3-MT, unlike those obtained for DOPAC and HVA,<br>correspond w to increase DOPAC and HVA, which unlike 3-MT were<br>not lowered by any dose of CGS 10746B. The changes in<br>3-MT, unlike those obtained for DOPAC and HVA,<br>correspond with decreases in dopamine neuron firing<br>rates and behaviora (15). MT, unlike those obtained for DOPAC and HVA,<br>rrespond with decreases in dopamine neuron firing<br>tes and behavioral indices of nigrostriatal suppression<br>5).<br>Overall, the resemblance of these minimal effects on<br>pamine release correspond with decreases in dopamine neuron firing<br>rates and behavioral indices of nigrostriatal suppression<br>(15).<br>Overall, the resemblance of these minimal effects on<br>dopamine release by atypical antipsychotics with thos

rates and behavioral indices of nigrostriatal suppression (15).<br>
Overall, the resemblance of these minimal effects on<br>
dopamine release by atypical antipsychotics with those<br>
described in section IV B for the D-1 compound (15).<br>
Overall, the resemblance of these minimal effects on<br>
dopamine release by atypical antipsychotics with those<br>
described in section IV B for the D-1 compounds SCH<br>
23390 and SKF 83566 (33, 59) suggests that D-1 rece dopamine release by atypical antipsychotics with those<br>described in section IV B for the D-1 compounds SCH<br>23390 and SKF 83566 (33, 59) suggests that D-1 receptor<br>antagonism may contribute to the antipsychotic mecha-<br>nism scribed in section IV B for the D-1 compounds SCH<br>390 and SKF 83566 (33, 59) suggests that D-1 receptor<br>tagonism may contribute to the antipsychotic mecha-<br>sm of atypical antipsychotics (14a, 17-19).<br>A very large number of antagonism may contribute to the antipsychotic mecha-

23390 and SKF 83566 (33, 59) suggests that  $D-1$  receptor<br>antagonism may contribute to the antipsychotic mecha-<br>nism of atypical antipsychotics  $(14a, 17-19)$ .<br>A very large number of experiments, reviewed above<br>and in tab nism of atypical antipsychotics (14a, 17-19).<br>A very large number of experiments, reviewed above<br>and in tabular form (table 9), corroborate the utility of<br>3-MT measurements for assessing dopamine release in<br>vivo. However, A very large number of experiments, reviewed above<br>and in tabular form (table 9), corroborate the utility of<br>3-MT measurements for assessing dopamine release in<br>vivo. However, some controversy concerning changes in<br>3-MT in and in tabular form (table 9), corroborate the utility of 3-MT measurements for assessing dopamine release in<br>vivo. However, some controversy concerning changes in<br>3-MT in the rat striatum after haloperidol has appeared<br>in 3-MT measurements for assessing dopamine release in<br>vivo. However, some controversy concerning changes in<br>3-MT in the rat striatum after haloperidol has appeared<br>in the literature. As expected from its blockade of D-2<br>auto vivo. However, some controversy concerning changes in 3-MT in the rat striatum after haloperidol has appeared<br>in the literature. As expected from its blockade of D-2<br>autoreceptors (62, 114, 115), this potent neuroleptic re 3-MT in the rat striatum after haloperidol has appeared<br>in the literature. As expected from its blockade of D-2<br>autoreceptors (62, 114, 115), this potent neuroleptic re-<br>liably augments striatal 3-MT levels for at least 8

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

**a**spet

<sup>178</sup> **WOOD AND ALTAR** 178 wood and<br>push-pull perfusates of cat caudate has been reported for sy<br>a number of neuroleptics including haloperidol (119). In 1 woop AND AI<br>push-pull perfusates of cat caudate has been reported for syst<br>a number of neuroleptics including haloperidol (119). In 100<br>the rat, however, haloperidol elevates DOPAC and HVA, auto wood AN<br>push-pull perfusates of cat caudate has been reported for<br>a number of neuroleptics including haloperidol (119). In<br>the rat, however, haloperidol elevates DOPAC and HVA,<br>but not 3-MT, at 1 h (145, 197, 202) or 2 h push-pull perfusates of cat caudate has been reported for<br>a number of neuroleptics including haloperidol (119). In<br>the rat, however, haloperidol elevates DOPAC and HVA,<br>but not 3-MT, at 1 h (145, 197, 202) or 2 h (191) aft push-pull perfusates of cat caudate has been reported for<br>a number of neuroleptics including haloperidol (119). In<br>the rat, however, haloperidol elevates DOPAC and HVA,<br>but not 3-MT, at 1 h (145, 197, 202) or 2 h (191) aft a number of neuroleptics including haloperidol (119). In<br>the rat, however, haloperidol elevates DOPAC and HVA<br>but not 3-MT, at 1 h (145, 197, 202) or 2 h (191) afte<br>even very high doses of 3 mg/kg. Haloperidol-induce<br>incre the rat, however, haloperidol elevates DOPAC and HVA,<br>but not 3-MT, at 1 h (145, 197, 202) or 2 h (191) after<br>even very high doses of 3 mg/kg. Haloperidol-induced<br>increases in 3-MT are obtained in the rat only in com-<br>bina but not 3-MT, at 1 h (145, 197, 202) or 2 h (191) after co<br>even very high doses of 3 mg/kg. Haloperidol-induced (10<br>increases in 3-MT are obtained in the rat only in com-<br>ac<br>bination with MAO inhibition with clorgyline (19 even very high doses of 3 mg/kg. Haloperidol-induced<br>increases in 3-MT are obtained in the rat only in com-<br>bination with MAO inhibition with clorgyline (191),<br>nialamide (41), or pargyline (102, 160). When sacrifice is<br>at increases in 3-MT are obtained in the rat only in combination with MAO inhibition with clorgyline (191), nialamide (41), or pargyline (102, 160). When sacrifice is at 8 to 16 min postadministration, however, haloperidol do bination with MAO inhibition with clorgyline (191),<br>nialamide (41), or pargyline (102, 160). When sacrifice is<br>at 8 to 16 min postadministration, however, haloperidol<br>does increase rat striatal 3-MT, by about 60% (145, 202 nialamide (41), or pargyline (102, 160). When sacrifice is<br>at 8 to 16 min postadministration, however, haloperidol<br>does increase rat striatal 3-MT, by about 60% (145, 202).<br>Similarly, only small and transient increases of at 8 to 16 min postadministration, however, haloperidol<br>does increase rat striatal 3-MT, by about 60% (145, 202).<br>Similarly, only small and transient increases of DA re-<br>lease from rat striatum have been measured with stri does increase rat striatal 3-MT, by about 60% (145, 202). tet:<br>Similarly, only small and transient increases of DA re-<br>lease from rat striatum have been measured with striatal CG<br>dialysis (106, 227) and push-pull perfusion Similarly, only small and transient increases of DA re-<br>lease from rat striatum have been measured with striatal C<br>dialysis (106, 227) and push-pull perfusion (149) after ph<br>haloperidol. Because striatal dopamine release i lease from rat striatum have been measured with striatal C<br>dialysis (106, 227) and push-pull perfusion (149) after<br>haloperidol. Because striatal dopamine release is only the<br>transiently increased after haloperidol treatmen dialysis (106, 227) and push-pull perfusion (149) after<br>haloperidol. Because striatal dopamine release is only<br>transiently increased after haloperidol treatment, it is<br>likely that an early induction of depolarization block haloperidol. Because striatal dopamine release is only transiently increased after haloperidol treatment, it is likely that an early induction of depolarization block of dopamine neurons by this potent neuroleptic (76) pre transiently increased after haloperidol treatment, it is morph<br>likely that an early induction of depolarization block of dopan<br>dopamine neurons by this potent neuroleptic (76) pre-<br>vents subsequent dopamine release. This i likely that an early induction of depolarization block of dopamine neurons by this potent neuroleptic (76) prevents subsequent dopamine release. This is consistent rawith the ability of the MAO inhibition technique to show dopamine neurons by this potent neuroleptic (76) prevents subsequent dopamine release. This is consistent with the ability of the MAO inhibition technique to show an increase in 3-MT, since the early increase in release wo vents subsequent dopamine release. This is consistent rat<br>with the ability of the MAO inhibition technique to show by (<br>an increase in 3-MT, since the early increase in release to t<br>would contribute to the accumulated pool with the ability of the MAO inhibition technique to show<br>an increase in 3-MT, since the early increase in release<br>would contribute to the accumulated pool of 3-MT. Thus,<br>rather than invalidating the usefulness of 3-MT as a an increase in 3-MT, since the early increase in release would contribute to the accumulated pool of 3-MT. Thus, rather than invalidating the usefulness of 3-MT as an index of dopamine release, these data reveal a species would contribute to the accumulated pool of  $3\text{-}MT$ . Thus,<br>rather than invalidating the usefulness of  $3\text{-}MT$  as an<br>index of dopamine release, these data reveal a species<br>difference in the actions of haloperidol on rat index of dopamine release, these data reveal a species<br>difference in the actions of haloperidol on rat striatal<br>dopamine release.<br>*D. DA Autoreceptor Agonists*<br>*1. Pharmacology*. When administered in doses high 1. The actions of haloperidol on rat striatal act<br>
pamine release. The release.<br> *PA Autoreceptor Agonists*<br>
1. *Pharmacology*. When administered in doses high (14<br>
pough to stimulate postsynaptic D-2 receptors in the 2

dopamine release. The community of the CD of the CD.<br>
D. DA Autoreceptor Agonists<br>
1. Pharmacology. When administered in doses high (1.<br>
enough to stimulate postsynaptic D-2 receptors in the nucleus accumbens and caudate-p nucleus accumbent agents and caudate-putament alones high and caudate-putamen, full dopamine agents accumbens and caudate-putamen, full dopamine agents such as apomorphine increase locomotor behav-D. DA Autoreceptor Agonists<br>1. Pharmacology. When administered in doses his<br>enough to stimulate postsynaptic  $D-2$  receptors in t<br>nucleus accumbens and caudate-putamen, full dopami<br>agonists such as apomorphine increase lo 1. Pharmacology. When administered in doses high<br>enough to stimulate postsynaptic D-2 receptors in the<br>nucleus accumbens and caudate-putamen, full dopamine<br>agonists such as apomorphine increase locomotor behav-<br>ior in rats enough to stimulate postsynaptic D-2 receptors in the<br>nucleus accumbens and caudate-putamen, full dopamine<br>agonists such as apomorphine increase locomotor behav-<br>ior in rats (52, 150). However, lower doses of dopamine<br>agon nucleus accumbens and caudate-putamen, full dopamine<br>agonists such as apomorphine increase locomotor behav-<br>ior in rats (52, 150). However, lower doses of dopamine<br>agonists and administration of dopamine autoreceptor<br>agoni agonists such as a<br>pomorphine increase locomotor behavior in rats  $(52, 150)$ . However, lower doses of dopamine<br>agonists and administration of dopamine autoreceptor<br>agonists (partial agonists) decrease locomotor behavior<br> agonists such as apomorphine increase locomotor behav-<br>
ior in rats  $(52, 150)$ . However, lower doses of dopamine<br>
agonists and administration of dopamine autoreceptor<br>
agonists (partial agonists) decrease locomotor behav agonists and administration of dopamine autoreceptor<br>agonists (partial agonists) decrease locomotor behavior<br>and striatal dopamine release (57, 83, 84, 177). The<br>locomotor suppression and decrease in dopamine release<br>occur agonists (partial agonists) decrease locomotor behavior delard striatal dopamine release  $(57, 83, 84, 177)$ . The malocomotor suppression and decrease in dopamine release  $14$  occur because of the selective activation of and striatal dopamine release (57, 83, 84, 177). The<br>locomotor suppression and decrease in dopamine release<br>occur because of the selective activation of presynapti<br>dopamine autoreceptors. This lowers the release an<br>synapti locomotor suppression and decrease in dopamine release<br>occur because of the selective activation of presynaptic<br>dopamine autoreceptors. This lowers the release an<br>synaptic concentrations of dopamine. The lessened stim<br>ulat dopamine autoreceptors. This lowers the release and<br>synaptic concentrations of dopamine. The lessened stim-<br>ulation of postsynaptic D-2 receptors attenuates loco-<br>motion. These low autoreceptor-selective doses of dopa-<br>min dopamine autoreceptors. This lowers the release and synaptic concentrations of dopamine. The lessened stim-<br>ulation of postsynaptic D-2 receptors attenuates loco-<br>ing motion. These low autoreceptor-selective doses of dopa synaptic concentrations of dopamine. The lessened stim-<br>ulation of postsynaptic D-2 receptors attenuates loco-<br>induction. These low autoreceptor-selective doses of dopa-<br>mine agonists also lower 3-MT levels in the rat and ulation of postsynaptic D-2 receptors attenue motion. These low autoreceptor-selective dose<br>mine agonists also lower 3-MT levels in the<br>mouse striatum and olfactory tubercle (4, 6, 8<br>accumulation of 3-MT after pargyline (1 otion. These low autoreceptor-selective doses of dopa-<br>ine agonists also lower 3-MT levels in the rat and<br>ouse striatum and olfactory tubercle (4, 6, 8) and the<br>cumulation of 3-MT after pargyline (102).<br>The subtle, and phy mine agonists also lower 3-MT levels in the rat and abduced mouse striatum and olfactory tubercle  $(4, 6, 8)$  and the accumulation of 3-MT after pargyline  $(102)$ .<br>The subtle, and physiologically relevant, modulation of d

mouse striatum and olfactory tubercle  $(4, 6, 8)$  and the accumulation of 3-MT after pargyline (102).<br>The subtle, and physiologically relevant, modulation of dopamine neuron activity by autoreceptors can be achieved with t accumulation of 3-MT after pargyline (102).<br>The subtle, and physiologically relevant, modulation<br>of dopamine neuron activity by autoreceptors can be<br>achieved with the D-2 receptor agonists apomorphine,<br>N-propylnorapomorphi The subtle, and physiologically relevant, modula<br>of dopamine neuron activity by autoreceptors can<br>achieved with the D-2 receptor agonists apomorph<br>N-propylnorapomorphine, bromocriptine, and lisur<br>and the partial D-2 agonis  $1.3.4.4\alpha.5.10\beta$ -hexahydro-4-propyl-2H-[1]benzopyrano achieved with the D-2 receptor agonists apomorphine,<br>N-propylnorapomorphine, bromocriptine, and lisuride,<br>and the partial D-2 agonists CGS 15855A and  $(+)$ -trans-<br>1,3,4,4 $\alpha$ ,5,10 $\beta$ -hexahydro-4-propyl-2H-[1]benzopyrano<br>[ N-propylnorapomorphine, bromocriptine, and lisuride,<br>and the partial D-2 agonists CGS 15855A and  $(+)$ -trans-<br>1,3,4,4 $\alpha$ ,5,10 $\beta$ -hexahydro-4-propyl-2H-[1]benzopyrano<br>[3,4-b]pyridin-7-ol (CGS 15873) (4, 8, 72) which have and the partial D-2 agonists CGS 15855A and  $(+)$ -trans-<br>1,3,4,4 $\alpha$ ,5,10 $\beta$ -hexahydro-4-propyl-2H-[1]benzopyrano<br>[3,4-b]pyridin-7-ol (CGS 15873) (4, 8, 72) which have at<br>least a 5-fold autoreceptor selectivity (93). Stim  $1,3,4,4\alpha,5,10\beta$ -hexahydro-4-propyl-2H-[1]benzopyrano<br>[3,4-b]pyridin-7-ol (CGS 15873) (4, 8, 72) which have at sin<br>least a 5-fold autoreceptor selectivity (93). Stimulation eth<br>of the dopamine autoreceptor attenuates do  $[3,4-b]$ pyridin-7-ol (CGS 15873) (4, 8, 72) which have<br>least a 5-fold autoreceptor selectivity (93). Stimulat<br>of the dopamine autoreceptor attenuates dopamine s<br>thesis (103), turnover (41, 57), nigrostriatal cell fir<br>(1), least a 5-fold autoreceptor selectivity (93). Stimulation<br>of the dopamine autoreceptor attenuates dopamine syn-<br>thesis (103), turnover (41, 57), nigrostriatal cell firing<br>(1), and the depolarization-evoked release of triti of the dopamine autoreceptor attenuates dopamine synthesis (103), turnover (41, 57), nigrostriatal cell firing (1), and the depolarization-evoked release of tritium-<br>labeled dopamine from striatal slices (114, 115, 173, 23

systemic apomorphine administration decreases by up to 4 ALTAR<br>systemic apomorphine administration decreases by up to<br>100% the release of dopamine in the striatum. These<br>autoreceptor-mediated decreases in dopamine release are ALTAR<br>systemic apomorphine administration decreases by up to<br>100% the release of dopamine in the striatum. These<br>autoreceptor-mediated decreases in dopamine release are<br>corroborated by 3-MT measurements. Apomorphine systemic apomorphine administration decreases by up to 100% the release of dopamine in the striatum. These autoreceptor-mediated decreases in dopamine release are corroborated by 3-MT measurements. Apomorphine (101), lisur systemic apomorphine administration decreases by up to 100% the release of dopamine in the striatum. These autoreceptor-mediated decreases in dopamine release are corroborated by 3-MT measurements. Apomorphine (101), lisur 100% the release of dopamine in the striatum. These<br>autoreceptor-mediated decreases in dopamine release are<br>corroborated by 3-MT measurements. Apomorphine<br>(101), lisuride, and bromocriptine (191) decrease 3-MT<br>accumulation autoreceptor-mediated decreases in dopamine release are<br>corroborated by 3-MT measurements. Apomorphine<br>(101), lisuride, and bromocriptine (191) decrease 3-MT<br>accumulation after pargyline. Apomorphine also lowers<br>3-MT level (101), lisuride, and bromocriptine (191) decrease 3-MT accumulation after pargyline. Apomorphine also lowers 3-MT levels of otherwise untreated rats (4, 53, 191, 202), rabbits (173), and mice (8, 33). Suppressions of stri (101), lisuride, and bromocriptine (191) decreaccumulation after pargyline. Apomorphine al 3-MT levels of otherwise untreated rats  $(4, 53,$ rabbits (173), and mice  $(8, 33)$ . Suppressions  $(3-MT$  following dipropyl-2-amino accumulation after pargyline. Apomorphine also lowers 3-MT levels of otherwise untreated rats  $(4, 53, 191, 202)$ , rabbits (173), and mice  $(8, 33)$ . Suppressions of striatal 3-MT following dipropyl-2-amino-6,7-dihydroxy-1 3-MT levels of otherwise untreated rats (4, 53, 191, 202),<br>rabbits (173), and mice (8, 33). Suppressions of striatal<br>3-MT following dipropyl-2-amino-6,7-dihydroxy-1,2,3,4-<br>tetrahydronaphthalene (ADTN), piribedil, ergocorni rabbits (173), and mice (8, 33). Suppressions<br>3-MT following dipropyl-2-amino-6,7-dihydro<br>tetrahydronaphthalene (ADTN), piribedil, e:<br>(191), LY 171555, CGS 15855A, the (-)-enai<br>CGS 15855 (CGS 16314A), (+)-N,n-propyl-3<br>phen 3-MT following dipropyl-2-amino-6,7-dihydroxy<br>tetrahydronaphthalene (ADTN), piribedil, erg(191), LY 171555, CGS 15855A, the (-)-enanti<br>CGS 15855 (CGS 16314A), (+)-N,n-propyl-3-(h<br>phenyl)piperidine [(+)-3-PPP] 6,7-dihydroxy tetrahydronaphthalene (ADTN), piribedil, erg<br>(191), LY 171555, CGS 15855A, the (-)-enant<br>CGS 15855 (CGS 16314A), (+)-N,n-propyl-3-(<br>phenyl)piperidine [(+)-3-PPP] 6,7-dihydroxy<br>thylaminotetralin (TL-99), and (-)N,n-propy<br>mo (191), LY 171555, CGS 15855A, the  $(-)$ -enantiomer of CGS 15855 (CGS 16314A),  $(+)$ -N,n-propyl-3-(hydroxy-phenyl)piperidine  $[ (+)$ -3-PPP] 6,7-dihydroxy-2-dimethylaminotetralin (TL-99), and  $(-)N$ ,n-propylnorapo-morphine (8, 3 CGS 15855 (CGS 16314A),  $(+)$ -N,n-p<br>phenyl)piperidine  $[ (+)$ -3-PPP] 6,7-<br>thylaminotetralin (TL-99), and  $(-)$ l<br>morphine (8, 33) are consistent with t<br>dopamine release by these compounds<br>Basal and pargyline-accumulated lev enyl)piperidine  $[(+)-3-PPP]$  6,7-dihydroxy-2-dime-<br>ylaminotetralin (TL-99), and  $(-)N,n$ -propylnorapo-<br>orphine (8, 33) are consistent with the suppression of<br>pamine release by these compounds.<br>Basal and pargyline-accumulated l

thylaminotetralin (TL-99), and  $(-)N,n$ -propylnorapo-<br>morphine  $(8, 33)$  are consistent with the suppression of<br>dopamine release by these compounds.<br>Basal and pargyline-accumulated levels of 3-MT in the<br>rat frontal cortex a morphine (8, 33) are consistent with the suppression of dopamine release by these compounds.<br>Basal and pargyline-accumulated levels of 3-MT in the rat frontal cortex and cingulate cortex are also lowered by CGS 15855A or a Basal and pargyline-accumulated levels of 3-MT in the<br>rat frontal cortex and cingulate cortex are also lowered<br>by CGS 15855A or apomorphine (9). This is in contrast<br>to the inability of cortical dopamine autoreceptors to<br>di rat frontal cortex and cingulate cortex are also lowered<br>by CGS 15855A or apomorphine (9). This is in contrast<br>to the inability of cortical dopamine autoreceptors to<br>directly modulate neocortical dopamine synthesis or me-<br> by CGS 15855A or apomorphine (9). This is in contrast<br>to the inability of cortical dopamine autoreceptors to<br>directly modulate neocortical dopamine synthesis or me-<br>tabolism (20, 21), although DA agonists have been pos-<br>tu to the inability of cortical dopamine autoreceptors to directly modulate neocortical dopamine synthesis or metabolism (20, 21), although DA agonists have been postulated to indirectly modulate these aspects of dopamine act directly modulate neocortical dopamine synthesis or metabolism (20, 21), although DA agonists have been postulated to indirectly modulate these aspects of dopamine activity through changes in dopamine release (69, 204). Th tabolism (20, 21), although DA agonists have been pos-<br>tulated to indirectly modulate these aspects of dopamine<br>activity through changes in dopamine release (69, 204).<br>That dopamine autoreceptor modulation of dopamine<br>rele tulated to indirectly modulate these aspects of dopamine activity through changes in dopamine release (69, 204).<br>That dopamine autoreceptor modulation of dopamine release is present in neocortical areas is also supported b activity through of<br>That dopamine<br>release is present<br>by in vitro studio<br>(143, 144, 179).<br>2. Tolerance sti **2. Tolerance studies are administration** of dopenine<br> **2. Tolerance studies. Repeated administration for 2 h**<br> **2. Tolerance studies. Repeated administration for 2 h**<br> **2. Tolerance studies. Repeated administration for 2** 

morphine (8, 33) are consistent with the suppression of copamine release by these compounds.<br>
Basal and pargyline-accumulated levels of 3-MT in the rat frontal cortex and cingulate cortex are also lowered by CGS 158556 or release is present in neocortical areas is also supported<br>by in vitro studies of the frontal and piriform cortices<br>(143, 144, 179).<br>2. Tolerance studies. Repeated administration for 2 h<br>(8) or constant delivery for 2 days by in vitro studies of the frontal and piriform cortices<br>
(143, 144, 179).<br>
2. Tolerance studies. Repeated administration for 2 h<br>
(8) or constant delivery for 2 days (4) of CGS 15855A or<br>
apomorphine lowers striatal and (143, 144, 179).<br>
2. Tolerance studies. Repeated administration for 2 1<br>
(8) or constant delivery for 2 days (4) of CGS 15855A of<br>
apomorphine lowers striated and olfactory tubercle 3-MT<br>
concentrations. After 14 days of 2. Tolerance studies. Repeated administration for 2 h (8) or constant delivery for 2 days (4) of CGS 15855A or apomorphine lowers striatal and olfactory tubercle 3-MT concentrations. After 14 days of administration, howeve (8) or constant delivery for 2 days (4) of CGS 15855A or<br>apomorphine lowers striatal and olfactory tubercle 3-MT<br>concentrations. After 14 days of administration, how-<br>ever, 3-MT is no longer suppressed by sustained agonis apomorphine lowers striatal and olfactory tubercle 3-MT<br>concentrations. After 14 days of administration, how-<br>ever, 3-MT is no longer suppressed by sustained agonist<br>delivery via Alzet minipumps of daily doses that proved<br> concentrations. After 14 days of administration, how-<br>ever, 3-MT is no longer suppressed by sustained agonist<br>delivery via Alzet minipumps of daily doses that proved<br>maximally effective at 2 days. In addition, tolerance af ever, 3-MT is no longer suppressed by sustained agonist<br>delivery via Alzet minipumps of daily doses that proved<br>maximally effective at 2 days. In addition, tolerance after<br>14 days to the release-suppressing properties exte maximally effective at 2 days. In addition, tolerance after 14 days to the release-suppressing properties extends to the inability of large, acute injections of either agonist to lower  $3-MT$ , even with the contribution of maximally effective at 2 days. In addition, toleran<br>14 days to the release-suppressing properties ext<br>the inability of large, acute injections of either<br>to lower 3-MT, even with the contribution of the<br>delivered drug (4). 14 days to the release-suppressing properties extends to<br>the inability of large, acute injections of either agonist<br>to lower 3-MT, even with the contribution of the pump-<br>delivered drug (4). Tolerance to the synthesis-supp the inability of large, acute injections of either agonist<br>to lower 3-MT, even with the contribution of the pump-<br>delivered drug (4). Tolerance to the synthesis-suppress-<br>ing (16), firing rate-suppressing (73), and antipsy to lower 3-MT, even with the contribute delivered drug (4). Tolerance to the ing (16), firing rate-suppressing (73) (181, 182) properties of apomorphine about 2 days of chronic administration. ing (16), firing rate<br>(181, 182) propertia<br>about 2 days of chrones<br>*E. CNS Stimulants*<br>A wide variety of A wide variety of apomorphine also occurs after that also intervalse out 2 days of chronic administration.<br>
CNS Stimulants<br>
A wide variety of central nervous system (CNS) stim-<br>
ants appear to act via increasing DA release

ulants appear to act via increasing DA release and/or<br>inhibiting DA uptake. In the case of amphetamine-type<br>inhibiting DA uptake. In the case of amphetamine-type E. CNS Stimulants<br>A wide variety of central nervous system (CNS) stim<br>ulants appear to act via increasing DA release and/o<br>inhibiting DA uptake. In the case of amphetamine-type<br>stimulants, inhibition of MAO may also contri E. CNS Stimulants<br>A wide variety of central nervous system (CNS) stim-<br>ulants appear to act via increasing DA release and/or<br>inhibiting DA uptake. In the case of amphetamine-type<br>stimulants, inhibition of MAO may also cont A wide variety of central nervous system (CNS) stimulants appear to act via increasing DA release and/or inhibiting DA uptake. In the case of amphetamine-type stimulants, inhibition of MAO may also contribute to their phar

*1. Uptake blockers.* The DA uptake blockers, nomifeninhibiting DA uptake. In the case of amphetami<br>stimulants, inhibition of MAO may also contri<br>their pharmacology.<br>1. Uptake blockers. The DA uptake blockers, n<br>sine, amfonelic acid, 1-{2-[bis(4-fluorophenyl)m<br>ethyl}-4-(3-ph etimulants, inhibition of MAO may also contribute to<br>their pharmacology.<br>1. Uptake blockers. The DA uptake blockers, nomifen-<br>sine, amfonelic acid, 1-{2-[bis(4-fluorophenyl)methoxy]<br>ethyl}-4-(3-phenylpropyl)piperazine(GBR their pharmacology.<br>
1. Uptake blockers. The DA uptake blockers, nomifensine, amfonelic acid, 1-{2-[bis(4-fluorophenyl)methoxy]<br>
ethyl}-4-(3-phenylpropyl)piperazine(GBR 12909), and<br>
cocaine, have been shown to increase ext 1. Uptake blockers. The DA uptake blockers, nomifensine, amfonelic acid,  $1-\{2-\text{bis}(4-\text{fluoropheny})\text{methony}}\$ ethyl}-4-(3-phenylpropyl)piperazine(GBR 12909), and cocaine, have been shown to increase extraneuronal DA, as assessed by sine, amfonelic acid, 1-{2-[bis(4-fluorophenyl)methoxy]<br>ethyl}-4-(3-phenylpropyl)piperazine(GBR 12909), and<br>cocaine, have been shown to increase extraneuronal DA,<br>as assessed by in vivo voltammetry (104), striatal dialysis ethyl}-4-(3-phenylpropyl)piperazine(GBR 12909), and<br>cocaine, have been shown to increase extraneuronal DA,<br>as assessed by in vivo voltammetry (104), striatal dialysis<br>(48), and steady-state 3-MT measurements (58, 145, 191, cocaine, have been shown to increase extraneuronal DA,<br>as assessed by in vivo voltammetry (104), striatal dialysis<br>(48), and steady-state 3-MT measurements (58, 145, 191,<br>202). The uptake blocker, benztropine, has also bee



PHARMACOLOGICAL REVIEWS

3-MT MEASUREMENTS AND DA RELEA:<br>tammetry (170) and striatal dialysis (48). However, in 2.<br>the one study of 3-MT steady-state levels, this compound com 3-MT MEASUREMENTS AND DA REL<br>tammetry (170) and striatal dialysis (48). However, in<br>the one study of 3-MT steady-state levels, this compound<br>was inactive. This finding is the one published discrep-3-MT MEASUREMENTS AND I<br>tammetry (170) and striatal dialysis (48). However,<br>the one study of 3-MT steady-state levels, this compou<br>was inactive. This finding is the one published discrep-<br>ancy for the relationship between tammetry (170) and striatal dialysis (48). However<br>the one study of 3-MT steady-state levels, this compo<br>was inactive. This finding is the one published disc<br>ancy for the relationship between basal 3-MT concentions and DA tammetry (170) and striatal dialysis (48). However, in<br>the one study of 3-MT steady-state levels, this compound<br>was inactive. This finding is the one published discrep-<br>ancy for the relationship between basal 3-MT concentr the one study of 3-MT steady-state levels, this compound combined was inactive. This finding is the one published discrep-<br>between ancy for the relationship between basal 3-MT concentra-<br>tions and DA release, and it clearl was inactive. This finding is the one published discrepancy for the relationship between basal 3-MT concentrations and DA release, and it clearly requires furthestudy. By monitoring 3-MT accumulation after MA<br>study. By mon tions and DA release, and it clearly requires further<br>study. By monitoring 3-MT accumulation after MAO<br>inhibition, desipramine was found to increase this proc-<br>ess in whole rat brain, as does cocaine (99). In the rabbit study. By monitoring 3-MT accumulation after MAO<br>inhibition, desipramine was found to increase this proc-<br>ess in whole rat brain, as does cocaine (99). In the rabbit<br>striatum, however, cocaine did not enhance 3-MT accu-<br>mu study. By monitoring 3-MT<br>inhibition, desipramine was i<br>ess in whole rat brain, as doe<br>striatum, however, cocaine d<br>mulation after MAOI (79).<br>The physiological importal hibition, desipramine was found to increase this proc-<br>in whole rat brain, as does cocaine (99). In the rabbit<br>riatum, however, cocaine did not enhance 3-MT accu-<br>ulation after MAOI (79).<br>The physiological importance of hi

ess in whole rat brain, as does cocaine (99). In the rabbit<br>striatum, however, cocaine did not enhance 3-MT accu-<br>mulation after MAOI (79).<br>The physiological importance of high affinity DA up-<br>take by dopaminergic nerve en striatum, however, cocaine did not enhance 3-MT accu-<br>mulation after MAOI (79).<br>The physiological importance of high affinity DA up-<br>take by dopaminergic nerve endings during normal syn-<br>ele-<br>aptic transmission has been a mulation after MAOI (79).<br>The physiological importance of high affinity DA up-<br>take by dopaminergic nerve endings during normal syn-<br>aptic transmission has been a controversial issue. High<br>affinity uptake has been demonstr The physiological importance of high affinity DA uptake by dopaminergic nerve endings during normal synaptic transmission has been a controversial issue. High affinity uptake has been demonstrated to limit the diffusive en take by dopaminergic nerve endings during normal synchtic transmission has been a controversial issue. High phenoment<br>affinity uptake has been demonstrated to limit the dif-<br>weight fusive entry of DA into striatal slices ( affinity uptake has been demonstrated to limit the diffusive entry of DA into striatal slices (13, 169). Similarly, inhibition of uptake into brain slices by cocaine and nomifensine increases DA overflow as assessed by vol affinity uptake has been demonstrated to limit the dif-<br>fusive entry of DA into striatal slices (13, 169). Similarly, in<br>inhibition of uptake into brain slices by cocaine and me<br>nomifensine increases DA overflow as assesse fusive entry of DA into striatal slices (13, 169). Similarly, in<br>inhibition of uptake into brain slices by cocaine and me<br>nomifensine increases DA overflow as assessed by volaci<br>tammetry (104). In contrast, in vivo stimula inhibition of uptake into brain slices by cocaine are nomifensine increases DA overflow as assessed by vo<br>tammetry (104). In contrast, in vivo stimulation of the MFB, in the presence of DA uptake blockers, has been unable nomifensine increases DA overflow as assessed by vol-<br>tammetry (104). In contrast, in vivo stimulation of the<br>MFB, in the presence of DA uptake blockers, has been<br>tal studies to reveal any differences in DA clearance moniunable to reveal any differences in DA clearance moniunable to reveal any differences in DA clearance moni-<br>tored by voltammetry (60). Studies of DA metabolism in<br>rat striatal slices after inhibition of high affinity uptake<br>3<br>by either decreasing sodium concentrations in the by either decreasing sodium concentrations in the medium or by the addition of nomifensine have indicated that, while these slices do not accumulate DA, as compared to normal slices, the metabolism of the labeled DA rat striatal slices after inhibition of high affinity uptake 3-MT<br>by either decreasing sodium concentrations in the me-<br>dium or by the addition of nomifensine have indicated of elev<br>that, while these slices do not accumula by either decreasing sodium concentrations in the medium or by the addition of nomifensine have indicated that, while these slices do not accumulate DA, as compared to normal slices, the metabolism of the labeled DA to DOP that, while these slices do not accumulate DA, as compared to normal slices, the metabolism of the labeled DA to DOPAC and HVA is only minimally affected (164). that, while these slices do not accumulate DA, as compared to normal slices, the metabolism of the labeled DA to DOPAC and HVA is only minimally affected (164). The conclusions from these studies were that high affinity DA pared to normal slices, the metabolism of the labeled DA<br>to DOPAC and HVA is only minimally affected (164).<br>The conclusions from these studies were that high affin-<br>ity DA uptake is only a minor route of DA inactivation<br>an to DOPAC and HVA is only minimally affected (164). So<br>The conclusions from these studies were that high affin-<br>ity DA uptake is only a minor route of DA inactivation<br>and that the bulk of DA metabolism is secondary to glial ity DA uptake is only a minor route of DA inactivation<br>and that the bulk of DA metabolism is secondary to glial<br>uptake. In fact, studies of the diffusional distance of<br>released DA indicate that this is less than 100,000 nm and that the bulk of DA metabolism is secondary to glial uptake. In fact, studies of the diffusional distance of released DA indicate that this is less than 100,000 nm (60); however, this value is much greater than the dis uptake. In fact, studies of the diffusional distance of preleased DA indicate that this is less than 100,000 nm 3.<br>(60); however, this value is much greater than the distance of the synaptic cleft (20 to 30 nm; 140). In ad released DA indicate that this is less than 100,000 nm 3-M<br>(60); however, this value is much greater than the dis-<br>tance of the synaptic cleft (20 to 30 nm; 140). In addition, mis<br>this diffusional distance was unaffected b (60); however, this value is much greater than the dis-<br>tance of the synaptic cleft  $(20 \text{ to } 30 \text{ nm}; 140)$ . In addition, miss<br>this diffusional distance was unaffected by inhibition of Thigh affinity DA uptake, by MAO inh tance of the synaptic cleft  $(20 \text{ to } 30 \text{ nm}; 140)$ . In addition, in<br>this diffusional distance was unaffected by inhibition of<br>high affinity DA uptake, by MAO inhibition, and by<br>COMT inhibition  $(60)$ , again indicating th this diffusional distance was unaffected by inhibition of<br>high affinity DA uptake, by MAO inhibition, and by<br>COMT inhibition (60), again indicating that metabolism<br>of released DA is mainly secondary to glial uptake. This<br>c high affinity DA uptake, by MAO inhibition, and by COMT inhibition (60), again indicating that metabolism of released DA is mainly secondary to glial uptake. This conclusion would be compatible with the astrocytic sheets w DMT inhibition (60), again indicating that metabolism<br>released DA is mainly secondary to glial uptake. This<br>inclusion would be compatible with the astrocytic a<br>eets which surround synapses within the CNS (140).<br>The degree of released DA is mainly secondary to glial uptake. This tained<br>conclusion would be compatible with the astrocytic acute sheets which surround synapses within the CNS (140). site of<br>The degree of activity of a given dopam

conclusion would be compatible with the astrocytic accesses which surround synapses within the CNS (140). sit<br>The degree of activity of a given dopaminergic pathway<br>may also affect the net effect of drug treatments on DA ( sheets which surround synapses within the CNS (140).<br>The degree of activity of a given dopaminergic pathway<br>may also affect the net effect of drug treatments on DA (<br>release. In a study of drug effects on DA release in the The degree of activity of a given dopaminergic pathway<br>may also affect the net effect of drug treatments on DA<br>release. In a study of drug effects on DA release in the<br>rat striatum (voltammetry) after either 1 s or 10 s of may also affect the net effect of drug treatments on DA (PCP) receptor demonstrate a stereospecific motor acti-<br>release. In a study of drug effects on DA release in the vation in rats which is accompanied by elevated DOPA release. In a study of drug effects on DA release in the rat striatum (voltammetry) after either 1 s or 10 s of 50-<br>Hz stimulation of the MFB, benztropine only potentiated<br>the 1-s and not the 10-s period of electrical stim rat striatum (voltammetry) after either 1 s or 10 s of 50-<br>Hz stimulation of the MFB, benztropine only potentiated picket 1-s and not the 10-s period of electrical stimulation In<br>(170, 171). These data clearly indicate tha Hz stimulation of the MFB, benztropine only potentiated projector is and not the 10-s period of electrical stimulation. In r (170, 171). These data clearly indicate that drug effects accuracy on DA release can be affected the 1-s and not the 10-s period of electrical stimulation In (170, 171). These data clearly indicate that drug effects accon DA release can be affected by the level of activity of PC dopaminergic neurons prior to drug admi (170, 171). These data clearly indicate that drug effects as on DA release can be affected by the level of activity of  $\,$  F dopaminergic neurons prior to drug administration. In  $\,$  n this regard, previous studies of s on DA release can be affected by the level of activity of dopaminergic neurons prior to drug administration. In this regard, previous studies of striatal synaptosomes had demonstrated that high affinity uptake of DA is inh dopaminergic neurons prior to drug administration. In n<br>this regard, previous studies of striatal synaptosomes had<br>demonstrated that high affinity uptake of DA is inhibited<br>under depolarizing conditions (86). These data su this regard, previous studies of striatal synaptosomes had<br>demonstrated that high affinity uptake of DA is inhibited<br>under depolarizing conditions (86). These data suggest<br>that under low levels of activity, high affinity D demonstrated that high affinity uptake of DA is inhibited cortica<br>under depolarizing conditions (86). These data suggest cate th<br>that under low levels of activity, high affinity DA uptake mesoco<br>is a significant process fo under depolarizi<br>that under low le<br>is a significant<br>that under high<br>may predominat

*2. Precursor supply.* Using the paradigm of MAOI in LEASE IN VIVO FROM NEURONS 179<br>2. Precursor supply. Using the paradigm of MAOI in<br>combination with L-DOPA administration, a correlation<br>between increased motor activity and both striatal and LEASE IN VIVO FROM NEURONS 179<br>2. Precursor supply. Using the paradigm of MAOI in<br>combination with L-DOPA administration, a correlation<br>between increased motor activity and both striatal and<br>nucleus accumbens 3-MT levels w 2. Precursor supply. Using the paradigm of MAOI in combination with L-DOPA administration, a correlation between increased motor activity and both striatal and nucleus accumbens 3-MT levels was noted (53). Increased 3-MT l 2. Precursor supply. Using the paradigm of MAOI<br>combination with L-DOPA administration, a correlatio<br>between increased motor activity and both striatal an<br>nucleus accumbens 3-MT levels was noted (53). I<br>creased 3-MT levels combination with L-DOPA administration, a correlation<br>between increased motor activity and both striatal and<br>nucleus accumbens 3-MT levels was noted (53). In-<br>creased 3-MT levels have also been noted in the brain-<br>stem and between increased motor activity and h<br>nucleus accumbens 3-MT levels was<br>creased 3-MT levels have also been not<br>stem and hypothalamus with the combi<br>and L-DOPA administration (23, 39).<br>Using brain dialysis, direct evidence ucleus accumbens 3-MT levels was noted (53). In-<br>eased 3-MT levels have also been noted in the brain-<br>em and hypothalamus with the combination of MAOI<br>d L-DOPA administration (23, 39).<br>Using brain dialysis, direct evidence creased 3-MT levels have also been noted in the brain-<br>stem and hypothalamus with the combination of MAOI<br>and L-DOPA administration (23, 39).<br>Using brain dialysis, direct evidence for increased DA<br>release has been obtained

tyrosine (58a). *3. DOPA administration (23, 39).*<br> *3. Daing brain dialysis, direct evidence for increased DA*<br> *Dase has been obtained after precursor loading with*<br> *3. DA releasers.* The early studies of Braestrup (34)<br> *3. DA release* 

tammetry (104). In contrast, in vivo stimulation of the of these stimulants, independent of class, elevated stria-<br>MFB, in the presence of DA uptake blockers, has been tal steady-state 3-MT levels (58, 127, 145, 191, 201, The conclusions from these studies were that high affin-<br>ity DA uptake is only a minor route of DA inactivation<br>nous stimulant, phenethylamine, which appears to be<br>and that the bulk of DA metabolism is secondary to glial<br> Using brain dialysis, direct evidence for increased DA<br>release has been obtained after precursor loading with<br>tyrosine (58a).<br>3. DA releasers. The early studies of Braestrup (34)<br>clearly indicated that amphetamine-like sti release has been obtained after precursor loading wit<br>tyrosine (58a).<br>3. DA releasers. The early studies of Braestrup (34<br>clearly indicated that amphetamine-like stimulants (am<br>phetamine, methamphetamine, and phenmetrazine tyrosine (58a).<br>
3. DA releasers. The early studies of Braestrup (34)<br>
clearly indicated that amphetamine-like stimulants (am-<br>
phetamine, methamphetamine, and phenmetrazine)<br>
were unique in that they decreased whole brai 3. DA releasers. The early studies of Braestrup (34)<br>clearly indicated that amphetamine-like stimulants (am-<br>phetamine, methamphetamine, and phenmetrazine)<br>were unique in that they decreased whole brain DOPAC<br>in the rat, clearly indicated that amphetamine-like stimulants (amphetamine, methamphetamine, and phenmetrazine)<br>were unique in that they decreased whole brain DOPAC<br>in the rat, while other stimulants increased this DA<br>metabolite (met phetamine, methamphetamine, and phenmetrazine)<br>were unique in that they decreased whole brain DOPAC<br>in the rat, while other stimulants increased this DA<br>metabolite (methylphenidate, nomifensine, amfonelic<br>acid, and piprado were unique in that they decreased whole brain DOPA<br>in the rat, while other stimulants increased this D.<br>metabolite (methylphenidate, nomifensine, amfoneli<br>acid, and pipradol). Subsequent studies indicated that a<br>of these in the rat, while other stimulants increased this DA<br>metabolite (methylphenidate, nomifensine, amfonelic<br>acid, and pipradol). Subsequent studies indicated that all<br>of these stimulants, independent of class, elevated striametabolite (methylphenidate, nomifensine, amfonelicacid, and pipradol). Subsequent studies indicated that all<br>of these stimulants, independent of class, elevated stria-<br>tal steady-state 3-MT levels (58, 127, 145, 191, 201, acid, and pipradol). Subsequent studies indicated that all<br>of these stimulants, independent of class, elevated stria-<br>tal steady-state 3-MT levels (58, 127, 145, 191, 201, 225)<br>and 3-MT accumulation after MAOI (77, 99). On of these stimulants, independent of class, elevated striatal steady-state 3-MT levels (58, 127, 145, 191, 201, 225) and 3-MT accumulation after MAOI (77, 99). One negative study for the effects of methylphenidate on stria and 3-MT accumulation after MAOI (77, 99). One negand 3-MT accumulation after MAOI (77, 99). One n<br>ative study for the effects of methylphenidate on stria<br>3-MT was reported (191). The elevated striatal 3-1<br>levels were also shown to correlate with the appeara<br>of elevated C ative study for the effects of methylphenidate on striatal 3-MT was reported (191). The elevated striatal 3-MT levels were also shown to correlate with the appearance of elevated CSF DA levels after amphetamine administrat 3-MT was reported (191). The elevated striatal 3-M<br>levels were also shown to correlate with the appearance of elevated CSF DA levels after amphetamine adminition in the rat (47). Amphetamine treatment has bee<br>shown to inc in the rat, while other stimulants increased this DA metabolite (methylphenidate, nomifensine, amfonelic acid, and pipradol). Subsequent studies indicated that all of these stimulants, independent of class, elevated stria of elevated CSF DA levels after amphetamine admin<br>tration in the rat (47). Amphetamine treatment has be<br>shown to increase DA release collected in striatal dia<br>sates by a number of laboratories (90, 215, 229) and<br>elevate 3tration in the rat (47). Amphetamine treatment has been<br>shown to increase DA release collected in striatal dialy-<br>sates by a number of laboratories (90, 215, 229) and to<br>elevate 3-MT in striatal dialysates (215). The endog shown to increase DA release collected in striatal dialy-<br>sates by a number of laboratories (90, 215, 229) and to<br>elevate 3-MT in striatal dialysates (215). The endoge-<br>nous stimulant, phenethylamine, which appears to be<br>c sates by a number of laboratories (90, 215, 229) and to<br>elevate 3-MT in striatal dialysates (215). The endoge-<br>nous stimulant, phenethylamine, which appears to be<br>contained within the rat nigrostriatal dopaminergic<br>pathway elevate 3-MT in striatal dialysates (215). The endo<br>nous stimulant, phenethylamine, which appears to<br>contained within the rat nigrostriatal dopamine<br>pathway (95), also releases DA, as indicated by eleva<br>3-MT levels (127). mous stimulant, phenethylamine, which appears to contained within the rat nigrostriatal dopaminergiathway (95), also releases DA, as indicated by elevation 3-MT levels (127). The possible modulatory or cotrans-mitter role contained within the rat nigre-<br>pathway (95), also releases DA, a<br>3-MT levels (127). The possible<br>mitter role of this trace amine is<br>mission warrants further study.<br>The site of action of these CNS mitter role of this trace amine in dopaminergic transmission warrants further study.<br>The site of action of these CNS stimulants is presum-

3-MT levels (127). The possible modulatory or cotransmitter role of this trace amine in dopaminergic transmission warrants further study.<br>The site of action of these CNS stimulants is presumably at the dopaminergic nerve e mitter role of this trace amine in dopaminergic transmission warrants further study.<br>The site of action of these CNS stimulants is presumably at the dopaminergic nerve ending. In the case of amphetamine, the DOPAC lowering mission warrants further study.<br>The site of action of these CNS stimulants is presumably at the dopaminergic nerve ending. In the case of amphetamine, the DOPAC lowering effect is also obtained in DA nerve endings in the r The site of action of these CNS stimulants is presumably at the dopaminergic nerve ending. In the case of amphetamine, the DOPAC lowering effect is also obtained in DA nerve endings in the rat striatum after an acute hemit ably at the dopaminergic nerve<br>amphetamine, the DOPAC lowe<br>tained in DA nerve endings in th<br>acute hemitransection, demonstratie of action for this drug (34).<br>4. PCP receptor agonists. Agonis approximation. the DOPAC lowering effect is also obined in DA nerve endings in the rat striatum after an ute hemitransection, demonstrating the presynaptic e of action for this drug (34).<br>4. *PCP receptor agonists*. Agonis % acute hemitransection, demonstrating the presynaptic<br>site of action for this drug  $(34)$ .<br>4. PCP receptor agonists. Agonists of the phencyclidine

acute hemitransection, demonstrating the presynaptic<br>site of action for this drug (34).<br>4. PCP receptor agonists. Agonists of the phencyclidine<br>(PCP) receptor demonstrate a stereospecific motor acti-<br>vation in rats which i site of action for this drug (34).<br>4. PCP receptor agonists. Agonists of the phencyclidine<br>(PCP) receptor demonstrate a stereospecific motor acti-<br>vation in rats which is accompanied by elevated DOPAC<br>and HVA in mesolimbic 4. PCP receptor agonists. Agonists of the phencyclidine (PCP) receptor demonstrate a stereospecific motor activation in rats which is accompanied by elevated DOPAC and HVA in mesolimbic and mesocortical dopaminergic projec (PCP) receptor demonstrate a stereospecific motor activation in rats which is accompanied by elevated DOPAC and HVA in mesolimbic and mesocortical dopaminergic projections, but not in the nigrostriatal pathway (31, 56). In vation in rats which is accompanied by elevated DOPAC<br>and HVA in mesolimbic and mesocortical dopaminergic<br>projections, but not in the nigrostriatal pathway (31, 56).<br>In recent studies of steady-state 3-MT levels and 3-MT<br>a and HVA in mesolimbic and mesocortical dopaminergi<br>projections, but not in the nigrostriatal pathway (31, 56)<br>In recent studies of steady-state 3-MT levels and 3-MT<br>accumulation after pargyline, the PCP receptor agonists<br>P methyl-5H-dibenzo $[a,d]$ cyclohepten-5,10-imine (MK In recent studies of steady-state 3-MT levels and 3-M<br>accumulation after pargyline, the PCP receptor agonist<br>PCP, dexoxadrol, ketamine, and  $10,11$ -dihydro-<br>methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (M<br>801), were found accumulation after pargyline, the PCP receptor agonists<br>PCP, dexoxadrol, ketamine, and  $10,11$ -dihydro-5<br>methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (MF<br>801), were found to increase these parameters in meso<br>cortical dopa PCP, dexoxadrol, ketamine, and 10,11-dihydro-5-<br>methyl-5H-dibenzo[ $a,d$ ]cyclohepten-5,10-imine (MK<br>801), were found to increase these parameters in meso-<br>cortical dopaminergic pathways (152). These data indi-<br>cate that PCP methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK<br>801), were found to increase these parameters in meso-<br>cortical dopaminergic pathways (152). These data indi-<br>cate that PCP receptor stimulation leads to activation of<br>meso 801), were found to increase these parameters in meso-<br>cortical dopaminergic pathways (152). These data indi-<br>cate that PCP receptor stimulation leads to activation of<br>mesocortical and mesolimbic DA pathways (66, 85) and<br>a cortical dopaminergic pathways (152). These data indicate that PCP receptor stimulation leads to activation of mesocortical and mesolimbic DA pathways (66, 85) and are consistent with the early reports of increased  $[^{14}$ cate that PCP receptor stimulation leads to activation of<br>mesocortical and mesolimbic DA pathways (66, 85) and<br>are consistent with the early reports of increased [<sup>14</sup>C]3-<br>MT formation from [<sup>14</sup>C]tyrosine in whole mouse b

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

180 **WOOD AND ALTAR**<br>WOOD AND ALTAR were observed after PCP which correlated with decreased action of intitiated DA release as assessed by in vivo voltammetry culline and b wood ANI<br>were observed after PCP which correlated with decreased<br>striatal DA release as assessed by in vivo voltammetry<br>(88). (88). Fre observed after PCP which correlated with decreased riatal DA release as assessed by in vivo voltammetry as.<br>
5. Lithium. Acute lithium has been reported to de-<br>
sase mouse whole brain 3-MT (135), while chronic

striatal DA release as assessed by in vivo voltammetry c<br>
(88).<br>
5. Lithium. Acute lithium has been reported to de-<br>
crease mouse whole brain 3-MT (135), while chronic d<br>
treatment for 11 days increases rat striatal 3-MT (88).<br>5. Lithium. Acute lithium has been reported to de-<br>crease mouse whole brain 3-MT (135), while chronic<br>treatment for 11 days increases rat striatal 3-MT levels<br>121). Similarly, 20 days of lithium treatment increase<br>r 5. Lithium. Acute lithium has been reported to decrease mouse whole brain  $3-MT$  (135), while chronic treatment for 11 days increases rat striatal  $3-MT$  levels (121). Similarly, 20 days of lithium treatment increase rat st crease mouse whole brain 3-MT (135), while chronic<br>treatment for 11 days increases rat striatal 3-MT levels<br>(121). Similarly, 20 days of lithium treatment increase<br>rat striatal and nucleus accumbens DOPAC levels (61).<br>Thes treatment for 11 days increases rat striatal 3-MT<br>(121). Similarly, 20 days of lithium treatment in<br>rat striatal and nucleus accumbens DOPAC level:<br>These data indicate that chronic lithium treatme<br>sults in both increased D Fract striatal and nucle<br>
These data indicate t<br>
sults in both increase<br>
F. CNS Depressants<br>
Alcohol decreases

hese data indicate that chronic lithium treatment re-<br>
lts in both increased DA synthesis and release.<br>
CNS Depressants<br>
Alcohol decreases the accumulation of 3-MT after<br>
rgyline treatment (116). Stable adenosine analogs h sults in both increased DA synthesis and release.<br>  $\begin{array}{r} \text{e} \text{x} \\ \text{f} \end{array}$ <br>  $\begin{array}{r} \text{F. CNS} \end{array}$  Depressants<br>
Alcohol decreases the accumulation of 3-MT after<br>
pargyline treatment (116). Stable adenosine analogs h F. CNS Depressants<br>Alcohol decreases the accumulation of 3-MT a<br>pargyline treatment (116). Stable adenosine analogs h<br>also been shown to decrease the postmortem accum<br>tion of striatal 3-MT in decapitated rats (133), to  $F$ . CNS Depressants<br>Alcohol decreases the accumulation of 3-MT after<br>pargyline treatment (116). Stable adenosine analogs have<br>also been shown to decrease the postmortem accumula-<br>tion of striatal 3-MT in decapitated rats Alcohol decreases the accumulation of  $3-MT$  after<br>pargyline treatment (116). Stable adenosine analogs have<br>also been shown to decrease the postmortem accumula-<br>tion of striatal  $3-MT$  in decapitated rats (133), to de-<br>crea pargyline treatment (116). Stable adenosine analogs have also been shown to decrease the postmortem accumulation of striatal 3-MT in decapitated rats (133), to decrease basal striatal 3-MT levels (214), and to antagoniz pa also been shown to decrease the postmortem accumulation of striatal 3-MT in decapitated rats (133), to de-<br>crease basal striatal 3-MT levels (214), and to antagonize (19<br>pargyline-dependent 3-MT accumulation in the rat st tion of striatal 3-MT in decapitated rats (133), to decrease basal striatal 3-MT levels (214), and to antagonize pargyline-dependent 3-MT accumulation in the rat striatum (214). The use of selected adenosine agonists and a crease basal striata<br>pargyline-depender<br>tum (214). The us<br>antagonists has streceptor mediated.<br>C. CABAcraice.

## **G.** *GABAergics*

tagonists has suggested that these actions are A-1 GI<br>ceptor mediated. (3)<br> $GABAergic$  modulation of the nigrostriatal pathway is<br>tremely complex in that GABA-A receptors have been  $\frac{1}{100}$ receptor mediated.  $\begin{array}{cc} (35 & (35) \\ (36) & (38) \\ (37) & (38) \\ (38) & (39) \\ (39) & (39) \\ (30) & (39) \\ (30) & (39) \\ (30) & (30) \\ (31) & (32) \\ (32) & (33) \\ (34) & (35) \\ (36) & (37) \\ (38) & (39) \\ (39) & (30) \\ (30) & (31) \\ (31) & (32) \\ (32) & (33) \\ (34) & (35) \\ (37) & (39) \\ (30) &$ G. GABAergics<br>
GABAergic modulation of the nigrostriatal pathway is<br>
extremely complex in that GABA-A receptors have been<br>
demonstrated on dopaminergic nerve endings within the<br>
striatum (40, 45), on dopaminergic cell bod GABAergics<br>
GABAergic modulation of the nigrostriatal pathway is<br>
extremely complex in that GABA-A receptors have been<br>
demonstrated on dopaminergic nerve endings within the<br>
striatum (40, 45), on dopaminergic cell bodies GABAergic modulation of the nigrostriatal pathway is<br>extremely complex in that GABA-A receptors have been<br>demonstrated on dopaminergic nerve endings within the<br>striatum (40, 45), on dopaminergic cell bodies in the<br>substant extremely complex in that GABA-A receptors have been<br>demonstrated on dopaminergic nerve endings within the<br>striatum (40, 45), on dopaminergic cell bodies in the<br>substantia nigra (109), and on nerve endings of afferents<br>to demonstrated on dopaminergic nerve endings within the striatum  $(40, 45)$ , on dopaminergic cell bodies in the substantia nigra  $(109)$ , and on nerve endings of afferents to the substantia nigra  $(153)$ . GABA-B receptors a (32). bstantia nigra (109), and on nerve endings of afferents<br>the substantia nigra (153). GABA-B receptors are also<br>esent within both the striatum and substantia nigra<br>2).<br>*1. GABA-A agonists*. The GABA-A agonists muscimol,<br>jic

to the substantia nigra (153). GABA-B recept<br>present within both the striatum and subst.<br>(32).<br>*1. GABA-A agonists*. The GABA-A agonists<br>kojic amine, 4,5,6,7-tetrahydroisoxazolo[5,4-c<br>ol (THIP), and progabide all dose depe present within both the striatum and substantia nigra (32).<br>
1. GABA-A agonists. The GABA-A agonists muscimol,<br>
kojic amine, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-<br>
ol (THIP), and progabide all dose dependently decr (32).<br>
1. GABA-A agonists. The GABA-A agonists muscimol, both<br>
is a strict and progabide all dose dependently decrease<br>
the levels of striatal 3-MT (205). The depressant action<br>
of progabide on striatal DA release has als 1.  $GABA-A$  agonists. The GABA-A agonists muscimol<br>kojic amine,  $4,5,6,7$ -tetrahydroisoxazolo $[5,4-c]$ pyridin-3<br>ol (THIP), and progabide all dose dependently decreas<br>the levels of striatal 3-MT (205). The depressant action<br>of kojic amine,  $4,5,6,7$ -tetrahydroisoxazolo $[5,4-c]$ pyridin-3-<br>ol (THIP), and progabide all dose dependently decrease<br>the levels of striatal 3-MT (205). The depressant action<br>of progabide on striatal DA release has also bee ol (THIP), and progabide all dose dependently decrease<br>the levels of striatal 3-MT (205). The depressant action<br>of progabide on striatal DA release has also been dem-<br>onstrated directly with push-pull perfusion studies in the levels of striatal 3-MT (205). The depressant action<br>of progabide on striatal DA release has also been dem<br>onstrated directly with push-pull perfusion studies in the<br>cat caudate (161). The effects of these agents on st of progabide on striatal DA release has also been demonstrated directly with push-pull perfusion studies in the treat<br>cat caudate (161). The effects of these agents on striatal MT  $\cdot$ <br>3-MT levels were antagonized by the onstrated directly with push-pull perfusion studies in the cat caudate (161). The effects of these agents on striatal 3-MT levels were antagonized by the GABA antagonist, picrotoxin, and lasted longer than 3 h (205). GABAcat caudate (161). The effects of these agents on striatal MT were found not to express tolerance (212).<br>
3-MT levels were antagonized by the GABA antagonist, The benzodiazepines clonazepam and nitrazepam, like<br>
picrotoxi 3-MT levels were antagonized by the GABA antagonist,<br>picrotoxin, and lasted longer than 3 h (205). GABA-A dia<br>effects on HVA are more complex. While muscimol, the<br>THIP, and kojic amine elevate DOPAC (205), THIP and of<br>mus picrotoxin, and lasted longer than 3 h (205). GABA-A<br>effects on HVA are more complex. While muscimol,<br>THIP, and kojic amine elevate DOPAC (205), THIP and<br>muscimol increase striatal HVA, while kojic amine and<br>progabide decr effects on HVA are more complex. While muscimol,<br>THIP, and kojic amine elevate DOPAC (205), THIP and<br>muscimol increase striatal HVA, while kojic amine and<br>progabide decrease HVA (205). The only consistent<br>changes in DA me muscimol increase striatal HVA, while kojic amine and<br>progabide decrease HVA (205). The only consistent<br>changes in DA metabolites with these inhibitory agents<br>were the decreases in 3-MT levels.<br>Using the paradigm of parent uscimol increase striatal HVA, while kojic amine and<br>ogabide decrease HVA (205). The only consistent<br>anges in DA metabolites with these inhibitory agents<br>are<br>the decreases in 3-MT levels.<br>Using the paradigm of parenteral i progabide decrease HVA (205). The only consistent<br>changes in DA metabolites with these inhibitory agents alt<br>were the decreases in 3-MT levels. act<br>lost using the paradigm of parenteral injections in acutely<br>hemitransected

changes in DA metabolites with these inhibitory agents activate were the decreases in 3-MT levels. Lymphered actively actively bend to the striatum, both THIP and kojic amine were shown to PAC act on GABA-A receptors withi were the decreases in 3-MT levels. acts and Using the paradigm of parenteral injections in acutely ben<br>hemitransected rats and using local drug injections into box<br>the striatum, both THIP and kojic amine were shown to PAO<br> Using the paradigm of parenteral injections in acutely<br>hemitransected rats and using local drug injections into<br>the striatum, both THIP and kojic amine were shown to<br>exact on GABA-A receptors within the striatum (205). In<br> hemitransected rats and using local drug injections in<br>the striatum, both THIP and kojic amine were shown t<br>act on GABA-A receptors within the striatum (205). I<br>marked contrast, muscimol decreases striatal 3-MT i<br>hemitrans the striatum, both THIP and kojic amine were shown to PAC<br>act on GABA-A receptors within the striatum (205). In Recen<br>marked contrast, muscimol decreases striatal 3-MT in increa<br>hemitransected rats but increases 3-MT after act on GABA-A receptors within the striatum (205). In Recent<br>marked contrast, muscimol decreases striatal 3-MT in increase<br>hemitransected rats but increases 3-MT after local injec-<br>tions into the striatum (205). This effec marked contrast, muscimol decreases striatal 3-MT in<br>hemitransected rats but increases 3-MT after local injec-<br>tions into the striatum (205). This effect in the striatum<br>agrees with studies of the effects of muscimol on DA hemitransected rats but increases 3-MT after local injections into the striatum (205). This effect in the striatum agrees with studies of the effects of muscimol on DA release in striatal slices in vitro (176a), but its po tions into the striatum  $(205)$ . This effect in the striatum agrees with studies of the effects of muscimol on DA crelease in striatal slices in vitro  $(176a)$ , but its potential  $\Gamma$  role in vivo is unknown since this dr

striatal DA release as assessed by in vivo voltammetry culline and by prior kainate lesions of striatal neurons (88).<br>
(205). In acutely hemitransected rats, parenteral musci-<br>
5. Lithium. Acute lithium has been reported t wood AND ALTAR<br>ecreased action of intrastriatal muscimol is antagonized by bicu-COMALTAR<br>action of intrastriatal muscimol is antagonized by bicu-<br>culline and by prior kainate lesions of striatal neurons<br>(205). In acutely hemitransected rats, parenteral musci-(205).<br>
ALTAR<br>
action of intrastriatal muscimol is antagonized by bic<br>
culline and by prior kainate lesions of striatal neuro<br>
(205). In acutely hemitransected rats, parenteral mus<br>
mol does not change striatal 3-MT levels action of intrastriatal muscimol is antagonized by bicu-<br>culline and by prior kainate lesions of striatal neurons<br>(205). In acutely hemitransected rats, parenteral musci-<br>mol does not change striatal 3-MT levels (205). The action of intrastriatal muscimol is antagonized by bicu-<br>culline and by prior kainate lesions of striatal neurons<br>(205). In acutely hemitransected rats, parenteral musci-<br>mol does not change striatal 3-MT levels (205). The culline and by prior kainate lesions of striatal neurons (205). In acutely hemitransected rats, parenteral muscimol does not change striatal 3-MT levels (205). These data argue for a modulation by muscimol of an undefined (205). In acutely hemitransected rats, pair mol does not change striatal 3-MT level data argue for a modulation by muscimol if feedback pathway with cell bodies in the nerve terminals in the substantia nigra. Local injecti bl does not change striatal 3-MT levels (205). These<br>ta argue for a modulation by muscimol of an undefined<br>edback pathway with cell bodies in the striatum and<br>rve terminals in the substantia nigra.<br>Local injections of both

data argue for a modulation by muscimol of an undefined<br>feedback pathway with cell bodies in the striatum and<br>nerve terminals in the substantia nigra.<br>Local injections of both muscimol and kojic amine into<br>the substantia n feedback pathway with cell bodies in the striatum and<br>nerve terminals in the substantia nigra.<br>Local injections of both muscimol and kojic amine into<br>the substantia nigra were also investigated (205). In these<br>experiments, nerve terminals in the substantia nigra.<br>
Local injections of both muscimol and kojic amine into<br>
the substantia nigra were also investigated (205). In these<br>
experiments, either compound decreased striatal 3-MT<br>
levels in Local injections of both muscimol and kojic amine into<br>the substantia nigra were also investigated (205). In these<br>experiments, either compound decreased striatal 3-MT<br>levels in a bicuculline-reversible manner. In summary, the substantia nigra were also investigated (205). In the experiments, either compound decreased striatal 3-N<br>levels in a bicuculline-reversible manner. In summa<br>GABA-A agonists decrease striatal DA release via a<br>tions wit periments, either compound decreased striatal 3-MT<br>vels in a bicuculline-reversible manner. In summary,<br>ABA-A agonists decrease striatal DA release via ac-<br>ons within both the striatum and substantia nigra.<br>2. GABA-B agoni

levels in a bicuculline-reversible manner. In summary GABA-A agonists decrease striatal DA release via actions within both the striatum and substantia nigra.<br>2. GABA-B agonists. The GABA-B agonist baclofen like GABA-A agon GABA-A agonists decrease striatal DA release via actions within both the striatum and substantia nigra.<br>2. GABA-B agonists. The GABA-B agonist baclofen,<br>like GABA-A agonists, decreases striatal 3-MT in con-<br>junction with tions within both the striatum and substantia nigra.<br>2. GABA-B agonists. The GABA-B agonist baclofen,<br>like GABA-A agonists, decreases striatal 3-MT in con-<br>junction with dramatic elevations in DOPAC and HVA<br>(191). This unc 2. GABA-B agonists. The GABA-B agonist baclofen,<br>like GABA-A agonists, decreases striatal 3-MT in con-<br>junction with dramatic elevations in DOPAC and HVA<br>(191). This uncoupling of DA synthesis and release is<br>similar to tha like GABA-A agonists, decreases striatal 3-MT in con-<br>junction with dramatic elevations in DOPAC and HVA<br>(191). This uncoupling of DA synthesis and release is<br>similar to that observed with GBL (58, 201). In addition,<br>drug junction with dramatic elevations in DOPAC and HVA<br>(191). This uncoupling of DA synthesis and release is<br>similar to that observed with GBL (58, 201). In addition,<br>drug effects on DA synthesis express cross-tolerance for<br>GB (191). This<br>similar to the similar to the similar of the SBL and the SSS, 71).<br> $3.$  Indirection milar to that observed with GBL (58, 201). In additional effects on DA synthesis express cross-tolerance for BL and baclofen, suggesting a common locus of action 5, 71).<br>3. *Indirect GABAergics*. The benzodiazepine, diazem

drug effects on DA synthesis express cross-tolerance for GBL and baclofen, suggesting a common locus of action (35, 71).<br>
3. *Indirect GABAergics*. The benzodiazepine, diazepam, decreases steady-state 3-MT levels (205, 211 GBL and baclofen, suggesting a common locus of action (35, 71).<br>
3. *Indirect GABAergics*. The benzodiazepine, diazepam, decreases steady-state 3-MT levels (205, 211, 212)<br>
and the accumulation of 3-MT after pargyline trea (35, 71).<br>
3. *Indirect GABAergics*. The benzodiazepine, diaze-<br>
pam, decreases steady-state 3-MT levels (205, 211, 212)<br>
and the accumulation of 3-MT after pargyline treatment<br>
(99, 211). Push-pull perfusion studies have 3. Indirect GABAergics. The benzodiazepine, diaze-<br>pam, decreases steady-state 3-MT levels (205, 211, 212)<br>and the accumulation of 3-MT after pargyline treatment<br>(99, 211). Push-pull perfusion studies have also shown<br>that pam, decreases steady-state 3-MT levels (205, 211, 21 and the accumulation of 3-MT after pargyline treatme (99, 211). Push-pull perfusion studies have also show that diazepam can antagonize the increased striatal D release and the accu<br>(99, 211). Pu<br>that diazepar<br>release from<br>toxin (46).<br>The action 9, 211). Push-pull perfusion studies have also shown<br>at diazepam can antagonize the increased striatal DA<br>lease from cat caudate after local perfusion with picro-<br>xin (46).<br>The actions of diazepam on striatal  $3-MT$  are ob

that diazepam can antagonize the increased striatal DA<br>release from cat caudate after local perfusion with picro-<br>toxin (46).<br>The actions of diazepam on striatal 3-MT are observed<br>at doses of 5 mg/kg or greater (218) and a release from cat caudate after local perfusion with picrotoxin (46).<br>
The actions of diazepam on striatal 3-MT are observed<br>
at doses of 5 mg/kg or greater (218) and are reversed<br>
both by the GABA antagonist, picrotoxin, a toxin (46).<br>The actions of diazepam on striatal 3-MT are observed<br>at doses of 5 mg/kg or greater (218) and are reversed<br>both by the GABA antagonist, picrotoxin, and the ben-<br>zodiazepine receptor antagonist, flumazenil (Ro I he actions of diazepain on striatal 3-MT are observed<br>at doses of 5 mg/kg or greater (218) and are reversed<br>both by the GABA antagonist, picrotoxin, and the ben-<br>zodiazepine receptor antagonist, flumazenil (Ro 151788;<br>20 at doses of 5 mg/kg or greater (218) and are reversed<br>both by the GABA antagonist, picrotoxin, and the ben-<br>zodiazepine receptor antagonist, flumazenil (Ro 151788;<br>205, 211). This decrease in striatal 3-MT lasts for more<br>t both by the GABA antagonist, picrotoxin, and the ben-<br>zodiazepine receptor antagonist, flumazenil (Ro 151788;<br>205, 211). This decrease in striatal 3-MT lasts for more<br>than 8 h and is accompanied by decreases in HVA but<br>wit zodiazepine receptor antagonist, flumazenil (Ro 151788;<br>205, 211). This decrease in striatal 3-MT lasts for more<br>than 8 h and is accompanied by decreases in HVA but<br>with no change in DOPAC (218, 219). In a 3-wk chronic<br>tre 205, 211). This decrease in striatal 3-MT lasts f<br>than 8 h and is accompanied by decreases in H<br>with no change in DOPAC (218, 219). In a 3-wk<br>treatment study, the actions of diazepam on st<br>MT were found not to express tole an 8 h and is accompanied by decreases in HVA but<br>th no change in DOPAC (218, 219). In a 3-wk chronic<br>eatment study, the actions of diazepam on striatal 3-<br>T were found not to express tolerance (212).<br>The benzodiazepines c

with no change in DOPAC (218, 219). In a 3-wk chronic<br>treatment study, the actions of diazepam on striatal 3-<br>MT were found not to express tolerance (212).<br>The benzodiazepines clonazepam and nitrazepam, like<br>diazepam, decr treatment study, the actions of diazepam on striatal 3-<br>MT were found not to express tolerance (212).<br>The benzodiazepines clonazepam and nitrazepam, like<br>diazepam, decrease striatal 3-MT and HVA; however,<br>these drugs also MT were found not to express tolerance (212).<br>The benzodiazepines clonazepam and nitrazepam, like<br>diazepam, decrease striatal 3-MT and HVA; however,<br>these drugs also decrease DOPAC (212). The significance<br>of these differen The benzodiazepines<br>diazepam, decrease str<br>these drugs also decreas<br>of these differences b<br>remains to be defined.<br>The benzodiazepine azepam, decrease striatal 3-MT and HVA; however,<br>ese drugs also decrease DOPAC (212). The significance<br>these differences between various benzodiazepines<br>mains to be defined.<br>The benzodiazepine antagonist, flumazenil, does

these drugs also decrease DOPAC (212). The significance<br>of these differences between various benzodiazepines<br>remains to be defined.<br>The benzodiazepine antagonist, flumazenil, does not<br>alter any striatal DA metabolite but d of these differences between various benzodiazepines<br>remains to be defined.<br>The benzodiazepine antagonist, flumazenil, does not<br>alter any striatal DA metabolite but does antagonize the<br>actions of benzodiazepine agonists ( remains to be defined.<br>The benzodiazepine antagonist, flumazen<br>alter any striatal DA metabolite but does ant<br>actions of benzodiazepine agonists (211). <sup>7</sup><br>benzodiazepine agonist, methylamide- $\beta$ -carb<br>boxylate (FG 7142), The benzodiazepine antagonist, flumazenil, does not<br>alter any striatal DA metabolite but does antagonize the<br>actions of benzodiazepine agonists (211). The inverse<br>benzodiazepine agonist, methylamide- $\beta$ -carboline-3-car-<br> alter any striatal DA metabolite but does antagonize the<br>actions of benzodiazepine agonists (211). The inverse<br>benzodiazepine agonist, methylamide- $\beta$ -carboline-3-car-<br>boxylate (FG 7142), which is anxiogenic, increases DO actions of benzodiazepine agonists (211). The inverse<br>benzodiazepine agonist, methylamide- $\beta$ -carboline-3-car-<br>boxylate (FG 7142), which is anxiogenic, increases DO-<br>PAC levels in the rat prefrontal cortex (PFC) (180).<br>R benzodiazepine agonist, methylamide- $\beta$ -carboline-3-carboxylate (FG 7142), which is anxiogenic, increases DC<br>PAC levels in the rat prefrontal cortex (PFC) (180<br>Recent studies using brain dialysis, have also detecte<br>incre boxylate (FG 7142), which is anxiogenic, increases DO-PAC levels in the rat prefrontal cortex (PFC) (180).<br>Recent studies using brain dialysis, have also detected<br>increased DA release in the PFC after FG 7142 (74).<br>4. GABA

PAC levels in the rat prefrontal cortex (PFC) (180).<br>Recent studies using brain dialysis, have also detected<br>increased DA release in the PFC after FG 7142 (74).<br>4. GABA transaminase inhibitors. The GABA trans-<br>aminase inhi Recent studies using brain dialysis, have also detected<br>increased DA release in the PFC after FG 7142 (74).<br>4. GABA transaminase inhibitors. The GABA trans-<br>aminase inhibitor, aminooxyacetic acid (AOAA), de-<br>creases striat increased DA release in the PFC after FG 7142 (74).<br>4. GABA transaminase inhibitors. The GABA trans-<br>aminase inhibitor, aminooxyacetic acid (AOAA), de-<br>creases striatal 3-MT levels with a parallel increase in<br>DA steady-sta 4. GABA transaminase inhibitors. The GABA transaminase inhibitor, aminooxyacetic acid (AOAA), dcreases striatal 3-MT levels with a parallel increase iDA steady-state levels (124% of control) but does no change DOPAC or HVA aminase inhibitor, aminooxyacetic acid (AOAA), decreases striatal 3-MT levels with a parallel increase in DA steady-state levels (124% of control) but does not change DOPAC or HVA (205). In rats with acute hemitransections

**a**spet

PHARMACOLOGICAL REVIEW

3-MT MEASUREMENTS AND DA RELE<br>indicating an action within the striatum, possibly at the wh<br>level of the dopaminergic nerve ending. Intraventricular cla 3-MT MEASUREMENTS AND DA<br>indicating an action within the striatum, possibly at the<br>level of the dopaminergic nerve ending. Intraventricular<br>administration of the GABA transaminase inhibitor, etl 3-MT MEASUREMENTS AND DA<br>indicating an action within the striatum, possibly at the<br>level of the dopaminergic nerve ending. Intraventricular<br>administration of the GABA transaminase inhibitor, eth-<br>anolamine-O-sulfate, also indicating an action within the striatum, possibly at the<br>level of the dopaminergic nerve ending. Intraventricular<br>administration of the GABA transaminase inhibitor, eth-<br>anolamine-O-sulfate, also has been reported to decr indicating an action within<br>level of the dopaminergic n<br>administration of the GABA<br>anolamine-O-sulfate, also h<br>striatal 3-MT levels (44).<br>5. Tolerance studies. The vel of the dopaminergic nerve ending. Intraventricul<br>lministration of the GABA transaminase inhibitor, et<br>lolamine-O-sulfate, also has been reported to decrea<br>riatal 3-MT levels (44).<br>5. *Tolerance studies*. The use of DA

administration of the GABA transaminase inhibitor, exercised and analytical 3-MT levels (44).<br>striated 3-MT levels (44).<br>5. Tolerance studies. The use of DA metabolite me-<br>urements to assess drug tolerance is extremely com anolamine-O-sulfate, also has been reported to decrease st<br>striatal 3-MT levels (44).<br>5. Tolerance studies. The use of DA metabolite meas-<br>urements to assess drug tolerance is extremely compli-<br>cated since, in many cases, striatal 3-MT levels (44). In c.<br>5. Tolerance studies. The use of DA metabolite meas-<br>urements to assess drug tolerance is extremely compli-<br>cated since, in many cases, there is a dissociation between<br>changes in indices of 5. Tolerance studies. The use of DA metabolite me<br>urements to assess drug tolerance is extremely come<br>cated since, in many cases, there is a dissociation betwe<br>changes in indices of DA metabolism and indices of<br>release (ta urements to assess drug tolerance is extremely complicated since, in many cases, there is a dissociation between an changes in indices of DA metabolism and indices of DA rangles (table 7). In the case of chronic (3 wk) ben cated since, in many cases, there is a dissociation between<br>changes in indices of DA metabolism and indices of DA<br>release (table 7). In the case of chronic  $(3 \text{ wk})$  benzodi-<br>in<br>azepine treatment, this dissociation is cle release (table 7). In the case of chronic  $(3 \text{ wk})$  benzodi-interpreted to involve a specific mu-2 isoreceptor antag-<br>azepine treatment, this dissociation is clear in that the onist action of these kappa agonists  $(207)$ . release (table 7). In the case of chronic (3 wk) benzo<br>azepine treatment, this dissociation is clear in that t<br>drug effects on HVA tolerated, while the decrease in<br>MT did not tolerate (212). Studies of subchronic (1 w<br>GABA azepine treatment, this dissociation is clear in that the<br>drug effects on HVA tolerated, while the decrease in 3-<br>MT did not tolerate (212). Studies of subchronic (1 wk)<br>GABA-A (THIP and kojic amine) and GABA-B (baclo-<br>haf drug effects on HVA tolerated, while the decrease in 3-<br>MT did not tolerate (212). Studies of subchronic (1 wk) rat. Re<br>GABA-A (THIP and kojic amine) and GABA-B (baclo-<br>have den<br>fen) agonist treatment have indicated tolera MT did not tolerate (212). Studies of subchronic (1 w<br>GABA-A (THIP and kojic amine) and GABA-B (bacl<br>fen) agonist treatment have indicated tolerance to t<br>drug effects on DOPAC and HVA (24) as well as L<br>steady-state levels GABA-A (THIP and kojic amine) and GABA-B (baclo-<br>fen) agonist treatment have indicated tolerance to the (9<br>drug effects on DOPAC and HVA (24) as well as DA (L<br>steady-state levels (71). Cross-tolerance between baclo-<br>fen, G fen) agonist treatment have indicated tolerance to the (9-<br>drug effects on DOPAC and HVA (24) as well as DA (D<br>steady-state levels (71). Cross-tolerance between baclo-<br>be fen, GBL, and HA-966 was also monitored with regard drug effects on DOPAC and HVA (24) as well as DA<br>steady-state levels (71). Cross-tolerance between baclo-<br>fen, GBL, and HA-966 was also monitored with regard<br>to enhanced DA synthesis (35, 71). However, no study<br>of DA relea steady-state levels (71). Cross-tolerance between bac.<br>fen, GBL, and HA-966 was also monitored with regato enhanced DA synthesis (35, 71). However, no stu<br>of DA release after chronic GABA-A or GABA-B agon<br>treatment has bee to enhanced DA synthesis (35, 71). However, no study DA release into rat brain dialysates have also demon-<br>of DA release after chronic GABA-A or GABA-B agonist strated that mu agonists dramatically increase DA col-<br>treatme of DA release after chronic GABA-A or GABA-B agonist strated that mu agonists dramatically increase DA col-<br>treatment has been conducted, thereby limiting specu-<br>lected in nucleus accumbens dialysates with no effect or<br>lat treatment has been conducted, thereby limiting specu-

## *H. Opiates and OpiOid Peptides*

of dopaminergic neurons.<br>
DA<br>
DO.<br>
DO.<br>
1. Striatal DA metabolism. Early studies of the effects piri-<br>
of morphine on striatal DOPAC and HVA (reviewed in active<br>
ref. 207 and 208) on the incorporation of radioactive (1R H. Opiates and Opioid Peptides<br>1. Striatal DA metabolism. Early studies of the effects<br>of morphine on striatal DOPAC and HVA (reviewed in<br>ref. 207 and 208) on the incorporation of radioactive<br>precursors into the DA pool (2 H. Opiates and Opioid Peptides<br>1. Striatal DA metabolism. Early studies of the effect<br>of morphine on striatal DOPAC and HVA (reviewed in<br>tef. 207 and 208) on the incorporation of radioactiv<br>precursors into the DA pool (27) 1. Striatal DA metabolism. Early studies of the effects of morphine on striatal DOPAC and HVA (reviewed in ref. 207 and 208) on the incorporation of radioactive precursors into the DA pool (27) and on L-DOPA accumulation ( of morphine on striatal DOPAC and HVA (reviewed in<br>ref. 207 and 208) on the incorporation of radioactive<br>precursors into the DA pool (27) and on L-DOPA accu-<br>mulation (139) indicated that DA metabolism was dra-<br>matically e ref. 207 and 208) on the incorporation of radioactive (precursors into the DA pool (27) and on L-DOPA accu-<br>mulation (139) indicated that DA metabolism was dramatically enhanced in both the rat and mouse striatum.<br>These d precursors into the DA pool (27) and on L-DOPA accu-<br>mulation (139) indicated that DA metabolism was dra-<br>matically enhanced in both the rat and mouse striatum.<br>These data, however, did not explain the differences of<br>indi mulation (139) indicated that DA metabolism was dra-<br>matically enhanced in both the rat and mouse striatum.<br>These data, however, did not explain the differences of<br>acute morphine (110) on motor behavior in these 2<br>species matically enhanced in both the rat and mouse striatum.<br>These data, however, did not explain the differences of<br>acute morphine (110) on motor behavior in these 2<br>species (i.e., motor activation in the mouse and motor<br>depre These data, however, did not explain the differences of indicate morphine (110) on motor behavior in these 2 expecies (i.e., motor activation in the mouse and motor oppression in the rat). In 1978, this issue was addresse acute morphine (110) on motor behavior in these 2 except<br>species (i.e., motor activation in the mouse and motor opioid<br>depression in the rat). In 1978, this issue was addressed cortica<br>in more depth when it was reported t species (i.e., motor activation in the mouse and m<br>depression in the rat). In 1978, this issue was addre<br>in more depth when it was reported that, while<br>incorporation of [<sup>3</sup>H]tyrosine into labeled rat striatal<br>and DOPAC oc depression in the rat). In 1978, this issue was addressed<br>in more depth when it was reported that, while the<br>incorporation of [<sup>3</sup>H] tyrosine into labeled rat striatal DA<br>and DOPAC occurred to a greater extent in D-Ala-Met in more depth when it was reported that, while the<br>incorporation of [<sup>3</sup>H] tyrosine into labeled rat striatal DA<br>and DOPAC occurred to a greater extent in D-Ala-Met-<br>enkephalin amide-treated animals, no change in the la-<br> incorporation of [<sup>3</sup>H]tyrosine into labeled rat striatal DA soliand DOPAC occurred to a greater extent in D-Ala-Metershephalin amide-treated animals, no change in the labeling of striatal 3-MT was detected (3). At the sa and DOPAC occurred to a greater extent in D-Ala-Met-<br>enkephalin amide-treated animals, no change in the la-<br>beling of striatal 3-MT was detected (3). At the same<br>time, enhanced striatal 3-MT levels were measured in<br>mouse enkephalin amide-treated animals, no change in the labeling of striatal 3-MT was detected (3). At the same<br>time, enhanced striatal 3-MT levels were measured in<br>mouse but not rat striatum after morphine (147, 224). A<br>compar beling of striatal 3-MT was detected (3). At the same<br>time, enhanced striatal 3-MT levels were measured in<br>mouse but not rat striatum after morphine (147, 224). A<br>comparison of mu and delta analgesics revealed increases<br>in time, enhanced striatal 3-MT levels were measured in  $Pr$ <br>mouse but not rat striatum after morphine (147, 224). A<br>comparison of mu and delta analgesics revealed increases<br>in striatal DOPAC and HVA in both the rat and mouse comparison of mu and delta analgesics revealed increase<br>in striatal DOPAC and HVA in both the rat and mouse<br>but an increase in 3-MT levels only in the mouse. In the<br>mouse, however, strain differences have been described<br>wi in striatal DOPAC and HVA in both the rat and mouse<br>but an increase in 3-MT levels only in the mouse. In the<br>mouse, however, strain differences have been described,<br>with strains lacking the motor stimulant effects of mor-<br> but an increase in 3-MT levels only in the mouse. In the mouse, however, strain differences have been described, with strains lacking the motor stimulant effects of morphine also lacking the increase in striatal 3-MT (147) mouse, however, strain differences have been described,<br>with strains lacking the motor stimulant effects of mor-<br>phine also lacking the increase in striatal 3-MT (147).<br>Local morphine injections indicated that the mouse st with strains lacking the motor stimulant effects of morphine also lacking the increase in striatal 3-MT (147).<br>Local morphine injections indicated that the mouse striatal 3-MT increases after morphine were the result of ac phine also lacking the increase in striatal 3-MT (147).<br>Local morphine injections indicated that the mouse stria-<br>tal 3-MT increases after morphine were the result of<br>activation of mu receptors in the substantia nigra (147 Local morphine injections indicated that the mouse stread 3-MT increases after morphine were the result activation of mu receptors in the substantia nigra (1-224), while the lack of effect of morphine on rat stria 3-MT ap tal 3-MT increases after morphine were<br>activation of mu receptors in the substanti<br>224), while the lack of effect of morphine c<br>3-MT appeared to be the result of a "presyr<br>ing" action within the striatum (27, 224).<br>The ago tivation of mu receptors in the substantia nigra (147, 4), while the lack of effect of morphine on rat striatal MT appeared to be the result of a "presynaptic clampe" action within the striatum (27, 224). The agonist/antag 224), while the lack of effect of morphine on rat striatal 3-MT appeared to be the result of a "presynaptic clamping" action within the striatum  $(27, 224)$ .<br>The agonist/antagonist analgesics also elevate striatal \_\_<br>DOPA

3-MT MEASUREMENTS AND DA RELEASE *IN VIVO* FROM NEURONS 181<br>indicating an action within the striatum, possibly at the which has been attributed to receptor dualism with this LEASE IN VIVO FROM NEURONS 181<br>which has been attributed to receptor dualism with this<br>class of opiates (94, 207, 208, 225). As with mu and delta LEASE IN VIVO FROM NEURONS 181<br>which has been attributed to receptor dualism with this<br>class of opiates (94, 207, 208, 225). As with mu and delta<br>agonists, the agonist/antagonist agents do not increase LEASE IN VIVO FROM NEURONS 181<br>which has been attributed to receptor dualism with this<br>class of opiates (94, 207, 208, 225). As with mu and delta<br>agonists, the agonist/antagonist agents do not increase<br>striated 3-MT levels which has been attributed t<br>class of opiates (94, 207, 208<br>agonists, the agonist/antage<br>striatal 3-MT levels (207).<br>In contrast, kappa agonis nich has been attributed to receptor dualism with this<br>ass of opiates (94, 207, 208, 225). As with mu and delta<br>onists, the agonist/antagonist agents do not increase<br>riatal 3-MT levels (207).<br>In contrast, kappa agonists do

class of opiates (94, 207, 208, 225). As with mu and de<br>agonists, the agonist/antagonist agents do not increa<br>striatal 3-MT levels (207).<br>In contrast, kappa agonists do not alter the levels<br>any of the DA metabolites but st agonists, the agonist/antagonist agents do not incre<br>striatal 3-MT levels (207).<br>In contrast, kappa agonists do not alter the level-<br>any of the DA metabolites but stereospecifically ant<br>onize the actions of mu and delta an striatal 3-MT levels (207).<br>In contrast, kappa agonists do not alter the levels of<br>any of the DA metabolites but stereospecifically antag-<br>onize the actions of mu and delta and agonist/antagonist<br>analgesics on nigrostriata In contrast, kappa agonists do not alter the levels of<br>any of the DA metabolites but stereospecifically antag-<br>onize the actions of mu and delta and agonist/antagonist<br>analgesics on nigrostriatal DA metabolism in both the<br> any of the DA metabolites but stereospecifically anto<br>onize the actions of mu and delta and agonist/antagon<br>analgesics on nigrostriatal DA metabolism in both t<br>rat  $(225)$  and the mouse  $(207)$ . This action has be<br>interpr onize the actions of mu and delta and agonis<br>analgesics on nigrostriatal DA metabolism<br>rat (225) and the mouse (207). This actio<br>interpreted to involve a specific mu-2 isorec<br>onist action of these kappa agonists (207).<br>2. relative is on nigrostriatal DA metabolism in both the t (225) and the mouse (207). This action has been terpreted to involve a specific mu-2 isoreceptor antag-<br>ist action of these kappa agonists (207).<br>2. *Mesolimbic and* 

rat. (225) and the mouse (207). This action has been<br>interpreted to involve a specific mu-2 isoreceptor antag-<br>onist action of these kappa agonists (207).<br>2. Mesolimbic and mesocortical DA metabolism in the<br>rat. Regional s interpreted to involve a specific mu-2 isoreceptor and<br>onist action of these kappa agonists (207).<br>2. Mesolimbic and mesocortical DA metabolism in<br>rat. Regional studies of opiate effects on DA metabol<br>have demonstrated tha onist action of these kappa agonists (207).<br>
2. Mesolimbic and mesocortical DA metabolism in the<br>
rat. Regional studies of opiate effects on DA metabolism<br>
have demonstrated that mu (222) and agonist/antagonist<br>
(94) analg 2. Mesolimbic and mesocortical DA metabolism in  $\tau$ <br>rat. Regional studies of opiate effects on DA metaboli<br>have demonstrated that mu (222) and agonist/antagon<br>(94) analgesics increase both DA synthesis/metaboli<br>(DOPAC) a rat. Regional studies of opiate effects on DA metabolism<br>have demonstrated that mu (222) and agonist/antagonist<br>(94) analgesics increase both DA synthesis/metabolism<br>(DOPAC) and release (3-MT) in the rat nucleus accum-<br>be have demonstrated that mu (222) and agonist/antagonist<br>(94) analgesics increase both DA synthesis/metabolism<br>(DOPAC) and release (3-MT) in the rat nucleus accum-<br>bens. In contrast, synthesis/metabolism is increased in<br>the  $(DOPAC)$  and release  $(3-MT)$  in the rat nucleus accum-<br>bens. In contrast, synthesis/metabolism is increased in (DOPAC) and release (3-MT) in the rat nucleus accum-<br>bens. In contrast, synthesis/metabolism is increased in<br>the septum, while release is unaltered (207). Studies of<br>DA release into rat brain dialysates have also demon-<br>st bens. In contrast, synthesis/metabolism is increased in<br>the septum, while release is unaltered (207). Studies of<br>DA release into rat brain dialysates have also demon-<br>strated that mu agonists dramatically increase DA col-<br> DA release into rat brain dialysates have also demonstrated that mu agonists dramatically increase DA colstrated that mu agonists dramatically increase DA collected in nucleus accumbens dialysates with no effect or small increases in striatal dialysate DA levels (57a).<br>Analysis of the actions of morphine on mesocortical DA me

1. *Striatal DA metabolism.* Early studies of the effects priform, and cingulate cortices. In contrast, neither DA <br>1. *Striatal DA metabolism*. Early studies of the effects metabolite was elevated in the entorhinal corte lected in nucleus accumbens dialysates with no effect of small increases in striatal dialysate DA levels (57a).<br>Analysis of the actions of morphine on mesocortica<br>DA metabolism (table 12) have demonstrated increased<br>DOPAC sman increases in striatal dialysate DA levels (57a).<br>
Analysis of the actions of morphine on mesocortical<br>
DA metabolism (table 12) have demonstrated increased<br>
DOPAC (105a, 105b) and 3-MT (222) in the prefrontal,<br>
pirif DA metabolism (table 12) have demonstrated increased<br>DOPAC (105a, 105b) and 3-MT (222) in the prefrontal,<br>piriform, and cingulate cortices. In contrast, neither DA<br>metabolite was elevated in the entorhinal cortex. The<br>act *(1R,5R,9R* )-5,9-dimethyl-2-(L-tetrahydrofurfuryl) piriform, and cingulate cortices. In contrast, neither DA<br>metabolite was elevated in the entorhinal cortex. The<br>actions of morphine were also reversed by  $(-)$ - $\alpha$ - $(1R,5R,9R)$ -5,9-dimethyl-2-(L-tetrahydrofurfuryl)-<br>2'-hy metabolite was elevated in the entorhinal cortex. The<br>actions of morphine were also reversed by  $(-)$ - $\alpha$ -<br> $(1R, 5R, 9R)$ -5,9-dimethyl-2-(L-tetrahydrofurfuryl)-<br>2'-hydroxy-6,7-benzomorphan (MR-2034) indicating<br>that, as in  $2'$ -hydroxy-6,7-benzomorphan (MR-2034) indicating that, as in the striatum (section IV H 1), these opiate effects are mu-2 receptor mediated (105b). These data indicate that the mesocortical dopaminergic pathways,  $(1R, 5R, 9R)$ -5,9-dimethyl-2-(L-tetrahydrofurfuryl)-2'-hydroxy-6,7-benzomorphan (MR-2034) indicating that, as in the striatum (section IV H 1), these opiate effects are mu-2 receptor mediated (105b). These data indicate  $2'$ -hydroxy-6,7-benzomorphan (MR-2034) indicating<br>that, as in the striatum (section IV H 1), these opiate<br>effects are mu-2 receptor mediated (105b). These data<br>indicate that the mesocortical dopaminergic pathways,<br>except that, as in the striatum (section IV H 1), these opia<br>effects are mu-2 receptor mediated (105b). These da<br>indicate that the mesocortical dopaminergic pathway<br>except for the entorhinal cortex (105a), receive pote<br>opioid inp effects are mu-2 recoindicate that the metrorior except for the entorior opioid inputs which cortical DA neurons.<br>The actions of ago dicate that the mesocortical dopaminergic pathways,<br>cept for the entorhinal cortex (105a), receive potent<br>ioid inputs which can increase the activity of meso-<br>rtical DA neurons.<br>The actions of agonist/antagonist analgesics

except for the entorhinal cortex (105a), receive potent<br>opioid inputs which can increase the activity of meso-<br>cortical DA neurons.<br>The actions of agonist/antagonist analgesics on me-<br>solimbic and mesocortical DA cells ar opioid inputs which can increase the activity of meso-<br>cortical DA neurons.<br>The actions of agonist/antagonist analgesics on me-<br>solimbic and mesocortical DA cells are also complex. In<br>the case of butorphanol, both DOPAC an

*in the rational control in the rat brain (94, 105a, 105b, 207)*<br>*in the rat brain (94, 105a, 105b, 207)*<br>*in man* 

Brain region	<b>DOPAC</b>	3-MT	
Nigrostriatal			
<b>Striatum</b>			
<b>Mesolimbic</b>			
Nucleus accum-			
bens			
Olfactory tubercle			
Septum			
Mesocortical			
Prefrontal cortex			
Pyriform cortex			
Cingulate cortex			
<b>Entorhinal cortex</b>			

\* Small increase at "high" doses.

Downloaded from [pharmrev.aspetjournals.org](http://pharmrev.aspetjournals.org/) at Thammasart University on December 8, 2012

HARM<br>REV

PHARMACOLOGICAL REVIEWS

increased in the nucleus accumbens (94); however, no wood M<br>increased in the nucleus accumbens (94); however, no<br>effect was observed in the olfactory tubercle or the pre-<br>frontal, piriform, or cingulate cortices (94). 182<br>increased in the nucleus accumbens  $(94)$ ; heffect was observed in the olfactory tubercle<br>frontal, piriform, or cingulate cortices  $(94)$ . effect was observed in the olfactory tubercle or the pre-<br>frontal, piriform, or cingulate cortices (94).<br>*I. Cholecystokinin* 

nervous system in the role of cholecystokinin and a last the role of cholecystokinin (CCK) in the wind in part because of the positive of this peptide to modulate the release of dopa-I. Cholecystokinin<br>Interest in the role of cholecystokinin (CCK) in the<br>nervous system has developed in part because of the<br>ability of this peptide to modulate the release of dopa-<br>mine in several forebrain areas. Peripher Interest in the role of cholecystokinin (CCK) in<br>nervous system has developed in part because of<br>ability of this peptide to modulate the release of d<br>mine in several forebrain areas. Peripheral administion<br>of the sulfated Interest in the role of cholecystokinin (CCK) in the<br>nervous system has developed in part because of the<br>ability of this peptide to modulate the release of dopa-<br>mine in several forebrain areas. Peripheral administra-<br>tion nervous system has developed in part because of ability of this peptide to modulate the release of domine in several forebrain areas. Peripheral adminition of the sulfated octapeptide of CCK (CCK-8S) creases the basal rele ability of this peptide to modulate the release of dopa-<br>mine in several forebrain areas. Peripheral administra-<br>pertion of the sulfated octapeptide of CCK (CCK-8S) de-<br>creases the basal release of dopamine from mesoaccummine in several forebrain areas. Peripheral administra-<br>tion of the sulfated octapeptide of CCK (CCK-8S) de-<br>correlate well with behavioral data where the direct<br>creases the basal release of dopamine from mesoaccum-<br>bens d tion of the sulfated octapeptide of CCK (CCK-8S) decreases the basal release of dopamine from mesoaccum-<br>combens dopamine neurons as determined with in vivo above<br>voltammetry (28, 113). However, increases in dopamine the<br> creases the basal release of dopamine from mesoaccu<br>bens dopamine neurons as determined with in vi<br>voltammetry (28, 113). However, increases in dopamin-<br>release have also been measured, with microdialysis,<br>the striatum and bens dopamine neurons as determined with in vivo alvertimentry (28, 113). However, increases in dopamine the release have also been measured, with microdialysis, in the striatum and accumbens following peripheral administ voltammetry (28, 113). However, increases in dopamine<br>release have also been measured, with microdialysis, in<br>the striatum and accumbens following peripheral admin-<br>istration of CCK-8S (159). We thus determined with 3-<br>MT release have also been measured, with microdialysis, in<br>the striatum and accumbens following peripheral admin-<br>istration of CCK-8S (159). We thus determined with 3-<br>MT measurements whether CCK-8S attenuates basal<br>dopamine the striatum and accumbens following peripheral admini-<br>istration of CCK-8S (159). We thus determined with 3-<br>MT measurements whether CCK-8S attenuates basal<br>dopamine release in the frontal cortex, olfactory tubercle,<br>or istration of CCK-8S (159). We thus determined with 3-<br>MT measurements whether CCK-8S attenuates basal of<br>dopamine release in the frontal cortex, olfactory tubercle,<br>or caudate-putamen and whether CCK-8S can reverse<br>the in MT measurements whether CCK-8S attenuates basal<br>dopamine release in the frontal cortex, olfactory tubercle,<br>or caudate-putamen and whether CCK-8S can reverse<br>the increase in striatal and limbic dopamine release<br>induced by dopamine release in the frontal cortex, olfactory tubercle,<br>or caudate-putamen and whether CCK-8S can reverse<br>the increase in striatal and limbic dopamine release<br>induced by pharmacological means  $(d$ -amphetamine or<br>halope the increase in striatal and limbic dopamine release<br>induced by pharmacological means  $(d$ -amphetamine or<br>haloperidol). These studies have been performed in both<br>the mouse  $(5, 7)$  and the rat  $(51)$  and indicate that CCKthe increase in striatal and limbic dopamine release<br>induced by pharmacological means  $(d$ -amphetamine or<br>haloperidol). These studies have been performed in both<br>the mouse  $(5, 7)$  and the rat  $(51)$  and indicate that CCKinduced by pharmacological means  $(d$ -amphetamine or haloperidol). These studies have been performed in both the mouse  $(5, 7)$  and the rat  $(51)$  and indicate that CCK-<br>8S decreases basal 3-MT levels in the striatum and f haloperidol). These studies have been performed in both<br>the mouse  $(5, 7)$  and the rat  $(51)$  and indicate that CCK-<br>8S decreases basal 3-MT levels in the striatum and<br>frontal cortex, and the olfactory tubercle at high do the mouse  $(5, 7)$  and the rat  $(51)$  and indicate that CCK-<br>8S decreases basal 3-MT levels in the striatum and<br>frontal cortex, and the olfactory tubercle at high doses<br>of the peptide. These effects were both dose and tim 8S decreases basal 3-MT levels in the striatum and<br>frontal cortex, and the olfactory tubercle at high doses  $201$ <br>of the peptide. These effects were both dose and time<br>dependent. Additionally, CCK-8S was found to dose CO<br> frontal cortex, and the olfactory tubercle at high doses<br>of the peptide. These effects were both dose and time<br>dependent. Additionally, CCK-8S was found to dose<br>dependently antagonize the increases in striatal and<br>olfactor treatment. pendent. Additionally, CCK-8S was found to dose compendently antagonize the increases in striatal and mateur factory tubercle 3-MT after amphetamine (15 mg/kg) postment.<br>Prior work with CCK has also shown that the sulfated

dependently antagonize the increases in striatal and machineous offsectory tubercle 3-MT after amphetamine  $(15 \text{ mg/kg})$  pend<br>treatment.<br>Prior work with CCK has also shown that the sulfated  $(6 \text{octapeptide decreases spontaneous dopamine release in drug})$ <br>the nucleus acc olfactory tubercle 3-MT after amphetamine  $(15 \text{ mg/kg})$  perceatment.<br>
Prior work with CCK has also shown that the sulfated<br>
octapeptide decreases spontaneous dopamine release in druce<br>
the nucleus accumbens (28, 113). Howev treatment.<br>
Prior work with CCK has also shown that the sulfated<br>
octapeptide decreases spontaneous dopamine release in<br>
the nucleus accumbens (28, 113). However, the CCK-8S<br>
effects on 3-MT are even more apparent when dop Prior work with CCK has also shown that the sulfated octapeptide decreases spontaneous dopamine release in the nucleus accumbens (28, 113). However, the CCK-8S effects on  $3$ -MT are even more apparent when dopamine releas octapeptide decreases spontaneous dopamine release in due nucleus accumbens (28, 113). However, the CCK-8S later effects on 3-MT are even more apparent when dopamine release is augmented by *d*-amphetamine or haloperidol. the nucleus accumbens (26, 115). However, the CCK-6S<br>effects on 3-MT are even more apparent when dopamine<br>release is augmented by d-amphetamine or haloperidol.<br>The reversals by CCK-8S of elevations in 3-MT following<br>halope release is augmented by *d*-amphetamine or haloperidol. the reversals by CCK-8S of elevations in 3-MT following phaloperidol or *d*-amphetamine were not simply additive the effects of the two drugs. Rather, the magnitude o The reversals by CCK-8S of elevations in 3-MT following<br>haloperidol or *d*-amphetamine were not simply additive<br>effects of the two drugs. Rather, the magnitude of the<br>CCK attenuation of elevated dopamine release following<br> haloperidol or *d*-amphetamine were not simply additive tiffects of the two drugs. Rather, the magnitude of the identical CCK attenuation of elevated dopamine release following either drug greatly exceeded the extent of 3 effects of the two drugs. Rather, the magnitude of the ic<br>CCK attenuation of elevated dopamine release following<br>either drug greatly exceeded the extent of 3-MT de-<br>creases obtained with CCK-8S alone. This was especially<br>t CCK attenuation of elevated dopamine release following<br>either drug greatly exceeded the extent of 3-MT de-<br>creases obtained with CCK-8S alone. This was especially<br>netrue in the olfactory tubercle, where CCK-8S had little<br> either drug greatly exceeded the extent of 3-MT of creases obtained with CCK-8S alone. This was especiatrue in the olfactory tubercle, where CCK-8S had lit or no effect on basal dopamine release but reversed t 200% increas creases obtained with CCK-8S alone. This was especial<br>true in the olfactory tubercle, where CCK-8S had litt<br>or no effect on basal dopamine release but reversed the<br>200% increase in release induced by *d*-amphetamin<br>Thus, true in the olfactory tubercle, where CCK-8S had little form<br>or no effect on basal dopamine release but reversed the<br>200% increase in release induced by *d*-amphetamine.<br>Thus, CCK-8S appears to more greatly suppress dopa-<br> or no effect on basal dopamine release but reversed  $200\%$  increase in release induced by  $d$ -amphetami<br>Thus, CCK-8S appears to more greatly suppress do<br>mine release when it has been augmented, either<br>membrane depolariza 200% increase in release induced by *d*-amphetamine.<br>
Thus, CCK-8S appears to more greatly suppress dopa-<br>
mine release when it has been augmented, either by<br>
membrane depolarization (haloperidol) or by impulse-<br>
independ Thus, CCK-8S appears to more greatly suppress do mine release when it has been augmented, either membrane depolarization (haloperidol) or by imputed potation (dependent release (d-amphetamine). This conclusions supported b mine release when it has been augmented, either by<br>membrane depolarization (haloperidol) or by impulse-<br>independent release (d-amphetamine). This conclusion<br>is supported by the ability of CCK to block potassium-<br>evoked, bu membrane depolarization (haloperidol) or by impulse-<br>independent release (*d*-amphetamine). This conclusion<br>is supported by the ability of CCK to block potassium-<br>evoked, but not basal, dopamine release from nucleus<br>accumb is supported by the ability of CCK to block potassium-<br>evoked, but not basal, dopamine release from nucleus MT is a DA metabolite generated subsequent to DA<br>accumbens slices in vitro (186, 187). These findings are<br>consiste evoked, but not basal, dopamine release from nucleus MI is a DA metabolite generated subsequent to DA accumbens slices in vitro (186, 187). These findings are release and that 3-MT measurements are a useful index consisten evoked, but not basal, dopamine release from nucleus accumbens slices in vitro (186, 187). These findings are release consistent with the proposed role of endogenous CCK as of a suppressor of forebrain dopamine neurons (6 accumbens slices in vitro (186, 187). These findings are consistent with the proposed role of endogenous CCK as a suppressor of forebrain dopamine neurons (67, 195) and that antipsychotic effects of CCK (134) may be attrib mesolimbic dopamine neurons (141, 156).

## WOOD AND ALTAR<br>ever, no **V. Summary of Known Limitations of 3-MT Measurements**

Interest in the role of cholecystokinin<br>I. Cholecystokinin a DA metabolite which is only generated subsequent to<br>I. Cholecystokinin and DA metabolite which is only generated subsequent to<br>Interest in the role of cholecysto LITAR<br>
V. Summary of Known Limitations of 3-MT<br>
Measurements<br>
The main tenet of the present review is that 3-MT is<br>
DA metabolite which is only generated subsequent to V. Summary of Known Limitations of 3-MT<br>Measurements<br>The main tenet of the present review is that 3-MT is<br>a DA metabolite which is only generated subsequent to<br>DA release by COMT, an enzyme which is not present Measurements<br>The main tenet of the present review is that 3-MT is<br>a DA metabolite which is only generated subsequent to<br>DA release by COMT, an enzyme which is not present<br>within dopaminergic neurons. This hypothesis is sup The main tenet of the present review is that 3-MT is<br>a DA metabolite which is only generated subsequent to<br>DA release by COMT, an enzyme which is not present<br>within dopaminergic neurons. This hypothesis is sup-<br>ported by t The main tenet of the present review is that 3-MT<br>a DA metabolite which is only generated subsequent<br>DA release by COMT, an enzyme which is not presen<br>within dopaminergic neurons. This hypothesis is sup<br>ported by the excel DA release by COMT, an enzyme which is not present DA release by COMT, an enzyme which is not present<br>within dopaminergic neurons. This hypothesis is sup-<br>ported by the excellent agreement between 3-MT meas-<br>urements and the levels of DA collected in push-pull<br>perfusates a within dopaminergic neurons. This hypothesis is sup-<br>ported by the excellent agreement between 3-MT meas-<br>urements and the levels of DA collected in push-pull<br>perfusates and brain dialysates. Additionally, these data<br>corre ported by the excellent agreement between 3-MT measurements and the levels of DA collected in push-pull<br>perfusates and brain dialysates. Additionally, these data<br>correlate well with behavioral data where the direct<br>compari urements and the levels of DA collected in push-pull<br>perfusates and brain dialysates. Additionally, these data<br>correlate well with behavioral data where the direct<br>comparisons have been made. However, as presented<br>above, s perfusates and brain dialysates. Additionally, these data<br>correlate well with behavioral data where the direct<br>comparisons have been made. However, as presented<br>above, several potential pitfalls must be considered in<br>the e correlate well with beha<br>comparisons have been in<br>above, several potential p<br>the evaluation of any new<br>of dopaminergic neurons.<br>(a) Monoamine oxidase

**above, several potential pitfalls must be considered in<br>
the evaluation of any new pharmacological manipulation<br>
of dopamine gic neurons.<br>
(a) Monoamine oridase inhibitors will increase 3-MT<br>
levels; therefore, any drug u** levels; therefore, any drug under study should be devoid the evaluation of any new pharmacological manipulation<br>of dopaminergic neurons.<br>(a) Monoamine oxidase inhibitors will increase 3-MT<br>levels; therefore, any drug under study should be devoid<br>of this action. An example of thi (a) Monoamine oxidase inhibitors will increase 3-MT levels; therefore, any drug under study should be devoid of this action. An example of this problem was an early study of N,N-dimethyltryptamine in which increased 3-MT l levels; therefore, any drug under study should be devoid<br>of this action. An example of this problem was an early<br>study of N,N-dimethyltryptamine in which increased 3-<br>MT levels were hypothesized to indicate a DA releasing<br> of this action. An example of this problem was an early<br>study of N,N-dimethyltryptamine in which increased 3-<br>MT levels were hypothesized to indicate a DA releasing<br>action for this agent (167). However, subsequent studies<br> MT levels were hypothesized to indicate a DA releasing<br>action for this agent (167). However, subsequent studies<br>clearly demonstrated that this effect was mainly the<br>result of monoamine oxidase inhibition (193). action for this agent (167). However, subsequent studies

201). *(b)* COMT inhibitors will decrease 3-MT levels (191, 01).<br>(c) Dietary factors which alter the activity of MAO or

result of monoamine oxidase inhibition (193).<br>
(b) COMT inhibitors will decrease 3-MT levels (19<br>
201).<br>
(c) Dietary factors which alter the activity of MAO of<br>
COMT can also complicate the interpretation of phar-<br>
macolog (b) COMT inhibitors will decrease 3-MT levels (19<br>201).<br>(c) Dietary factors which alter the activity of MAO<br>COMT can also complicate the interpretation of phanacological studies. For example, COMT is a Mg-opendent enzyme, 201).<br>
(c) Dietary factors which alter the activity of MAO or<br>
COMT can also complicate the interpretation of phar-<br>
macological studies. For example, COMT is a Mg-de-<br>
pendent enzyme, such that in Mg-deficient rats striat (c) Dietary factors which alter the activity of MAC<br>COMT can also complicate the interpretation of ph<br>macological studies. For example, COMT is a Mg-<br>pendent enzyme, such that in Mg-deficient rats stric<br>3-MT levels are dec macological studies. For example, COMT is a Mg-dependent enzyme, such that in Mg-deficient rats striatal 3-MT levels are decreased (unpublished observations).<br>(d) Species and pathway differences, with regard to drug effect 3-MT levels are decreased (unpublished observations).

lated. *(d)* Species and pathway differences, with regard to drug effects, should always be tested and not extrapolated.<br> *(e)* Although there are no published drug effects on the clearance of 3-MT, this should be considered as a

(d) Species and pathway differences, with regard to<br>drug effects, should always be tested and not extrapo-<br>lated.<br>(e) Although there are no published drug effects on<br>the clearance of 3-MT, this should be considered as a<br>p drug effects, should always be tested and not extrapolated.<br>
(e) Although there are no published drug effects on<br>
the clearance of 3-MT, this should be considered as a<br>
possible site of action for some drugs, especially si (e) Although there are no published drug effects<br>the clearance of 3-MT, this should be considered as<br>possible site of action for some drugs, especially sir<br>the dynamics of this metabolite pool demonstrate sign<br>icant specie e clearance of 3-MT, this should be considered as a<br>ssible site of action for some drugs, especially since<br>e dynamics of this metabolite pool demonstrate signif-<br>int species differences (216).<br>(*f*) Inability to measure 3-

possible site of action for some drugs, especially since<br>the dynamics of this metabolite pool demonstrate signif-<br>icant species differences (216).<br> $(f)$  Inability to measure 3-MT associated with the<br>incertohypothalamic dop the dynamics of this metabolite pool demonstrate signif-<br>icant species differences (216).<br>(*f*) Inability to measure 3-MT associated with the<br>incertohypothalamic dopaminergic pathway, since the<br>nerve endings are juxtaposed icant species differences (216).<br>
(*f*) Inability to measure 3-N<br>
incertohypothalamic dopaminen<br>
nerve endings are juxtaposed to<br>
form classical synapses (130a).<br>
When these potential pitfalls ( $f$ ) Inability to measure 3-MT associated with the certohypothalamic dopaminergic pathway, since the revelondings are juxtaposed to blood vessels and do rem classical synapses (130a). When these potential pitfalls are al incertohypothalamic dopaminergic pathway, since the<br>nerve endings are juxtaposed to blood vessels and do not<br>form classical synapses (130a).<br>When these potential pitfalls are all taken into consid-<br>eration, reliable interp

nerve endings are juxtaposed to<br>form classical synapses (130a).<br>When these potential pitfalls<br>eration, reliable interpretation<br>DA release should be possible. When these potential pitfalls are all taken into consideration, reliable interpretation of the effects of drugs on DA release should be possible.<br>VI. Conclusions

ation, reliable interpretation of the effects of drugs on<br>A release should be possible.<br>VI. Conclusions<br>A thorough review of the literature indicates that 3-<br>T is a DA metabolite generated subsequent to DA DA release should be possible.<br>
VI. Conclusions<br>
A thorough review of the literature indicates that 3-<br>
MT is a DA metabolite generated subsequent to DA<br>
release and that 3-MT measurements are a useful index VI. Conclusions<br>A thorough review of the literature indicates that 3-MT is a DA metabolite generated subsequent to DA<br>release and that 3-MT measurements are a useful index<br>of DA release in vivo. Furthermore, the simplicity A thorough review of the literature indicates that 3-MT is a DA metabolite generated subsequent to DA release and that 3-MT measurements are a useful index of DA release in vivo. Furthermore, the simplicity of 3-MT measure A thorough review of the literature indicates that 3-<br>MT is a DA metabolite generated subsequent to DA<br>release and that 3-MT measurements are a useful index<br>of DA release in vivo. Furthermore, the simplicity of 3-<br>MT measu MT is a DA metabolite generated subsequent to DA<br>release and that 3-MT measurements are a useful index<br>of DA release in vivo. Furthermore, the simplicity of 3-<br>MT measurements, as compared to brain dialysis or<br>push-pull pe release and that 3-MT measurements are a useful index<br>of DA release in vivo. Furthermore, the simplicity of 3-<br>MT measurements, as compared to brain dialysis or<br>push-pull perfusion methods, will lead to an increase in<br>the dopaminergic pathways in the CNS.



- 1. AGHAJANIAN, G. K., AND BUNNEY, B. S.: Dopamine autoreceptors: phar-<br>
macological characterization by microiontophoretic single cell recordin<br>
macological characterization by microiontophoretic single cell recordin S-MI MEASUREMENTIS AND DA REI<br>REFERENCES<br>macological characterization by microiontophoretic single cell recording<br>studies. Naunyn-Schmiedeberg's Arch. Pharmacol. 297: 1-10, 1977.
- REFERENCES<br>
1. AGHAJANIAN, G. K., AND BUNNEY, B. S.: Dopamine autoreceptors: pharmacological characterization by microiontophoretic single cell recording<br>
studies. Naunyn-Schmiedeberg's Arch. Pharmacol. 297: 1-10, 1977.<br>
2 macological characterization by microiontophoretic single cell recording<br>studies. Naunyn-Schmiedeberg's Arch. Pharmacol. 297: 1-10, 1977.<br>BD, Y., JAVOY, F., AND YOUDIM, M. B. H.: Monoamine oxidase and<br>aldehyde dehydrogenas 2. AGER, Y., JAVOY, F., AND YOUDIM, M. B. H.: Monoamine oxidase and aldehyde dehydrogenase activity in the striatum of rats after 6-hydroxy-<br>dopamine lesion of the nigrostriatal pathway. Br. J. Pharmacol. 48: 175-<br>3. ALGER
- 
- aldehyde dehydrogenase activity in the striatum of rats after 6-hydroxy-<br>dopamine lesion of the nigrostriatal pathway. Br. J. Pharmacol. 48: 175-<br>178, 1973.<br>3. ALGERI, S., BRUNELLO, N., CALDERINI, A., AND CONSOLAZIONE, A.: 5. ALTAR, C. A., BERNER, B., BEALL, R., CARLSEN, S. F., AND BOYAR, W. C.:<br>
Dopemine release and metabolism after chronic delivery of selective or<br>
non-selective dopamine autoreceptor agonists. Mol. Pharmacol. 33: 690-<br>
65.
- Suppression of dopamine release and metabolism after chronic delivery of selective or non-selective dopamine autoreceptor agonists. Mol. Pharmacol. 33: 690–695, 1988.<br>
5. ALTAR, C. A., AND BOYAR, W. C.; Brain CCK-B recepto
- s. ALTAR, C. A., AND BOYAR, W. C.: Brain CCA-B receptors mediate the<br>suppression of dopamine release by cholecystokinin. Brain Res. (in press),<br>1988.<br>6. ALTAR, C. A., BOYAR, W. C., OEI, E., AND WOOD, P. L.: Dopamine<br>autore attereceptors modulate the in vivo release of dopamine in the frontal, cingulate and entorhinal cortices. J. Pharmacol. Exp. Ther. 242: 115-120, 1987.<br>
7. ALTAR, C. A., BOYAR, W. C., OBI, E., AND WOOD, P. L.: Cholecystokin
- 
- 7. ALTAR, C. A., BOYAR, W. C., OEI, E., AND WOOD, P. L.: Cholecystokinin<br>attenuates basal and drug-induced increases of limbic and striatal dopa-<br>mine release. Brain Res. 460:76-82, 1988.<br>8. ALTAR, C. A., BOYAR, W. C., AND
- 
- **10. ALTAR, C. A., AND HAUSER, K.: Topography of substantia nigra innervation**<br> **10. ALTAR, C. A., AND HAUSER, K.: Topography of substantia nigra innervation**<br> **10. ALTAR, C. A., JOYCE, J. N., AND MARSHALL, J. F.: Function** 9. ALTAR, C. A., AND HAUSER, K.: Topography of substantia nigra innervation<br>by D1 receptor-containing striatal neurons. Brain Res. 410: 1-11, 1987.<br>10. ALTAR, C. A., JOYCE, J. N., AND MARSHALL, J. F.: Functional organizati
- 
- nigrostriatal lesions: implications for behavioral recovery from brain in press), 1988.<br>
12. ALTAR, C. A., MARIEN, M. R., AND MARSHALL, J. F.: Time course of<br>
adaptations in dopamine synthesis, metabolism, and release following<br>
nigrostriatal lesions: implications for behavioral recovery from
- injury. J. Neurochem. 48: 390–399, 1987.<br>
13. ALTAR, C. A., AND MARSHALL, J. F.: Neostriatal dopamine uptake and<br>
reversal of age-related movement disorders with dopamine uptake inhi-<br>
itors. In Central Determinants of Age
- reversal of age-related movement disorders with dopamine uptake inhibitors. In Central Determinants of Age-related Declines in Motor Function, ed. by J. Joseph, pp. 343–354, New York Academy, New York, 1987.<br>FIRE, C. A., O ing of 6-hydroxydopamine or gamma-hydroxybutyrate in awake rats. Neuropharmacology 23: 309-318, New York headers. Neuropharmacology 23: 309-318, 1987.<br>14a. ALTAR, C. A., O'NEIL, S., AND MARSHALL, J. F.: Sensorimotor impair
- and neostriatal dopamine metabolite elevations result from intranigra<br>injection of 6-hydroxydopamine or gamma-hydroxybutyrate in awake rats<br>
Neuropharmacology 23: 309-318, 1987.<br>
LTAR, C. A., WASLEY, A. M., BOYAR, W. C., L ALTAR, C. A., WASLEY, A. M., BOYAR, W. C., LIEBMAN, J., GERHARDT, S., AND WOOD, P. L.: Dopamine neurochemical profile of atypical anti-<br>psychotics resembles that of D-1 antagonists. Naunyn-Schmiedeberg's<br>Arch. Pharmacol. 3 **EXAMPLY THE TEXT CONSULTER IN A SET AND WOOD, P. L.: Dopamine neurochemical profile of atypical antipsychotics resembles that of D-1 antagonists. Naunyn-Schmiedeberg's Arch. Pharmacol. 338: 162-168, 1988.<br>
TRAR, C. A., WA**
- psychotics resembles that of D-1 antagonists. Naunyn-Schmiedeberg's<br>Arch. Pharmacol. 338: 162-168, 1988.<br>
15. ALTAR, C. A., WASLEY, A. M., LIEBMAN, J., GERHARDT, S., KIM, H.,<br>
WELCH, J. J., AND WOOD, P. L.: CGS 10746B: an
- WELCH, J. J., AND WOOD, P. L.: CGS 10746B: an atypical antipsychotic<br>candidate that selectively decreases dopamine release at behaviorally<br>effective doese. Life Sci. 39: 699-705, 1986.<br>16. ANDEN, N.-E., GRABOWSKA-ANDEN, E.
- tion of autoreceptors on dopamine neurons in different brain regions of<br>rats treated with gammabutyrolactone. J. Neural Trans. 58: 143-152,<br>1983.<br>17. ANDERSEN, P. H., AND BRAESTRUP, C.: Evidence for different states of th
- 18. ANDERSEN, P. H., GRONVALD, F. C., AND JANSEN, J. A.: A comparison between dopamine-stimulated adenylate cyclase and <sup>3</sup>H-SCH 23390 binding in the rat striatum. Life Sci. 37: 1971–1983, 1985. an adenylate cyclase-coupled state of the D1 receptor. J. Neurochem. 47:<br>
1822–1831, 1986.<br>
18. ANDERSEN, P. H., GRONVALD, F. C., AND JANSEN, J. A.: A comparison<br>
between dopamine-stimulated adenylate cyclase and <sup>3</sup>H-SCH
- an adenyiate cyclese-coupled state or the D1 receptor. J. Neurochem. 47:<br>
1822–1831, 1986.<br>
18. ANDERSEN, P. H., GRONVALD, F. C., AND JANSEN, J. A.: A comparison<br>
between dopamine-stimulated adenyiate cyclase and <sup>3</sup>H-SCH 19. ANDERSEN, P. H., NIELSEN, E. B., GRONVALD, F. C., AND BRAESTRUP, C.:<br>
Some atypical neuroleptics inhibit [<sup>1</sup>H]SCH 23390 binding in vivo. Eur.<br>
J. Pharmacol. 120: 143-144, 1986.<br>
20. BANNON, M. J., AND ROTH, R. H.: Pha
- 
- meurons. Pharmacol. Rev. 35: 53-68, 1983.<br>
21. BANNON, M. J., WOLF, M. E., AND ROTH, R. H.: Pharmacology of dopamine neurons innervating the prefrontal, cingulate, and piriform cortices. Eurol. J. Pharmacol. 92: 19. Therma
- NNNON, M. J., WOLF, M. E., AND ROTH, R. H.: Pharmacology of dopamine neurons innervating the prefrontal, cingulate, and piriform cortices. Eur.<br>J. Pharmacol. 92: 119-125, 1983.<br>RETHOLINI, G.: Differential effect of neurole neurons innervating the prefrontal, cingulate, and piriform cortices. Eur.<br>J. Pharmacol. 92: 119-125, 1983.<br>22. BARTHOLINI, G.: Differential effect of neuroleptic drugs on dopamine turn-<br>over in the extrapyramidal and limb
- 
- 

- of GABAergic agonists elevates  $[^3H]GABA$  binding and produces tolerance in striatal dopamine catabolism. Brain Res. 335: 169-173, 1985.<br>25. BERNHEIMER, H., BIRKMAYER, W., HORNYKIEWICZ, O., JELLINGER, K., AND SETTELBERGER, and Huntington. Clinical, morphological, and neurochemical correlations. **J. Neural.** Sci. **20: 415-455, 1973.** 26. BE8SON, **M. J.,** CHERAMY, **A.,** FELTZ, **P., AND GLOWINSKI,** J.: Dopamine:
- AND SEITELBERGER, F.: Brain dopamine and the syndromes of Parkinson<br>and Huntington. Clinical, morphological, and neurochemical correlations.<br>J. Neurol. Sci. 20: 415–456, 1973.<br>esson, M. J., CHERAMY, A., FELTZ, P., AND GLOW
- and Huntington. Clinical, morphological, and neurochemical correlations.<br>
J. Neurol. Sci. 20: 415-455, 1973.<br>
26. BESSON, M. J., CHERAMY, A., FELTZ, P., AND GLOWINSKI, J.: Dopamine:<br>
spontaneous and drug induced release fr spontaneous and drug induced release from the caudate nucleus in the cat. Brain Res. 32: 407–424, 1971.<br>GcIO, G., CASA, M., CORDA, M. G., DIBELLO, C., AND GESSA, G. L.:<br>Stimulation of dopamine synthesis in caudate nucleus **527.** Blach Mes. 32: 407-424, 1971.<br>
28. Blach M, CoRA, M. G., DIBELLO, C., AND GESSA, G. L.:<br>
Stimulation of dopennine synthesis in caudate nucleus by intrastriatal<br>
enkephalins and antagonism by naloxone. Science (Wash.
- 
- enkephalins and antagonism by naloxone. Science (Wash. DC) 200: 552-<br>554, 1978.<br>28. BLAHA, C. D., PHILLIPS, A. G., AND LANE, R. F.: Reversal by cholecysto-<br>kinin of apomorphine-induced inhibition of dopamine release in the nucleus accumbens of the rat. Regul. Pept. 17: 301-310, 1987.<br>ANK, C. L., SASA, S., ISERNHAGEN, R., MEYERSON, L. R., WASSIL, D.,<br>WONG, P., MODAK, A. T., AND STAVINOHA, W. B.: Levels of novembershine<br>in each dopenine in mou 29. BLANK, C. L., SASA, S., ISERNHAGEN, R., MEYERSON, L. R., WASSIL, D., WONG, P., MODAK, A. T., AND STAVINOHA, W. B.: Levels of norepinephrine and dopamine in mouse brain regions following microwave irradiation—rapid post
- rine and dopamine in mouse brain regions following microwave irradiation—rapid post-mortem degradation of striatal DA in decapitated ani-<br>mals. J. Neurochem. 33: 213–219, 1979.<br>UM, M., MCEWEN, B. S., AND ROBERTS, J. L.: Tr 30. BLUM, M., MCEWEN, B. S., AND ROBERTS, J. L.: Transcriptional analysis<br>of tyrosine hydroxylase gene expression in the tuberinfundibular dope-<br>minergic neurons of the rat acruate nucleus after estrogen treatment. J.<br>Biol
- 
- of tyrosine hydroxylase gene expression in the tuberinfunduous do-<br>minergic neurons of the rat arcuste nucleus after estrogen treatment. J.<br>Biol. Chem. 262: 817-821, 1987.<br>31. BOWERS, M. B., AND HOFFMAN, F. J.: Homovanilli
- macology 84: 136-137, 1984.<br>
32. BOWERY, N. G., HUDSON, A. L., AND PRICE, G. W.: GABA-A and GABA-<br>
B receptor site distribution in the rat central nervous system. Neuroscience 20: 365-383, 1987.<br>
33. BOYAR, W. C., AND ALTA 33. BOYAR, W. C., AND ALTAR, C. A.: Modulation of dopamine release by D2<br>but not D1 receptor agonists and antagonists. J. Neurochem. 48: 824-<br>831, 1987.<br>34. BRAESTRUP, C.: Biochemical differentiation of amphetamine vs. met
- 
- Altar, pp. 53–78, Alan R. Liss, New York, 1986.<br>
11. ALTAR, C. A., AND MARIEN, M. R.: Preservation of dopamine release in the<br>
denervated striatum: implications for Parkinson's disease. Neurosci. Lett.<br>
2. ALTAR, C. A., MA phenidate and nomifensine in rats. J. Pharm. Pharmacol. 29: 463-470,<br>1977.<br>35. BROXTERMAN, H. J., NOACH, E. K., VAN VALKENBURG, C. F. M., AND<br>WIJLING, A.: Cross-tolerance of dopamine metabolism to baclofen,<br>gamma-butyrolac **35.** BROXTERMAN, H. J., NOACH, E. K., VAN VALKENBURG, C. F. M., AND WILLING, A.: Cross-tolerance of dopamine metabolism to baclofen,<br>gamma-butyrolactone, and HA-966 in the striatum and olfactory tubercle<br>of the rat. Life
	- PSYCHERMAN, H. J., VANVALKENBURG, C. F. M., AND NOACH, E. L.: HA-<br>966 effects on striatal dopamine metabolism: implications for dopamine<br>compartmentation. J. Pharm. Pharmacol. 32: 67-69, 1980.<br>77. BURKI, H. R.: Effects of
	- compartmentation. H. R.: Effects of fluperlapine on dopaminergic systems in rat brain.<br>Phychopharmacologia 89: 77-84, 1986.<br>38. BURKI, H. R., RUCH, W., AND ASPER, H.: Effects of clozapine, thioridazine,
	- compartmentation. J. Pharm. Pharmacol. 32: 67-69, 1980.<br>
	JRKI, H. R.: Effects of fluperlapine on dopaminergic systems in rat brain.<br>
	Psychopharmacologia 89: 77-84, 1986.<br>
	JRKI, H. R., RUCH, W., AND ABPER, H.: Effects of cl 137. BURKI, H. K.: Effects of tuperlapine on copaminergic systems in rat oral Psychopharmacologia 89: 77-84, 1986.<br>
	23. BURKI, H. R., RUCH, W., AND AsPER, H.: Effects of clozapine, thioridaxin<br>
	perlapine, and haloperidol o
	- JRKI, H. R., RUCH, W., AND ASPER, H.: Effects of clozapine, thioridaxine, perlapine, and haloperidol on the metabolism of the biogenic amines in the brain of the rat. Psychopharmacologia 41: 27-33, 1975.<br>
	JU, N. T.: Relati **40. CAMPOCHIARO, P., T., Relationship between catechol-o-methyltransferase and phenolsulfotransferase in the metabolism of dopamine in the rat brain. J.<br>Neurochem. 45: 1612–1619, 1985.<br>40. CAMPOCHIARO, P., SCHWARTZ, R., A**
	- 136: 501-511, 1977.<br> **41. CAMPOCHIARO, P., SCHWARTZ, R., AND COYLE, J. T.: GABA receptor**<br> **40. CAMPOCHIARO, P., SCHWARTZ, R., AND COYLE, J. T.: GABA receptor**<br>
	binding in rat striatum: localization and effects of denervat
	- MPOCHIARO, P., SCHWARTZ, R., AND COYLE, J. T.: GABA receptor<br>binding in rat striatum: localization and effects of denervation. Brain Res.<br>136: 501–511, 1977.<br>RESSON, A., AND LANDQVIST, M.: Effect of chlorpromazine or halop 136: 501-511, 1977.<br>
	136: 501-511, 1977.<br>
	41. CARLSSON, A., AND LINDQVIST, M.: Effect of chlorpromazine or haloperidol<br>
	on formation of 3-methoxytyramine and normetanephrine in mouse brain.<br>
	Acta Pharmacool. Toxicol. 20: 1
	- of 3-methoxytyramine and normation of 3-methoxytyramine in brain.<br>Acta Pharmacol. Toxicol. 20: 140–144, 1963.<br>22. CARLSSON, A., LINDQVIST, M., AND KEHR, W.: Postmortal accumulation<br>of 3-methoxytyramine in brain. Naunyn-Sch
	- neus and automorphism. M., AND KEHR, W.: Postmortal accumulation<br>of 3-methoxytyramine in brain. Naunyn-Schmiedeberg's Arch. Pharma-<br>col. 284: 365-372, 1974.<br>RELSSON, A., AND WINBLAD, B.: Influence of age and time interval of 3-methoxytyramine in brain. Naunyn-Schmiedel<br>col. 284: 365–372, 1974.<br>KRLSSON, A., AND WINBLAD, B.: Influence of age and<br>death and autopsy on dopamine and 3-methoxytyra<br>basal ganglia. J. Neural Trans. 38: 271–276, 1976.
	- col. 284: 365-372, 1974.<br>
	43. CARESON, A., AND WINELAD, B.: Influence of age and time interval between<br>
	death and autopsy on dopamine and 3-methoxytyramine levels in human<br>
	basal ganglia. J. Neural Trans. 38: 271-276, 1976 death and autopsy on dopamine and 3-methoxytyramine levels in hossal ganglia. J. Neural Trans. 38: 271–276, 1976.<br>
	INTABENI, F., BUGATTI, A., GROPPETTI, A., MAGGI, A., PARENTI, M.<br>
	RACAGNI, G.: GABA and dopamine: their mut **basal ganglia. J. Neural Trans. 38:** 271–276, 1976.<br> **Sensitive Press,** P. BUGATTI, A., GROPPETTI, A., MAGGI, A., PARENTI, M., AND<br>
	RACAGNI, G.: GABA and dopamine: their mutual regulation in the nigro-<br>
	striatal system. I **York, 1979.** R. S. GABA and dopamine: their mutual regulation in the nigred strindard system. *In* GABA-Neurotranemitters, ed. by P. Krogsgaard-La sen, J. Scheel-Kruger, and H. Kofod, pp. 107-117, Academic Press, Ne York,
	- GABA, beta-adrenergic and H. Kofod, pp. 107-117, Academic Press, New<br>York, 1979.<br>KANG, R. S. L., TRAN, V. T., AND SNYDER, S. H.: Neurotransmitter<br>receptor bicalizations: brain season induced alterations in benzodiazepine,<br> 46. CHANG, R. S. L., TRAN, V. T., AND SNYDER, S. H.: Neurotransmitt<br>receptor localizations: brain lesion induced alterations in benzodiazepin<br>GABA, beta-adrenergic, and histamine H1-receptor binding. Brain Re<br>190: 95-110, receptor localizations: brain lesion induced alterations in benzodiazepine,<br>
	GABA, beta-adrenergic, and histamine H1-receptor binding. Brain Res.<br>
	190: 95-110, 1980.<br>
	46. CHERAMY, A., NIEOULLON, A., AND GLOWINSKI, J.: Bloc
	- GABA, beta-adrenergic, and histamine H1-receptor binding. Brain Res.<br>
	46. CHERAMY, A., NIEOULLON, A., AND GLOWINSKI, J.: Blockade of the picro-<br>
	toxin-induced in vivo release of dopamine in the cat caudate nucleus by<br>
	diaz
	- toxin-induced in vivo release of dopamine in the cat caudate nucleus by diazepam. Life Sci. 20: 811-816, 1977.<br>
	47. CHIURH, C. C., ZAVADIL, A. P., AND MARKEY, S. P.: Increase of striatal 3-<br>
	methoxytyramine but not of homo
	- in rat striated 3-<br>in rate, C. C., ZAVADIL, A. P., AND MARKEY, S. P.: Increase of striatal 3-<br>methoxytyramine but not of homovanillic acid following administration<br>of d-amphetamine or decapitation. Fed. Proc. 37: 509 (abst of *d*-amphetamine or decapitation. Fed. Proc. 37: 509 (abst. 1554), 1978.<br>48. CHURCH, W. H., JUSTICE, J. B., AND BYRD, L. D.: Extracellular dopamine<br>in rat striatum following uptake inhibition by cocaine, nomifensine, and SUREL, W. H., JUSTICE, J. B., AND BYRD, L. D.: Extracellular dopamine<br>in rat striatum following uptake inhibition by cocaine, nomifensine, and<br>benztropine. Eur. J. Pharmacol. 139: 345-348, 1987.<br>MINO, M., PONZIO, F., ACHIL
	- in rat striatum following uptake inhibition by cocaine, non-<br>henztropine. Eur. J. Pharmacol. 139: 345–348, 1987.<br>MINO, M., PONZIO, F., ACHILLI, G., VANTINI, G., PEREGC<br>S., AND GARATTINI, S.: Dopaminergic effects of buspiro

spet

- 184 **WOOD AND ALTAR**<br>184 **WOOD AND ALTAR**
- WOOD AND A<br>50. COMMISSIONG, J. W.: Monoamine metabolites: their relationship to monominergic neuronal activity. Biochem. Pharmacol. 34: 1127–1131, 1985.<br>51. Cost, C., ALTAR, C. A., AND WOOD, P. L.: Effects of cholecystokin WOOD AND ALTAR<br>50. COMMISSIONG, J. W.: Monoamine metabolites: their relationship to mon-<br>6ffectominergic neuronal activity. Biochem. Pharmacol. 34: 1127-1131, 1985.<br>51. Cost, C. A., ATAR, C. A., AND WOOD, P. L.: Effects of So. COMMISSIONG, J. W.: Monoamine metabolites: their relationship to mon-<br>
commenter neuronal activity. Biochem. Pharmacol. 34: 1127-1131, 1985.<br>
51. Cost, A.I.T.R., C. A., AND WOOD, P. L.: Effects of cholecystokinin on<br>
a
- acetylcholine turnover and dopamine release in the rat frontal cortex and<br>striatum. Neuropharmacology (in press), 1988.<br>52. COSTALL, B., NAYLOR, R. J., AND NOHRIA, V.: Climbing behavior induced<br>by apomorphine in mice: a po
- activity. Burnopharmacology (in press), 1988.<br>
Scarcial. B., NAVIOR, R. J., AND NOHRIA, V.: Climbing behavior induced<br>
by apomorphine in mice: a potential model for the detection of neuroleptic<br>
activity. Eur. J. Pharmacol by apomorphine in mice: a potential model for the detection of neuroleptic activity. Eur. J. Pharmacol. 50: 39-50, 1978.<br>AVIES, C. L., AND HEAL, D. J.: Determination of 3-methoxytyramine in<br>rat brain by HPLC with electroch **53. DAVIES, C. L., AND HEAL, D. J.: Determination of 3-methoxytyramine in**<br>rat brain by HPLC with electrochemical detection and its correlation with<br>dopamine function after administration of a monoamine oxidase inhibitor<br>
- and homovanillic acid in rat striatum. J. Neurochem. 47: 1919-1923, 1986.<br>
54. DEDEK, J., BAUMES, R., TIEN-DUC, N., GOMENI, R., AND KORF, J.: Turn-<br>
over of free and conjugated (sulphonyloxy)dialydroxyphenylacetic acid<br>
an type A form of monoamine oxidase within R. AND KORF, J.:<br>cover of free and conjugated (sulphonyloxy)dihydroxyphenylacetiand<br>homovanillic acid in rat striatum. J. Neurochem, 33: 687-695,<br>sMAREST, K. T., SMITH, D. L., AND AZ
- over of free and conjugated (sulphonyloxy)dihydroxyphenylacetic acid and homovanillic acid in rat striatum. J. Neurochem, 33: 687-695, 1979.<br>55. DEMAREST, K. T., SMITH, D. L., AND AZZARO, A. J.: The presence of the type A
- **ROTH, R. H.: Meson Inc. 1. AND AZZARO, A. J.: The presence of the type A form of monoamine oxidase within nigrostriatal dopamine-containing neurons. J. Pharmacol. Exp. Ther. 215: 461-468, 1980.<br>
<b>ROTH, A. Y., TAM, S.-Y.,** type A form of monoamine oxidase within nigrostriatal dopamine-containing neurons. J. Pharmacol. Exp. Ther. 215: 461-468, 1980.<br>56. DEUTCH, A. Y., TAM, S.-Y., FREEMAN, A. S., BOWERS, M. B., JR., AND<br>ROTH, R. H.: Mesolimbic
- 
- CHIARA, A. M., PORCEDDU, M. L., FRATTA, W., AND GESSA, G. L.:<br>Postsynaptic receptors are not essential for dopaminergic feedback regu-<br>lation. Nature (Lond.) 267: 270-272, 1977.<br>DICHIARA, G., AND IMPERATO, A.: Opposite eff 57a. DICHIARA, G., AND IMPERATO, A.: Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal<br>caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244: 1067-1080,<br>1
- exudate of freely moving rats. J. Pharmacol. Exp. Ther. 244: 1067-1080, 1988.<br>
58. DIGIULIO, A. M., GROPPETTI, A., CATTABENI, F., GALLI, C. L., MAGGI, A., ALGERI, S., AND PONZIO, F.: Significance of dopamine metabolites in
- ALGERI, S., AND PONZIO, F.: Significance of dopamine metabolites in the<br>evaluation of drugs acting on dopaminergic neurons. Eur. J. Pharmacol.<br>52: 201-278, 1978.<br>59. DURING, M. J., ACWORTH, I. N., AND WURTMAN, R. J.: Effec
- DURING, M. J., ACWORTH, I. N., AND WURTMAN, R. J.: Effects of systemic L-tyrosine on dopamine release from rat corpus striatum and nucleus accumbent. Brain Res. 452: 378-380, 1988.<br>accumbents in the state in the striate in **rat. Science (Wash. DC)** 221: 78-380, 1988.<br> **SP. EWING, A. G., BIGELOW, J. C., AND WIGHTMAN, R. M.: Direct in vivo<br>
monitoring of dopamine released from two striatal compartments in the<br>
rat. Science (Wash. DC) 221: 169-**
- monitoring of dopamine released from two striatal compartments in the<br>rat. Science (Wash. DC) 221: 169-171, 1983.<br>60. EWING, A. G., AND WIGHTMAN, R. M.: Monitoring the stimulated release<br>of dopamine with in vivo voltammetr
- 60. EWING, A. G., AND WIGHTMAN, R. M.: Monitoring the stimulated release<br>of dopamine with in vivo voltammetry. II. Clearance of released dopamine<br>from extracellular fluid. J. Neurochem. 43: 570-577, 1984.<br>61. FADDA, F., SE
- 62. FARNEBO, L., AND HAMBERGER, B.: Drug-induced changes in the release of  $^{740-708}$ , 1974.<br>
<sup>3</sup>H-monoamines from field stimulated rat brain slices. Acta Physiol. 87. HORNKIEWICZ, O.: Parkinson's disease: from brain homo
- related compounds by electron capture chemical ionization GC-MS. *In* CNS sumulants with phencycliane on dopamine release using in vivo<br>Mass Spectrometry in Biomedical Research, ed. by S. J. Gaskell, pp. 403-<br>441, John Wil 641, FAULL, K. F., AND BECK, O.: Quantification of neurotransmitters and<br>related compounds by electron capture chemical ionization GC-MS. In<br>Mass Spectrometry in Biomedical Research, ed. by S. J. Gaskell, pp. 403-<br>441, Joh
- Felated compounds by electron capture chemical ionization GC-MS. In<br>Mass Spectrometry in Biomedical Research, ed. by S. J. Gaskell, pp. 403-<br>441, John Wiley & Sons, New York, 1986.<br>GARRATTI, P., ALGERI, S., BENFENATI, F., 64. **FERRETTI, P., ALGERI, S., BENFENATI, F., CIMINO, M., FERRETTI, C., GARRATTIT, M., AND LIPARTITI, M.: Biochemical effects of minaprine on striatal dopaminergic neurons in rats. J. Pharm. Pharmacol. 36: 48-50, 1984.<br>198** ganglia functions. Annu. Rev. Gerontol. Geriat. J. Pharmacol. 36: 48-50, 1984.<br>65. Finction C. E., RANDALL, P. K., AND MARSHALL, J. F.: Aging and basal ganglia functions. Annu. Rev. Gerontol. Geriat. 2: 49-85, 1981.<br>66. FR
- 
- 65. FINCH, C. E., RANDALL, P. K., AND MARSHALL, J. F.: Aging and basal<br>ganglia functions. Annu. Rev. Gerontol. Geriat. 2: 49-85, 1981.<br>66. FRENCH, E. D., PILAPIL, C., AND QUIRION, R.: Phencyclidine binding sites<br>in the nuc
- reduction of dopamine turnover in discreased following lesions of the mesolimbic dopamine system. Eur. J.<br>Pharmacol. 116: 1–9, 1985.<br>XXE, K., ANDERSON, K., LOCATELLI, V., AGNATI, L. F., HOKFELT, T.,<br>SKIRBOLL, L., AND MUTT, Pharmacol. 116: 1-9, 1985.<br>
67. FUXE, K., ANDERSON, K., LOCATELLI, V., AGNATI, L. F., HOKFELT, T., SKIRBOLL, L., AND MUTT, V.: Cholecystokinin peptides produce marked<br>
reduction of dopamine turnover in discrete areas in th
- 
- autoreceptors: studies in vivo. J. Pharmacol. Exp. Theorem. 23. Pharmacol. A., AND GROPPETTI, A.: A mass fragmentographic assay of 3-methoxytyr-<br>amine in rat brain. J. Neurochem. 27: 795–798, 1976.<br>LLOWAY, M. P., WOLF, M. 89. GALLOWAY, M. P., WOLF, M. E., AND ROTH, R. H.: Regulation of dopamine synthesis in the medial prefrontal cortex is mediated by release modulating autoreceptors: studies in vivo. J. Pharmacol. Exp. Ther. 236: 689-698, 1
- synthesis in the medial prefrontal cortex is mediated by release modulating<br>autoreceptors: studies in vivo. J. Pharmacol. Exp. Ther. 236: 689-698,<br>1986.<br>70. GERHARDT, S., GERBER, R., AND LIEBMAN, J. M.: SCH 23390 dissociat
- from conventional neuroleptics in apomorphine climbing and primate<br>acute dyskinesia models. Life Sci. 37: 2355-2363, 1985.<br>71. GIANUTSOS, G., AND MOORE, K. E.: Tolerance to the effects of baclofen<br>and gamma-butyrolactone o
- From conventional neuroleptics in apomorphine climbing and primate<br>acute dyskinesia models. Life Sci. 37: 2355-2363, 1985.<br>71. GLANUTSOS, G., AND MOORE, K. E.: Tolerance to the effects of baclofen<br>and gamma-butyrolactone o 72. GLAESSER, B. S., BERRY, J. C., BOYAR, W. C., LOVELL, R. A., BR. WALDER, A., LOO, P., STONE, G., KALINSKY, H., AND HUTCHISON, A Dopamine autoreceptor activity of CGS 15855A. Soc. Neurosci. A 11: 501, 1985.<br>
11: 501, B.
- 

effects of repeated administration of apomorphine, EMD 23 448, and (+) 3.PPP on A9 neurons. Soc. Neurosci. Abstr. **<sup>1</sup> 1:** 116, 1985.

- ALTAR<br>
effects of repeated administration of apomorphine, EMD 23 448, and (+)<br>
3-PPP on A9 neurons. Soc. Neurosci. Abstr. 11: 116, 1985.<br>
74. GOLDSTEIN, L. E., BRADBERRY, C. W., ROTH, R. H., AND BUNNEY, B. S.:<br>
Simultaneou 3-PPP on A9 neurons. Soc. Neurosci. Abstr. 11: 116, 1985.<br>
74. GOLDSTEIN, L. E., BRADBERRY, C. W., ROTH, R. H., AND BUNNEY, B. S.:<br>
Simultaneous in vivo measurements of dopamine release and metabolism<br>
in the rat medial pr
- 
- Antischizophrenic drugs of the dipnehylbutylpiperidine type act as cal-<br>cium channel antagonists. Proc. Natl. Acad. Sci. USA 80: 5122-5125,<br>1983.<br>RACE, A. A., AND BUNNEY, B. S.: Opposing effects of striatonigral feedback<br>p
- 1983.<br>
77. GRACE, A. A., AND BUNNEY, B. S.: Opposing effects of striatonigral feedback<br>
pathways on midbrain dopamine cell activity. Brain Res. 333: 271-284,<br>
1985.<br>
77. GROPPETTI, A., ALGERI, S., CATTABENI, F., DIGIULIO, pathways on midbrain dopamine cell activity. Brain Res. 333: 271–284,<br>1985.<br>ROPPETTI, A., ALGERI, S., CATTABENI, F., DIGIULIO, A. M., GALLI, C. L.,<br>PONZIO, F., AND SPANO, P. F.: Changes in specific activity of dopamine<br>met
- 77. GROPPETTI, A., ALGERI, S., CATTABENI, F., DIGIULIO, A. M., GALLI, C. L.,<br>PONZIO, F., AND SPANO, P. F.: Changes in specific activity of dopamine<br>metabolites as evidence of a multiple compartmentation of dopamine in<br>stri 78. GROPPETTI, A., PARENTI, M., GALLI, C. L., BUGATTI, A., CATTABENI, F.,<br>DIGIULIO, A. M., AND RACAGNI, G.: 3-Methoxytyramine and different<br>neuroleptics: dissociation from HVA and DOPAC. Life Sci. 23: 1763-<br>1768, 1978.<br>29.
- lation. Nature (Lond) 267: 270-272, 1977.<br>
macol. 134: 257-264, 1987.<br>
TOG, 134: 257-264, 1987.<br>
TOG, IL.: FRATTA, W., AND GESSA, G. L.: TOG, SHARMAN, D. F., AND TEGERDINE, P. R.: Some observations on the estimation of 3-m
	- vations on the estimation of 3-methoxytyramine in brain tissue. Br. J.<br>Pharmacol. 42: 505-511, 1971.<br>80. HEFTI, F., MELAMED, E., AND WURTMAN, R. J.: Partial lesions of the<br>dopaminergic nigroetriatal system in rat brain: bi vations on the estimation or 3-methoxytyramine in orain tissue. Br. J.<br>Pharmacol. 42: 505-511, 1971.<br>80. HEFTI, F., MELAMED, E., AND WURTMAN, R. J.: Partial lesions of the<br>dopaminergic nigrostriatal system in rat brain: bi
	-
	- dopaminergic nigrostriatal system in rat brain: biochemical characteriza-<br>tion. Brain Res. 195: 123-137, 1980.<br>81. HENN, F. A., AND HAMBERGER, A.: Glial cell function: uptake of transmitter<br>substances. Proc. Natl. Acad. Sc
	- substances. Proc. Natl. Acad. Sci. USA 68: 2686-2690, 1971.<br>
	82. HITZEMAN, R. J., LOH, H. H., AND DOMINO, E. F.: Effect of phencyclidine<br>
	on the accumulation of <sup>14</sup>C-catecholamines formed from <sup>14</sup>C-tyrosine.<br>
	Arch. Int. **81:** 89-99, 1983. Arch. Int. Pharmacodyn. 202: 252-258, 1973.<br>
	83. HJORTH, S., CARLSSON, A., AND CLARK, D.: Central dopamine agonist and<br>
	antagonist actions of the enantiomers of 3-PPP. Psychopharmacology<br>
	81: 89-99, 1983.<br>
	84. HJORTH, S. A
	- JORTH, S., CARLSSON, A., AND CLARK, D.: Central dopamine agonist and<br>antagonist actions of the enantiomers of 3-PPP. Psychopharmacology<br>10RTH, S. A., CARLSSON, A., WIKSTROM, H., LUNDBERG, P., SANCHEZ,<br>D., HACKSELL, U., ARV autoreceptors. Life Sci. 28: 1225-1238, 1983.<br> **28:** 89. 1983.<br> **28:** B. A., CARLSSON, A., WIKSTROM, H., LUNDBERG, P., SANCHEZ,<br>
	D., HACKSELL, U., ARVIDSSON, L.-E., SVENSSON, U., AND NILSON, J. L.<br>
	G.: 3-PPP, a new central
	- G.: 3-PPP, a new centrally acting DA-receptor agonist with selectivity for<br>autoreceptors. Life Sci. 28: 1225-1238, 1981.<br>86. Horver, T., LJuNoDAHL, A., FUXE, K., AND JOHANSSON, O.: Dopamine<br>nerve terminals in the rat limbi
	- DRYELT, I., LJUNGDAHL, A., FUXE, K., AND JOHANSSON, O.: LOpamine<br>earve terminals in the rat limbic cortex: aspects of the dopamine hypoth-<br>esis of schizophrenia. Science (Wash. DC) 184: 177-179, 1974.<br>DLTZ, R. W., AND COYL merve terminais in the rat limbic cortex: aspects of the copamine nypothesis of schizophrenia. Science (Wash. DC) 184: 177–179, 1974.<br>DLTZ, R. W., AND COYLE, J. T.: The effects of various salts, temperature, and the alkalo 36. HOLTZ, R. W., AND COYLE, J. T.: The effects of various salts, temperature,<br>and the alkaloids veratridine and brachotoxin on the uptake of [<sup>3</sup>H]<br>dopamine into synaptosomes from rat striatum. Mol. Pharmacol. 10:<br>746–758
	-
	-
	-
	- **phase high performance liquid chromatography with electrochemical de-**<br>**istry.** Neuropharmacology 19: 587-590, 1980.<br> **istry.** Neuropharmacology 19: 587-590, 1980.<br> **iPERATO, A., AND DICHIARA, G.: Trans-striatal dialysis** 90. IMPERATO, A., AND DICHIARA, G.: Trans-striatal dialysis coupled to reverse<br>phase high performance liquid chromatography with electrochemical de-<br>tection: a new method for the study of the in vivo release of endogenous<br>
	- EXECH, E. D., PILAPIL, C., AND QUIRION, R.: Phencyclidine-induced hyperactivity are and phencyclidine-induced hyperactivity are assessment and phencyclidine-induced hyperactivity are assessment and phencyclidine-induced hy **Example 12339 Stimulates which controls while the D-1 agonist SCH**<br>detection: a new method for the study of the in vivo release of endogenous<br>dopamine and metabolites. J. Neurosci. 4: 966-977, 1984.<br>PERATO, A., MULAS, A.,
		-
		- release in the dorsal caudate of freely moving rats. Eur. J. Pharmacol.<br>142: 177-182, 1987.<br>92. ISHKAWA, K., SHIBANOKI, S., SAITO, S., AND MCGAUGH, J. L.: Effect of<br>microwave irradiation on monoamine metabolism in dissecte WOOD, P. L.: The dopamine autoreceptor agonist, CGS 15855A, modu-Brain Res. 240: 158–16<br>ENGAR, S., HAUSLER, A<br>WOOD, P. L.: The dopa<br>lates striatal dopamine<br>cology (in press), 1988.<br>ENGAR, S., KIM, H. S., A **93. IYENGAR, S., HAUSLER, A., KIM, H. S., MARIEN, M., ALTAR, C. A., AND**<br>
		WOOD, P. L.: The dopamine autoreceptor agonist, CGS 15855A, modulates striatal dopamine metabolism and prolactin release. Neuropharma-<br>
		cology (in
		- accumbens of the rat. Neurosci. 1988.<br> **A. IYENGAR, S., KIM, H. S., AND WOOD, P. L.: Agonist action of the agonist/**<br>
		antagonist analgesic: butorphanol on dopamine metabolism in the nucleus<br>
		accumbens of the rat. Neurosci.
		- antagonist analgesic butorphanol on dopamine metabolism in the nucleus<br>accumbens of the rat. Neurosci. Lett. 77: 226–230, 1987.<br>95. JURIO, A. V.: Lesion of selected brain areas as a tool for the demonstration<br>of some trace
		-
		- of some trace biogenic amines neural pathways. Gen. Pharmacol. 18: 1-<br>5, 1987.<br>96. KAAKKOLA, S., MANNISTO, P. T., AND NISSINEN, E.: Striatal membrane-<br>bound and soluble catechol-o-methyl-transferase after selective lesions the rat. J. Neural. Trans. 69: 221–228, 1987.<br>the rat. J. Neural. Trans. 69: 221–228, 1987.<br>AN, J. P., MOUGET-GONIOT, C., BIZIERE, K., LADINSKY, H., AND GAR-<br>ATTINI, S.: Minaprine, a new atypical stimulant of dopaminergic 97. KAN, J. P., MOUGET-GONIOT, C., BIZIERR, K., LADINSKY, H., AND GAR ATTINI, S.: Minaprine, a new atypical stimulant of dopaminergic neuro transmesions. II. Evidence for dual pre- and post-synaptic mechanisms of action. I
		-

spet

spet

 $\overline{\mathbb{O}}$ 

- 
- 3-MT MEASUREMENTS AND DA RELI<br>chemical demonstration of catechol-o-methyltransferase in mammalian<br>brain. Brain Res. 167: 241-250, 1979.<br>99. KARASAWA, T., FURUKAWA, K., OCHI, V., AND SHIMIZU, M.: Monoamine<br>metabolites as i MRASAWA, T., FURUKAWA, K., OCHI, V., AND SHIMIZU, M.: Monoamine metabolites as indicators of the effect of centrally acting drugs on mono-amine release in rat brain. Arch. Int. Pharmacodyn. 231: 261-273, 1978. ATO, T., DON 100. KATO, T., DONG, B., ISHII, K., AND KINEMUCHI, H.: Brain dialysis: in vivo metabolism of dopamine and serotonin by monoamine oxidase A but not B in the striatum of unrestrained rats. J. Neurochem. 46: 1277-1282, 1986.<br>
- 
- 
- metabolism of dopamine and serotonin by monoamine oxidase A but not<br>
B in the striatum of unrestrained rats. J. Neurochem. 46: 1277-1282,<br>
1986.<br>
101. KEHR, W.: 3-Methoxytyramine as an indicator of impulse-induced dopamine hydroxylase activity. J. Pharm. Pharmacol. 24: 744-747, 1972.<br>103. KEHR, W., CARLSSON, A., LINDQVIST, M., MAGNUSSON, T., AND ATACK,<br>C.: Evidence for a receptor-mediated feedback control of striatal tyrosine<br>129.<br>104. KELLY
- EHR, W., CARLSSON, A., LINDQVIST, M., MAGNUSSON, T., AND ATACK, C.: Evidence for a receptor-mediated feedback control of striatal tyrosine hydroxylase activity. J. Pharm. Pharmacol. 24: 744-747, 1972.<br>BLLY, R. S., AND WEIG C.: Evidence for a receptor-mediated feedback control of striatal tyrosine<br>hydroxylase activity. J. Pharm. Pharmacol. 24: 744–747, 1972.<br>104. KELLY, R. S., AND WRIGHTMAN, R. M.: Detection of dopamine overflow<br>and diffusion
- nos. RELY, R. S., AND WRIGHTMAN, R. M.: Detection of dopamine overlowing<br>and diffusion with voltammetry in slices of rat striatum. Brain Res. 423:<br>79-87, 1987.<br>105. KILTS, C. D., VRBANAC, J. J., RICKERT, D. E., AND RECH, R fragmentographic determination of 3,4-dihydroxyphenylethylamine and<br>4-hydroxy-3-methoxyphenethylamine in the caudate nucleus. J. Neuro-<br>chem. 28: 465-467, 1977.<br>105a. KIM, H. S., IYENGAR, S., AND WOOD, P. L.: Opiate action
- 
- KIM, H. S., IYENGAR, S., AND WOOD, P. L.: Opiate actions on mesocortidopamine metabolism in the rat. Life Sci. 39: 2033–2036, 1986.<br>KIM, H. S., IYENGAR, S., AND WOOD, P. L.: Reversal of the actions<br>morphine on mesocortical dopamine metabolism in the rat. Life Sci. 39: 2033-2036, 1986.<br>
105b. KIM, H. S., IYENGAR, S., AND WOOD, P. L.: Reversal of the actions of<br>
morphine on mesocortical dopamine metabolism in the rat by the kappa<br>
agonist MR-2
- 
- Syncy Correlation in guinea-pig spinal cord. However, the matrices of department of drugs on the in vivo release of dopamine and its metabolites. Jpn. J.<br>Pharmacol. 40: 57-67, 1986.<br>107. KONDO, M., FUJIWARA, H., AND TANAKA or drugs on the in vivo release of dopamine and its metabolites. Jpn. J.<br>
Pharmacol. 40: 57-67, 1986.<br>
107. KoNDO, M., FUJIWARA, H., AND TANAKA, C.: Dopamine release and pre-<br>
synaptic dopaminergic regulation in guinea-pig
- 
- **BRAIN SEA. 194: 536-539, 1980.**<br> **BRAIN SEA. 1980.** 2007. ALTERT M.J., AND LIEBERMANN, A. N.: The effect of specific brain lesions on the high affinity binding of GABA in the substantia nigra.<br>
Brain Res. 194: 536-539, 19
- dopamine metabolism: he high affinity binding of GABA in the substantia nigra.<br>Brain Res. 194: 536-539, 1980.<br>110. KUSCHINSKY, K., AND HORNYKIEWICZ, O.: Effects of morphine on striatal<br>dopamine metabolism: possible mechani
- 
- CNSCHINSKY, K., AND HORNYKIEWICZ, O.: Elfects of morphine on striatal dopenine metabolism: possible mechanism of its opposite effect on locomine modern accumbens and mice. Eur. J. Pharmacol. 26: 41-50, 1974.<br>
111. LANE, R. as a possible mechanism of action. Blectrochemistry in vivo: application to CNS pharmacology. Ann. NY Acad. Sci. 473: 47-63, 1986.<br>NR, R. F., AND BLAHA, C. D.: Chronic haloperidol decreases dopaminelease in striatum and nu
- CNS pharmacology. Ann. NY Acad. Sci. 473: 47-63, 1986.<br>
112. LANE, R. F., AND BLAHA, C. D.: Chronic haloperidol decreases dopamine<br>
release in striatum and nucleus accumbens in vivo: depolarization block<br>
as a possible mec
- analysis of cholecystokinin-induced inhibition of dopamine release in the nucleus caudatus. Brain Res. 397: 200-204, 1986.<br>
EHMANN, J., BRILEY, M., AND LANGER, S. Z.: Characterization of dopamine autoreceptor and tritium l analysis of choiecystokinin-induced inhibition of dopamine release in the<br>nucleus caudatus. Brain Res. 397: 200–204, 1986.<br>114. LEHMANN, J., BRILEY, M., AND LANGER, S. Z.: Characterization of dopa-<br>mine autoreceptor and tr
- mine autoreceptor and tritium labeled spiperone binding sites in vitro<br>with classical and novel dopamine receptor agonists. Eur. J. Pharmacol.<br>88: 11–26, 1983.<br>**EHMANN, J., AND LANGER, S. Z.: The pharmacological distinctio** 116. LEHMANN, J., AND LANGER, S. Z.: The pharmacological distinction between central pre- and postsynaptic dopamine receptors: implications for the pathology and therapy of schizophrenia. *In* Advances in Dopamine Research
- pathology and therapy of schizophrenia. *In* Advances in Dopam<br>search, ed. by M. Kohaska et al., Pergamon, Oxford, 1982.<br>116. LiLPgUBT, S., AND CARLSSON, A.: Alteration of central cateche<br>macol. 30: 728-730, 1978.<br>117. LIN
- LJEQUIST, S., AND CARLSSON, A.: Alteration of central catecholamine metabolism following acute administration of ethanol. J. Pharm. Pharmacol. 30: 728-730, 1978.<br> **RDVALL, O., AND BJORKLUND, A.: Dopamine-** and norepine phr IFFREE ASSEMBLY OF AND DESCRIPTION THE REAL DRIVER CHARGED MANUSCRIPTION (NURSE AND PRESS, NEW YORK, 1983.<br>
118. LINDVALL, O., BJORKLUND, A., AND FALCK, B.: Fluorescence microscopy<br>
118. LINDVALL, O., BJORKLUND, A., AND FA
- 
- **endogenous catecholamines into the perfusate of discrete microscopy**<br>of biogenic amines in Methods in Neurobiology, ed. by R. Lahue, vol. 2,<br>pp. 365-431, Plenum Press, New York, 1981.<br>119. LLOYD, K. G., AND BARTHOLINI, G.
- endogenous catecholamines into the perfusate of discrete brain areas of<br>the cat in vivo. Experientia (Basel) 31: 560-562, 1975.<br>120. LOOPUJUT, L. D., AND VAN DER KOOY, D.: Simultaneous ultrastructural<br>localization of chole encogenous catecnolamines into the pertusate of discrete brain areas of<br>the cat in vivo. Experientia (Basel) 31: 560-562, 1975.<br>120. LOOPUJUIT, L. D., AND VAN DER KOOY, D.: Simultaneous ultrastructural<br>localization of chol
- Fractivity in nerve fibers of the rat nucleus accumbens. Neurosci. Lett.<br>
88: 329–334, 1985.<br>
121. MAGGI, A., AND ENNA, S. J.: Regional alterations in rat brain neurotransmitter Release in Vivo, John<br>
22. MARSDEN, C. A.: M 121. MAGGI, A., AND ENNA, S. J.: Regional alterations in rat brain neurotransmitter systems following chronic lithium treatment. J. Neurochem. 34:<br>888-892, 1980.<br>122. MARSDEN, C. A.: Measurement of Neurotransmitter Release
- 
- 

3-MT MEASUREMENTS AND DA RELEASE IN VIVO FROM NEURONS 185<br>
f catechol-o-methyl transferase and monoamine<br>
-250. 1979. Catechol-o-methyl transferase and monoamine<br>
-250. 1979. Catechol-o-methyl transferase and monoamine<br>
ox

- **CEASE IN VIVO FROM NEURONS** 185<br>and raphe lesions on the catechol-o-methyl transferase and monoamine<br>oxidase activities in the rat striatum. Eur. J. Pharmacol. 19: 35-42, 1972.<br>124. MARSHALL, J. F.: Somatosensory inattent **tracerebral 6-OHDA injections:** spontaneous recovery and pharmacological control. Brain Sea. 177: 311-324, 1979.<br>
124. MARSHALL, J. F.: Somatoensory inattention after dopamine-depleting in<br>
tracerebral 6-OHDA injections: spontaneous recovery and pharmacolog<br>
cal control. Brain Res. 177: 311
- 
- next disorders of aging. Brain Res. 379: 112-117, 1986.<br>
125. MARSHALL, J. F., AND ALTAR, C. A.: Striatal dopamine uptake and move-<br>
126. MARSHALL, J. F., AND ALTAR, C. A.: Striatal dopamine uptake and move-<br>
126. MCKENZI, ARSHALL, J. F., AND ALTAR, C. A.: Striatal dopamine uptake and movement disorders of aging. Brain Res. 379: 112–117, 1986.<br>CKENZI, G. M., AND SZERB, J. C.: The effect of dihydroxyphenylalanine,<br>pheniprazine, and d-amphetam ment disorders of aging. Brain Res. 379: 112-117, 1986.<br>126. McKENZI, G. M., AND SZERB, J. C.: The effect of dihydroxyphenylalanine,<br>pheniprazine, and d-amphetamine on the in vivo release of dopamine<br>from the caudate nucle
- 
- 128. McQuADE, P. S., AND WOOD, P. L.: The effects of administration of meta-tyramine and para-tyramine on dopamine and its metabolites in the rat striatum. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 8: 705-709, 1984.
- 129. MICHAEL, A. C., IKEDA, M., AND JUSTICE, J. B.: Dynamics of recovery of releasable dopamine following electrical stimulation of the medial fore-<br>brain bundle. Neurosci. Lett. 76: 81-86, 1987. 128. McQuade, P. S., AND WOOD, P. L.: The effects of administration of meta-<br>tyramine and para-tyramine on dopamine and its metabolites in the rat<br>striatum. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 8: 705-709, 1984.<br>12
- 130a. Moraldie. Neurosci. Lett. 76: 81-86, 1987.<br>
130. MICHAEL, A. C., JUSTICE, J. B., AND NEILL, D. B.: In vivo voltammetric<br>
determination of the kinetics of dopamine metabolism in the rat. Neurosci.<br>
Lett. 56: 365-369,
- determination of the kinetics of dopamine metabolism in the rat. Neurosci.<br>
Lett. 56: 365-369, 1985.<br>
130a. MOORE, K. E., DEMAREST, K. T., AND LOOKINGLAND, K. J.: Stress,<br>
prolactin, and hypothalamic dopaminergic neurons. determination of the kinetics of dopamine metabolism in the rat. Neurosc<br>Lett. 56: 365-369, 1985.<br>130a. MOORE, K. E., DEMAREST, K. T., AND LOOKINGLAND, K. J.: Stree<br>prolactin, and hypothalamic dopaminergic neurons. Neuroph
- 130a. MOORE, K. E., DEMAREST, K. T., AND LOOKINGLAND, K. J.: Stress,<br>prolactin, and hypothalamic dopaminergic neurons. Neuropharmacology<br>26: 801-807, 1987.<br>131. MORTIMER, J. A., AND WEBSTER, D. D.: Comparison of extrapyram
- 
- motor function in normal aging and Parkinson's disease. In Advances in<br>Neurogerontology: The Aging Nervous System, ed. by J. A. Nortimer, F.<br>J., Pirozzolo, and G. S. Maletta, pp. 217-241, Karger, New York, 1982.<br>132. Mos,
- voltammetric investigations into the action of HA-966 on central dop<br>minergic neurons. Brain Res. 207: 465-470, 1981.<br>133. MYERS, S., AND PUGSLEY, T. A.: Decrease in rat striatal dopamine synthes<br>and metabolism in vivo by nists. Brain Res. 375: 193-197, 1986.<br>
134. NAIR, N. P. V., LaL, S., AND BLOOM, D. M.: Cholecystokinin and schizo-<br>
phrenia. Perspectives on etiology of psychiatric disorders: brain neuro-<br>
transmission and neuro-peptides.
- nists. Brain Res. 375: 193-197, 1986.<br>AIR, N. P. V., LAL, S., AND BLOOM, D. M.: Cholecystokinin and schizo-phrenia. Perspectives on etiology of psychiatric disorders: brain neuro-<br>transmission and neuropeptides. Prog. Brai
- 136. OzAWA, H., AND MIYAUCHI, T.: Potentiating effect of lithium chloride on methamphetamine-induced stereotypy in mice. Eur. J. Pharmacol. 41:<br>2136. PALKOVITS, M., AND BROWNSTEIN, M. J.: Microdissection of brain areas by
- motor activity in rats and mice. Eur. J. Pharmacol. 26: 41-50, 1974.<br>
110. KUSCHINSKY, K., AND HORNYKIEWICZ, O.: Effects of morphine on striatal<br>
110. KUSCHINSKY, K., AND HORNYKIEWICZ, O.: Effects of morphine on striatal<br> methanology in mice. Eur. J. Pharmacol. 41:<br>
213-216, 1977.<br>
213-216, PALKOVITS, M., AND BROWNSTEIN, M. J.: Microdissection of brain areas<br>
by the punch technique. In Brain Microdissection Techniques, ed. by A.<br>
C. Cuello, 197. PATRICK, R. L., AND BARCHAS, J. D.: Dopamine synthesis in rat striatal synaptosomes. II. Dibutyryl cyclic adenosine 3',5'-monophosphoric acid and 6-methylenetetrahydropterine-induced synthesis increases without an inc
	- in curease in endogenous dopamine release. J. Pharmacol. Exp. Ther.<br>197: 97-104, 1976.<br>138. PELTON, E. W., KIMELBERG, H. K., SHIPHERD, S. V., AND BOURKE, R. S.:<br>Dopamine and norepinephrine uptake and metabolism by astrogli
	-
	- 138. PELTON, E. W., KIMELBERG, H. K., SHIPHERD, S. V., AND BOURKE, R. S.:<br>Dopamine and norepine-phrine uptake and metabolism by astroglial cells<br>in culture. Life Sci. 26: 1655–1663, 1981.<br>139. PERSSON, S. A.: Effect of mor Philadelphia, 1976. 141. Philadelphia, 1976. 14
	-
	- release by cholecystokinin: relevance to schizophrenia. Trends Pharmacol. Philadelphia, 1976.<br>
	Philadelphia, 1976.<br>
	Philadelphia, 1986.<br>
	Philadelphia, 1986.<br>
	141. PHILLIPS, A. G., LANR, R. F., AND BLAHA, C. D.: Inhibition notical Trans. A. G., LANE, R. F., AND BLAHA, C. D.: Inhibition of dopamine release by cholecystokinin: relevance to schizophrenia. Trends Pharmacol. Sci. 7: 126-128, 1986. PLANTJE, J. P., DUCARTJE, F. A., VERHEIJDEN, F. H LEBLAD, E., AND CARLSSON, A.: In vivo effects of the calcium antagonist<br>nimodipine on dopamine metabolism in mouse brain. J. Neural Trans.<br>66: 171-187, 1986.<br>LANTIE, J. F., DIJCKS, F. A., VERHEIJDEN, F. H., AND STOOF, J.<br>C
	- **VANTIE, J. F., DIJCKS, F. A., VERHEIJDEN, F. H., AND STOOF, J.** C.: Stimulation of D2 dopamine receptors in rat mesocortical areas inhibits the release of [<sup>3</sup>H]dopamine. Eur. J. Pharmacol. 114: 401-402, 1985.<br>LANTIE, J.
	- 144. PLANTJE, J. F., STEINBUSCH, H. W. M., SCHIPPER, J., DIJCKS, F. A., VERHEIJDEN, P., AND STOOP, J. C.: D-2 dopamine receptors regulate the release of [<sup>3</sup>H]dopamine in rat cortical regions showing dopamine immu-C.:Stimulation of D2 dopamine receptors in rat mesocortical areas inhibits<br>the release of [\*H]dopamine. Eur. J. Pharmacol. 114: 401-402, 1985.<br>144. PLANTJE, J. F., STEINBUSCH, H. W. M., SCHIPPER, J., DUCKS, F. A.,<br>VERHELID
	- metabolites, W. Neuroscience 20: 157-168, 1987.<br>
	145. PONZIO, F., ACHILLI, G., PEREGO, C., AND ALGERI, S.: Differential effects<br>
	of certain dopamine gic drugs on the striatal concentration of dopamine<br>
	metabolites, with sp of certain dopaminergic drugs on the striatal concentration of dopamine<br>metabolites, with special reference to 3-methoxytyramine. Neurosci. Lett.<br>27: 61-67, 1981.<br>146. PORTIG, P. J., AND VOGT, M.: Release into the ventricl
	-
	- strains of mices: behavioral and biochemical correlations. J. Physiol. (Lond<br>
	147. RACAGNI, C., BRUNO, F., IULIANO, E., AND PAOLETTI, R.: Differential<br>
	148. RACKHAM, A., Wood, P. L., AND Hudgins. J. Pharmacol.<br>
	148. RACKHA
	- arginivity to morphine-induced analgesia and motor activity in two inbred<br>strains of mice: behavioral and biochemical correlations. J. Pharmacol.<br>Exp. Ther. 2009: 111-116, 1979.<br>148. RACKHAM, A., WooD, P. L., AND HUDGIN, R
	-

PHARM<br>REV

- release or encogenous copamine and its metaoolites from rat striatum as<br>drugs. Pharm. Weekbl. Sci. Ed. 6: 153-158, 1983.<br>Amphetamines A., AND MUNKVARD, I.: Biochemical, anatomical, and psycholog-<br>ical investigations of ste drugs. Pharm. Weekbl. Sci. Ed. 5: 153-158, 1983.<br>
150. RANDRUP, A., AND MUNKVARD, I.: Biochemical, anatomical, and psychological investigations of stereotyped behavior induced by amphetamines. In Amphetamines and Related C
- 
- Amphetamnes and Keiated Compounds, ed. by E. Costa and S. Garattini,<br>
p. 695-713, Rawns Press, New York, 1970.<br>
151. RANJE, C., AND UNGERSTEDT, U.: High correlations between number of<br>
dopamine cells, dopamine levels, and 83-93, 1977.<br>
162. RAO, T. S., KIM, H. S., LEHMANN, J., MARTIN, L. L., AND WOOD. P. L.:<br>
Selective activation of meaocortical dopaminergic pathways by phencyclic<br>
dire (PCP) receptor agonistic: tentative evidence for PCP r
- 
- 
- 154. RINNE, U. K., SONNIEN, V., AND HYYPPA, M.: Effect of 1-dopa on brain 170<br>monoamines and their metabolites in Parkinson's disease. Life Sci. 10:<br>549–557, 1971.<br>155. RYPT, A. J. RANCIS, A., AND ROTH, J. A.: Distinct cel monoamnes and their metabolites in Farkinson's disease. Lue Sci. 10:<br>165. Rivert, A. J., FRANCIS, A., AND ROTH, J. A.: Distinct cellular localization<br>of membrane-bound and soluble forms of catechol-o-methyltranaferase in<br>b
- **behavior produced and soluble forms of actechol-o-methyltransferase in**<br>
of membrane-bound and soluble forms of catechol-o-methyltransferase in<br>
behavior, T. E., AND BECKER, J. B.: Enduring changes in brain and<br>
behavior 156. ROBINSON, T. E., AND BECKER, J. B.: Enduring changes in brain and<br>behavior produced by chronic amphetamine administration: a review and<br>evaluation of animal models of amphetamine psychosis. Brain Res. 11:<br>157-198, 198
- evaluation of animal models of amphetamine psychosis. Brain 157-198, 1986.<br>156a. RoBINSON, T. E., AND WHISHAW, I. Q.: Striatal dopamine release<br>with microdialysis following unilateral nigrostriatal damage. So<br>noci. Abst. 1 YOBINSON, T. E., AND WHISHAW, I. Q.: Striatal dopamine release asset with microdialysis following unilateral nigrostriatal damage. Soc. Nosci. Abst. 13: A67.5, 1987.<br>
rosci. Abst. 13: A67.5, 1987.<br>
ylacetic acid in the mou
- ronal metabolism of dopamine? Br. J. Pharmacol. Abst. 13: A67.5, 1987.<br>
157. Roffler-Tarlov, S., Sharman, D. F., and Tergerdine, P.: 3,4-Dihydroxyphen-<br>
158. Rottic acid in the mouse striatum: a reflection of intra-and ext
- flow of the release and synthesis of P. S.4-Dihydroxyphen-<br>placetic acid in the mouse striatum: a reflection of intra- and extraneu-<br>ronal metabolism of dopamine? Br. J. Pharmacol. 42: 343-351, 1971.<br>Drug, R. H., WallTERS, ylacetic acid in the mouse striatum: a reflection of intra- and extraneuronal metabolism of dopamine? Br. J. Pharmacol. 42: 343-351, 1971.<br>
1707. H. H., WALTERS, J. R., AND AGHAJANIAN, G. K.: Effect of impulse<br>
flow on the
- 168. KOTH, K. H., WALTERS, J. K., AND AGHAJANIAN, G. K.: Effect of impulse<br>flow on the release and synthesis of DA in the rat striatum. In Frontiers<br>in Catecholamine Research, ed. by S. H. Snyder and E. Usdin, pp. 567-<br>574 **674, Pergamon Press, New York, 1973.**<br>1974, Pergamon Press, New York, 1973.<br>A., AND FUXE, K.: Effects of cholecysotokinin peptides and neurotensin<br>on dopamine release and metabolism in the rostral and caudal part of the<br>n 160. A., AND FUXE, K.: Effects of cholecysotokinin peptides and neurotensin<br>on dopamine release and metabolism in the rostral and caudal part of the<br>nucleus accumbens using intracerebral dialysis. Neurochem. Int. 10: 509-<br> A., AND FUXE, K.: Effects of cholecysotokinin peptides and neurotensin<br>on dopamine release and metabolism in the rostral and caudal part of the<br>nucleus accumbens using intracerebral dialysis. Neurochem. Int. 10: 509-<br>520,
- nucleus accumbens using intracerebral dialysis. Neurochem. Int. 10: 509-520, 1987.<br>160. SALLER, C. F., AND SALAMA, A. I.: 3-Methoxytyramine accumulation: effects of typical neuroleptics and various atypical compounds. Naun
- ILLER, C. F., AND SALAMA, A. I.: 3-Methoxytyramine accumulation: effects of typical neuroleptics and various atypical compounds. Naunyn-Schmie-deberg's Arch. Pharmacol. 334: 125-132, 1986.<br>KATTON, B., ZIVKOVIC, B., DEDEK, receptor stimulation. III. Effect of program of SL 76002) on NE, DA, and IR 76002) on NE, DA, and Transport, R., and DARTHOLINI, G.: German arminolativity acid (GABA) Transport, R., And BARTHOLINI, G.: Gammac-aminolativity 161. SCATTON, B., ZIVKOVIC, B., DEDEK, J., LLOYD, K. G., CONSTANTINIDIS, J.,<br>TISSOT, R., AND BARTHOLINI, G.: Gamma-aminobutyric acid (GABA)<br>receptor stimulation. III. Effect of progabide (SL 76002) on NE, DA, and<br>5-HT turn
- lateral nigrostriatal damage. Pharmacol. Biochem. Bapt. 1981. 2007.<br>
B88, 1982.<br>
HALLERT, T., UPCHURCH, M., LOBAUGH, N., FARRAR, R., SPIRDUSO, W., GULLIAM, P., VAUGHN, D., AND WILCOX, R.: Tactile extinction: distin-<br>
guish GULLIAM, P., VAUGHN, D., AND WILCOX, R.: Tactile extinction: distin-<br>guishing between sensorimotor and motor asymmetries in rats with uni-<br>lateral nigrostriatal damage. Pharmacol. Biochem. Behav. 16: 455-462,<br>183. SCHOEPP,
- 
- notatynaptic glial cell metabolism by both the type A and B forms of<br>monoamine oxidase. J. Neurochem. 40: 1340-1348, 1983.<br>164. SCHOEPP, D. D., AND AEZARO, A. J.: Further studies on the nature of<br>postsynaptic dopemine upta
- 
- dependency and investigation of a possible role for carrier-mediated<br>uptake into serotonin neurons. J. Neurochem. 44: 1747-1752, 1985.<br>165. SHEEL-KRUGER, J.: Studies on the accumulation of o-methylated dopamine<br>and noradre 166. SHEEL-KRUGER, J.: Studies on the accumulation of o-methylated dopamine<br>and noradrenaline in the rat brain following various neuroleptics, thy-<br>moleptics, and aceperone. Arch. Int. Pharmacodyn. 195: 372–378, 1972.<br>166. moleptics, and aceperone. Arch. Int. Pharmacodyn. 195: 372-378, 1972.<br>166. SKAPER, S. D., ADELSON, G. L., AND SEEGMILLER, J. E.: Metabolism of biogenic amines in neuroblastoma and glioma cells in culture. J. Neurochem. 27:
- 
- chem. 27: 1065-1072, 1976.<br>
19: Chem. 27: 1065-1072, 1976.<br>
19: Expressed synthesis of striatal dopamine by N,N-dimethyl-<br>
tryptamine. Life Sci. 21: 1597-1602, 1977.<br>
168. SPARKS, D. L., SLEVIN, J. T., AND HANSAKER, J. C.:
- 
- 170. STAMFORD, J. A., KRUK, Z. L., AND MILLAR, J.: Measurement of stimulated
- J.: Increased dopamine efflux from striatal slices during development and<br>after nigrostriatal bundle damage. Neuroscience 7: 1648-1654, 1967.<br>170. STAMFORD, J. A., KRUK, Z. L., AND MILLAR, J.: Measurement of stimulated<br>dop dopamine release by in vivo voltammetry: the influence of stimulus duration on drug responses. Neurosci. Lett. 69: 70–73, 1986.<br>KAMPORD, J. A., KRUK, Z. L., AND MILLAR, J.: Accommodation of rate in introduction and the med
- WOOD AND ALTAR<br>
striatum as 172. STANLEY, M., AND WILK, S.: Striatal DOPAC elevation predicts antipsy-<br>
dministered chotic efficacy of metoclopramide. Life Sci. 24: 1907-1912, 1979. **TAR**<br>FANLEY, M., AND WILK, S.: Striatal DOPAC elevation predicts an<br>chotic efficacy of metoclopramide. Life Sci. 24: 1907–1912, 1979.<br>FARKE, K., REIMANNM, W., ZUMSTEIN, A., AND HERTTING, G.: Eff
	- 172. STANLEY, M., AND WILK, S.: Striatal DOPAC elevation predicts antipsychotic efficacy of metoclopramide. Life Sci. 24: 1907–1912, 1979.<br>173. STARKE, K., REIMANNM, W., ZUMSTEIN, A., AND HERTTING, G.: Effect of dopamine r **rabbit caudate in vitro. Naunyn-Schmiddel Life Sci. 24: 1907–1912, 1979.**<br> **173. STARKE, K., REIMANNM, W., ZUMSTEIN, A., AND HERTTING, G.: Effect of**<br>
	dopamine receptor agonists and antagonists on release of dopamine in t
	- dopamine receptor agonists and antagonists on release of dopamine in the<br>rabbit caudate nucleus in vitro. Naunyn-Schmiedeberg's Arch. Pharmacol.<br>305: 27-36, 1978.<br>174. STARKE, K., SPAETH, L., LANG, J. D., AND ADELUNG, C.: in vitro comparison of presynaptic and postsynaptic dopamine receptors<br>in the rabbit caudate nucleus. Naunyn-Schmiedeberg's Arch. Pharmacol.<br>323: 298-306, 1983.<br>1983. 298-306, 1983.<br>synaptosom.al localization of monoamine 174. STARKE, K., SPAETH, L., LANG, J. D., AND ADELUNG, C.: Further functional<br>in vitro comparison of presynaptic and postsynaptic dopamine receptors<br>in the rabbit caudate nucleus. Naunyn-Schmiedeberg's Arch. Pharmacol.<br>323
	-
	- TENSTROM, A., HARDY, J., AND ORELAND, L.: Intra- and extra-dopamine-<br>symaptocomal localization of monoamine oxidase in striatal homogenates<br>from four species. Biochem. Pharmacol. 36: 2931-2935, 1987.<br>coor, J. C., DE BOER, 178. STOOP, J. C., DE BOER, T., SMINIA, P., AND MULDER, A. H.: Stimulation of D2 dopamine receptors in rat neostriatum inhibits the release of acetyl choline and dopamine but does not affect the release of GABA, glutamate
	- choline and dopamine but does not affect the release of GABA, glutamate<br>or serotonin. Eur. J. Pharmacol. 84: 211-214, 1982.<br>176a. STOOF, J. C., DEN BRELIEN, E. J. S., AND MULDER, A. H.: GABA<br>modulates the release of dopami and route of the route of dopenine and acetylcholine from rat caudate modulates the release of dopenine and acetylcholine from rat caudate nucleus slices. Eur. J. Pharmacol. 27: 35-42, 1979. 177. STROMBOM, U.: Catecholamin
	-
	- regions: a combined fluorescent regions: A compared fluorescent retrograde tracer and interest and route of tyrosine hydroxylation in mouse brain. Naunyn-Schiedeberg's Arch. Pharmacol. 292: 167-173, 1976.<br>
	178. SwaNSON, L study in the rat. Brain Sea. Bull 9: 321-353, 1982.<br>
	179. SWANSON, L. W.: The projections of the ventral tegmental area and adjacent<br>
	regions: a combined fluorescent retrograde tracer and immunofluorescence<br>
	study in the r
	- autoreceptors modulate dopamine release from the projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res. Bull. 9: 321-353
	-
	- 179. TALMACIU, R. K., HOFFMAN, I. S., AND CUBEDDUX, L. X.: Dopamine<br>autoreceptors modulate dopamine release from the prefrontal cortex. J.<br>Neurochem. 47: 805-817, 1986.<br>180. TAM, S.-Y., AND ROTH, R. H.: Selective increase Biochem. Pharmacol. 34: 1595-1598, 1985.<br>
	181. TAMMINGA, C. A., DEFRAITES, E. G., GOTTS, M. D., AND CHASE, T. N.:<br>
	Apomorphine and N-n-propylnorapomorphine in the treatment of schir-<br>
	ophrenia. In Apomorphine and Other Dop Apomorphine and N-n-propylnorapomorphine in the treatment of schizophrenia *In* Apomorphine and Other Dopaminometics, ed. by G. U. Corsis and F. L. Geesa, pp. 49-56, Raven Press, New York, 1981.<br>182. TAMMINGA, C. A., GOTTS
	-
	- propylinoraporphine. Arch. Gen. Propaminometics, ed. by G. U. Corsis<br>and F. L. Gessa, pp. 49-56, Raven Press, New York, 1981.<br>182. TAMMINGA, C. A., GOTTS, M. D., GUNVANT, K. T., ALPHREE FOR SONG<br>FOSTER, N. L.: Dopamine ago
	- catecholamine containing neurones in the rat brain. J. Neurochem. 17:<br>269-278, 1970.<br>184. VAMENBURG, C. F. M., NOACH, E. L., AND WIJLING, A.: Involvement<br>of the nerve impulse flow in the release of extragranular dopamine.
	- electrochemical detection, and liquid scintillation counting. J. Neurosci.<br>Methods 11: 29-38, 1964. J. Pharmacol. 57: 191-199, 1979.<br>
	185. VAN VALKENBURG, C., VAN DER KROGT, J., MOLEMAN, P., VAN BERKUM,<br>
	H., TJADEN, U., AND DE JONG, J.: A procedure to measure the specific<br>
	activities of dopamine and its metabolites in ra
	- **186. VOIGT, M. M., AND WANG, R. Y.: In vivo release of dopamine in the nucleus accumbens of the rat: modulation by cholecystokinin. Brain Res. 296:<br>189–193, 1984.<br>187. VoIGT, M. M., WANG, R. Y., AND WESTFALL, T. C.: The e**
	-
	- **from cat brain following** electrical stimulation of the effects of cholecystokinin on the in vivo release of newly synthesized [<sup>4</sup>H]dopamine from the nucleus accumbens of the rat. J. Neurosci. 5: 2744–2749, 1985.<br>DN VOIG 188. VON VOIGTLANDER, P. F., AND MOORE, K. E.: The release of <sup>2</sup>H-dopamine<br>from cat brain following electrical stimulation of the substantia nigra and<br>caudate nucleus. Neuropharmacology 10: 733-741, 1971.<br>189. VULTO, A. G
	- caudate nucleus. Neuropharmacology 10: 733-741, 1971.<br>189. VULTO, A. G., SHARP, T., AND UNGERSTEDT, U.: Rapid postmortal increase<br>in extracellular concentration of dopamine in the rat brain as assessed by NO VOIGTLANDER, P. F., AND MOORE, K. E.: The release of "H-dopamine from cat brain following electrical stimulation of the substantia nigra and caudate nucleus. Neuropharmacology 10: 733–741, 1971.<br>ULTO, A. G., SHARP, T.,
	- from cat brain following electrical stimulation of the substantia nigra and<br>from cat brain following electrical stimulation of the substantia nigra and<br>caudate nucleus. Neuropharmacology 10: 733-741, 1971.<br>189. VULTO, A. G 190. VULTO, A. G., WESTERNBERG, H. G. M., MEUER, L. B. A., AND VERSTEEG,<br>D. H. G.: The dopamine metabolite 3-methoxytyramine is not a suitable<br>indicator of dopamine release in the rat brain. J. Neurochem. 47: 1387-<br>1393, 1
	- release in the rathrain. J. Neurochem. 47: 1387-1393, 1986.<br>
	191. WALDMEIER, P. C., LAUBER, J., BLUM, W., AND RICHTER, W. J.: 3-<br>
	Methoxytyramine: its suitability as an indicator of synaptic dopenine<br>
	relevance of preferen
	- **EXUST THE MESOLICE CONSTRUMERS AND MESTER, W. J.:** Methoxytyramine: its suitability as an indicator of synaptic dopaminelesse. Naunyn-Schiedeberg's Arch. Pharmacol. 315: 219-225, 1981. ALDMEER, P. C., AND MATRER, L.: On t Methoxytyramine: its suitability as an indicator of synaptic dopamine<br>release. Naunyn-Schiedeberg's Arch. Pharmacol. 315: 219–225, 1981.<br>192. WALDMEIER, P. C., AND MAITRE, L.: On the relevance of preferential<br>increases of release. Naunyn-Schiedeberg's Arch. Pharmacol. 315: 219–225, 1981.<br>
	192. WALDMEIER, P. C., AND MAITRE, L.: On the relevance of preferential<br>
	increases of mesolimbic versus striatal dopamine turnover for the predic-<br>
	tion o
	- tion of antipsychotic activity of psychotropic drugs. J. Neurochem. 27: 589-597, 1976.<br>
	193. WALDMETER, P. C., AND MATTRE, L.: Neurochemical investigations of the interaction of N,N-dimethyltryptamine with the dopaminergic
- after nigrostriatal bundle damage. Neuroscience 7: 1648-1654, 1987.<br>
2. State of the postmortem interval. J. Forenaic Sci. 193. WALDMETER, P. C., AND MATTRE, L.: Neurochemical investigations of the postmanner as a gauge of NEURONS: S.C., AND MATTRE, L.: Neurochemical investigations of the interaction of N,N-dimethyltryptamine with the dopaminergic system in rat brain. Psychopharmacology 52: 137-144, 1977.<br>ALTTRES, J. R., ROTH, R. H., AND AGH The UNIX CONSTRAINS TO THE THE SUPPORT THE SUPPORT THE SUPPORT THE SUPPORT THE SUPPORT THAN A SUPPORT THE SUPPORT THAN A SUPPORT THAN A SUPPORT THAN THE SUPPORT THAN THE SUPPORT THAN A SUPPORT THAN THE SUPPORT THAN A SUPPO nourons: similar biochemical and histochemical effects of gamma-hydrox-<br>neurons: similar biochemical and histochemical effects of gamma-hydrox-<br>butyrate and acute lesions of the nigrostriatal pathway. J. Pharmacol.<br>Exp. Th
	-
	- Exp. Ther. 186: 630–639, 1973.<br>195. WANG, R. Y., WHITE, F. J., AND VOIGT, M. M.: Cholecystokinin, dopamine,<br>and schizophrenia. Trends Pharmacol. Sci. 5: 436–438, 1984.<br>196. WELLER, M. E., ROSE, S., JENNER, P., AND MASDEN,

ARMA

- 197. WESTERINK, B. H. C.: Effects of drugs on the formation of 3-methos tyramine, a dopamine metabolite, in the substantia nigra, striatum, 3-MT MEASUREMENTS AND DA I<br>tyramine, a dopamine metabolite, in the substantia nigra, striatum, nu-<br>cleus accumbens, and tuberculum olfactorium of the rat. J. Pharm. Phar-**Cleus accumbens, and tuberculum olfactorium of 3-methody-tyramine, a dopamine metabolite, in the substantia nigra, striatum, nucleus accumbens, and tuberculum olfactorium of the rat. J. Pharm. Pharmeol. 31: 94-99, 1979.<br>** tyramine, a dopamine metabolite, in the substantia nigra, striatum, nucleus accumbens, and tuberculum olfactorium of the rat. J. Pharm. Pharmacol. 31: 94-99, 1979.<br>
198. WESTERINK, B. H. C.: Sequence and significance of do
- 
- 
- macol. 31: 94-99, 1979.<br>
198. WESTERINK, B. H. C.: Further studies on the sequence of dopamine metabolism in the rat brain. Eur. J. Pharmacol. 56: 313-322, 1979.<br>
199. WESTERINK, B. H. C.: Sequence and significance of dopa
- 199. WESTERINK, B. H. C.: Sequence and significance of dopamine metabolism<br>in the rat brain. Neurochem. Int. 7: 221-227, 1985.<br>200. WESTERINK, B. H. C., DAMSMA, G., ROLLEMA, H., DE VRIES, J. B., AND<br>HORN, A. S.: Scope and methoxytyramine in the rat striatum by HPLC with electrochemical detection: implications for the eequence in the cerebral metabolism of dopamine. J. Neurochem. 38: 342-347, 1982.<br>ESTERINK, B. H. C., AND SPAAN, S. J.: On th
- release. J. Neurochem. 38: 342-347, 1982.<br>202. WESTERINK, B. H. C., AND SPAAN, S. J.: On the significance of endogenous<br>3-methoxytyramine for the effects of centrally acting drugs on dopamine<br>3-methoxytyramine for the effe
- dopamine. J. Neurochem. 38: 342-347, 1982.<br>
202. WESTERINK, B. H. C., AND SPAAN, S. J.: On the significance of endogenous<br>
3-methoxytyramine for the effects of centrally acting drugs on dopamine<br>
release in the net brain.
- 204. **WoLF,** M. E., **AND ROTH,** R. H.: Dopamine neurons projecting **to the medial** prefrontal cortex possess release-modulating autoreceptors. **Neurophar-**
- macology 26: 1053-1059, 1987.<br>
204. Wol.F, M. E., AND ROTH, R. H.: Dopamine neurons projecting to the medial<br>
prefrontal cortex possess release-modulating autoreceptors. Neurophar-<br>
2020. Wood, P. L.: Actions of GABAergic macology 26: 1053-1059, 1987.<br>
206. Woon, P. L.: Actions of GABAergic agents on dopamine metabolism in the<br>
nigrostriatal pathway of the rat. J. Pharmacol. Exp. Ther. 222: 674–679,<br>
1982.<br>
206. Woon, P. L.: A selected ion
- 
- 1982.<br>
206. Woon, P. L.: A selected ion monitoring assay for dopamine and its metab-<br>
olites using negative chemical ionization. Biomed. Mass Spec. 9: 302-306,<br>
224.<br>
1982.<br>
207. Woon, P. L.: Opioid regulation of CNS dopam
- 207. Woon, P. L.: Opioid regulation of CNS dopaminergic pathways: a review ropharmacology 21: 1305-1310, 1982.<br>
of methodology, receptor types, regional variations, and species differ-<br>
ences. Peptides 4: 595-601, 1983.<br>
2 or methodology, receptor types, regional variations, and species dirferences. Peptides 4: 595-601, 1983.<br>
208. Wood, P. L.: The significance of multiple CNS opioid receptor types: a<br>
review of critical considerations relat
- noon, P. L.: The significance of multiple CNS opioid receptor types: a review of critical considerations relating to technical details and anatomy in the study of central opioid actions. Peptides 9: 49-55, 1988. Coros, P. 209. WOOD, P. L., ALTAR, C. A., AND KIM, H. S.: Presynaptic inhibitionigrostriatal dopamine release in the mouse: lack of cross-tolerance tween apomorphine, GBL, and CGS 10746B. Life Sci. 42: 1503-1<br>1988.<br>210. WOOD, P. L., nigrostriatal dopamine release in the mouse: lack of cross-tolerance between apomorphine, GBL, and CGS 10746B. Life Sci. 42: 1503-1506, 1988.<br>1988. Life Sci. 42: 1503-1506, 1986.<br>1988. Life Sci. 42: 1503-1506, 1990. P. L.,
- 
- 211. WooD, P. L, **ETIENNE,** P., LAL, S., **AND NeiR,** N. P. V.: GABAergic regulation of nigrostriatal neurons: coupling of benzodiazepine and GABA 117-124, 1986.<br>
receptors. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 6: 471-474, 229. ZETTERSTROM, T., AND UNGERSTRDT, U.: Effects of apomorphine Frog. Neuro-Psychopharmacol. Biol. Psychiat. 8: 471-474, 1982.<br>The Members. Psychopharmacol. Biol. Psychiat. 6: 471-474, P., 2000, P. L., ETIENNE, P., LAL, S., AND NAIR, N. P. V.: Benzodiazepines<br>212. Wood, P. L., ETIENNE,
- 
- 213. WOOD, P. L., KIM, H. S., AND ALTAR, C. A.: In vivo assessment of dopamine and norepinephrine release in rat neocortex: gas chromatography-mass and GABAergic regulation of nigrostriatal neurons: lack of tolerance and GABAergic regulation of nigrostriatal neurons: lack of tolerance Prog. Neuro-Psychopharmacol. Biol. Psychiat. 8: 779-783, 1984. 000, P. L., KIM, H. S and GABAergic regulation of nigrostriatal neurons: lack of toleran<br>Prog. Neuro-Psychopharmacol. Biol. Psychiat. 8: 779–783, 1984.<br>COD, P. L., KIM, H. S., AND ALTAR, C. A.: In vivo assessment of dopam<br>and norepinephrine rel
- **214. WooD,** P. L., **KIM,** H. S., **BOYAR,** W. C., **AND HU'rcHlsoN,** A.: Inhibition E IN VIVO FROM NEURONS 187<br>
oon, P. L., Kim, H. S., Boyar, W. C., and Hurchison, A.: Inhibition<br>
of rat nigrostriatal dopamine release by adenosine receptor agonists: Al<br>
receptor mediation. Neuropharmacology (in press), 1 receptor mediation. Neuropharmacology (in press), 1988.<br>214. Woon, P. L., Kim, H. S., Boyar, W. C., AND HUTCHISON, A.: Inhibition<br>of rat nigrostriatal dopamine release by adenosine receptor agonists: A1<br>receptor mediation. COD, P. L., KIM, H. S., BOYAR, W. C., AND HUTCHISON, A.: Inhibition<br>of rat nigrostriatal dopamine release by adenosine receptor agonists: A1<br>receptor mediation. Neuropharmacology (in press), 1988.<br>Coop, P. L., KIM, H. S.,
- of rat nigrostriatal dopamine release by adenosine receptor agonists: A1<br>receptor mediation. Neuropharmacology (in press), 1988.<br>215. Woon, P. L., KIM, H. S., AND MARIEN, M. R.: Intracerebral dialysis: direct<br>evidence for release. Life Sci. 41: 1–5, 1987.
- striates. Life Sci. 41: 1-5, 1987.<br>
216. Woon, P. L., KIM, H. S., STOCKLIN, K., AND RAO, T. S.: Dynamics of the<br>
striatal 3-MT pool in rat and mouse striatum: species differences as<br>
assessed by steady-state measurements a 216. Wood, P. L., KIM, H. S., STOCKLIN, K., AND RAO, T. S.: Dynamics of the
- tetrahydrocarbazolamine neuroleptica. Prog. Neuro-Psychopharmacol.
- Biol. Psychiat. 8: 773-777, 1984.<br>Joon, P. L., McQuane, P. S., ETIENNE, P., LAL, S., AND NAIR, N. P. V.:<br>Differential actions of classical and atypical neuroleptics on mouse nigro-218. WOOD, P. L., MCQUADE, P. S., ETIENNE, P., LAL, S., AND NAIR, N. P. V.:<br>Differential actions of classical and atypical neuroleptics on mouse nigro-<br>striatal neurons. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 7: 765-218. WOOD, P. L., MCQUADE, P. S., ETIENNE, P., LAL, S., AND NAIR, N. P. V.:<br>Differential actions of classical and atypical neuroleptics on mouse nigro-<br>striatal neurons. Prog. Neuro-Psychopharmacol. Biol. Psychiat. 7: 765-
- 219. WOOD, P. L., NAIR, N. P. V., AND BOZARTH, M.: Striatal 3-methoxytyramine as an index of dopamine release: effects of electrical stimulation.<br>Neurosci. Lett. 32: 291-294, 1982.<br>220. WoOD, P. L., NAIR, N. P. V., LAI, S.
- 
- 
- Neurosci. Lett. 32: 291-294, 1962.<br>
220. Woon, P. L., NAIR, N. P. V., LAL, S., AND ETIENNE, P.: Buspirone, a<br>
potential atypical neuroleptic. Life Sci. 33: 269-273, 1963.<br>
221. Woon, P. L., AND PERLOQUIN, A.: Increases in
- mesocortical but not mgrostriatal dopamine release in the rat. Life Sci.<br>
223. WooD, P. L., AND RAO, T. S.: Differential actions on dopamine synthesis<br>
and release in the rat striatum after cessation of impulse flow with G comparison. The rat and mouse in the rat attriatum after cessation of impulse flow with GB or TTX (submitted), 1988.<br>
or TTX (submitted), 1988.<br>
or TTX (submitted), 1988.<br>
the rat and mouse: the role of nigral and striatal
- ropharmacology 21: 1305-1310, 1982. 224. Wood, P. L., AND RICHARD, J. W.: Morphine and nigrostriatal function in the rat and mouse: the role of migral and striatal opiate receptors. Neuromenology 21: 1305-1310, 1982. Wood,
- the rat and mouse: the role of nigral and striatal opiate receptors. Neu ropharmacology 21: 1305-1310, 1982.<br>Coop, P. L., SOTLAND, M., RICHARD, J. W., AND RACKHAM, A.: Action<br>of mu, kappa, sigma, delta, and agonist/antagon
- **226. Woon, P. L., SOTLAND, M., RICHARD, J. W., AND RACKHAM, A.: Actions**<br>of mu, kappa, sigma, delta, and agonist/antagonist opiates on striatal<br>dopaminergic function. J. Pharmacol. Exp. Ther. 215: 697-703, 1980.<br>226. Yong
- on the turnover and release of dopamine in rat striatum. J. Pharmacol.<br>Exp. Ther. 231: 38-42, 1984.<br>227. ZETTERSTROM, T., SHARP, T., AND UNGERSTEDT, U.: Effect of neuroleptic<br>drugs on striatal dopamine release and metaboli studied by intracerebral dialysis. Eur. J. Pharmacol. 106: 27-37, 1985.
- on the turnover and release of dopamine in rat striatum. J. Pharmacol.<br>Exp. Ther. 231: 38-42, 1984.<br>227. ZETTERSTROM, T., SHARP, T., AND UNGERSTEDT, U.: Effect of neuroleptic drugs on striatal dopamine release and metaboli drugs on striatal dopamine release and metabolism in the awake rat<br>drugs on striatal dopamine release and metabolism in the awake rat<br>studied by intracerebral dialysis. Eur. J. Pharmacol. 106: 27-37, 1985.<br>228. ZETTERSTROM
- 
- I. Pharmacol. 934:<br>
in rat striatum in vivo. Naunyn-Schmiedeberg's Arch. Pharmacol. 934:<br>
229. **ZETTERSTROM**, T., AND UNGERSTRDT, U.: Effects of apomorphine on the<br>
in vivo release of dopamine and its metabolites, studied metrical and the metabolites, studied by brain dialysis.<br>
230. ZIGMOND, M. J., AND STRICKER, E. M.: Adaptive properties of monoaminergic neurons. *In* Handbook of Neurochemistry, ed. by A. Lajtha, vol. 9, pp. 87-107, Plenu GMOND, M. J., AND STRICKER, E. M.: Adaptive properties of monergic neurons. In Handbook of Neurochemistry, ed. by A. Lajthapp. 87-107, Plenum Press, New York, 1985.<br>DMSTERN, A., KARDUCK, W., AND STARKE, K.: Pathways of dom
- 

lspet

**REVIEW** 

ARMACOLOGI