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RECEPTOR ADAPTATIONS TO CENTRALLY ACTING DRUGS

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INTRODUCTION

Although most psychoactive drugs are used chronically in patients, the majority of preclinical psychopharmacological investigations utilize acute treatments. However, over the past few years it has generally been realized that the chronic effects of drugs may differ quite considerably from their acute influences. There is thus obvious clinical importance to gaining a biochemical understanding of the phenomena of tolerance, addiction, and withdrawal. These phenomena may result in part from changes in the number and affinity of CNS neurotransmitter and drug receptors (1). This review focuses on studies of CNS receptors identified by radioligand binding techniques and the influences of chronic drug treatments upon their number and affinity. Behavioral, biochemical, and electrophysiological studies are referred to when they enhance our understanding of the underlying receptor processes but these areas of research are not the main focus of this review. Many of the studies to be discussed were instigated as the result of clinical or behavioral observations. It is, however, important to emphasize that apparent changes in physiological responsivity may result from processes either proximal or distal to the neurotransmitter receptor. It is also attractive to assume that an increase in receptor number will be associated with an increased physiological responsiveness of the system under study. However, it is unclear as yet whether this is a necessary sequela of such change. For example, an increase in the number of presynaptic autoreceptors that regulate the release of neurotransmitter could result in a diminished synaptic response. This is an important consideration as the locations of many

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binding sites for neurotransmitter receptor radioligands have yet to be precisely localized.

A number of factors must be taken into account when considering the results of radioligand receptor binding studies. Since radioligand binding can change as the result of alterations of receptor affinity and/or receptor number, it is important that saturation studies are undertaken to distinguish between these two possibilities. It is also important to demonstrate that the apparent receptor alterations are not due to nonspecific perturbations such as changes in nonspecific binding or to toxic effects of the chronic treatments. Additionally, radioligand binding studies are complicated by the fact that both radiolabeled agonists and antagonists can be utilized to label the "same" physiological receptor. However, it is now apparent that some ^{3}H-agonists may label distinct receptors or different functional states of receptors than are labeled by antagonists (2). Other considerations, common to all chronic drug studies, include the frequency and duration of drug administration (3), and whether the phenomenon of interest is investigated while animals are maintained on the drug (tolerance) or following cessation of drug treatment (withdrawal). In some situations, however, investigations can only be carried out following a withdrawal period because the chronically administered drug directly binds to the receptor under study.

α-ADRENERGIC RECEPTORS

α-Adrenergic receptors have been divided into two categories (4) based on physiological and pharmacological experiments: α_1 receptors mediate the classic postsynaptic effects of norepinephrine (NE) in the peripheral nervous system; α_2 receptors are located presynaptically on NE terminals in the sympathetic nervous system and inhibit the release of NE. Recently, it has become apparent that in some instances α_2 receptors may also be located postsynaptically (5,6). α_1 receptors have been proposed to be selectively labeled with ^{3}H-WB4101, a potent α antagonist (7), although this selectivity has been questioned (8). It is unclear whether α_2 receptors of the presynaptic variety have been selectively labeled or not. ^{3}H-Clonidine (^{3}H-CLON) (7) and ^{3}H-*para*-amino-clonidine (^{3}H-PAC) (9), both α_2 agonists, label two populations of high affinity binding sites which have the pharmacological specificity of α_2 receptors. However, 6-hydroxydopamine lesions that remove noradrenergic presynaptic terminals fail to reduce the binding of ^{3}H-CLON or ^{3}H-PAC (5). Thus, if these ligands label α_2 receptors these receptors must exist majorally on postsynaptic elements separate from noradrenergic nerve terminals. Although this question has yet to be resolved, the effects of chronic drugs on α receptors must consider these populations of sites separately.

Antidepressants

Chronic treatments with tricyclic antidepressants, some of which are potent NE reuptake inhibitors, have been found either to slightly increase (10) or to have no effect on the α_1 receptor binding or ^{3}H-WB4101 (11,12). These treatments, however, were sufficient to down-regulate β receptor binding (see below). This finding is somewhat surprising since all the tricyclic antidepressants used [imipramine, desipramine (DMI), and amitriptyline] have relatively high affinity for α_1 receptor sites (13,14). As the tricyclics appear to be antagonists of α_1 receptors, one might have expected chronic treatment with these drugs to lead to a significant up-regulation of α_1 receptor sites. Surprisingly, it is the α_2 receptors that are up-regulated following antidepressant treatment, even though the tricyclics and other antidepressants have quite low affinity for α_2 sites (15,16). Thus, chronic treatment with DMI leads to an increase in α_2 receptor binding concurrent with a decrease in β receptor binding (16). Although ^{3}H-dihydroergocryptine labels both α_1 and α_2 receptors, its binding is reported to be unaffected by chronic DMI treatment (17).

The effects of antidepressants on α_2 receptors were initially hypothesized to be secondary to their effects on β receptors. In in vitro experiments, incubation of rat cerebral cortical slices with the β agonist, isoproterenol (ISO), causes an increase in α_2 receptor binding in addition to a decrease in β receptor binding (18). These effects are rapid, occurring within 30 min, and are reversible. Additionally, both effects show a parallel time course and can be selectively blocked by β receptor antagonists. Since, in similar in vitro experiments, a down-regulation of β receptors is apparent after incubation with antidepressants drugs (19), it is tempting to speculate that the effects of antidepressants on α_2 receptors in vivo are the result of an initial β receptor activation caused by increased synaptic levels of NE (18). Interestingly, ^{3}H-WB4101 binding sites are not altered during these treatments. Similar results were obtained in vivo where a seven day intraventricular infusion of ISO led to increased ^{3}H-PAC binding and decreased β receptor binding (20). Since the majority of these α_2 receptor binding sites do not appear to be located on NE terminals, it is conceivable that these α_2 receptors are located on the postsynaptic cells in close proximity to the affected β receptors.

Surprisingly, a subchronic treatment with iprindole, an antidepressant which does not affect NE uptake (21–23) and which has only low affinity for α_2 receptor sites (24), led to a 35% increase in the maximum binding capacity (B_{max}) of ^{3}H-PAC (25). This occurred without any changes in β receptor binding indicating that it may be possible for α_2 receptors to be modulated by antidepressants through mechanisms other than β receptor

modulation. Treatment with amphetamine also produced similar increases in α_2 receptor binding. However, concurrent administration of the two drugs decreased β receptors but the drugs' effects on α_2 receptors were not additive (25). These findings question the hypothesis (18) that postsynaptic β and α_2 receptors are functionally linked. Reisine et al (25) suggests that because of their physiological role, the α_2 receptors may rapidly adapt to changes in NE levels before *observable* changes in β receptors occur. Indeed, in the experiments by Maggi et al (18) the increase in α_2 receptors had an earlier onset than the decrease in β receptors. Similarly, short treatments with the α_2 antagonist, yohimbine, or DMI will increase α_2 receptors but only their combination will also decrease β receptors (16).

These receptor binding studies suggest that an α_2 receptor up-regulation may be related to the therapeutic effects of antidepressants. However, a number of other studies suggest that this hypothesis is too simplistic. For example, Crews & Smith (26) found that chronic DMI administration to rats led to an apparent physiological subsensitivity of α_2 receptors in atrial strips. Similar findings have been reported in the brain in electrophysiological experiments. Svensson & Usdin (27), recording from locus coeruleus neurons that can be inhibited by intravenous administration of clonidine or tricyclic antidepressants, found an apparent *subsensitivity* of α_2 receptors which developed after chronic

sions have been drawn by McMillen et al (28) and Huang (29). However, the inhibition and stabilization of locus coeruleus cell firing found in these experiments is unlikely to be the primary mechanism of antidepressant activity since iprindole is quite inactive in decreasing the firing of these cells (30). The α_2 receptors examined electrophysiologically are located on the cell bodies of noradrenergic neurons. However, the α_2 receptors labeled by radioligands and up-regulated by chronic antidepressant treatment are probably postsynaptic and thus may be modulated in a different manner.

Miscellaneous Drugs

Reserpine treatment increases both CNS α_1 and α_2 receptors (31). Interestingly, a recent study has reported the induction of α_2 binding sites in the rat salivary gland following reserpinization (32). Prior to reserpine treatment, there were no detectable α_2 receptors. Rosenblatt et al (11) report that chronic lithium treatment also increases α receptors but this is controversial (33). Behavioral experiments in mice chronically treated with the dopamine antagonist haloperidol (HAL) suggested that supersensitive adrenergic receptors were induced in the CNS (34,35). Although the interpretation of such experiments is complicated, Muller & Seeman (36) report that chronic HAL treatment increased ^{3}H-WB4101 binding in the cerebral cortex.

β-ADRENERGIC RECEPTORS

Agonists

Only one study has utilized chronic treatment with directly acting β agonists (20). Isoproterenol (ISO) was infused continuously by an intraventricular cannula for seven days, reducing the binding of the β-adrenergic antagonist, ^{3}H-dihydroalprenolol (^{3}H-DHA), by 40%. In an in vitro analogue of this experiment, rat cerebral cortical slices were incubated with ISO and a rapid, reversible down-regulation of β receptor binding occurred (18,19). Amphetamines and cocaine act as indirect agonists by increasing the synaptic levels of NE. It might be expected that chronic treatment with these agents would also lead to a down-regulation of β receptors. Indeed, Baudry et al (37) showed that treatment of mice for 6–15 days with amphetamine (~6 mg/kg/day in drinking water) resulted in a 30% decrease in NE-stimulated cAMP production in cortical membranes. Two other low dose studies also reported decreased β receptors after chronic amphetamine (38,39). However, Banerjee et al (38) found that chronic high dose amphetamine led to a 80% *increase* in ^{3}H-DHA binding 12 hr after the last drug injection. Since chronic high dose amphetamine depletes the brain of NE (40), it can be argued that low dose amphetamine treatment down-regulates β receptors because of increased synaptic levels of NE but high dose treatment diminishes the amount of NE available for release, leading to a compensatory up-regulation of β receptor number. However, since both acute and chronic cocaine treatments lead to an increase in ^{3}H-DHA binding (38), other mechanisms must be involved. Chronic treatment with psychomotor stimulants causes reverse tolerance to induced stereotyped behavior and locomotor activity (40–44). Since NE is involved in the control of locomotor activity it is an attractive hypothesis to suggest that these behavioral alterations may be related to β receptor up-regulation.

Antidepressants

NE reuptake inhibition by tricyclic antidepressants might well be expected to down-regulate β receptors. A number of studies have now reported this phenomenon for most of the tricyclics presently in clinical use for both β receptor binding and NE- and ISO-stimulated adenylate cyclase activity [for reviews see (45–48)]. The most detailed studies have been conducted using chronic DMI treatment (49). As few as two injections of DMI can lead to a significant decrease in β receptor binding (50). With daily injections of DMI, effects are maximal (40% decrease in B_{max}) at about one week and are maintained with continued treatment (17). Following cessation of chronic DMI treatment, β receptor binding recovers within one week (51). Cortical β receptors appear most sensitive to these effects (17,24). Studies

of NE-stimulated adenylate cyclase activity parallel the direction, time course, and in general the quantitative changes in β receptor binding (46, 47,51). That the effects of DMI are probably due to the increased synaptic levels of NE has been demonstrated by the lack of β receptor down-regulation in animals in which presynaptic NE terminals have been removed (51,52). Supporting this hypothesis, concurrent administration of the β receptor antagonist propranolol also blocked the receptor decrease caused by DMI (51). Monoamine oxidase inhibitors, which also increase synaptic levels of NE, down-regulate β receptors as well (39,51,53).

In in vitro experiments, a 1 hr incubation of rat cerebral cortex slices with various antidepressants produced a reversible 30% decrease in ^{3}H-DHA binding (19). Incubation with ISO was also able to produce a rapid and reversible loss of β receptors; moreover, the subsensitivity due to DMI and ISO were nonadditive. This reversible loss of β receptor sites may be an initial phase of the β receptor down-regulation by antidepressants seen in vivo. The decrease in β receptor binding caused by chronic DMI treatment in vivo, however, is not reversible in vitro (54). These studies suggest that the decrease in β receptors produced in vitro is similar to the effects identified by Lefkowitz's group in the frog erythrocyte (6), whereas the nonreversible effects following chronic DMI treatment may well represent losses of receptors due to internalization (55).

Utilizing the β antagonist ^{125}I-iodohydroxybenzylpindolol and computer analysis of its displacement by selective β_1 and β_2 antagonists, Minneman et al (56) were able to demonstrate that chronic DMI treatment reduced the number of β_1 receptors but not β_2 receptors in the cortex. In similar studies, they demonstrated that neonatal 6-hydroxydopamine treatment resulted in a selective increase in β_1 receptors in the adult cerebral cortex (56). They suggest that β_1 receptors are neuronally innervated whereas β_2 receptors are not.

Two antidepressants were thought to be exceptions to these general findings. Nisoxetine is a potent NE reuptake inhibitor, but in one study it was found not to down-regulate β receptor binding (24); nor was it found to decrease the NE-stimulated adenylate cyclase (56,57). However, this appears to be the result of its short duration of action as multiple doses of this antidepressant have now been shown to cause β receptor subsensitivity (47). On the other hand iprindole, a potent antidepressant, does not inhibit NE reuptake (21–23) yet causes down-regulation of β receptors to a similar extent as DMI (51). Interestingly, its effect depend on the presence of presynaptic NE terminals since the down-regulation of β receptors is blocked by prior 6-hydroxydopamine treatment (51). It has been suggested that iprindole acts by increasing the release of NE rather than blocking its reuptake (51). Other atypical antidepressants include mianserine, a 5HT

antagonist, and trazodone; both of them down-regulate β receptors but their interaction with presynaptic NE terminals is at present unclear (58).

A down-regulation of the adenylate cyclase apparently is not always paralleled by down-regulation of receptor binding. Chronic foot shock stress will lead to a decreased cyclase response to NE in cerebral cortex slices, but this is not paralleled by any change in β receptor binding (45). This decreased efficacy of noradrenergic transmission is also seen electrophysiologically where chronic DMI treatment reduces the ability of NE to inhibit Purkinje cells (59).

All pharmacological antidepressants share the ability to decrease the number of β receptors. Is this phenomenon relevant to their antidepressant activity? It is well known that although the effects of these agents on NE uptake occur immediately following acute administration, their antidepressant activity takes several weeks to develop. Similarly, although the tricyclic antidepressants initially increase NE synaptic activity following acute administration, their chronic administration leads to decreased noradrenergic transmission (51,57,60,61). The time course of the down-regulation of β receptors may parallel the development of their antidepressant activity in man. Electroconvulsive shock treatment in man is a potent antidepressant therapy. Its neurochemical mechanism of action is unclear. Electroconvulsive shocks have been reported to affect several biochemical parameters of central noradrenergic transmission which increase synaptic levels of NE and thus might be expected to initiate receptor down-regulation. Three studies in reporting down-regulation of β receptor binding following daily electroconvulsive shock, support the hypothesis that down-regulation of β receptors is important in the therapeutic activity of antidepressant agents (62–64). The extent of the down-regulation is about the same as that caused by chronic antidepressants; however, the effect of ECS is rapid and occurs following only three days of twice a day treatment. Norepinephrine-stimulated adenylate cyclase is also reduced and to an even greater extent than the decrease in β receptors (46).

These new findings stand in marked contrast to the original "catecholamine hypothesis of affective disorders" which suggested depression was the result of decreased adrenergic transmission. Major evidence for this hypothesis was based on the fact that tricyclic antidepressants acutely increase noradrenergic transmission by blocking catecholamine reuptake processes and could correct this deficit. Although the down-regulation of NE receptors caused by tricyclic antidepressants is in all probability mediated as a secondary effect of their influences on reuptake, it now appears probable that it is the receptor down-regulation per se, and the subsequent decrease in noradrenergic transmission, that is responsible for the therapeutic effect of these drugs. The search for a unitary hypothesis to explain the effects of

a diverse group of therapies is an attractive pursuit and in this circumstance appears reasonably successful. However, the identification of specific binding sites for some antidepressants that can be down-regulated by chronic DMI treatment suggests that these various compounds may have multiple mechanisms of action (12). The relationship of these binding sites to the mechanism of action of antidepressant drugs is unclear, especially in light of the finding that platelets from nontreated depressed patients exhibit lower levels of ^{3}H-imipramine binding than controls (65). Furthermore, the up-regulation of α_2 receptors also appears relevant to antidepressant action (see above). Studies of human postmortem brains from depressed patients utilizing β receptor, α receptor, and ^{3}H-imipramine binding are obviously going to throw important light on the mechanisms involved in depression and its amelioration.

If indeed down-regulation of β receptors is in part responsible for the therapeutic efficacy of antidepressants, a reasonable hypothesis might be that β receptor up-regulation is in part responsible for the etiology of depression. Reserpine is considered to be a good model of depression in animals and although it depletes catecholamines (another major cornerstone supporting the original catecholamine hypothesis of affective disorders) it also causes an up-regulation of β receptors (33,66,67). Lithium is able to counteract this up-regulation of β receptors (33), and it probably does this without reversing the reserpine-induced catecholamine depletion. However, lithium does not enhance the β receptor down-regulation caused by imipramine (11). It is now well established that lithium is effective in the treatment of mania and may also have some antidepressant activity. A number of studies have investigated the effects of chronic lithium treatment on β adrenergic receptors and report little (11) or no effect (68). In a study investigating the effects of lithium on cortical NE-stimulated adenylate cyclase, Ebstein et al (69) found that three weeks of lithium treatment produced a decrement in NE-induced cAMP accumulation, but after two days of withdrawal cyclase activity was back to control levels. However, in an electrophysiological study, Siggins & Schultz (59) found that whereas acute lithium antagonizes the effect of NE inhibition of Purkinje cells, chronic lithium actually enhances the effects of NE. These effects are thus divergent to the actions of DMI.

If down-regulation of β receptors is in part responsible for the therapeutic effects of antidepressants it would be advantageous if this desensitization could be produced more rapidly. Two studies have reported that combined antidepressant and α_2 antagonist treatment increases the rate and perhaps enhances the degree of β receptor desensitization. Paul & Crews (70) found that combined treatment of DMI and phenoxybenzamine produced a significant 14% decrease in β receptors following a single administration

whereas treatment with DMI alone took six days before a significant decrease was found. Similarly, Reisine et al (16) found that combined treatment of yohimbine and DMI also down-regulated β receptors within four days although treatment with either drug alone did not alter β receptor binding. A possible mechanism for this potentiation is that the α_2 blockers antagonize the presynaptic inhibition of NE release, thus enhancing synaptic NE levels above those produced by DMI treatment alone. Two other drug combinations also produce a rapid down-regulation of β receptors but at present the mechanism of their potentiation is unclear. Iprindole and amitriptyline (16) and iprindole-amphetamine (25) combinations both down-regulate β receptors following three days of treatment. Neither drug individually alters β receptor binding over that time period. Iprindole does modify the metabolism of amphetamine (71), reducing the *p*-hydroxylation of amphetamine and thus increasing its half-life in the brain. However, these studies utilized 20 mg/kg of amphetamine per day, a high dose, which if enhanced further by iprindole might have been expected to lead a receptor up-regulation (see above) rather than a more rapid down-regulation. On the other hand both the iprindole-amphetamine treatment and the iprindole-amitriptyline treatment would be expected to enhance synaptic NE levels above and beyond that produced by each drug separately, as their mechanisms of action are different, thus leading to more rapid desensitization.

Miscellaneous Drugs

Treatment of rats with the α_2 agonist clonidine increases ISO-stimulated cAMP production in the brain stem where clonidine may exert antihypertensive effects (72). However, ^{3}H-DHA binding is unchanged. In another study, treatment of spontaneously hypertensive rats with clonidine by continuous infusion for two weeks resulted in a marked decrease in NE-stimulated adenylate cyclase activity in the cortex (73). Other brain regions were not investigated. Overstreet & Yamamura (74) report that after 21 days of treatment with clonidine, rats become tolerant to the locomotor depression produced by this agent. Tolerance development was correlated with an *increase* in β receptor binding in the cortex. The development of tolerance could be blocked by concomitant administration of yohimbine, an α_2 antagonist, and this also blocked the increase in ^{3}H-DHA binding. The increase in β receptors may be an important determinant of tolerance development to clonidine.

Some behavioral manifestations of ethanol withdrawal are similar to those seen in thyrotoxicosis where there is evidence to suggest a peripheral β receptor supersensitivity. Furthermore, propranolol, a β blocker, can control some of these withdrawal signs. Banerjee et al (75) have shown that chronic ethanol reduces brain adrenergic receptors *before* withdrawal.

Twenty-four hours into withdrawal, the β receptors had returned to control levels but after two and three days the receptors were increased by approximately 70%. These studies suggest that increased β receptor sensitivity may contribute to the hyperexcitable state of withdrawal in chronic alcoholism and may provide a rationale for the use of β antagonists in the management of the ethanol withdrawal syndrome. Similarly, rats withdrawn from chronic morphine treatment show an increase in cortical NE and ISO-stimulated adenylate cyclase and in ^{3}H-DHA binding (76). As morphine is known to decrease noradrenergic transmission, it would appear that this up-regulation may be the result of disuse hypersensitivity. Chronic treatment with propranolol also leads to disuse hypersensitivity as evidenced by an increase in both ^{3}H-DHA binding (77) and the NE-stimulated adenylate cyclase (73). On the other hand, chronic estradiol can down-regulate β receptors (78) through unknown mechanisms.

DOPAMINE RECEPTORS

Antagonists

The response of dopamine (DA) receptors to chronic treatment with DA antagonists has great clinical relevance. In schizophrenics, a semi-irreversible side effect, tardive dyskinesia, develops during chronic neuroleptic therapy (79). It is characterized by involuntary movements of the tongue, mouth, face, and extremities, and develops after months or years of treatment with DA antagonists. The symptoms can be reduced by increasing the dose of neuroleptic drug, only to have them reappear at a later date. Discontinuation of the neuroleptic drug serves only to exacerbate the symptoms, as does treatment with DA agonists. This spectrum of effects led Klawans to suggest that tardive dyskinesia might result from a DA antagonist-induced, DA receptor supersensitivity (80). Support for this hypothesis came from behavioral experiments utilizing rodents treated with neuroleptics for a few days to several weeks. Although the animals did not demonstrate spontaneous aberrant motor behavior, they did develop an enhanced behavioral sensitivity to apomorphine, a directly acting DA agonist (reviewed in 79,81).

A DA receptor supersensitivity after such neuroleptic treatments has been demonstrated directly with radioligand binding experiments (82). A number of researchers have since replicated the findings of this study (reviewed in 83). Indeed, treatments with DA antagonists, such as HAL or fluphenazine, for periods of between one and three weeks result in a 25% increase in the number of DA receptor sites labeled with ^{3}H-butyrophenones (82) or ^{3}H-pimozide (84) following a short 5–7 day withdrawal period. Withdrawing the drug for more than 1–2 weeks results in a complete

reversal of the receptor increase (82). Several experiments (85–89) have been conducted utilizing longer treatments, more closely approximating the clinical situation. These longer treatment periods led to greater increases in the B_{max} of DA receptor binding. During 1-yr treatment periods, without withdrawal, rats eventually produce spontaneous movements (86). There is a decreased affinity (probably resulting from residual drug in the membrane preparation) and an increased B_{max} for the binding of ^{3}H spiperone (^{3}H-SPIP), a DA antagonist (87). Upon withdrawal of drug, enhanced behavioral responses disappear within a one month period. The increase in B_{max} for ^{3}H-SPIP binding, however, was maintained for up to three months following drug removal although the dissociation constant (K_D) reverted to control levels by two weeks.

Baldessarini & Tarsy (79), however, have questioned the relevance of this animal model to tardive dyskinesia as the effects develop so rapidly and are reversible. The exact temporal relationship of receptor with behavioral changes further questions their direct association. For example, rats show enhanced responsiveness to DA agonists following a *single* injection of a DA antagonist (90,91) and this is not mirrored by changes in DA receptor properties determined in radioligand binding experiments (92). If not responsible for tardive dyskinesia, these receptor changes may be responsible for the tolerance to the cataleptic and extrapyramidal side effects initially apparent on administration of neuroleptics in animals (93) or in man. Of interest is the finding that treatment of nursing rats with neuroleptics will increase ^{3}H-SPIP binding in the neonates (94,95) whereas neuroleptic administration to the mothers during pregancy results in a decreased number of ^{3}H-SPIP binding sites in the offspring (95).

Following chronic neuroleptic treatment, the binding of ^{3}H-DA is increased to approximately the same extent as radiolabeled antagonist binding (96,97). However, in studies utilizing other agonist ^{3}H-ligands, much smaller increases in binding are seen (98,99; I. Creese, unpublished results; M. Goldstein, personal communication). It has been suggested that ^{3}H-DA agonists, under some conditions, preferentially label receptors associated with adenylate cyclase (100–102), although, a number of studies have reported no change in DA-stimulated adenylate activity following chronic neuroleptic treatment (103,104), but this is controversial (87,105,106). Under other in vitro conditions ^{3}H-DA-agonists may label autoreceptors (107), although this is also controversial (98,102). There is some question as to whether autoreceptors on DA terminals in the striatum can become supersensitive since the effects of DA agonists on DA synthesis and release from synaptosomes is unchanged following chronic neuroleptic treatment (108). However, under some conditions it appears that chronic neuroleptics can produce terminal autoreceptor supersensitivity, as the effect of DA agonists

on presynaptic tyrosine hydroxylase activity, in the absence of impulse flow, is enhanced following chronic fluphenazine (109). Indeed, presynaptic autoreceptors, at least on the DA cell bodies in the substantia nigra, become supersensitive following chronic HAL treatment as measured electrophysiologically (110). Current studies in this area are reported in a recent symposium proceeding (111).

Although studies in the pituitary indicate that chronic neuroleptic blockade will enhance the effectiveness of DA agonists in inhibiting prolactin release (112,113), chronic HAL treatment in rats is reported to result in a decrease in pituitary DA receptor binding (114). This is surprising since pituitary DA receptors appear in part to be regulated in a similar manner to CNS DA receptors. For instance, removal of DA from the pituitary, by lesioning the basal hypothalamus, results in enhanced mammotroph sensitivity to DA agonists (115), and both CNS and pituitary DA receptors are regulated in a smaller manner by guanine nucleotides (102). However, in patients with tardive dyskinesia, there is no evidence for pituitary DA receptor supersensitivity as they have an apparently normal (116) or reduced (117) prolactin response. These studies need to be extended as there is now good evidence that distinct DA receptor subtypes exist in the CNS and periphery (102).

Of potential clinical interest is the finding that lithium prevents the development of DA receptor supersensitivity following chronic neuroleptic treatment (118, 119). The concurrent treatment of rats with lithium blocks the receptor supersensitivity as measured by ^{3}H-SPIP binding as well as the behavioral supersensitivity (120,121). Chronic lithium alone does not affect DA receptor binding or the DA sensitive adenylate cyclase (118,122). Lithium is also able to antagonize the development of supersensitive autoreceptors on DA cell bodies in the substantia nigra as measured electrophysiologically (110). In contrast to the ability of lithium to antagonize DA antagonist-induced supersensitivity, it actually enhances the behavioral supersensitivity seen following chronic reserpine treatment (123); however, receptor numbers were not examined directly. Conversely, lithium does not alter reserpine-induced increases in α receptors (33).

Other drugs besides directly acting DA antagonists can increase DA receptor number. For example, reserpine, which blocks storage of DA, is as effective as DA antagonists in increasing DA receptor number (82). The GABA agonist THIP, which probably inhibits DA neuron firing by a mechanism similar to γ-butyrolactone (124), also increases DA receptor binding and behavioral sensitivity following a 12 day treatment (J. Hyttel and A. Christensen, personal communication). An intriguing finding recently reported is that DA receptors demonstrate diurnal variations in number with an ultradian rhythm exhibiting peaks at 2:00 A.M. and 2:00 P.M., and an amplitude of about 75% (125). Chronic imipramine modifies

the rhythm such that the two peaks occur 4 hr later with the amplitude and average binding being decreased. The relationship of these receptor changes with the ability of chronic antidepressant treatment to prevent the inhibitory effect of small doses of apomorphine on DA synthesis and motor activity (126) is unclear, but it does suggest that chronic antidepressants can modify both pre- and postsynaptic DA receptor function.

Agonists

Similar to other neurotransmitter receptors, DA receptors can be down-regulated after exposure to agonists. It is impossible to expose CNS DA receptors directly to DA using a peripheral injection; however, DA infused intrastriatally for seven days caused a decrease in ^{3}H-HAL binding (127). Receptors can be exposed to endogenous DA by treatment with amphetamine which releases DA and blocks its reuptake. We have found that amphetamine treatment for five days results in a 20% decrease in the maximum number of ^{3}H-SPIP binding sites in rat striatum with a smaller change in ^{3}H-agonist binding (D. Sibley et al, in preparation). When rats were treated for 20 days with amphetamine, a slightly greater loss of ^{3}H-SPIP binding was found (128). In a similar experiment, a 14 day treatment with amphetamine or the directly acting DA agonist apomorphine did not reduce ^{3}H-HAL binding but did produce a 20–25% decrease in ^{3}H-apomorphine binding to DA receptors (129). Peripherally administered L-Dopa is directly converted to DA within the CNS and a three week treatment with L-Dopa was found to reduce ^{3}H-HAL binding (130) and greatly reduce the DA-sensitive adenylate cyclase. However, List et al (131) did not detect a change in ^{3}H-SPIP binding after a five day treatment with L-Dopa. Many ergots possess DA agonist activity, and the chronic treatment with bromocriptine (130,132) or pergolide (133) reduces striatal ^{3}H-SPIP or ^{3}H-HAL binding sites. The DA-sensitive adenylate cyclase measured in caudate slices was also markedly reduced by bromocriptine treatment (130,132). However, the DA-sensitive adenylate cyclase measured in striatal *homogenates* was not reduced by this treatment (132), suggesting that the subsensitive state depends on a special form of the receptor confined by other membrane components disrupted upon homogenization. In contrast, other studies report that bromocriptine treatment does not alter striatal DA receptor binding (131,133). The decrease in receptors caused by bromocriptine must be regarded with suspicion, as bromocriptine has been suggested to be an irreversible or slowly reversible dopaminergic ligand (134).

A number of functional experiments are in keeping with the binding results. For example, Scatton & Worms (135) report that repeated treat-

ment with apomorphine dipivaloyl ester produces an apparent subsensitivity of DA receptors as measured behaviorally or by changes in DA turnover. Similarly, Schwartz et al (136) review studies demonstrating that the dopaminergically mediated hypothermia in mice exhibits classical tolerance following agonist treatments.

If DA agonist treatment can down-regulate normal DA receptors, it might well be expected that DA-agonists would down-regulate receptors that had been up-regulated by other mechanisms. Both behavioral (93a,137) and binding experiments suggest that this is true. Following the up-regulation of DA receptors as the result of chronic HAL treatment (see above), a five day administration of bromocriptine or L-Dopa was able to reverse the increase in ^{3}H-DA binding caused by chronic HAL treatment and block the increase in DA-stimulated adenylated cyclase activity following chronic trifluperazine treatment. L-Dopa treatment might be useful in modulating up-regulated DA receptors in man found following chronic neuroleptic therapy in schizophrenia (138–140) and may thus be a successful therapy for tardive dyskinesia (96). Similarly, in Parkinson's disease the "on-off" response sometimes with L-Dopa therapy may result from a down-regulation by L-Dopa of the up-regulated receptors caused by the dopaminergic denervation in this disease. The stopping of L-Dopa therapy intermittently may allow these down-regulated receptors to increase in sensitivity, with the patient becoming sensitive to L-Dopa therapy once more (141).

Chronic DA agonist treatment, however, seems to be more complex than the above studies would indicate. Completely contradictory results have been found in both behavioral and receptor binding studies. For example, a one to two week treatment of rats with cocaine, which blocks DA reuptake, increases the behavioral response to cocaine and causes an increase in striatal ^{3}H-SPIP binding (142). Similarly, a five week treatment of rats with cocaine or amphetamine increases striatal ^{3}H-DA binding (143). Chronic L-Dopa treatment was also found to increase the number of ^{3}H-SPIP binding sites (144). Although these experiments reporting an up-regulation of DA receptor binding following chronic agonist treatment are in marked contrast to the studies discussed above, there is behavioral evidence to suggest that long-term administration of DA agonists can lead to progressive augmentation of their behavioral effects. For example, the locomotor activity and stereotypy response of rodents to amphetamine or apomorphine is potentiated during chronic agonist treatment (40–42, 44, 145). Enhanced sensitivity to agonists is also seen electrophysiologically following long-term amphetamine administration (146).

Since chronic amphetamine treatments have been shown to deplete the brain of DA and DA uptake sites (40,147), an attractive hypothesis to reconcile these apparently paradoxical effects would be to suggest that

following chronic agonist treatment there is an effective depletion of DA leading to up-regulation of receptor sites. However, this does not explain why animals would show enhanced responsiveness to drugs that depend on endogenous stores of DA for their effectiveness. Additionally, a single injection of a DA agonist can enhance future responsiveness to agonist administration (91,136). This potentiation following a single apomorphine injection can last for up to two weeks, can be blocked by neuroleptics, and depends on the presence of presynaptic DA terminals. One explanation may be that the effect of agonist administration is to desensitize presynaptic DA autoreceptors, thus increasing the effectiveness of future agonist administration by reducing the presynaptic negative feedback. Although this could be a satisfactory hypothesis to explain the behavioral phenomena, it would not explain the increase in DA receptor binding seen following agonist pretreatment. However, following agonist pretreatment Muller & Seeman (129) reported a decrease in ^{3}H-apomorphine binding, which they feel binds to presynaptic receptors. Conversely, Friedhoff et al (96) found no effect of L-Dopa treatment on ^{3}H-DA binding in rats. These studies may represent an area where binding experiments may not "explain" behavioral phenomena. Also, the divergent results seen in the binding experiments suggest that when these studies are replicated the binding of multiple agonist and antagonist ^{3}H-ligands be undertaken in an attempt to resolve these conflicting results.

Miscellaneous Drugs

Although dopamine receptor binding is reported to be unaltered by chronic ethanol administration, withdrawal of mice from chronic ethanol treatment results in a decreased responsiveness of striatal but not mesolimbic DA sensitive adenylate cyclase (148). This subsensitivity is not apparent while the animals are maintained on ethanol but becomes evident during the withdrawal period. It seems probable that ethanol influences the membrane coupling between DA receptor sites and the catalytic units of adenylate cyclase. In keeping with this apparent down-regulation of DA receptors, other physiological and behavioral experiments demonstrate a dopaminergic subsensitivity during ethanol withdrawal (148–151). Other studies have produced conflicting results with longer treatments (152,153). Interestingly, Lai et al (154) found that three days of treatment with ethanol intubation following a unilateral 6-hydroxydopamine lesion in the substantia nigra was able to reduce the development of behavioral dopaminergic supersensitivity.

The effects of opiates on DA systems in the brain are numerous (155) and may in part be mediated by opiate receptors that exist on DA nerve terminals (156). It would not be surprising if DA receptors were modified in response to chronic opiate treatment. Behavioral data indeed suggest that

a dopaminergic hypersensitivity may emerge following chronic opiate administration (157–159) although this has been questioned in other behavioral and electrophysiological studies (160,161). Few DA receptor binding studies have been conducted. In one study (162), morphine administration by subcutaneous pellet for six days resulted in a small but significant increase in the binding of the DA antagonist ^{3}H-domperidone. These animals exhibited a marked behavioral supersensitivity to apomorphine. In another study (163), ^{3}H-SPIP binding was determined in striatal tissue after rats were made dependent with low or high dose morphine pellet implantation. Low dose dependence resulted in a decrease in binding affinity while the higher dose treatment resulted in a higher affinity but with reduced number of binding sites. The DA-sensitive adenylate cyclase is unchanged or decreased following chronic opiate administration (163,164).

Behavioral and clinical data suggest that estrogen may modulate DA receptors. For example, injection of large doses of estrogen has been reported to increase the duration of stereotypy induced by DA agonists (165). Additionally, stereotypy duration was reduced in guinea pigs after ovariectomy (166), as was the in vitro response of adenylate cyclase to DA in homogenates prepared from the striata of ovariectomized rats (167). Although estrogen has multiple effects on DA metabolism and can increase the penetration of dopaminergic drugs into the CNS (168), estrogen does appear to modulate DA receptor sensitivity (169,170). High dose treatment with estradiol six days before behavioral or biochemical measurements were made increased the stereotypy response to amphetamine or apomorphine and increased the binding of ^{3}H-SPIP (169). This does not seem to be the result of effects of estrogen on presynaptic DA metabolism since estrogen is able to increase the number of DA receptors previously up-regulated by DA denervation (170). The mechanism by which estrogen affects postsynaptic DA receptors is unknown but it is reported that prior removal of the pituitary blocks the effect of estrogen on ^{3}H-SPIP binding (170). The interaction between estrogen, DA receptors, and dopaminergic drugs is obviously complex since *combined* chronic treatments with HAL and estrogen can enhance behavioral responsiveness to apomorphine but treatment with estrogen *following* a chronic HAL treatment will attenuate the drug-induced stereotypy (171).

SEROTONIN RECEPTORS

Antidepressants

Serotonergic systems may be involved in the mechanism of action of antidepressant drugs, some of which are very potent inhibitors of serotonin (5HT) reuptake. However, few studies have been conducted investigating the effects of chronic antidepressant treatment on 5HT receptors. Further-

more, studies that have been performed have produced conflicting results. Two studies report marked 30–65% decreases in the number of ^{3}H-5HT receptor binding sites following a three week antidepressant treatment (24, 172). The former study found the frontal cortex to be more sensitive to the drug effects than the striatum or hippocampus. These effects probably result from increased synaptic 5HT levels since these uptake inhibitors have extremely low affinity for ^{3}H-5HT binding sites (14). Consistent with this hypothesis, 5HT specific A-type monoamine oxidase inhibitors (MAOI) decrease ^{3}H-5HT binding while B-type MAOI do not (173). Surprisingly, chronic treatment with fluoxetine, a potent 5HT uptake inhibitor, was ineffective in reducing ^{3}H-5HT binding in any brain region (24,173). However, when fluoxetine treatment was combined with the more potent NE uptake inhibitor, nisoxetine, a significant decrease in frontal cortex 5HT binding was found (24). However, in other studies, DMI and clorimipramine (17,173) were ineffective in altering ^{3}H-5HT binding.

These studies stand in contrast to electrophysiological and behavioral studies which report an enhanced sensitivity to 5HT following chronic antidepressant treatment. De Montigny & Aghajanian (174) report a selective increase in the inhibitory response of forebrain neurons to 5HT applied by microiontophoresis after chronic antidepressant treatment. Interestingly, iprindole was as effective as the tricyclic antidepressant drugs in inducing sensitization of forebrain postsynaptic 5HT receptors although it is not a 5HT uptake inhibitor. Conversely, fluoxetine, a potent 5HT uptake inhibitor, did not modify serotonergic sensitivity. In a behavioral study (175), four week treatment of mice with imipramine or amitriptyline resulted in an enhanced serotonergic head twitching response. These findings were reminiscent of the effects of chronic amphetamine on DA receptor binding where an enhanced behavioral response is noted concurrently with decreased receptor binding (see above). It is now apparent, however, that there are at least two types of 5HT receptor. One is labeled selectively by ^{3}H-5HT, the other by ^{3}H-spiperone; both are labeled by ^{3}H-LSD (176). It is thus possible that the behavioral and electrophysiological serotonergic responses are mediated by receptors selectively labeled by ^{3}H-SPIP as opposed to ^{3}H-5HT. Only one study has investigated the effects of chronic antidepressants on serotonergic ^{3}H-SPIP binding (12). However, since antidepressants have reasonable affinity for ^{3}H-LSD binding sites (14,177), it is possible that residual drug might have masked any enhanced ^{3}H-SPIP binding sites. It is important that future investigations of 5HT receptors utilize both ^{3}H-5HT and ^{3}H-SPIP as ligands.

Agonists and Antagonists

One of the characteristics of LSD (a mixed 5HT agonist/antagonist) is the rapid tolerance that develops to its repeated administration in animals and

man. However, this does not appear to be mediated by a change in the ability of LSD to inhibit the activity of raphe serotonergic neurons (178), but to a decreased sensitivity of postsynaptic serotonergically sensitive neurons (179). Trulson & Jacobs (180) demonstrated that repeated administration of LSD resulted in a 20–25% decrease in maximal ^{3}H-5HT and ^{3}H-LSD receptor binding in both forebrain and brainstem areas. There was also a 25% increase in the K_D for ^{3}H-5HT binding but no effect on ^{3}H-LSD receptor affinity. In contrast, chronic treatment of rats with the 5HT precursor 5-hydroxytryptophan did not alter the binding of ^{3}H-5HT to cortical membranes (181).

Chronic treatment with D-fenfluramine (182), a long-lasting 5HT releaser, caused a significant decrease in the number of ^{3}H-5HT binding sites in some brain regions, which was associated with a decrease in the anorexic effect of the 5HT agonist, *m*-chlorophenylpiperazine (182). Conversely, the chronic administration of the 5HT antogonist, methergoline, led to a significant increase in ^{3}H-5HT binding and was associated with an increase in the anorexic effect of *m*-chlorophenylpiperazine. However, in a similar study (181), methergoline had no effect on cortical ^{3}H-5HT binding. On the other hand, Klawans et al (183) have demonstrated behavioral supersensitivity to 5HT agonists following chronic receptor blockade with methysergide.

Other Drugs

Chronic treatment with reserpine, which depletes 5-HT stores, or *p*-chlorophenylalanine, a 5-HT synthesis inhibitor, elicited 20–300% increases in ^{3}H-5HT binding in numerous brain regions (184). ^{3}H-LSD binding was also increased to a lesser extent. Acute treatments with these drugs resulted in much smaller effects, suggesting that the receptor binding increases seen after chronic treatment resulted from on increase in receptor numbers rather than a depletion of endogenous 5-HT bound to receptors. In behavioral studies, these treatments also enhance the serotonergic responsiveness of mice (182). In contrast, chronic but not acute lithium resulted in a 40–50% decrease in ^{3}H-5HT binding in hippocampus and striatum although not in the hypothalamus and cortex (68). Since this receptor alteration is noted only after chronic administration it may be related to the therapeutic action of lithium in the prophylaxis of recurrent manic-depressive psychosis.

Although haloperidol is almost inactive at ^{3}H-5HT binding sites (184), chronic HAL leads to a slight increase of specific ^{3}H-5HT binding in the striatum, although it has no effect in other regions (36). Interestingly, a four day treatment with chlorpromazine (a potent DA antagonist but with moderate 5-HT receptor affinity) resulted in enhanced serotonergic responsiveness in mice (185). An abundant literature suggests an interaction of

serotonergic systems with the acute and chronic effects of opiates. Although the myenteric plexus of the guinea pig ileum becomes more sensitive to 5HT following chronic opiate treatment (186), binding studies in both the guinea pig ileum and brain did not uncover changes in either ^{3}H-LSD or ^{3}H-5HT binding (187).

MUSCARINIC ACETYLCHOLINE RECEPTORS

Anticholinesterases

Muscarinic ACh receptors on cultured nerve cells (188,189) have been shown to be down-regulated by acute exposure to agonists. Thus, it is not surprising that CNS muscarinic ACh receptors are also subject to up- and down-regulation. Studies utilizing chronic exposure to directly acting agonists have not been undertaken, but administration of anticholinesterases has enabled the effects of enhanced exposure to endogenously released ACh to be investigated. Tolerance develops to the behavioral effects of these anticholinesterase agents, and behavioral experiments suggest that this may result from subsensitivity to ACh (190). Recent studies have demonstrated that there is a significant decrease in the number of muscarinic cholinergic receptors labeled by the antagonist ^{3}H-quinuclidinyl benzilate (^{3}H-QNB) following chronic treatment with the irreversible anticholinesterase diisopropylflurophosphate (DFP) (191–193). DFP alterations of ^{3}H-QNB binding were blocked by concurrent administration of physostigmine, a reversible cholinesterase inhibitor that protects cholinesterase from irreversible phosphorylation by DFP. Furthermore, chronic atropine administration concurrent with DFP treatment blocked the decrease of striatal ^{3}H-QNB binding. These results indicate that the receptor changes were the result of enhanced synaptic ACh levels. The time course of the attenuation of the pharmacological effects caused by DFP correlated with a time course for decreased ^{3}H-QNB binding in the striatum. Surpisingly, although behavioral tolerance also occurs following the chronic treatment with a reversible carbamate anticholinesterase, physostigmine, ^{3}H-QNB binding is reported to be unaltered (74). Although the affinity of antagonists for cholinergic receptors are unaffected by DFP treatment, the affinity of agonists for ^{3}H-QNB binding are reduced by about twofold (193). More detailed analysis of the displacement curves indicated that agonists displace ^{3}H-QNB binding in a biphasic manner suggestive of both high and low affinity binding sites. About 25% of the ^{3}H-QNB binding is displaced with high affinity by agonists. The ratio of the agonist affinities for the low and high affinity displacement of ^{3}H-QNB (K_L/K_H) has been suggested to correlate with agonist efficacy (194). This ratio was reduced for agonists following chronic DFP treatment, suggesting that agonist efficacy is decreased (193).

Barbiturates and Ethanol

Administration of sodium barbital to rats in their drinking water for 40 weeks increased ^{3}H-QNB binding by 56% (194a). At three days following withdrawal, the number of spontaneous convulsions in the abstinence period was greatest, decreasing to 0 at 12 days of withdrawal. The increase in receptor binding was also lost 12 days after withdrawal. A supersensitivity towards the temperature reducing effect of pilocarpine during abstinence followed a similar time course after barbital treatment. In a less severe chronic paradigm, ^{3}H-QNB binding was significantly reduced by 30% in the cerebellum but not in any other brain region studied. This effect did not appear specific to barbiturates since chronic treatment with diazepam produced a similar effect (195).

A seven day ethanol diet induced seizures and convulsions in mice following ethanol withdrawal, especially during the first 24 hr. ^{3}H-QNB binding was increased at the termination of the ethanol treatment by ~25% in hippocampus and 14% in the cortex although not in the striatum (196). This may relate to the ability of ethanol to reduce ACh release. These increases in ^{3}H-QNB binding were lost 24 hr after ethanol withdrawal. However, the functional relationship between changes in cholinergic receptors and these physiological events is unclear since atropine does not diminish the severity of ethanol withdrawal seizures in mice (197).

Miscellaneous Drugs

Chronic blockade of cholinergic transmission in the rat with atropine results in tolerance to atropine-induced activity. This is accompanied by a small but significant increase in the B_{max} of ^{3}H-QNB binding (198). Similarly, deficiency of the ACh precursor, choline, induces a 30% increase in ^{3}H-QNB binding (H. I. Yamamura, personal communication). It is somewhat surprising that ^{3}H-QNB binding is increased following these treatments since, unlike many other neurotransmitter receptors, denervation of cholinergic receptors in the CNS has not been associated with receptor up-regulation (199).

Following chronic treatment with HAL, the locomotor stimulation produced by the muscarinic antagonist, dexetimide, is enhanced (200). Conversely, the reduction in locomotor activity produced by the cholinergic agonist pilocarpine is reduced. In a similar study chronic HAL decreased the depression of locomotor activity produced by cholinergic agonists while allowing a previously ineffective dose of atropine to produce marked stimulation (201). These studies suggest that chronic HAL may produce a hyposensitivity of central muscarinic receptors. However, Kobayashi et al (202) was unable to demonstrate any alterations in caudate or hippocampal ^{3}H-QNB binding following HAL treatment. Similar negative findings have

been reported by Muller & Seeman (36). These changes may result from alterations in the dopaminergic/cholinergic balance within the striatum which is known to modulate locomotor activity. Chronic reserpine (203) and tricyclic antidepressant (24) treatments are also reported not to influence ^{3}H-QNB binding sites.

Behavioral (158) and electrophysiological (204,205) experiments suggest that a supersensitivity of cholinergic receptors develops following chronic morphine treatment. However, Overstreet reported a decrease in ^{3}H-QNB binding 24 hr after withdrawal from morphine, although there was no change in ^{3}H-QNB binding 30 min after the last morphine injection (74). Moreover, the tolerant rats were supersensitive to the behavioral effects of centrally or peripherally administered pilocarpine, whereas the morphine withdrawn rats were subsensitive to the behavioral effects of pilocarpine. Thus, the changes in receptor binding correlated with the behavioral subsensitivity observed in the withdrawal state but not the behavioral supersensitivity observed in the tolerant state.

GABA RECEPTORS

Few studies have investigated the effects of chronic drug treatments on GABA receptors in the CNS. One study (195) found that treatment with diazepam or phenobarbital resulted in a 65% decrease in striatal ^{3}H-GABA binding although no changes were found in other brain areas. This decrease in GABA receptor binding may be associated with the ability of both drugs to enhance GABAergic synaptic transmission. In contrast, Gale demonstrated that chronic treatment with HAL or chlorpromazine increased the binding of ^{3}H-GABA in the substantia nigra of rats (206). No change was found in the striatum. Kobayashi et al (202) were also unable to demonstrate an alteration of ^{3}H-GABA binding in the striatum after chronic HAL treatment. Since cutting the striato-nigral GABAergic pathways also increases GABA receptors in the substantia nigra it is tempting to suggest that the relative deficit of GABA transmission in the nigra caused by chronic neuroleptic treatment (207) is responsible for this effect. On the other hand, chronic clozapine, an atypical neuroleptic that does not cause catalepsy in animals and is devoid of Parkinson-like extrapyramidal side effects in man, does not increase nigral GABA receptor binding (206). This may be associated with the ability of clozapine to increase rather than decrease the turnover rate of GABA in the substantia nigra compared to classical neuroleptics (207). It is tempting to speculate that these modifications of nigral GABA receptors may be responsible for some of the clinical consequences of long-term neuroleptic administration, although the relationship of these receptor changes to the decreased ability of imidazol-4-

acetic acid, a GABA agonist, to inhibit locomotor activity of mice following chronic HAL treatment is unclear (208).

Chronic lithium treatment for three weeks reduces striatal GABA receptor binding by 68% and hypothalamic GABA receptor binding by 36% with no changes in the cortex, cerebellum, or hippocampus (68). In contrast, acute lithium treatment does not influence GABA receptor binding, and at concentrations up to 0.1 mM lithium has no effect on GABA receptor binding in vitro. That the effect of chronic lithium treatment on GABA receptor binding may be of some importance in the therapeutic action of lithium is suggested by the finding that it is observed only in certain brain regions.

BENZODIAZEPINE RECEPTORS

Surprisingly, few chronic benzodiazepine administration studies have been undertaken since the identification of benzodiazepine receptors in the CNS. Thus, the involvement of receptor alterations in the well-known tolerance development to the sedative effects of benzodiazepines has not been ascertained. Furthermore, five studies conducted to date have produced disparate results. In one series of studies the B_{max} of ^{3}H-diazepam binding in rat cortex was reduced by 15% following 7–10 days of twice daily injections with large doses of flurazepam. The K_D was almost doubled but could be reversed by washing the tissue, suggesting that it resulted from residual flurazepam (209, 210). In another study, diazepam was administered in the food (equivalent to 175 mg/kg for 35 days), and an initial decrease in ^{3}H-flunitrazepam binding was found one and two days after treatment but increased binding was observed between days three and seven of withdrawal (211). In yet another experiment, diazepam (90 mg/kg/day) or lorazepam (60 mg/kg/day) were administered orally for eight weeks and binding was investigated 5 and 11 days after treatment (212). There were no statistically significant alterations in receptor binding. Similarly, treatment with diazepam at a low dose (3 mg/kg/day for 30 days) also produced no changes in benzodiazepine receptor binding (195). Thus, at this point it is impossible to draw conclusions from these conflicting series of experiments. It should be remembered, however, that although tolerance develops to the sedative effects of benzodiazepines, tolerance does not develop to their antianxiety effects. Thus, regional differences in benzodiazepine receptor responses to chronic treatment may suggest their differential involvement in mediating these two pharmacological effects.

Since there is well-established clinical and experimental evidence for potentiation of acute and chronic effects of ethanol by other central nervous system depressants including the benzodiazepines, Karobath et al (213) investigated the effects of long-term ethanol administration on benzodiaze-

pine receptor binding. Receptor binding was investigated without a withdrawal period and no changes in ^{3}H-flunitrazepam binding were detected in any of eight brain regions investigated. The enhancing effect of GABA on benzodiazepine binding was also unaffected by the ethanol treatment. Thus, these results suggest that the nature of the well-recognized clinical interaction between benzodiazepine and ethanol is not mediated through primary binding sites for the benzodiazepines.

OPIATE/ENDORPHIN RECEPTORS

The identification of opiate receptors by radioligand binding techniques (214–216) made it possible to test the hypothesis that tolerance and dependence following chronic opiate administration was the result of changes in receptor number (1). While there is a decreased sensitivity to opiate agonists during chronic morphine administration there is an increased sensitivity to antagonists (217). The identification of the reciprocal effects of sodium on the binding of opiate agonists and antagonists (218) invited the hypothesis that tolerance was due to reciprocal changes in opiate agonist and antagonist receptors. However, numerous experiments have been performed investigating this question and it is apparent that no major change in opiate receptor number occurs during either chronic opiate administration or withdrawal. Initial experiments did find increases in opiate receptors following chronic opiate administration (219–221), but these receptor changes did not correlate with the development of tolerance or physical dependence. Furthermore, acute treatments with either agonists or antagonists produced similar receptor increases. It appears that the enhanced receptor binding resulted from the administered opiates displacing the endogenous ligands from receptors in vivo thus uncovering more sites to be labeled in vitro. Studies by Davis et al (222), utilizing brainstem slices, did demonstrate a change in the affinity of ^{3}H-morphine binding after chronic morphine; however, it is unclear whether residual morphine was removed from the brain slices. The general consensus is that neither the affinity nor receptor density is significantly changed during the development of tolerance whether receptors are labeled with agonists or antagonists (223–225). A number of researchers have felt that receptor changes may indeed occur in vivo but that they are lost during the homogenization process for in vitro binding studies. In vivo labeling of opiate receptors utilizing tail vein injections of ^{3}H-opiates have been utilized to investigate this possibility, but no evidence for a change in the binding properties of opiate receptors in vivo in tolerant rats has been demonstrated (224,226).

In spite of the lack of demonstrable receptor changes in binding experiments, it is clear that the responsiveness of individual neurons to opiates does indeed change during tolerance (reviewed in 227). Furthermore,

Schultz et al (228) have demonstrated that chronic treatment of guinea pigs with the antagonist naloxone increased the sensitivity to opioids in the longitudinal muscle-myenteric plexus preparation of the ileum. This was associated with an increase in the number of opiate receptors measured with the agonist ^{3}H-etorphine in both the periphery and CNS. In neuroblastoma-glioma hybrid cells, morphine is able to inhibit the stimulation of adenylate cyclase by prostaglandin E_1. During chronic exposure to morphine, the cells become tolerant to this inhibition and upon withdrawal of morphine show an enhanced cAMP production suggesting that this receptor-effector system may mediate some of the aspects of opiate tolerance and withdrawal (229). The recent identification of distinct types of opiate receptors by radioligand binding techniques and pharmacological effects (230–232) and which have different CNS localizations and regulatory mechanisms suggest that receptor changes in opiate tolerance should be reinvestigated.

CONCLUDING COMMENTS

It is significant that the molecular mechanisms responsible for the varied receptor changes reported in this review have yet to be elucidated. The heterogeneity of CNS tissue and the inability to quantitate the precise exposure of receptors to drugs in vivo provides obstacles for such detailed investigations. However, in the periphery rapid progress is being made in understanding the processes involved in receptor changes in response to chronic exposure to agonists. For example, receptor internalization appears to be of critical importance in the regulation of peptide and protein receptors (233) and has already been suggested as important in the development of subsensitivity in peripheral β receptors (55). Other studies of peripheral β receptors have demonstrated the importance of the formation of a high affinity agonist binding state of the receptor as a prerequisite for receptor activation and down-regulation by exposure to agonists (234). Indeed, down-regulation of peripheral β receptors may be a two-step phenomenon involving an initial uncoupling of adrenegic receptors from adenylate cyclase followed by an actual decrease in receptor number (6,235). These studies of β adrenergic agonist binding and the involvement of guanine nucleotides in regulating the high affinity agonist binding state of the β receptor have demonstrated the crucial role of receptor-effector coupling mechanisms in determining physiological responsiveness. Influences of guanine nucleotides on CNS receptor binding are reminiscent of these effects (e.g. 102) and suggest that similar processes are involved. Indeed, as progress in this important and exciting area of research develops, it is likely to become apparent that the biochemical mechanisms responsible for receptor regulation in the CNS are not unlike those in the periphery.

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