Ann. Rev. Pharmacol. Toxicol. 1980. 20:111–27

PHARMACOLOGY OF CENTRAL SEROTONIN NEURONS

◆6762

Ray W. Fuller

The Lilly Research Laboratories, Indianapolis, Indiana 46206

INTRODUCTION

Serotonin (5-hydroxytryptamine), formed enzymatically by the 5-hydroxylation of L-tryptophan and the subsequent decarboxylation of 5-hydroxy-L-tryptophan, appears to function as a neurotransmitter or neuromodulator in mammalian brain. Histofluorescence and other techniques have been used to map the neuronal tracts in rat brain that contain serotonin (see 1). Various functional roles of serotonin-forming neurons have been elucidated or suggested based on their anatomic localization or on results obtained by experimental modification of their function. The purpose of this paper is to assess our ability at present to intervene pharmacologically in serotonin neuron function, i.e. to determine with what specificity and with what consequences brain serotoninergic systems can be altered by drugs.

HOW BRAIN SEROTONIN NEURONS FUNCTION

The serotonin neuron is generally thought to operate as illustrated schematically in Figure 1. Drugs may alter this process at several sites. First, they may act directly on the synaptic receptor to mimic (serotonin agonists) or to antagonize (serotonin antagonists) the action of serotonin. Alternatively, drugs may increase or decrease the amount of serotonin that acts on the receptor. Drugs that increase serotonin stores (monoamine oxidase inhibitors or serotonin precursors), release serotonin, or inhibit the neuronal reuptake mechanism all lead to increased stimulation of synaptic

0362-1642/80/0415-0111$01.00

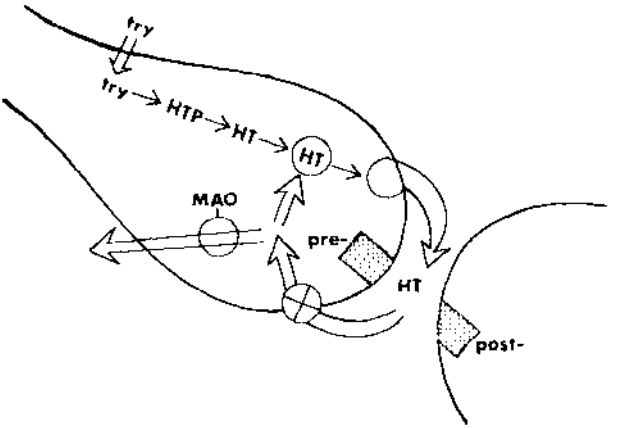

Figure 1 Postulated function of a serotonin neuronal system. Serotonin is synthesized by 5-hydroxylation of L-tryptophan (try) and subsequent decarboxylation of 5-hydroxy-L-tryptophan (HTP). Serotonin (HT) is stored in intraneuronal vesicles from which it is released upon nerve impulse into the synaptic cleft. There it may combine reversibly with receptors that exist not only postsynaptically (action on these receptors completes the process of neurotransmission across this synapse) but also presynaptically. The presynaptic autoreceptors apparently modulate the synthesis and release of serotonin by the serotoninergic neuron. The action of serotonin on synaptic receptors is terminated when it is pumped back into the serotonin neuron, where it may either be reutilized in storage granules or degraded enzymatically by monoamine oxidase, the major metabolite being 5-hydroxyindoleacetic acid (5-HIAA).

receptors by serotonin itself. Drugs that deplete stores of serotonin either by impairing the storage mechanism or by inhibiting the synthesis of serotonin would, by decreasing the availability of serotonin for release by nerve impulse, diminish neurotransmission through this pathway. Drugs that act by most of these mechanisms have been identified and studied.

TYPES OF DRUGS THAT ACT ON SEROTONIN NEURONS

Drugs Leading to Stimulation of Serotonin Receptors

DIRECT AGONISTS Drugs that mimic the action of serotonin receptors classically have been studied with isolated peripheral tissues (e.g. uterus or ileum) that respond to serotonin. The possibility that serotonin receptors in the periphery might differ from those in brain must be considered, though in general drugs that act on peripheral serotonin receptors seem also to act on the brain. Recently, radioligand binding has been introduced as a technique for studying several types of receptors in brain, and the binding of

tritiated serotonin or lysergic acid diethylamide is now used to study serotonin receptors in brain directly. Characteristic functional effects may also be used as indicators of serotonin receptor stimulation, such as head twitch in mice (2), extensor hindlimb reflex in acutely spinalized rats (3), and "serotonin behavioral syndrome" in rats (see 4, 5).

Figure 2 depicts two classes of drugs that appear to stimulate serotonin receptors, these classes being indolic compounds and certain substituted piperazines. The former group includes bufotenin, N,N-dimethyl-5-methoxytryptamine and several chemically related compounds (6–9), and the latter group includes quipazine (10, 11), MK-212 (12), and 1-(*m*-trifluoromethylphenyl)-piperazine (13). MK-212 (14) and quipazine (11, 15–17) also have presynaptic effects on serotonin neurons, and 1-(*m*-trifluoromethylphenyl)-piperazine may act more purely as a postsynaptic agonist (18) than these other substituted piperazines.

INDIRECT-ACTING AGENTS (UPTAKE INHIBITORS, RELEASERS, INHIBITORS OF DEGRADATION, PRECURSORS) Drugs that inhibit the neuronal reuptake mechanism on serotonin neurons have been known for several years. The first drugs found to inhibit serotonin uptake also inhibited the uptake of catecholamines, especially norepinephrine, and so could not be used to manipulate serotonin neurons specifically. In recent years, how-

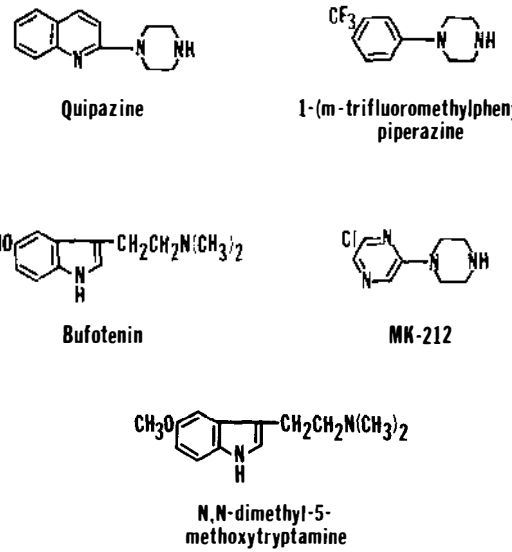

Figure 2 Structures of some direct-acting serotonin agonists.

ever, uptake inhibitors that are selective or specific for the uptake pump on serotonin neurons have been described. Figure 3 lists several of these. Fluoxetine was the first compound reported to have this selectivity (19, 20); although fluoxetine can inhibit the uptake of catecholamines in vitro when added at concentrations much higher than those required to inhibit serotonin uptake, doses that can be used in vivo inhibit only serotonin uptake with no detectable effects on catecholamine uptake. Subsequently, zimelidine (21), pirandamine (22), fluvoxamine (23), paroxetine and related compounds (24), citalopram (25), Org 6582 (26), *p*-bromo-EXP 561 (27), and

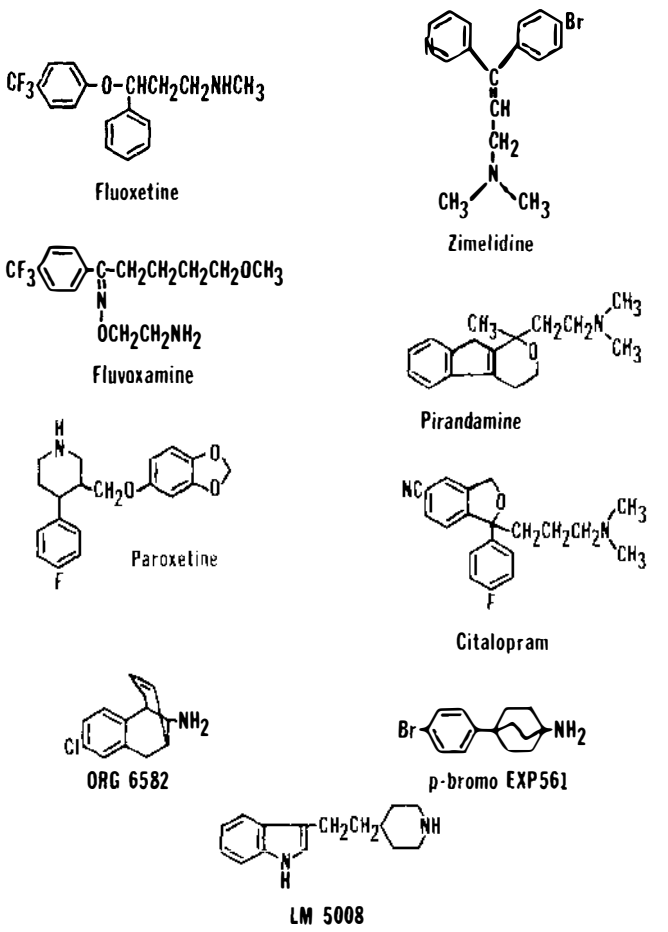

Figure 3 Structures of some selective inhibitors of serotonin uptake.

LM 5008 (28) have been reported to be similarly selective in inhibiting serotonin uptake.

The uptake inhibitors in Figure 3 have little or no ability to release serotonin from intraneuronal granular stores. Other agents that are competitive inhibitors of the serotonin uptake pump on the neuronal membrane also release serotonin from intraneuronal stores. The most widely studied of these agents are fenfluramine (see 4, 13) and *p*-chloroamphetamine and numerous analogues of it (29). Reserpine, tetrabenazine, and some other agents release serotonin but also release other biogenic amines; some of their initial pharmacologic effects may be due to amine release but cannot be attributed specifically to serotonin.

Inhibitors of monoamine oxidase increase neuronal stores of serotonin, which apparently results in increased concentrations of serotonin in the synaptic cleft due to the release of larger quantities per nerve impulse. Numerous monoamine oxidase inhibitors are known, but none affect serotonin neurons selectively (that is, they also increase dopamine, norepinephrine, epinephrine, and other biogenic amines).

L-Tryptophan and 5-hydroxy-L-tryptophan, the two precursors of serotonin, have been used to increase brain serotonin concentration. Precursor loading can enhance central serotonin function, but the use of each of these precursors has certain disadvantages. Only a small fraction of a dose of L-tryptophan is metabolized to serotonin, so the doses of tryptophan that have to be used to increase serotonin are relatively high. Alteration of transport or metabolism of other amino acids, or of processes like protein synthesis in which tryptophan is involved, may occur. Additionally, some of the quantitatively more major metabolites of tryptophan (such as kynurenine) reach high concentrations under conditions of tryptophan loading, and kynurenine or excess tryptophan may inhibit tryptophan conversion to serotonin (30). The use of 5-hydroxy-L-tryptophan is complicated by the fact that it requires only the aromatic L-amino acid decarboxylase for conversion to serotonin. This enzyme is not restricted to serotonin-forming neurons, so administration of 5-hydroxy-L-tryptophan leads to the formation of serotonin cells that do not normally form it. Serotonin formed from administered 5-hydroxy-L-tryptophan can influence catecholamine neuron function, for example, by displacing catecholamines from storage granules (31). This problem of specificity can be avoided by using low doses of 5-hydroxy-L-tryptophan, which increase serotonin principally in serotonin neurons (32), in combination with selective inhibitors of serotonin uptake; an uptake inhibitor like fluoxetine enhances only those actions of 5-hydroxy-L-tryptophan that are mediated by serotonin neurons (the only neurons that have a serotonin uptake pump).

The foregoing discussion indicates that selective uptake inhibitors, releasers, and precursors are the most useful means of selectively enhancing serotoninergic neurotransmission by increasing the synaptic concentrations of the endogenous neurotransmitter.

Drugs That Impair Serotonin Neuron Function

RECEPTOR ANTAGONISTS Drugs that block serotonin action on receptors have been identified by the same means as serotonin agonists, i.e. using peripheral tissues that respond to serotonin, radiolabeled ligand binding, or functional tests. Among compounds that block serotonin receptors are those shown in Figure 4 (some of these have serotonin *agonist* activity in

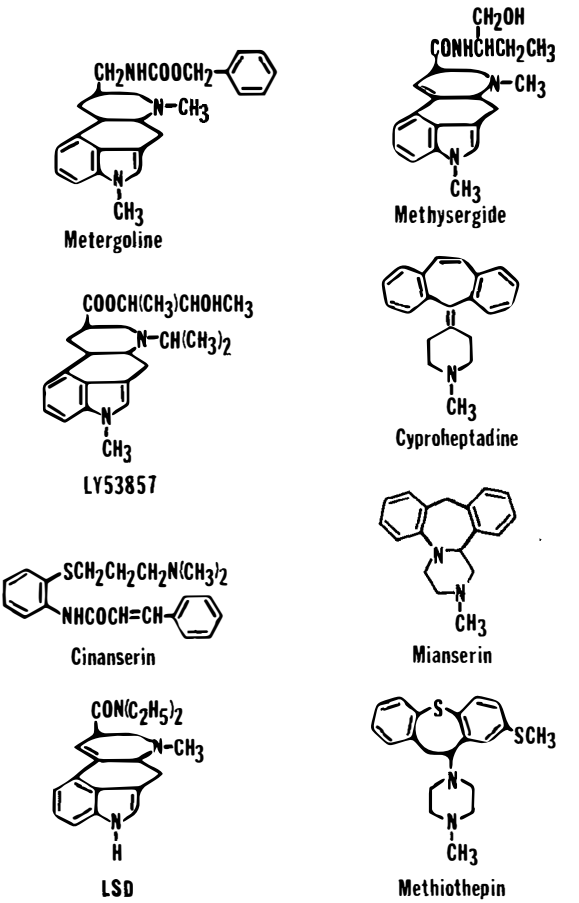

Figure 4 Structures of some serotonin receptor antagonists.

certain experimental situations). Representing the most commonly studied serotonin antagonists are metergoline (33–35), methysergide (36, 37), cyproheptadine (38), cinanserin (39, 40), mianserin (41, 42), lysergic acid diethylamide (LSD) (43), and methiothepin (44). LY53857 is a related compound from our laboratories that is a potent serotonin antagonist in vitro and in vivo. A compound not included in the figure is trazodone, which may have both agonist and antagonist actions on serotonin receptors (45). Some uncertainty about the ability of these agents to block serotonin receptors in brain has persisted, principally because of the lack of univerally accepted criteria of block of brain serotonin receptors. However, most or all of the compounds in Figure 4 do antagonize 5-hydroxy-L-tryptophan–induced head twitch in mice, the extensor hindlimb reflex in rats, and other effects attributed to serotonin receptor stimulation.

Aghajanian and his colleagues (see 6) have studied the ability of antagonists to block the effect of microiontophoresed serotonin in various brain regions. When cinanserin, cyproheptadine, methysergide, metergoline, and methiothepin were tested microiontophoretically on neurons in the raphe and on neurons in areas known to be innervated by serotonin-containing terminals, they were found not to block but instead to mimic the inhibitory effects of serotonin. In some brain regions the antagonists did block the excitatory effect of iontophoretically applied serotonin, but this excitatory effect was not considered to be a synaptic action. Thus electrophysiological findings with serotonin antagonists have not always been straightforward.

Antagonists of dopamine and norepinephrine receptors cause a compensatory increase in the turnover of dopamine and norepinephrine in brain (see 46). A similar increase in serotonin turnover could be expected to result from block of central serotonin receptors and has been looked for after treatment with putative serotonin antagonists. Methiothepin does increase brain serotonin turnover (44, 46–48), but in general the other drugs in Figure 4 do not (49, 50). The inability of these other drugs to increase serotonin turnover remains unexplained, since many experimental data affirm their ability to block central serotonin receptors. Methiothepin is not an ideal drug for use in blocking serotonin receptors because it also appears to block dopamine and norepinephrine receptors (46), and its elevation of serotonin turnover may not be solely a consequence of serotonin receptor blockade (48).

INHIBITORS OF SYNTHESIS AND DEPLETORS Although serotonin synthesis could be inhibited by blocking either of the two enzymes involved, only tryptophan 5-hydroxylase has been a useful target for inhibition because the aromatic L-amino acid decarboxylase is not restricted to serotonin neurons and is present in large excess so that its activity would have to be

inhibited almost completely in order for serotonin synthesis to be decreased substantially. *p*-Chlorophenylalanine is the most widely used inhibitor of serotonin synthesis. This compound is only a weak competitive inhibitor of tryptophan hydroxylase in vitro but causes an irreversible decrease in tryptophan hydroxylase activity in vivo lasting for several days. However, *p*-chlorophenylalanine has to be used at high doses and interferes with amino acid transport processes, with phenylalanine hydroxylation, and probably with functions of neurons other than serotonin neurons to some extent. These other effects may complicate the interpretation of data obtained with this inhibitor of serotonin synthesis, though it remains a useful tool for lowering brain serotonin concentration.

Depletors of serotonin that act by mechanisms other than or in addition to inhibition of serotonin synthesis include *p*-chloroamphetamine, fenfluramine, and reserpine. The effects of reserpine and reserpine-like drugs, as mentioned before, are not confined to serotonin neurons. *p*-Chloroamphetamine and fenfluramine act more selectively on serotonin neurons. After initially releasing serotonin into the synaptic cleft (4), they decrease serotonin stores and presumably lead to a functional deficit of serotonin at the receptor.

NEUROTOXINS 5,6- and 5,7-Dihydroxytryptamines are actively transported into serotonin neurons by means of the membrane uptake pump and cause rapid irreversible destruction of serotonin neurons. These compounds have been widely used to lesion serotonin neurons chemically. A recent *Annal of the New York Academy of Sciences* (Volume 305, 1978) deals exclusively with serotonin neurotoxins and provides up-to-date reviews of various characteristics of these drugs. *p*-Chloroamphetamine and fenfluramine, in addition to the initial release and later reversible depletion of serotonin stores, then lead to irreversible and long-lasting decreases not only in serotonin content but also in other markers of serotonin neurons (tryptophan hydroxylase activity and serotonin uptake). While there is controversy about the histologic changes that accompany these effects particularly with fenfluramine, both fenfluramine and *p*-chloroamphetamine can produce long-lasting depleting effects on serotonin neurons.

PHYSIOLOGIC ROLES AND PHARMACOLOGIC MODIFICATION OF SEROTONIN NEURONS

The availability of drugs like direct agonists, uptake inhibitors, and releasers that selectively enhance serotoninergic neurotransmission and of drugs like antagonists, inhibitors of synthesis, depletors, and neurotoxins that selec-

tively impair serotoninergic neurotransmission has been of great help in exploring functional roles of serotonin neurons in brain. Serotonin neurons are postulated to be involved in the control of various types of behavior and of certain other functions of the central nervous system. Some of the more widely studied of these physiologic roles, particularly those which pharmacologic evidence has been prominent in establishing, are discussed below. These in turn suggest some therapeutic uses or possibilities for agents that intervene in central serotonin neuronal function.

A role of serotonin in the etiology of mental depression and in the antidepressant effects of drugs has been postulated, but, despite extensive studies, has not been supported by compelling evidence [for a recent review, see (51)]. Some workers have found abnormally low concentrations of serotonin in post mortem brain samples or of 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressed patients, but others have failed to confirm these abnormalities. Some evidence suggests that there may be a bimodal distribution pattern for 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressed patients (52) and that only a particular subgroup of depressed patients are deficient in central serotonin function (53). Some investigators have reported antidepressant responses to serotonin precursors, L-tryptophan or 5-hydroxy-L-tryptophan, but others have not found such effects. The possibility that enhanced serotonin function accounts for or contributes to the antidepressant actions of tricyclic uptake inhibitors or of monoamine oxidase inhibitors has been considered. One of the more convincing arguments for this was the finding that inhibition of serotonin synthesis but not catecholamine synthesis antagonized the antidepressant action both of tranylcypromine (54) and of imipramine (55). The recent availability of uptake inhibitors selective for serotonin (not affecting norepinephrine) may aid greatly in proving or disproving a role of serotonin in antidepressant activity. Both zimelidine (56, 57) and fluvoxamine (58) have been reported to have antidepressant efficacy in humans, though only limited data have so far been published.

Animal behavior in which serotonin neurons have been suggested to participate include conflict behavior (39) and other types of operant behavior (59), sexual activity (60), ingestive behavior (see below), and muricidal behavior in rats. Recent experimental findings in the last area include inhibition of muricide by serotonin uptake inhibitors (61, 62) and by direct or indirect serotonin agonists (62) and enhancement of muricide by raphe lesions (63) and by *p*-chlorophenylalanine (64), these latter effects being reversed by 5-hydroxy-L-tryptophan.

Experimental modification of central serotonin neurons has been associated with changes in feeding behavior (for review see 65). The anorectic

action of MK-212 (66) and of fenfluramine (67) is thought to be mediated by direct and indirect stimulation of serotonin receptors, respectively. Fluoxetine combined with 5-hydroxy-L-tryptophan has a potent and long-lasting anorectic effect in rats (68). Wurtman & Wurtman (69, 70) found that fenfluramine, fluoxetine, and MK-212 selectively suppressed non-protein caloric intake in rats, whereas the anorectic drug amphetamine (which does not act through a serotoninergic mechanism) decreased both protein and total calorie consumption. The selective reduction of non-protein caloric intake might be an advantageous property of an anti-obesity drug.

Serotonin neurons in the central nervous system appear to be involved in pain (for review see 71) and in the analgesic effect of some drugs (71, 72) and of acupuncture (73). Antagonism of serotonin function interferes with the analgesic effect of morphine [see, for example (72, 74–76)], etorphine (77), and enkephalin analogues (78), whereas enhancement of serotonin function potentiates morphine analgesia (79–82) or produces analgesia (82, 83) and reduces hyperalgesia (84) directly.

Numerous studies have supported a role of serotonin neurons in the hypothalamic control of pituitary function. For example, a stimulatory effect of serotonin in the secretion of two pituitary hormones—prolactin and ACTH—has been demonstrated by pharmacologic studies. Serum prolactin in rats is elevated when brain serotonin function is enhanced by the combination of fluoxetine and 5-hydroxy-L-tryptophan (85, 86) or by fenfluramine (87). Serum prolactin in rats is also elevated by direct-acting serotonin agonists like quipazine (88), 1-(*m*-trifluoromethylphenyl)-piperazine (18), and some indolealkylamines including bufotenin and N,N-dimethyl-5-methoxytryptamine (89). Stimulation of ACTH release, as evidenced by a rise in serum corticosterone, has also been reported with fluoxetine alone or in combination with 5-hydroxy-L-tryptophan (90, 91), with quipazine (92), and with 1-(*m*-trifluoromethylphenyl)-piperazine (18). The effect of quipazine was prevented by pretreatment with metergoline (92). The elevation of serum corticosterone following enhanced serotonin function is presumably initiated by increased release of corticotropin-releasing factor from the hypothalamus (93). Cyproheptadine has been reported to have therapeutic benefit in patients with Cushing's disease and to reduce elevated ACTH levels in other patients (94).

There are similar kinds of evidence for a role of serotonin neurons in the hypothalamic control of other pituitary hormones such as growth hormone, thyrotropin, and luteinizing hormone (see 95, 96).

Serotonin neurons in brain may contribute to the central regulation of cardiovascular function, especially in the control of blood pressure (see 97).

Recently we found that fluoxetine, particularly when given in combination with 5-hydroxy-L-tryptophan, has a pronounced antihypertensive effect in spontaneously hypertensive or DOCA hypertensive rats (98) and in anesthetized normotensive dogs (D. R. Holland, personal communication). Fenfluramine has been observed to have antihypertensive effects clinically (99), possibly through reduction of central sympathetic outflow (100) as a consequence of enhanced brain serotonin neuronal function. Blatt et al (101) reported that MK-212 and other purported central serotoninergic agents diminished cardiac susceptibility to ventricular fibrillation. The effect of MK-212 was blocked by metergoline. They suggested that an increase in central serotoninergic activity inhibits the flow of arrhythmogenic sympathetic nerve traffic from the brain to the heart.

There is evidence that serotonin neurons are involved in the catalepsy induced by neuroleptic drugs. For instance, neuroleptic-induced catalepsy is reduced by impairment of serotoninergic function, e.g. medial or dorsal raphe lesions (102), *p*-chlorophenylalanine (103), cyproheptadine (104) or 5,7-dihydroxytryptamine (105) and is enhanced by facilitating serotoninergic neurotransmission, e.g. direct-acting agonists and uptake inhibitors (106, 107).

Another brain function in which serotonin neurons seem to be involved is thermoregulation (108). Hyperthermia caused by fenfluramine in rats kept in a warm room is suggested to be due to hyperstimulation of serotonin receptors (109) and may be a useful test system for evaluating serotonin antagonists. Another such system is the antagonism of hyperthermia induced by the intracerebroventricular injection of serotonin in rabbits (110). Serotonin clearly is not of crucial importance in all experimental modifications of body temperature, however. Antagonism of reserpine hypothermia by uptake inhibitors seems to depend on enhanced noradrenergic rather than enhanced serotoninergic activity (111).

A role of serotonin in myoclonus (involuntary jerking of a muscle or limb) has been suggested. Therapeutic benefit of 5-hydroxy-L-tryptophan in patients with posthypoxic intention myoclonus has been obtained by numerous investigators (see 112, 113). Recently, drug-induced myoclonus in animals has been reported to be antagonized by 5-hydroxy-L-tryptophan or other agents that enhance central serotoninergic function (114). On the other hand, enhanced serotoninergic function can *induce* myoclonic movements in guinea pigs (115) and in 5,7-dihydroxytryptamine-treated rats (116), and 5-hydroxytryptophan is reported to have caused myoclonic-like spasms in some infants with Down's syndrome (117). Further investigation is needed to clarify the relationship between serotonin neurons and myoclonus (see 118).

Enhancement of central serotoninergic function may be of benefit in Parkinson's disease to offset some of the psychiatric side effects encountered when L-dopa is used (see 119, 120).

SUMMARY

Drugs with improved potency and specificity are becoming available for the pharmacologic manipulation of serotonin neurons in brain. Both enhancement and impairment of serotoninergic function can now be achieved by drugs acting through different mechanisms. Drugs of this sort are not only valuable tools for exploring functional roles of serotonin neurons but they have real or potential value in the treatment of diseases like mental depression, obesity, myoclonus or other movement disorders, pain, hypertension, and endocrine dysfunction.

Literature Cited

1. Azmitia, E. C. 1978. The serotonin-producing neurons of the midbrain median and dorsal raphe nuclei. In *Handbook of Pharmacology, Vol. 9, Chemical Pathways in the Brain,* ed. L. L. Iversen, S. D. Iversen, S. H. Snyder, pp. 233–312. New York: Plenum
2. Corne, S. J., Pickering, R. W., Warner, B. T. 1963. A method for assessing the effects of drugs on the central actions of 5-hydroxytryptamine. *Br. J. Pharmacol.* 20:106–20
3. Meek, J., Fuxe, K., Anden, N.-E. 1970. Effects of antidepressant drugs of the imipramine type on central 5-hydroxytryptamine neurotransmission. *Eur. J. Pharmacol.* 9:325–32
4. Trulson, M. E., Jacobs, B. L. 1976. Behavioral evidence for the rapid release of CNS serotonin by PCA and fenfluramine. *Eur. J. Pharmacol.* 36:149–54
5. Sloviter, R. S., Drust, E. G., Connor, J. D. 1978. Specificity of a rat behavioral model for serotonin receptor activation. *J. Pharmacol. Exp. Ther.* 206:339–47
6. Haigler, H. J., Aghajanian, G. K. 1977. Serotonin receptors in the brain. *Fed. Proc.* 36:2159–64
7. Green, A. R., Grahame-Smith, D. G. 1978. Processes regulating the functional activity of brain 5-hydroxytryptamine: Results of animal experimentation and their relevance to the understanding and treatment of depression. *Pharmakopsychiatry* 11:3–16
8. Bennett, J. P., Jr., Snyder, S. H. 1976. Serotonin and lysergic acid diethylamide binding in rat brain membranes: relationship to postsynaptic serotonin receptors. *Mol. Pharmacol.* 12:373–89
9. Fillion, G. M. B., Rousselle, J.-C., Fillion, M.-P., Beaudoin, D. M., Goiny, M. R., Deniau, J.-M., Jacob, J. J. 1978. High-affinity binding of ^{3}H 5-hydroxytryptamine to brain synaptosomal membranes: Comparison with ^{3}H lysergic acid diethylamide binding. *Mol. Pharmacol.* 14:50–59
10. Hong, E., Sancilio, L. F., Vargas, R., Pardo, E. G. 1969. Similarities between the pharmacological actions of quipazine and serotonin. *Eur. J. Pharmacol.* 6:274–80
11. Green, A. R., Youdim, M. B. H., Grahame-Smith, D. G. 1976. Quipazine: Its effects on rat brain 5-hydroxytryptamine metabolism, monoamine oxidase activity and behaviour. *Neuropharmacology* 15:173–79
12. Clineschmidt, B. V., McGuffin, J. C. 1978. Pharmacological differentiation of the central 5-hydroxytryptamine-like actions of MK-212 (6-chloro-2-[1-piperazinyl]-pyrazine), p-methoxyamphetamine and fenfluramine in an *in vivo* model system. *Eur. J. Pharmacol.* 50:369–75
13. Fuller, R. W., Snoddy, H. D., Mason, N. R., Molloy, B. B. 1978. Effect of 1-(m-trifluoromethylphenyl)-piperazine on ^{3}H-serotonin binding to membranes from rat brain *in vitro* and on serotonin turnover in rat brain *in vivo*. *Eur. J. Pharmacol.* 52:11–16
14. Clineschmidt, B. V., Totaro, J. A. Pflueger, A. B., McGuffin, J. C. 1978. Inhibition of the serotoninergic uptake system by MK-212 (6-chloro-2-[1-piperazinyl]-

pyrazine). *Pharmacol. Res. Commun.* 10:219–28
15. Fuller, R. W., Snoddy, H. D., Perry, K. W., Roush, B. W., Molloy, B. B., Bymaster, F. P., Wong, D. T. 1976. The effects of quipazine on serotonin metabolism in rat brain. *Life Sci.* 18:925–34
16. Hamon, M., Bourgoin, S., Enjalbert, A., Bockaert, J., Hery, F., Ternaux, J. P., Glowinski, J. 1976. The effects of quipazine on 5-HT metabolism in the rat brain. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 294:99–108
17. Jacoby, J. H., Howd, R. A., Levin, M. S., Wurtman, R. J. 1976. Mechanisms by which quipazine, a putative serotonin receptor agonist, alters brain 5-hydroxyindole metabolism. *Neuropharmacology* 15:529–34
18. Fuller, R. W., Clemens, J. A. 1979. 1-(m-Trifluoromethylphenyl)-piperazine, a serotonin agonist, increases serum corticosterone and prolactin concentration in rats. *IRCS Med. Sci.* 7:106
19. Wong, D. T., Horng, J. S., Bymaster, F. P., Hauser, K. L., Molloy, B. B. 1974. A serotonin uptake specific inhibitor: Lilly 110140, 3-(p-trifluoromethyphenoxy)-N-methyl-3-phenylpropylamine. *Life Sci.* 15:471–79
20. Fuller, R. W., Perry, K. W., Snoddy, H. D., Molloy, B. B. 1974. Comparison of the specificity of 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine and chlorimipramine as amine uptake inhibitors in mice. *Eur. J. Pharmacol.* 28:233–36
21. Ross, S. B., Ogren, S.-O., Renyi, A. L. 1976. (Z)-Dimethylamino-1-(4-bromophenyl)-1-(3-pyridyl)propene (H102/09), a new selective inhibitor of the neuronal 5-hydroxytryptamine uptake. *Acta Pharmacol. Toxicol.* 39:152–66
22. Pugsley, T., Lippmann, W. 1976. Effects of tandamine and pirandamine, new potential antidepressants, on the brain uptake of norepinephrine and 5-hydroxytryptamine and related activities. *Psychopharmacology* 47:33–41
23. Claassen, V., Davies, J. E., Hertting, G., Placheta, P. 1977. Fluvoxamine, a specific 5-hydroxytryptamine uptake inhibitor. *Br. J. Pharmacol.* 60:505–16
24. Buus Lassen, J. 1978. Potent and long-lasting potentiation of two 5-hydroxytryptophan-induced effects in mice by three selective 5-HT uptake inhibitors. *Eur. J. Pharmacol.* 47:351–58
25. Hyttel, J. 1978. Effect of a specific 5-HT uptake inhibitor, citalopram (Lu 10–171), on ^{3}H-5-HT uptake in rat brain synaptosomes *in vitro*. *Psychopharmacology* 60:13–18
26. Mireylees, S. E., Goodlet, I., Sugrue, M. F. 1978. Effects of Org 6582 on monoamine uptake *in vitro*. *Biochem. Pharmacol.* 27:1023–27
27. Fuller, R. W., Snoddy, H. D., Perry, K. W., Bymaster, F. P., Wong, D. T. 1978. Studies on 4-(p-bromophenyl)-bicyclo-(2,2,2)-octan-1-amine as an inhibitor of uptake into serotonin neurons. *Neuropharmacology* 17:815–18
28. Le Fur, G., Kabouche, M., Uzan, A. 1978. On the regional and specific serotonin uptake inhibition by LM 5008. *Life Sci.* 23:1959–66
29. Fuller, R. W. 1978. Structure-activity relationships among the halogenated amphetammes. *Ann. NY Acad. Sci.* 305:147–57
30. Gal, E. M., Young, R. B., Sherman, A. D. 1978. Tryptophan loading: Consequent effects on the synthesis of kynurenine and 5-hydroxyindoles in rat brain. *J. Neurochem.* 31:237–44
31. Yunger, L. M., Harvey, J. A. 1976. Behavioral effects of L-5-hydroxytryptophan after destruction of ascending serotonergic pathways in the rat: The role of catecholaminergic neurons. *J. Pharmacol. Exp. Ther.* 196:307–15
32. Fuxe, K., Butcher, L. L., Engel, J. 1971. DL-5-Hydroxytryptophan-induced changes in central monoamine neurons after peripheral decarboxylase inhibition. *J. Pharm. Pharmacol.* 23: 420–24
33. Ferrini, R., Glasser, A. 1965. Antagonism of central effects of tryptamine and 5-hydroxytryptophan by 1,6-dimethyl-8β-carbobenzyloxy-aminomethyl-10α-ergoline. *Psychopharmacology* 8:271–76
34. Sastry, B. S. R., Phillis, J. W. 1977. Metergoline as a selective 5-hydroxytryptamine antagonist in the cerebral cortex. *Can. J. Physiol. Pharmacol.* 55:130–33
35. Fuxe, K., Ogren, S.-O., Agnati, L. F., Jonsson, G. 1978. Further evidence that methergoline is a central 5-hydroxytryptamine receptor blocking agent. *Neurosci. Lett.* 9:195–200
36. Gyermek, L. 1961. 5-Hydroxytryptamine antagonists. *Pharmacol. Rev.* 13:399–439
37. Karja, J., Karki, N. T., Tala, E. 1961. Inhibition by methysergid of 5-hydroxytryptophan toxicity to mice. *Acta Pharmacol. Toxicol.* 18:255–62
38. Stone, C. A., Wenger, H. C., Ludden, C. T., Stavorski, J. M., Ross, C. A. 1961. Antiserotonin-antihistaminic

properties of cyproheptadine. *J. Pharmacol. Exp. Ther.* 131:73–84
39. Furgiuele, A. R., High, J. P., Horowitz, Z. P. 1965. Some central effects of SQ 10,643 [2,3-(dimethylaminopropylthio)-cinnamanilide hydrochloride], a potent serotonin antagonist. *Arch Int. Pharmacodyn.* 155:225–35
40. Geller, I., Hartmann, R. J., Croy, D. J., Haber, B. 1974. Attenuation of conflict behavior with cinanserin, a serotonin antagonist: reversal of the effect with 5-hydroxytryptophan and α-methyltryptamine. *Res. Commun. Chem. Pathol. Pharmacol.* 7:165–74
41. Vargaftig, B. B., Coignet, J. L., de Vos, C. J., Grijsen, H., Bonta, I. L. 1971. Mianserin hydrochloride: Peripheral and central effects in relation to antagonism against 5-hydroxytryptamine and tryptamine. *Eur. J. Pharmacol.* 16: 336–46
42. Maj, J., Sowinska, H., Baran, L., Gancarczyk, L., Rawlow, A. 1978. The central antiserotonergic action of mianserin. *Psychopharmacology* 59:79–84
43. Boakes, R. J., Bradley, P. B., Briggs, I., Dray, A. 1969. Antagonism by LSD to effects of 5-HT on single neurons. *Brain Res.* 15:529–31
44. Monachon, M.-A., Burkard, W. P., Jalfre, M., Haefely, W. 1972. Blockade of central 5-hydroxytryptamine receptors by methiothepin. *Naunyn-Schmiedeberg's Arch Pharmacol.* 274:192–97
45. Maj, J., Palider, W., Rawlow, A. 1979. Trazodone, a central serotonin antagonist and agonist. *J. Neural Transm.* 44:237–48
46. Fuller, R. W., Steinberg, M. 1976. Regulation of enzymes that synthesize neurotransmitter monoamines. *Adv. Enzyme Regul.* 14:347–90
47. Fuller, R. W., Perry, K. W. 1974. Methiothepin elevation of 5-hydroxyindoleacetic acid levels in various anatomic regions of rat brain. *Brain Res.* 70:369–71
48. Jacoby, J. H., Shabshelowitz, H., Fernstrom, J. D., Wurtman, R. J. 1975. The mechanisms by which methiothepin, a putative serotonin receptor antagonist, increases brain 5-hydroxyindole levels. *J. Pharmacol. Exp. Ther.* 195:257–64
49. Jacoby, J. H., Poulakos, J. J., Bryce, G. F. 1978. On the central anti-serotoninergic actions of cyproheptadine and methysergide. *Neuropharmacology* 17: 299–306
50. D'Amico, D. J., Patel, B. C., Klawans, H. L. 1976. The effect of methysergide on 5-hydroxytryptamine turnover in whole brain. *J. Pharm. Pharmacol.* 28:454–56
51. Murphy, D. L., Campbell, I. C., Costa, J. L. 1978. The brain serotonergic system in the affective disorders. *Prog. Neuro-Psychopharmacol.* 2:1–31
52. Asberg, M., Bertilsson, L., Tuck, D., Cronholm, B., Sjoqvist, F. 1973. Indoleamine metabolites in the cerebrospinal fluid of depressed patients before and during treatment with nortriptyline. *Clin. Pharmacol. Ther.* 14:277–86
53. Van Praag, H. M., Korf, J. 1974. Serotonin metabolism in depression: Clinical application of the probenecid test. *Int. Pharmacopsychiatry* 9:35–51
54. Shopsin, B., Friedman, E., Gershon, S. 1976. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patient. *Arch. Gen. Psychiatry* 33: 811–19
55. Shopsin, B., Gershon, S., Goldstein, M., Friedman, E., Wilk, S. 1975. Use of synthesis inhibitors in defining a role for biogenic amines during impramine treatment in depressed patients. *Psychopharmacol. Comm.* 1:239–49
56. Benkert, O., Laakman, G., Ott, L., Strauss, A., Zimmer, R. 1977. Effect of zimelidine (H 102/09) in depressive patients. *Arzneim.-Forsch.* 27:2421–23
57. Cox, J., Moore, G., Evans, L. 1978. Zimelidine: A new antidepressant. *Prog. Neuro-Psychopharmacol.* 2:379–84
58. Saletu, B., Schjerve, M., Grunberger, J., Schanda, H., Arnold, O. H. 1977. Fluvoxamine—a new serotonin re-uptake inhibitor: First clinical and psychometric experiences in depressed patients. *J. Neural Transm.* 41:17–36
59. Aprison, M. H., Hingtgen, J. N., McBride, W. J. 1975. Serotonergic and cholinergic mechanisms during disruption of approach and avoidance behavior. *Fed. Proc.* 34:1813–22
60. Meyerson, B. J., Malmnas, C. O. 1978. Brain monoamines and sexual behavior. In *Biological Determinants of Sexual Behaviour,* ed. J. B. Hutchison, pp. 521–54. New York: Wiley
61. Marks, P. C., O'Brien, M., Paxinos, G. 1978. Chlorimipramine inhibition of muricide: The role of the ascending 5-HT projection. *Brain Res.* 149: 270–73
62. Gibbons, J. L., Glusman, M. 1979. Effects of quipazine, fluoxetine, and fenfluramine on muricide in rats. *Fed. Proc.* 38:257
63. Yamamoto, T., Ueki, S. 1978. Effects of drugs on hyperactivity and aggression

induced by raphe lesions in rats. *Pharmacol. Biochem. Behav.* 9:821–26
64. Gibbons, J. L., Barr, G. A., Bridger, W. H., Leibowitz, S. F. 1978. Effects of para-chlorophenylalanine and 5-hydroxytryptophan on mouse killing behavior in killer rats. *Pharmacol. Biochem. Behav.* 9:91–98
65. Blundell, J. E. 1977. Is there a role for serotonin (5-hydroxytryptamine) in feeding? *Int. J. Obesity* 1:15–42
66. Clineschmidt, B. V., McGuffin, J. C., Pflueger, A. B., Totaro, J. A. 1978. A 5-hydroxytryptamine-like mode of anorectic action for 6-chloro-2-[1-piperazinyl]-pyrazine (MK-212). *Pharmacology* 62:579–89
67. Garattini, S., Samanin, R. 1978. Amphetamine and fenfluramine, two drugs for studies on food intake. *Int. J. Obesity* 2:349–51
68. Goudie, A. J., Thornton, E. W., Wheeler, T. J. 1976. Effects of Lilly 110140, a specific inhibitor of 5-hydroxytryptamine uptake, on food intake and on 5-hydroxytryptophan-induced anorexia. Evidence for serotoninergic inhibition of feeding. *J. Pharm. Pharmacol.* 28:318–20
69. Wurtman, J. J., Wurtman, R. J. 1977. Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. *Science* 198: 1178–80
70. Wurtman, J. J., Wurtman, R. J. 1979. Drugs that enhance central serotoninergic transmission diminish elective carbohydrate consumption by rats. *Life Sci.* 24:895–904
71. Messing, R. B., Lytle, L. D. 1977. Serotonin-containing neurons: Their possible role in pain and analgesia. *Pain* 4:1–21
72. Yaksh, T. 1979. Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. *Brain Res.* 160:180–85
73. Han, C.-S., Chou, P.-H., Lu, C.-C., Lu, L.-H., Yang, T.-H., Jen, M.-F. 1979. The role of central 5-hydroxytryptamine in acupuncture analgesia. *Sci. Sin.* 22:91–104
74. York, J. L., Maynert, E. W. 1978. Alterations in morphine analgesia produced by chronic deficits of brain catecholamines or serotonin: Role of analgesimetric procedure. *Psychopharmacology* 56:119–25
75. Dickenson, A. H., Oliveras, J.-L., Besson, J.-M. 1978. Role du noyau Raphe Magnus dans l'analgesie morphinique: Etudes par microinjections intracerebrales chez le rat. *C. R. Acad. Sci. Paris* 287:955–58
76. Deakin, J. F. W., Dostrovsky, J. O. 1978. Involvement of the periaqueductal grey matter and spinal 5-hydroxytryptaminergic pathways in morphine analgesia: effects of lesions and 5-hydroxytryptamine depletion. *Br. J. Pharmacol.* 63:159–65
77. Miranda, F., Candelaresi, G., Samanin, R. 1978. Analgesic effect of etorphine in rats with selective depletions of brain monoamines. *Psychopharmacology* 58: 105–9
78. Lee, R. L., Sewell, R. D. E., Spencer, P. S. J. 1978. Importance of 5-hydroxytryptamine in the antinociceptive activity of the leucine-enkephalin derivative, D-Ala^2-Leu^5-enkephalin (BW 180C), in the rat. *Eur. J. Pharmacol.* 47:251–53
79. Larson, A. A., Takemori, A. E. 1977. Effect of fluoxetine hydrochloride (Lilly 110140), a specific inhibitor of serotonin uptake, on morphine analgesia and the development of tolerance. *Life Sci.* 21:1807–12
80. French, E. D., Vasquez, S. A., George, R. 1978. Potentiation of morphine hyperthermia in cats by pimozide and fluoxetine hydrochloride. *Eur. J. Pharmacol.* 48:351–56
81. Sugrue, M. F., McIndewar, I. 1976. Effect of blockade of 5-hydroxytryptamine re-uptake on drug-induced antinociception in the rat. *J. Pharm. Pharmacol.* 28:447–48
82. Messing, R. B., Phebus, L., Fisher, L. A., Lytle, L. D. 1975. Analgesic effect of fluoxetine hydrochloride (Lilly 110140), a specific inhibitor of serotonin uptake. *Psychopharmacol. Commun.* 1:511–21
83. Yaksh, T. L., Wilson, P. R. 1979. Spinal serotonin terminal system mediates antinociception. *J. Pharmacol. Exp. Ther.* 208:446–53
84. Messing, R. B., Fisher, L. A., Phebus, L., Lytle, L. D. 1976. Interaction of diet and drugs in the regulation of brain 5-hydroxyindoles and the response to painful electric shock. *Life Sci.* 18: 707–14
85. Krulich, L. 1975. The effect of a serotonin uptake inhibitor (Lilly 110140) on the secretion of prolactin in the rat. *Life Sci.* 17:1141–44
86. Clemens, J. A., Roush, M. E., Fuller, R. W. 1978. Evidence that serotonin neurons stimulate secretion of prolactin releasing factor. *Life Sci.* 22:2209–14

87. Quattrone, A., Di Renzo, G., Schettini, G., Tedeschi, G., Scopacasa, F. 1978. Increased plasma prolactin levels induced in rats by d-fenfluramine: Relation to central serotonergic stimulation. *Eur. J. Pharmacol.* 49:163–67
88. Meltzer, H. Y., Fang, V. S., Paul, S. M., Kaluskar, R. 1976. Effect of quipazine on rat plasma prolactin levels. *Life Sci.* 19:1073–78
89. Meltzer, H. Y., Fessler, R. G., Simonovic, M., Fang, V. S. 1978. Stimulation of rat prolactin secretion by indolealkylamine hallucinogens. *Psychopharmacology* 56:255–59
90. Fuller, R. W., Snoddy, H. D., Molloy, B. B. 1975. Potentiation of the L-5-hydroxytryptophan-induced elevation of plasma corticosterone levels in rats by a specific inhibitor of serotonin uptake. *Res. Commun. Chem. Pathol. Pharmacol.* 10:193–96
91. Fuller, R. W., Snoddy, H. D., Molloy, B. B. 1976. Pharmacologic evidence for a serotonin neural pathway involved in hypothalamus-pituitary-adrenal function in rats. *Life Sci.* 19:337–46
92. Fuller, R. W., Snoddy, H. D., Clemens, J. A. 1978. The effect of quipazine, a serotonin receptor agonist, on serum corticosterone concentration in rats. *Endocrine Res. Commun.* 5:161–71
93. Jones, M. T., Hillhouse, E. W. 1977. Neurotransmitter regulation of corticotropin-releasing factor *in vitro*. *Ann. NY Acad. Sci.* 297:536–58
94. Krieger, D. T. 1977. Serotonin regulation of ACTH secretion. *Ann. NY Acad. Sci.* 297:527–34
95. Smythe, G. A. 1977. The role of serotonin and dopamine in hypothalamic-pituitary function. *Clin. Endocrinol.* 7:325–41
96. Weiner, R. I., Ganong, W. F. 1978. Role of brain monoamines and histamine in regulation of anterior pituitary secretion. *Physiol. Rev.* 58:905–76
97. Antonaccio, M. J. 1977. Neuropharmacology of central mechanisms governing the circulation. In *Cardiovascular Pharmacology,* ed. M. J. Antonaccio, pp. 131–65. New York: Raven
98. Fuller, R. W., Holland, D. R., Yen, T. T., Stamm, N. B. 1979. Antihypertensive effects of fluoxetine and L-5-hydroxytryptophan in rats. *Life Sci.* 25:1237–42
99. Tuomilehto, J., Siltanen, H., Jespersen, S. 1977. A study on the effect of fenfluramine in obese, hypertensive patients treated with β-adrenergic blocking agents. *Curr. Ther. Res.* 22:821–27
100. De La Vega, C. E., Slater, S., Ziegler, M. G., Lake, C. R., Murphy, D. L. 1977. Reduction in plasma norepinephrine during fenfluramine treatment. *Clin. Pharmacol. Ther.* 21:216–21
101. Blatt, C. M., Rabinowitz, S. H., Lown, B. 1979. Central serotonergic agents raise the repetitive extrasystole threshold of the vulnerable period of the canine ventricular myocardium. *Circ. Res.* 44:723–30
102. Costall, B., Fortune, D. H., Naylor, R. J., Marsden, C. D., Pycock, C. 1975. Serotonergic involvement with neuroleptic catalepsy. *Neuropharmacology* 14:859–68
103. Kostowski, W., Gumulka, W., Czlonkowski, A. 1972. Reduced cataleptogenic effects of some neuroleptics in rats with lesioned midbrain raphe and pretreated with parachlorophenylalanine. *Brain Res.* 48:443–46
104. Maj, J., Mogilnicka, E., Przewlocka, B. 1975. Antagonistic effect of cyproheptadine on neuroleptic-induced catalepsy. *Pharmacol. Biochem. Behav.* 3:25–27
105. Carter, C. J., Pycock, C. J. 1978. A study of the sites of interaction between dopamine and 5-hydroxytryptamine for the production of fluphenazine-induced catalepsy. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 304:135–39
106. Carter, C. J., Pycock, C. J. 1977. Possible importance of 5-hydroxytryptamine in neuroleptic-induced catalepsy in rats. *Br. J. Pharmacol.* 60:267P
107. Balsara, J. J., Jadhar, J. H., Chandorkar, A. G. 1979. Effects of drugs influencing central serotonergic mechanisms on haloperidol-induced catalepsy. *Psychopharmacology* 62:67–69
108. Myers, R. D., Waller, M. B. 1978. Thermoregulation and serotonin. In *Serotonin in Health and Disease,* Vol. II, *Psychological Regulation and Pharmacological Action,* ed. W. B. Essman, pp. 1–67. New York: Spectrum
109. Sulpizio, A., Fowler, P. J., Macko, E. 1978. Antagonism of fenfluramine-induced hyperthermia: a measure of central serotonin inhibition. *Life Sci.* 22:1439–46
110. Girault, J.-M. T., Jacob., J. J. 1979. Serotonin antagonists and central hyperthermia produced by biogenic amines in conscious rabbits. *Eur. J. Pharmacol.* 53:191–200
111. Slater, I. H., Rathbun, R. C., Kattau, R. 1979. Role of 5-hydroxytryptaminergic and adrenergic mechanism in antagonism of reserpine-induced hypothermia

in mice. *J. Pharm. Pharmacol.* 31: 108–10
112. Van Woert, M. H., Rosenbaum, D., Howieson, J., Bowers, M. B., Jr. 1977. Long-term therapy of myoclonus and other neurologic disorders with L-5-hydroxytryptophan and carbidopa. *N. Engl. J. Med.* 296:70–75
113. Magnussen, I., Dupont, E., Engbaek, F., de Fine Olivarius, B. 1978. Post-hypoxic intention myoclonus treated with 5-hydroxytryptophan and an extracerebral decarboxylase inhibitor. *Acta Neurol. Scand.* 57:289–94
114. Hwang, E. C., Van Woert, M. H. 1979. p,p'-DDT-Induced myoclonus: Serotonin and alpha noradrenergic interaction. *Res. Commun. Chem. Pathol. Pharmacol.* 23:257–66
115. Volkman, P. H., Lorens, S. A., Kindel, G. H., Ginos, J. Z. 1978. L-5-Hydroxytryptophan-induced myoclonus in guinea pigs: A model for the study of central serotonin-dopamine interactions. *Neuropharmacology* 17:947–55
116. Stewart, R. M., Campbell, A., Sperk, G., Baldessarini, R. J. 1979. Receptor mechanisms in increased sensitivity to serotonin agonists after dihydroxytryptamine shown by electronic monitoring of muscle twitches in the rat. *Psychopharmacology* 60:281–89
117. Coleman, M. 1971. Infantile spasms associated with 5-hydroxytryptophan administration in patients with Down's syndrome. *Neurology* 21:911–19
118. Chadwick, D., Hallett, M., Jenner, P., Marsden, C. D. 1978. 5-Hydroxytryptophan-induced myoclonus in guinea pigs. *J. Neurol. Sci.* 35:157–65
119. Fahn, S., Snider, S., Prasad, A. L. N., Lane, E., Makadon, H. 1975. Normalization of brain serotonin by L-tryptophan in levodopa-treated rats. *Neurology* 25:861–65
120. Rabey, J. M., Vardi, J., Askenazi, J. J., Streifler, M. 1977. L-Tryptophan administration in L-dopa-induced hallucinations in elderly Parkinsonian patients. *Gerontology* 23:438–44