SEROTONIN AND CENTRAL NERVOUS SYSTEM FUNCTION

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Alterations in the transport, metabolism, storage, release, or postsynaptic activity of serotonin (5-HT) attend the administration of many drugs that influence functions mediated by the central nervous system (CNS). Moreover, considerable biochemical evidence links serotonergic mechanisms to the regulation of such diverse activities as sleep and body temperature, as well as to the pathophysiology of human ills ranging from schizophrenia and depression to epilepsy and parkinsonism. Nevertheless, the exact relationship of central indoleamines to any of these issues cannot be said to be clear in even a single instance.

In the absence of any unifying concept sufficient to encompass the welter of suggested functions of brain 5-HT, perhaps it is time to ask whether this indoleamine plays any role in the mammalian CNS. Is 5-HT merely some useless vestige of our phylogenetic past, compliantly yielding to the actions of drugs affecting neuronal mechanisms, yet itself devoid of any significant physiologic activity? Such a question arises as a consequence of recent data indicating that pharmacologic agents affecting central indoleamines are less specific than originally thought, as well as from the realization that available techniques afford correlational rather than direct evidence in support of a causal relationship between 5-HT and physiologic events outside the serotonergic neuron.

In this review, critical consideration is first given to the experimental strategies applied to the study of serotonergic systems within the CNS. Evidence purporting to relate 5-HT to specific physiologic and pathologic mechanisms, particularly those affected by drugs, is then examined in light of these methodologic limitations. Anatomic, metabolic, and neurophysiologic data on 5-HT have not been emphasized since they have been the subject of several recent reviews (1–5).

METHODOLOGY

Attempts to evaluate the functional role of 5-HT in the mammalian CNS may be grouped into pharmacologic, physical, and biochemical approaches: (*a*) changes in function may be examined following the administration of a drug believed to exert a relatively specific action on serotonergic mechanisms; (*b*) alterations in function may be studied following stereotaxic lesioning or electrical stimulation of areas rich in 5-HT containing nerve cell bodies or processes;

(*c*) changes in levels of the amine or its metabolites and precursors may be studied in body fluids or CNS tissues during experimentally-induced or naturally-occurring alterations in body function. Data deriving from each of these strategies have their own characteristic set of strengths and weaknesses.

Most early pharmacologically-based studies of 5-HT function in brain utilized drugs such as reserpine or monoamine oxidase (MAO) inhibitors which affect CNS levels of all monoamines. More recent observations have focused on drugs believed to act more specifically on serotonergic neurons. Most important in this regard are the metabolic precursors of 5-HT, L-tryptophan and 5-hydroxytryptophan (5-HTP). Since systemically administered 5-HTP increases brain 5-HT, in part owing to a selective accumulation by neurons (6, 7), the central pharmacologic effects of this amino acid have often been attributed to an enhancement of 5-HT mediated neuronal transmission. On the other hand, loading doses of 5-HTP not only lead to substantial 5-HT accumulations in cells that do not ordinarily contain this indoleamine, but also interfere with catecholamines and their precursors for transport, storage, and metabolism within the CNS (8–10). In view of evidence that considerable exogenously administered 5-HTP may be taken up nonspecifically and metabolized abnormally (11), 5-HTP induced changes in CNS function may largely reflect actions on catecholaminergic or other central neurohumoral systems. The administration of L-tryptophan, on the other hand, might be expected to contribute more specifically to 5-HT stores within serotonergic neurons, since tryptophan hydroxylase, unlike the enzyme that decarboxylates 5-HTP, probably occurs only in cells normally containing 5-HT (9, 11, 12). Systemically administered L-tryptophan can lead to increased brain 5-HT levels, since tryptophan hydroxylase ordinarily is not saturated with its substrate (12–14).

While the blood brain barrier prevents the entry of systemically-administered 5-HT into the CNS, in some experiments the amine has been injected directly into the cerebrospinal fluid (CSF) pathways or the cerebral parenchyma. Under such circumstances 5-HT has been assumed to affect synaptic activity in much the same way as does the endogenous amine. However, the artificial flooding of small areas of brain may not mimic the effects of the minute quantities of transmitter normally released. Furthermore, one can never be certain whether the response to injected 5-HT is due to an action on pathways normally involved in the function being observed or even whether the injected 5-HT acts only at synapses where 5-HT may be the physiologic neuromediator.

The opposite pharmacologic approach to studies of central serotonergic mechanisms is to administer drugs that selectively inhibit indoleamine synthesis or block 5-HT receptors. Parachlorophenylalanine (PCPA) is a potent inhibitor of tryptophan hydroxylase and leads to a profound reduction in brain 5-HT levels (15). Its actions are not entirely specific, however, since PCPA can compete with transport mechanisms for tryptophan, phenylalanine, and other amino acids (14), and produces small depletions of brain catecholamines (15, 16). PCPA also inhibits phenylalanine hydroxylase and thus leads to increased levels of phenylalanine and abnormal metabolites of this amino acid. Furthermore,

PCPA is decarboxylated in brain to parachlorophenylethylamine and it has been suggested that the stimulant effects of this amine might have some functional significance (17). Since 5-HT levels are not totally depleted after PCPA treatment, it is also possible that a small amount of residual or newly-formed 5-HT could maintain effective activity in serotonergic systems. Some of these same considerations may apply to other less completely studied drugs that reduce brain 5-HT, including 5,6-dihydroxytryptamine (18), α-methyltryptophan, 19), α-propyldopacetamide (20, 21) and the parachloroamphetamines (16, 22).

A number of other drugs have been employed as pharmacologic tools to study central serotonergic mechanisms. For example, one approach has been to increase serotonergic effects by blocking neuronal reuptake. Chlorimipramine and imipramine have been shown to have relatively greater effects in inhibiting 5-HT rather than catecholamine uptake as compared to desipramine and nortriptyline, which are more effective blockers of norepinephrine uptake (23, 24). On the other hand, both drug groups have the capacity to affect both systems at least partially, and the exploitation of their biochemical differences has yet to be thoroughly evaluated in physiologic systems. The same may be said for drugs suggested to act specifically as 5-HT receptor blockers, e.g. methysergide and 2′-(3-dimethylaminopropylthio)-cinnamilide (cinanserin), or as direct receptor stimulators, e.g. 2-(1-piperazinyl) quinoline maleate (quipazine). Furthermore, the possibility of a direct or indirect effect of these drugs on catecholaminergic receptors should not be excluded. The difficulty in finding a drug that acts exclusively on serotonergic mechanisms remains the crucial limitation to pharmacologically based investigations of 5-HT mediated neural function.

The two major physical techniques for the in vivo study of CNS function are lesion formation and electrical stimulation. With respect to serotonergic mechanisms, it has been found that lesioning the midbrain raphe, an area where most 5-HT containing nerve cell bodies are located, markedly depletes forebrain 5-HT (25), whereas electrical stimulation of this area accelerates the synthesis and release of cerebral 5-HT (26, 27). Nevertheless, both these methods may affect fibers that merely traverse the area as well as those destined to terminate there. It is doubtful whether electrical stimulation can selectively activate nuclei, since axons have a lower electrical threshold than do cell bodies. Techniques based on destruction of CNS tissues essentially study the functional capacity of those parts left intact; it must remain an assumption that the destroyed area originally performed the destroyed function.

The third major approach to the study of serotonergic mechanisms involves biochemical or histofluorescent techniques to estimate steady state levels of the amine or its rate of turnover. Although numerous studies have sought to correlate 5-HT concentrations in animal or human brain at autopsy to antemortem function, it is now apparent that the in vivo estimation of 5-HT turnover may provide more useful information relative to the functional state of serotonergic neurons (28). In situations where it may be inconvenient or impossible to obtain cerebral tissues, measurements have been made of changes in 5-HT transport and metabolism in blood platelets (29–31) and of alterations in CSF levels of 5-hydro-

xyindoleacetic acid (5-HIAA) (32–34). The relationship between 5-HIAA concentrations in CSF and those in the cerebral parenchyma appears fairly close, but needs further substantiation both in the experimental animal and in man. Recently, attempts to study monoamine turnover in the CNS have used probenecid, which inhibits the active transport of organic acids such as 5-HIAA from the CSF compartment (35–37). Under such circumstances, the rate of rise of 5-HIAA in CSF may provide an index to the rate of formation of this 5-HT metabolite and thus to the central turnover of the parent amine. The validity of results obtained using this technique has yet to receive rigorous confirmation.

Temperature Regulation

Attempts to study the participation of serotonergic mechanisms in the regulation of body temperature through the intracranial installation of 5-HT or its precursors have yielded markedly variable results. For example, 5-HT reportedly causes a rise in body temperature in the cat, dog, and monkey (38–41), but a decline in temperature in the rat, mouse, rabbit, ox, and sheep (42–46). 5-HT or 5-HTP injected intracisternally into the unanesthetized rabbit has a temperature-lowering effect more readily obtained with small doses and a temperature-elevating effect more readily obtained with larger doses (47); the intraventricular injection of small doses of 5-HTP reportedly produces a fall followed by a rise in temperature (47). A similar biphasic response to 5-HT has also been observed in the cat (48). The diverse effects of the injection of 5-HT or its immediate precursor into the CSF pathways or anterior hypothalamus may thus relate not only to species differences but also to differences in the concentrations of these substances at their point of action as well as to the conditions under which the observations are made.

Several reports indicate that 5-HT turnover in rat brain is accelerated during exposure to elevated environmental temperatures and depressed while the animals are kept in a cold environment (49–51). More recent studies of brain 5-HT levels in mice after prolonged exposure to cold have shown a brief initial increase followed by a marked decrease (52). In warm environments the changes were reversed. Evidence from depletion experiments using an inhibitor of 5-HT synthesis indicates that the activity of brain 5-HT neurons decreases for some days in a cold environment but returns gradually to control levels after the animals have acclimated. Conceivably, the temporary changes in 5-HT metabolism that appear soon after alterations in ambient temperature may be the primary reactions that initiate the peripheral adaptive changes associated with acclimation to different environmental temperatures. Although it is generally assumed that body temperature is regulated by structures in the preoptic area and hypothalamus, Simmonds (53) has reported that high environmental temperatures lead to an immediate acceleration in 5-HT turnover in the cortex plus hippocampus as well as in preoptic and hypothalamic tissues of the rat; a delayed rise in 5-HT turnover occurs in the striatum. Central serotonergic pathways involved in the immediate response to heat may thus differ from those involved in slower and presumably longer term adjustments to a hot environment.

Myers and coworkers (54) have recently observed that the amount of 5-HT in a perfusate collected from the anterior preoptic area of an unanesthetized monkey exposed to a cold environment increases substantially above resting levels. Since warming had no effect on 5-HT release, the results suggest that 5-HT-containing neuronal systems in the anterior hypothalamus may play a role in activating heat production mechanisms in the primate. A similar conclusion was suggested by the blockade, following PCPA or reserpine, of the ability of rabbits to reduce the hyperthermia produced by pyrogen administration (55), although PCPA treatment alone did not produce hypothermia (56). The administration of PCPA to a patient with carcinoid syndrome induced hypothermia (57), although this drug had no observable effect on body temperature in patients with Huntington's chorea (58).

Neuroendocrine Function

It is generally believed that the hormonal secretions of the anterior pituitary are controlled by releasing or inhibitory factors, which are synthesized by hypothalamic neurosecretory cells and carried from their axonal terminals in the median eminence to the anterior pituitary by the hypophyseal portal vessels. Available evidence suggests that 5-HT participates in the control of the releasing factor cells, possibly by acting at synapses on these cells or in the multisynaptic pathways leading to them (59).

Several studies indicate that central 5-HT containing neurons may play a role in gonadotropin regulation. The injection of 5-HT into ventricular CSF decreases serum levels of luteinizing hormone (60, 61). The suggestion that 5-HT may interfere with the liberation of luteinizing hormone releasing factor is supported by the inhibitory effect of 5-HT on ovulation in rodents (62, 63). In ovariectomized rats, however, PCPA can replace progesterone in restoring estrous behavior (64) and reportedly induces pseudopregnancy (65). Kamberi et al (66) have recently reported that intraventricularly administered 5-HT or melatonin (which causes a rapid but brief increase in brain 5-HT) appears to stimulate the release of prolactin but inhibit the release of follicle stimulating hormone in rats. When melatonin or 5-HT was infused into the anterior pituitary by way of a cannulated portal vessel, the release of neither follicle-stimulating hormone nor prolactin seemed to be effected. This suggests that the amines may have acted to suppress the discharge of prolactin-inhibiting factor and follicle-stimulating hormone releasing factor.

Serotonergic mechanisms have also been implicated in the regulation of adrenocorticotropic hormone (ACTH). Implantation of 5-HT into certain areas of hypothalamus causes an apparent stimulation of ACTH secretion as indicated by an acute rise in plasma corticosteroid levels (67, 68). On the other hand, depletion of brain monoamines by the systemic administration of reserpine also leads to a rise in plasma corticosterone levels (69), although a more selective decrease in brain 5-HT with PCPA failed to achieve the same result (70). α-Ethyltryptamine, which may act by stimulating central 5-HT receptors, exerts a strong inhibiting action on ACTH secretion (71). It has also been reported that

hydrocortisone or dexamethasone restores cerebral 5-HT turnover to normal or even supernormal rates in rats in which 5-HT turnover was reduced following adrenalectomy (72, 73). These observations suggest that the inhibitory feedback action of glucocorticoids on ACTH secretion is mediated by central 5-HT-containing neurons, possibly owing to the influence of the adrenal steroids on tryptophan hydroxylase activity (72). It would thus appear that serotonergic neurons in the CNS are influenced by the activity of the pituitary-adrenal axis and that the central serotonergic systems in turn may participate in the modulation of ACTH regulation.

SLEEP

The most internally consistent body of information supporting a role for 5-HT in mechanisms controlling sleep derives from studies in the cat. PCPA, in doses that produce an 80–90% decrease in brain 5-HT synthesis, regularly precipitates nearly total insomnia (74–77). Both rapid eye movement (REM) and nonrapid eye movement (NREM) sleep are almost completely eliminated. In addition, the waking state produced is accompanied by regular ponto-geniculo-occipital activity, a phenomenon seen primarily during REM sleep in normal animals. Reserpine has previously been shown to produce effects similar to those elicited by PCPA (78). The degree of 5-HT depletion in brain correlates closely with the reduction in NREM sleep (74, 77). 5-HTP injected intravenously in doses that restore brain 5-HT to 60% of normal yields a temporary restoration of normal sleep patterns (74, 77). In addition, the chronic administration of 5-HTP prevents PCPA-induced insomnia (79). Larger 5-HTP doses after PCPA pretreatment produce an abnormal sleep pattern with a suppression of REM sleep, possibly owing to an effect of 5-HTP on nonserotonergic (possibly catecholaminergic) neurons (76).

That the changes observed with PCPA result from direct effects on 5-HT mediated neural transmission is supported by studies in cats with destructive lesions in the raphe areas. Subtotal lesions (80–90% destruction) which produce marked reductions in 5-HT synthesis, release, and metabolism, but no change in 5-HT levels, are associated with a period of total wakefulness lasting several days (75). This is supplanted by a combined diminution of NREM sleep, absent REM sleep, and the appearance of ponto-geniculo-occipital activity. Less extensive lesions produce less insomnia, with some REM sleep occurring if the amount of NREM sleep exceeds 15% of the total sleep time. Neither these lesions nor PCPA treatment were found to be accompanied by any significant change in norepinephrine or dopamine levels (75).

In the monkey, PCPA produces a selective decrease in NREM sleep without an attendant change in REM sleep (80). The administration of PCPA (3–4 gm/day) to patients with carcinoid tumors leads to a consistent reduction in REM time; NREM sleep is essentially unchanged, and 5-HTP (4 mg/kg) given orally to one individual during PCPA treatment failed to modify the sleep patterns further (81). In another clinical study, 5-HTP prolonged REM sleep approximately 20% in normal individuals given oral doses of 600 mg at bedtime; NREM sleep was slightly reduced (82). 5-HTP in a smaller intravenous dose was similarly effective

in increasing REM sleep in one study (83) but not in another (84). L-tryptophan (4–10 gm) given to normals produced a decrease in sleep latency without changing the duration of REM and NREM time (85). Another study, however, reported that similar doses of L-tryptophan led to increased NREM and decreased REM sleep (86). The marked reduction of REM sleep produced by L-dopa (87) and the increase in REM time produced by the catecholamine synthesis inhibitor α-methylparatyrosine (88) indicate that sleep patterns can hardly be considered a function regulated by serotonergic mechanisms alone. The bulk of the available evidence does, however, provide a fairly coherent argument supporting a special relationship between serotonergic mechanisms and the maintenance of NREM sleep (76, 89).

Seizure Disorders

PCPA, reserpine, and other depletors of brain monoamines lower the threshold to experimentally induced seizures (90–95). Reserpine has also been found to antagonize the anticonvulsant action of diphenylhydantoin (96, 97) and chlordiazepoxide (98). Conversely, MAO inhibitors, which elevate brain monoamines, exert an anticonvulsant effect when administered alone (90, 92, 99) or in combination with 5-HTP (90, 92). 5-HTP has also been reported to reverse the reserpine induced antagonism to the anticonvulsant activity of chlordiazepoxide (98). 5-HTP by itself, or in combination with a peripheral decarboxylase inhibitor, also appears to possess some anticonvulsant activity (90, 92, 94). The potential importance of many of these observations may be compromised by the relatively poor correlation between the time course of drug induced alterations in brain 5-HT levels and the maximum changes in convulsive thresholds (95).

Somewhat more convincing data in support of a role for 5-HT in modulating seizure susceptibility derives from experiments in certain inbred strains of mice which are prone to sound-induced convulsions. In these animals, drugs that lower levels of 5-HT or catecholamines increase the susceptibility to audiogenic seizures, whereas drugs that raise levels of these monoamines tend to protect against such seizures (100, 101). The time of maximum effect on seizure threshold corresponds closely to the time of maximum effect on amine levels. In addition, brain 5-HT turnover is accelerated at the time of maximal convulsive responsiveness to a sound stimulus, possibly due to impaired 5-HT storage within presynaptic terminals (102).

In addition to the difficulties that beset all studies of 5-HT function in the mammalian CNS, several unique problems tend further to complicate the interpretation of data relative to seizure thresholds. First, most laboratory investigations of convulsions involve the use of rodents, and therefore effects on body temperature, which can influence seizure susceptibility, must always be considered. Second, attempts to relate altered 5-HT concentrations to seizure thresholds is complicated by the multiplicity of methods used for inducing convulsions. Finally, it should be noted that toxic doses of many chemical substances including those with anticonvulsant activity may produce convulsions, whereas anticonvulsant activity of a broad spectrum of drugs given at toxic

dose levels is relatively rare. Future attempts to study monoamines in small areas of brain in relation to convulsive thresholds might clarify the apparent relationship between monoamines and seizure susceptibility. With the possible exception of certain carbonic anhydrase inhibitors (103), there is relatively little data to suggest that an effect on serotonergic mechanisms plays a major role in determining the potency of anticonvulsants now in general usc (104).

Extrapyramidal Function

Biochemical and pharmacologic observations indicate that a defect in 5-HT containing neuronal systems may play a role in the pathogenesis of parkinsonism. The 5-HT content of the basal ganglia is substantially reduced (105) and 5-HIAA levels in the CSF of patients with this disorder tend to be diminished (106). In addition, an inverse relationship between the rate of 5-HIAA accumulation in lumbar CSF during the administration of probenecid and the clinical severity of parkinsonian signs has been reported (37). In animals, unilaterally placed mesencephalic lesions induce extrapyramidal signs in the contralateral limbs and diminish 5-HT concentrations in the ipsilateral striatum (107–109).

Studies using monoamine precursors, on the other hand, suggest that a diminution in 5-HT mediated neuronal function may ameliorate parkinsonian signs. L-dopa, the most effective agent now available for the symptomatic relief of this disorder, is generally assumed to act by replenishing central dopamine stores. In the experimental animal, however, L-dopa loading has also been shown to reduce brain 5-HT (110). Furthermore, L-tryptophan or 5-HTP exacerbate parkinsonism (111, 112). The administration of PCPA to parkinsonian patients at doses that substantially reduce lumbar CSF levels of 5-HIAA but not homovanillic acid has no consistent effect on cardinal parkinsonian signs (113). Although there are reports of histopathologic changes in brain stem areas believed to be rich in 5-HT containing nerve cell bodies (114), the apparent ability of MAO inhibitors to restore brain 5-HT but not dopamine to normal levels in parkinsonian patients (115) indicates that altered 5-HT metabolism in this disorder may reflect functional rather than structural changes.

The possible involvement of 5-HT in the pathogenesis of Huntington's disease is suggested by the reported ability of reserpine to diminish and 5-HTP to exacerbate the choreatic movements that occur in these patients (116, 117). The characteristic neuropathological feature of this disorder is a pronounced degeneration of small nerve cells in corpus striatum, a region containing high concentrations of 5-HT as well as other monoamines. However, no abnormalities in steady-state levels or probenecid-induced accumulations of 5-HIAA in the CSF of Huntington's chorea patients have been found (118, 119). Furthermore, neither L-tryptophan nor PCPA appears to affect motor function in these patients (58, 119).

Mental Deficiency

Reduced circulating (platelet) 5-HT levels have been reported in patients with phenylketonuria (120) and Down's syndrome (121–123) as well as in some studies of children with primary infantile autism (124–126) and minimal brain dys-

function (127, 128). Low platelet 5-HT concentrations in Down's syndrome may in part relate to a defect in the uptake and binding of the amine (122, 129, 130), possibly owing to a defect in platelet ATP (122). Recent evidence suggesting that the conversion of intravenously infused tryptophan to 5-HIAA (131) and the activity of MAO (130) are normal in patients with Down's syndrome supports this view. In patients with phenylketonuria, however, the metabolism of intravenously-administered tryptophan to 5-HIAA is reduced by about 30%, suggesting that an inhibition of tryptophan hydroxylase by the excess of phenylalanine in the tissues may contribute to the reduction in circulating 5-HT levels (132). Hyperphenylalanemia may also affect the uptake of tryptophan from the gut as well as into the CNS.

The relationship between reported alterations in the transport, metabolism, or storage of 5-HT in peripheral tissues and the mental defect in these disorders remains uncertain. No studies of 5-HT metabolism in the CNS of patients with phenylketonuria have been reported; animal models of this disorder, involving the administration of high doses of phenylalanine or PCPA from birth, have had only limited success in mimicking the human mental defect (133–135). In patients with Down's syndrome, basal CSF levels of 5-HIAA and probenecid-induced accumulations of this 5-HT metabolite do not appear abnormal (123, 136, 137). Moreover, therapeutic trials of 5-HTP in patients with Down's syndrome have not been reported to alter the mental defect (137, 138).

Aggression and Hypersexuality

Rats given PCPA exhibit increased aggressive and mouse-killing activity (139, 140), which can be reduced by treatment with either 5-HTP or the MAO inhibitor pargyline. Cats apparently do not exhibit this behavioral change (141). Furthermore the irritability and aggressiveness induced by isolation in mice (142) or by septal lesions in rats (143) have been reported to be diminished by PCPA.

Similar differences in response to indoleamine-modifying manipulations are observed in studies of sexual behavior, emphasizing the need for careful consideration of the particular behavioral model used, the means for measuring behavioral change, and the importance of species differences in comparing results from different studies. In male rats treated with PCPA, increased mounting behavior in adult animals and increased grooming behavior and social play in juvenile animals was observed by Shillito (144). 5-HTP antagonized these effects of PCPA. Similarly, Tagliamonte and coworkers (145) reported compulsive sexual activity in PCPA-treated male rats which was enhanced by an MAO inhibitor and abolished by 5-HTP. On the basis that PCPA plus pargyline altered brain levels of catecholamines but not 5-HT, Gessa and coworkers (146) suggested that sexual behavior may be regulated by a combination of indoleamine and catecholamine effects, with 5-HT inhibiting and catecholamines stimulating sexually-related activity. The exact relationship of the behavior induced by PCPA or PCPA plus an MAO inhibitor to normal sexual behavior in rodents has been questioned, since no study has demonstrated increased ejaculatory frequency in these animals, although decreased ejaculatory latency and increased mounting of

females (whether in estrous or not) have been observed in some studies (139, 147) but not in others (148).

One study in cats also documented increased mounting by males during PCPA treatment (149), while in monkeys no changes in sexual activity or aggressive behavior with PCPA were observed (80, 150–152). In two patient groups treated with PCPA, observers' ratings yielded no suggestion of increased sexual interest or activity (58, 153), nor did one of these patient groups reveal any enhanced interest in sex on a self-rating scale (153).

Affective Disorders

Some biochemical evidence suggesting a state of central 5-HT depletion in patients with affective disorders has been obtained during the last 5 years. Reduced CSF levels of 5-HIAA have been observed in some studies of depressed and manic patients (4, 154–157), but not in others (158–161). Brain levels of 5-HT and 5-HIAA have also been reported to be lower in suicides than in control subjects (162–164).

Clinical data concerning the antidepressant efficacy of L-tryptophan are conflicting (165–169). Although Coppen and coworkers reported that L-tryptophan was as effective as electroconvulsive therapy (167) or imipramine (169), other workers have not found that it was a useful antidepressant in the majority of patients treated (4, 170–172), despite evidence that platelet 5-HT stores and possibly central 5-HT turnover (estimated from the effect of probenecid on 5-HIAA levels in CSF) were increased (173, 174). However, van Praag & Korf (175) have recently suggested that only a specific subgroup of depressed patients, identified on the basis of low CSF 5-HIAA levels, may respond to L-tryptophan.

Two double-blind studies with 5-HTP failed to demonstrate significant antidepressant effects (176, 177). The antidepressant efficiency of the different tricyclic drugs does not appear to vary systemically with their relative ability to block 5–HT uptake (e.g. imipramine) as opposed to norepinephrine uptake (e.g. desipramine or nortriptyline) into neuronal tissues and human platelets (23, 178).

In studies of manic patients, L-tryptophan has been reported to decrease hyperactive behavior (179, 180). PCPA and methysergide were ineffective, or made some patients worse (156, 179), although some early studies suggested a beneficial effect of methysergide (181, 182). L-tryptophan, unlike L-dopa (183), does not precipitate hypomanic episodes in bipolar depressed patients (179).

Pain Perception and Narcotic Analgesics

There is considerable diversity of opinion as to the participation of serotonergic mechanisms in pain perception or in the central pharmacologic actions of narcotic analgesics. It has been reported that PCPA increases sensitivity to painful stimuli in rats (184) but not in mice or rabbits (185, 186). The systemic administration of 5-HTP to rats abolished the PCPA effect. Lesions placed in the midbrain raphe nuclei of the rat, which diminish forebrain 5-HT, increase the sensitivity to shock and reduce the analgetic effect of morphine (187). Reserpine-

induced antagonism to morphine analgesia may also relate to 5-HT depletion, since the intraventricular injection of this amine restores morphine's analgetic action (188). The analgetic effect of morphine and several other narcotic analgesics is reported to be potentiated by 5-HTP (186, 189) and reduced by PCPA (186, 190) in some studies but not in others (185, 191).

The acute administration of morphine accelerates brain 5-HT turnover in rats (192), but not in mice (193). During chronic treatment with morphine, 5-HT turnover in rodent brain has been reported to increase (194–196) or remain unchanged (197, 198). Although there seems to be some relation between the development of tolerance and increased brain 5-HT turnover in mice (193, 194, 196), the relationship between central 5-HT metabolism and physical dependence appears unsettled (194, 197–199). Discrepancies in experimental results with respect to the development of tolerance and physical dependence in part reflect species differences as well as the manner in which morphine is administered (193, 196). Central 5-HT turnover may be reduced in addicts receiving methadone, as judged by 5-HIAA levels in CSF (200, 201).

The possibility of a cross-relationship between narcotic addiction and alcoholism on the basis of a common mechanism related to acetaldehyde condensation reactions with biogenic amines has recently been suggested (202, 203). Some tetrahydroisoquinolines formed from catecholamines bear a close structural relationship to addictive alkaloids such as morphine (202), and also have some similarities to amines in regard to transport, storage, and release at nerve endings (204, 205). Moreover, the formation of tetrahydro-β-carbolines from tryptophan derivatives has been described, and one such compound has been shown to be formed in vivo (206).

Psychotic Behavior

Most evidence linking indoleamines to psychotic behavior is derived from studies of indole-ring containing compounds with hallucinogenic or psychotomimetic properties, e.g. D-lysergic acid diethylamide (LSD) and N,N-dimethyltryptamine (DMT). Smythies, Benington & Morin (207) have suggested that psychotomimetic agents share structural features requisite for antagonistic activity at serotonergic receptor sites, the most specifically spelled-out development of the original proposals of Gaddum (208) and Woolley & Shaw (209) that the anti-5-HT properties of LSD might be responsible for its CNS effects. More recently, Brawley & Duffield (210) concluded that a decrease in 5-HT turnover resulting ultimately from post-synaptic effects is most closely associated with the behavioral actions of hallucinogenic agents as compared to their nonactive congeners. Snyder and coworkers have suggested that the activity of all psychotomimetic agents is in part dependent upon their structural resemblance to LSD (211, 212).

Data upon which the LSD 5-HT hypothesis for the mechanism of psychotomimetic drug effects is based resembles that supporting the role of indoleamines in other CNS processes: Pretreatment with reserpine or with PCPA potentiates the effects of LSD, whereas MAO inhibitors decrease LSD effects (207). In

addition, LSD applied iontophoretically inhibits the firing of 5-HT containing cells in the raphe nuclei (213, 214). Most evidence (215–218) favors the explanation that LSD prevents the release of 5-HT from serotonergic neurons, resulting in a small increase in brain 5-HT levels (219), a decrease in 5-HIAA (220), and the expected reduction in 5-HT turnover (221). It should be noted that at relatively low doses LSD mimics rather than inhibits the excitatory effects of 5-HT in the CNS (214).

DMT has similar effects in decreasing 5-HT release, increasing raphe 5-HT, and reducing the increase in 5-HIAA formation usually seen after raphe stimulation (220, 222, 223). DMT is of special interest because, like its parent amine, tryptamine (224, 225), it has recently been shown to be produced in brain tissues from several species, including man (225–227). DMT may also occur in human urine, especially after treatment with MAO-inhibiting drugs (228).

6-Hydroxylation, another metabolic pathway for tryptamine, has recently been demonstrated to exist in the rabbit (229). This pathway is of special interest because 5,6-dihydroxytryptamine, a compound potentially capable of formation via this pathway, has some relatively specific effects on serotonergic neurons, including the production of long-lasting amine depletion. The mechanism of action of this drug may be similar to that proposed for 6-hydroxydopamine in catecholaminergic neurons (18). Although only acute behavioral effects of 5,6-dihydroxytryptamine have been observed (18), the recent demonstration of reduced cellular MAO levels in schizophrenic and bipolar manic-depressive patients (230) suggests a mechanism analogous to that postulated for 6-hydroxydopamine by Stein & Wise (231) in that continuing destruction of monoaminergic neurons by 5,6-dihydroxytryptamine might provide a model for the study of progressive or recurrent mental states related to such monoamine-modulated functions as arousal activity, mood, and reward mechanisms (231, 232).

CONCLUSIONS

Drugs or procedures that affect brain 5-HT have been found to be associated with changes in a variety of centrally mediated functions. In fewer instances, spontaneous or experimentally-induced changes in behavioral or motor processes have been correlated with alterations in cerebral 5-HT metabolism. Experimental data now available do not, however, permit the unequivocal conclusion that any one function examined, or any one drug effect, is mediated principally by serotonergic mechanisms.

Nonetheless, the bulk of available information is compatible with the hypothesis that 5-HT may play an active role in the function of the mammalian CNS. The very multiplicity of centrally mediated functions associated with 5-HT would appear to indicate that this monoamine has the same mechanism of action in several neuronal pathways and that the specificity of its action derives from the anatomic constraints imposed by the neuronal systems in which 5-HT is found. As with other monoamines presumed to have a neuromediator function in the CNS, a more precise delineation of 5-HT's role must await further advances in technical approaches to the study of the mammalian brain.

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