9. Mechanism of action of hallucinogenic drugs: focus upon postsynaptic serotonergic receptors

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INTRODUCTION

Hallucinogens are among the most interesting drugs because their behavioral and psychological effects are not only profound but also multifaceted. Furthermore, it is often difficult to predict the exact nature of their effects. This is perhaps best exemplified by the fact that the effects of these drugs are thought by some to reflect the complex inner workings of the human mind (i.e. 'psychedelic' or mind-manifesting). They are also thought by some to mimic various forms of idiopathic psychoses (i.e. 'psychotomimetic'). Whether or not this is true, studying these compounds may still provide important insights into the basic processes underlying psychopathologies because they produce rapid and dramatic alterations in mood and perception. Finally, the hallucinogens, along with some of the opiates and neuropeptides, are of interest because, on a dose basis, they are among the most potent psychoactive agents known.

An issue that one must always confront when discussing hallucinogenic drugs is which compounds to include in the category and which to exclude. I do not believe that there is a definitive answer to this question since it would ultimately be dependent on establishing necessarily arbitrary criteria for what constitutes a hallucination. Also, from a practical point of view, it seems unlikely that we would be able to derive a global theoretical framework that would encompass all the drugs that would fall into a broad definition of hallucinogen (e.g. one that would include cannabis, phencyclidine, scopolamine, cyclazocine, etc.). Therefore, I have chosen to sidestep this definitional issue and to focus on a group of drugs that are almost universally considered hallucinogens, and that may have a common mode of action. I shall restrict the discussion to 'LSD-like' hallucinogens, i.e. those whose psychological and behavioral effects in humans mimic those of lysergic acid diethylamide (LSD) and whose effects in humans show at least unidirectional cross-tolerance with LSD (1–10). It is also worth noting that indications of cross-tolerance are taken as presumptive evidence for a common mechanism of action. Applying

these two criteria allows us to include parent compounds such as psilocin, N,N-dimethyltryptamine (DMT), mescaline, and 2,5-dimethoxy-4-methylamphetamine (DOM), and their derivatives.

Theories regarding the mechanism of action of hallucinogenic drugs have historically focused on the brain serotonin system. Although other neurotransmitters, such as dopamine, have been implicated in the action of these drugs, the primary emphasis has consistently been on serotonin. Initially, hallucinogens were hypothesized to function as serotonin antagonists. This was based on pharmacological studies which examined the peripheral effects of these compounds (11, 12). The emphasis then shifted to an action directly upon brain serotonin-containing neurons. Support for this derived primarily from experiments examining changes in brain neurochemistry and electrophysiological studies of serotonin-containing neurons in anesthetized animals (13-15). In the present chapter, I argue in favor of a third hypothesis: that the effects of hallucinogenic drugs can best be understood by considering their action directly upon neurons postsynaptic to serotonin-containing neurons. This conclusion is based largely on studies employing behavioral pharmacology and single unit analyses of serotonin-containing neurons in freely moving animals. In the process of drawing these conclusions, I shall also review recent behavioral, pharmacological, neurochemical, and electrophysiological studies of the role of various neurotransmitter systems in the action of hallucinogenic drugs. This review is not intended, however, to be a comprehensive survey, rather it is a critical analysis of a limited number of studies, with a focus on a particular hypothesis.

Since the initial proposal that LSD might act simply by blocking the action of serotonin, the complexity of hypotheses regarding the mechanism of action of hallucinogenic drugs has grown in parallel with our understanding of the complexities of the CNS. Therefore, one of the dominant themes of this chapter will be an attempt to delineate the variety of modes through which the hallucinogens may alter synaptic transmission. For example, the drugs may act presynaptically (on dendrites, cell body, or nerve terminal) and/or postsynaptically; their actions at these various cellular sites may be on any of a variety of neurotransmitter receptors or their subclasses; and their effects on these receptors may be as agonists (excitatory, inhibitory, and/or modulatory) and/or antagonists.

Many excellent review articles describing aspects of research on hallucinogenic drugs not covered in this chapter are available: early research on serotonin and hallucinogenic drugs (13); general behavioral effects of these drugs in animals (16); the role of neurotransmitters other than serotonin (17); structure-activity relationships and the action of hallucinogens on various structures within the CNS (18); and the effects of these drugs in humans (10). There are also a number of books dealing with various aspects of hallucinogenic drugs, for example: those concerned primarily with mechanistic issues (19, 20); those dealing primarily with the behavioral and phenomenological aspects of these drugs (21); and those covering both types of issues (22, 23).

As a final point in this introductory section, it may be useful to summarize some of the effects in humans that appear to be common to ergot-, phenylethylamine-, and indole-derivative hallucinogens such as LSD, psilocin, DMT, mescaline and

DOM (10,18):
Sensory-perceptual: altered sensations of colors, sounds, shapes, and so forth, ultimately developing into complex, often multimodal, hallucinations.
Psychic: rapid, and often profound, alterations of affect (depression, elation, blunting, etc.), depersonalization, and dream-like feelings.
Somatic: dizziness, weakness, tremor, nausea, and hyperreflexia.

I have chosen, somewhat arbitrarily, to divide the experimental material in this review into four sections: (1) neurochemistry, (2) pharmacology, which includes simple behavioral analyses and receptor binding studies, (3) behavior, and (4) electrophysiology (single unit studies).

NEUROCHEMISTRY

Examination of the effects of hallucinogenic drugs upon brain neurochemistry began in the early 1960's. Freedman (24) reported that the systemic administration of LSD to rats produced a small, but significant, increase in brain levels of serotonin. Neither brom-LSD nor the levo-isomer of LSD, both of which are, at best, weak psychoactively, elicited this change in brain serotonin. This demonstration of the differential *central* action of LSD and brom-LSD was important because Cerletti and Rothlin (25) had challenged the presumed importance of serotonin in the action of LSD (11, 12) on the basis of a similar serotonin antagonist action of LSD and brom-LSD in the *periphery*. Several years later, in an extension of the initial study, Freedman's laboratory reported that, in addition to increasing brain levels of serotonin, LSD decreased brain levels of serotonin's major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (26).

During the past ten years a number of studies have examined the mechanisms through which LSD increases serotonin levels and decreases 5-HIAA levels in the CNS, as well as other aspects of LSD's effect upon central serotonin and catecholamine neurotransmission. In addition, the effects of other hallucinogenic drugs on various aspects of monoamine neurotransmission have been examined.

One of the most consistent findings is that LSD decreases the release of brain serotonin in rats both in vivo (27, 28) and in vitro (29–32). Since decreased release in the in vitro studies can be demonstrated in brain slices containing serotonin axon terminals, but no serotonergic cell bodies, LSD must be exerting a direct effect on serotonin release, which is independent of any release effect mediated by a suppression of serotonergic neuronal activity (see below). Several studies have shown also that LSD decreases the synthesis of brain serotonin in mice (33) and rats (31, 34, 35). This action is not shared by brom-LSD (33, 34). Unlike the effect of LSD on serotonin release, which can be seen in tissue slices devoid of serotonergic cell bodies, the decreased synthesis cannot be demonstrated in such slices (31). Finally, LSD, but not brom-LSD, decreases the turnover of brain serotonin (33, 36).

In general, experiments employing other hallucinogenic drugs report results similar to those studies described above which employed LSD. Psilocybine, DMT, 5-methoxy-DMT (5-MeODMT), and DOM all have been found to increase brain

serotonin levels and/or decrease serotonin turnover (as measured by decreased 5-HIAA levels or by some other neurochemical method) (37–42). The one exception to this has been the results with mescaline. Freedman, Gottleib and Lovell (36) have reported that low doses of mescaline decreased 5-HIAA levels, whereas high doses increased 5-HIAA levels. Consistent with this high-dose effect, Tilson and Sparber (27) have reported that mescaline increased release and/or re-uptake of brain serotonin. Tonge and Leonard (43), however, reported the opposite result, i.e., mescaline increased brain serotonin levels and decreased brain 5-HIAA levels. These inconsistent results with mescaline may be attributable partly, as we shall see later, to its exerting an LSD-like effect on one subset of serotonin neurons, and an amphetamine-like effect on another subset of these neurons. In addition, mescaline's action on other brain neurotransmitters, such as norepinephrine, may exert an additional indirect effect upon brain serotonin.

The preponderance of experiments that have examined the effects of hallucinogenic drugs on neurotransmitter systems other than serotonin have been restricted, almost exclusively, to the study of brain catecholamines. In general, they have found increased release or turnover of norepinephrine with little effect on dopamine. Decreased levels of brain norepinephrine and/or increased norepinephrine release or turnover have been observed following administration of LSD (36, 44–46), DOM (41, 47), mescaline (46), psilocybine (38, 45), and 5-MeODMT (40). In most of these studies, a higher dose of the test drug was needed in order to produce a significant effect on norepinephrine as compared to that necessary to affect brain serotonin. Also, a few studies have reported little or no effect of hallucinogenic drugs on brain norepinephrine. For example, Peters (48) found that LSD had no effect on norepinephrine level or synthesis; Tilson and Sparber (27) reported that mescaline had no effect on norepinephrine release or re-uptake; and Anden et al. (38) reported that DMT had no effect on norepinephrine turnover. These discrepant findings remain, at present, unexplained.

Several neurochemical studies have implicated dopamine in the action of LSD. Persson (49) reported that LSD increased its rate of synthesis, but exerted no significant effect on dopamine turnover. Von Hungen et al. (50) concluded that LSD exhibited dopamine agonist properties, on the basis of evidence that LSD, but not brom-LSD, stimulated adenylate cyclase activity in particulate preparations from rat corpus striatum. This action was shared by dopamine and blocked by specific dopamine antagonists such as haloperidol. Mescaline, DMT, and psilocin were ineffective in this neurochemical assay. More recently, Hetey and Quiring (32) have reported that LSD also decreased the depolarization-induced release of dopamine in rat nucleus accumbens in vitro.

It is worth noting that most of the neurochemical changes described in this section are of rather small magnitude, generally of the order of 20-30% changes from baseline. However, this in itself does not represent a serious obstacle for implicating such effects as important mediators of hallucinogenesis, since there is little available information concerning the magnitude of a neurochemical change that is *necessary* for producing an important functional effect.

Several points can be made in summarizing this section: (1) These data indicate that while some hallucinogens affect brain dopamine, and some affect brain

norepinephrine, all of them appear to have an effect on brain serotonin. (2) Several of the neurochemical effects of the hallucinogens can occur independently from an action upon the cell body, i.e., without a concomitant change in neuronal discharge rate. For example, LSD induces a decrease in serotonin release which outlasts its depression of serotonergic unit activity (28). (3) It is important to keep in mind that in order to produce most of these neurochemical effects, significantly larger drug doses are required than are necessary to produce behavioral changes in the same species (see below). (4) It should also be pointed out that the strength of the conclusions that can be drawn on the basis of these neurochemical studies is somewhat lessened by the fact that they are almost exclusively correlative in nature. Few attempts have been made at establishing cause and effect relationships. (5) Finally, the neurochemical studies of hallucinogenic drugs conducted to date appear, generally, to have been of limited value in attempts to provide definitive answers to questions regarding mechanisms of action.

PHARMACOLOGY

Several rather disparate topics will be brought together in this section under the rubric of pharmacology. First, we shall discuss the influence of hallucinogenic drugs upon specific receptor binding of agonist and antagonist ligands for various neurotransmitter systems, as well as receptor binding studies in which the hallucinogens themselves are employed as ligands. In this context we shall also describe studies which have employed autoradiographic methods to examine the anatomical localization of binding sites for these drugs in the CNS. Second, we shall discuss theoretical considerations of the neuronal receptor sites for the actions of hallucinogens. This will consist of a brief description of structure-activity relationships. Finally, we shall discuss the ability of hallucinogens to elicit or influence simple behavioral or electrophysiological effects that are presumed to reflect alterations of synaptic transmission in specific neurochemical systems.

As with most other studies of hallucinogenic drugs, experiments employing specific receptor binding have focused primarily upon the serotonergic and catecholaminergic systems. The initial studies in this field examined the specific binding of (^{3}H)-d-LSD. Bennett and Aghajanian (51) have reported that serotonin was approximately 1000 times more potent than dopamine in displacing (^{3}H)-LSD from its binding sites in homogenates of rat brain tissue. In keeping with this schema, the indole nucleus hallucinogen, DMT, and the serotonin antagonist, methysergide, were effective in displacing (^{3}H)-LSD, whereas the phenylethylamine hallucinogens, DOM and mescaline, were less effective. These authors also examined GABA, norepinephrine, glutamate and histamine and found them all to be ineffective at displacing (^{3}H)-LSD. The binding appeared to be stereospecific since l-LSD, the psychoactively weak isomer, was only about 1/10,000 as potent as d-LSD in displacing (^{3}H)-d-LSD. Lesions of the raphe nuclei which destroyed serotonergic neurons and their axon terminals had no effect on the amount of (^{3}H)-LSD binding in rat forebrain homogenates, which implies that this binding is not associated with presynaptic receptors (i.e. receptors at any of a variety of sites on serotonergic neurons). These general results were soon confirmed by Bennett and

Snyder (52) and Lovell and Freedman (53). Bennett and Snyder (52) examined a large number of compounds and found that various indole nucleus hallucinogens and serotonin antagonist drugs were effective in displacing (^{3}H)-LSD from its binding sites in rat cortex. Somewhat puzzling was their finding that brom-LSD, a psychoactively weak congener of LSD, was as effective as d-LSD in displacing (^{3}H)-d-LSD. An important additional piece of information on this latter issue was provided by Bennett and Snyder (54) who reported that although brom-LSD was as effective as LSD in displacing (^{3}H)-LSD binding, it was only 1/10 as effective as LSD in displacing (^{3}H)-serotonin binding.

Several studies have specifically examined the effect of hallucinogenic drugs upon receptor binding in the dopamine system. In support of behavioral and neurochemical data indicating that LSD may exert dopamine agonist actions, Burt et al. (55) have reported that d-LSD had substantial affinity for (^{3}H)-dopamine binding sites in calf striatal tissue. By contrast, psilocin, DMT, DOM, and mescaline were ineffective. Again, somewhat surprisingly, they found that brom-LSD was also effective in displacing (^{3}H)-dopamine. Creese et al. (56) found that LSD binds to dopamine antagonist, as well as agonist, receptor sites*, which implies that it may possess mixed agonist-antagonist actions. Once again, brom-LSD was also active at both sites, however, the pattern was somewhat different: brom-LSD was less effective as a dopamine agonist and more effective as a dopamine antagonist than d-LSD. Somewhat in contrast to these results of Creese et al. (56), Whitaker and Seeman (57) found that LSD was not very active in competitively blocking dopamine antagonist binding.

More recently, a good deal of attention has been directed toward studying the interaction of hallucinogenic drugs with both a serotonin agonist receptor (labelled with (^{3}H)-serotonin) and a serotonin antagonist receptor (labelled with various ligands, e.g. (^{3}H)-spiperone, (^{3}H)-mianserin, etc.). Additionally, it is assumed by some that (^{3}H)-LSD may label both the agonist and antagonist forms of the serotonin receptor. Peroutka and Snyder (58) have reported that LSD was equally effective in binding to serotonin agonist and antagonist receptors. They also reported that brom-LSD and methysergide had less affinity for the agonist receptor and greater affinity for the antagonist receptor than LSD. Therefore, a shift in favor of antagonist receptor binding may decrease a compound's hallucinogenic potency. The classical serotonin antagonists cyproheptadine, cinanserin, and mianserin competed effectively for serotonin antagonist binding sites (labelled with (^{3}H)-spiperone). In a follow-up to these studies, Peroutka and Snyder (59) have reported that mianserin binds to the serotonin antagonist receptor with great affinity. The importance of this fact will be more apparent later, when we discuss the ability of mianserin and other serotonin antagonist drugs to block the behavioral effects of hallucinogenic drugs.

Rogawski and Aghajanian (60) have hypothesized that LSD may bind to a distinct

* By 'antagonist receptor' I do not mean to imply that an antagonist is the endogenous ligand, but that pharmacological antagonists display a much greater affinity for this receptor than do the endogenous agonist ligands. Therefore, these receptors can be much more effectively studied by employing labelled antagonist drugs, and, in this way, they can be differentiated from the receptors heavily labelled by the agonist.

serotonin receptor which is located directly on the dendrites and/or perikarya of serotonergic neurons. They argue on the basis of the existing literature that this receptor is probably not labelled by either (^{3}H)-serotonin or (^{3}H)-spiperone, but that it may be labelled by (^{3}H)-d-LSD. Presumably, the reason why the amount of (^{3}H)-d-LSD binding is not altered by the destruction of serotonergic neurons is because the number of binding sites on these particular neurons represents a very small proportion of the total number of receptor sites where (^{3}H)-d-LSD binds.

As a final note on the subject of specific receptor binding, two studies have recently reported interactions between various hallucinogens and the H_1 (64) and the H_2 (65) histamine receptors. The compounds appear to be much more active at the H_1 site. However, in both studies, brom-LSD displayed as much activity as d-LSD.

A number of studies have examined the anatomical distribution of [^{3}H]-d-LSD binding through the use of autoradiography. This has been investigated in a variety of animals, including mouse, rat, and monkey, and the general results have been quite consistent across species. Areas of the cerebral cortex and corpus striatum are most heavily labelled, subcortical areas, especially in the limbic system, are the next most heavily labelled, while the brainstem and cerebellum display the least (^{3}H)-d-LSD binding (51, 52, 54, 61–63). The low level of binding in the brainstem is of particular interest because the raphe nuclei, where the perikarya of most serotonergic neurons are clustered, were among the areas examined. These results, plus the fact that there is very little change in overall binding following the destruction of serotonergic neurons, suggest that the binding occurs postsynaptic to serotonergic cells.

The relationship of these LSD binding sites to the binding sites for neurotransmitters such as serotonin and dopamine, remains somewhat obscure. However, a recent experiment by Meibach et al. (66) has provided some important information on this issue. They compared the autoradiographic localization of LSD in untreated tissue with tissue to which unlabelled serotonin had been added. A difference in LSD binding in these two sets of tissues was attributed to binding to serotonin receptors, since it is assumed that the higher concentration of unlabelled serotonin would compete with the (^{3}H)-d-LSD for serotonin receptor sites. In many areas (e.g. hippocampus, septal area, pons, medulla and cortical layers III and IV) the labelled LSD was almost completely displaced by serotonin, while in other areas (e.g. striatum, substantia nigra, and cortical layers, I, II and VI) it was substantially less effective or ineffective. The approach could obviously be extended to an examination of the contributions of a variety of other neurotransmitter receptors to the binding of LSD and other hallucinogens.

What general conclusions can we draw on the basis of these receptor binding studies? First, an action at dopamine receptors does not appear to be a necessary condition for a drug to act as a hallucinogen. This is based on the fact that many hallucinogens have little affinity for either the agonist or antagonist dopamine receptor. The fact that LSD, the most potent hallucinogen, has an affinity for both dopamine receptors may imply that such an action may contribute to the potency of a hallucinogenic drug's effect. On the other hand, all of the hallucinogens have an affinity for the serotonin antagonist and/or agonist receptor, and the degree of affinity shows a general correlation with the hallucinogenic potency of the compounds. Second, although it appears somewhat problematic that brom-LSD has

been shown to be as effective as LSD in a number of binding studies, a closer examination indicates that their agonist-antagonist ratios are consistently different. In both dopamine and serotonin receptor binding studies, LSD has a greater affinity for the agonist receptor and less affinity for the antagonist receptor than brom-LSD. Indeed, this agonist-antagonist ratio may be one of the critical variables that determines whether, and to what degree, a compound will exert hallucinogenic actions. Finally, since virtually none of the binding occurs on presynaptic serotonergic neurons, it is clear that a preponderance of this binding occurs on neurons postsynaptic to serotonergic neurons. The anatomical distribution of LSD binding sites also supports this conclusion. As alluded to above, this concept of the direct postsynaptic actions of hallucinogenic drugs will be a dominant theme in this review.

A number of investigators have hypothesized, on the basis of structure-activity relationships, that the various hallucinogenic drugs may act upon a common receptor (67–69). Much of this speculation is based upon stereochemical analysis of the three-dimensional conformation that theoretically might be assumed by the nucleus and side chains of molecules of the various ergot-, indole-, and phenylethylamine-hallucinogens. The receptor in question is variously assumed to have a shape that would effectively bind compounds with either an indole or catechol nucleus structure, or a larger receptor with combined sites that would accommodate molecules of both types of compounds (69–73). 'Activity', in these analyses, is assessed in a variety of ways, including peripheral pharmacological action, behavioral or physiological effects in animals, and psychoactive potency in humans. On the basis of these types of analyses, alone, it is difficult to come to any definitive conclusions regarding the mechanisms of action of hallucinogens. However, they have made us aware of the possibility that various classes of hallucinogens may act on a common receptor. As with many approaches, it can be extremely useful if employed in conjunction with other types of experiments.

In the final portion of this section on pharmacology I shall describe the effects of hallucinogenic drugs on simple behavioral and electrophysiological measures. We shall also examine the evidence that these effects are mediated by actions upon specific neurotransmitter systems.

Anden et al. (36) were among the first to suggest that LSD exerted a direct serotonin agonist effect in the CNS. This conclusion was based on experiments in which LSD increased the magnitude of the hindlimb extensor reflex in spinal rats, an effect that is also produced by a variety of manipulations known to elevate serotonergic neurotransmission. This group of investigators later reported that similar effects were produced by psilocybine and DMT (38). Evidence that these were direct effects of these hallucinogens is provided by experiments which show that prior depletion of endogenous stores of CNS serotonin has no effect on LSD's ability to influence the extensor reflex (36, 38). Further evidence that these effects of LSD are attributable to a serotonin agonist action is indicated by their blockade with classical serotonin antagonist drugs (74).

In an attempt to extend this type of analysis and to employ a response with greater neurochemical specificity than the extensor reflex, we studied the ability of LSD to elicit the 'serotonin syndrome'. This syndrome is considered a behavioral assay for

increased activity in serotonin-mediated synapses (75, 76). The syndrome is observed in rats and other species, and consists most conspicuously of tremor, rigidity, Straub tail, hindlimb abduction, reciprocal forepaw treading, and lateral head weaving. Evidence that the presence of this constellation of behavioral signs reflects increased serotonergic transmission is detailed in a review by Jacobs (76). We reported that intraperitoneal administration of LSD effectively produced this syndrome in rats (ED_{50} = 600 μg/kg) (77). Further evidence for the specificity of this effect was provided by a study which showed that the specific destruction of serotonin nerve terminals, by the neurotoxin 5,7-dihydroxytryptamine, resulted in a supersensitive response to LSD. Evidence that this was a direct serotonin agonist effect of LSD was provided by experiments in which we showed that prior depletion of endogenous stores of brain serotonin had no influence on LSD's effectiveness (77).

This line of investigation has been continued more recently by Sloviter et al. (78). They reported that unlike LSD, brom-LSD did not elicit the syndrome, even in very high doses. In fact, pretreatment with brom-LSD had a significant blocking effect on the response to LSD. These authors also reported that classical serotonin antagonist drugs such as methysergide, metergoline, and mianserin blocked the serotonin syndrome induced by the short-acting hallucinogen 5-MeODMT. Finally, in an important extension of this line of investigation, they found that the direct serotonin agonist actions of indole nucleus hallucinogens also generalized to phenylethylamine hallucinogens. Both mescaline and DOM produced the syndrome and these effects were not blocked by prior depletion of endogenous stores of brain serotonin.

Two other sets of experiments which have employed the serotonin syndrome in the study of hallucinogenic drugs deserve mention. As described above, the fact that LSD elicits this sydrome, and that this is not affected by prior serotonin depletion, implies that LSD exerts a direct postsynaptic serotonin agonist effect (77). In this same study, we have reported that the repeated daily administration of LSD led to a dramatic tolerance to the behavioral response to this drug: day 1 ED_{50} = 600 μg/kg, day 5 ED_{50} = 1860 μg/kg. Thus, we demonstrated that LSD did not only have a direct postsynaptic serotonergic action, but that tolerance to the syndrome response might also be mediated postsynaptically. This is of particular interest since we have also reported (79, 80) that tolerance to LSD is not mediated by an altered presynaptic response (i.e., a change in the sensitivity of serotonergic neurons to LSD – these data will be described more fully in a later section). This lack of change in serotonergic neurons during tolerance is also supported by microspectrofluorimetric analyses of LSD-induced increases in serotonin fluorescence in serotonergic cell bodies (80a). In an attempt to directly examine whether tolerance to the serotonin syndrome-inducing effects of LSD was mediated by an alteration of postsynaptic receptor sensitivity, we carried out an experiment employing receptor binding. Repeated administration of LSD to rats (100 μg/kg every six hours for four days) resulted in significant decreases in the number of binding sites for both (^{3}H)-serotonin and (^{3}H)-LSD in both the forebrain and brainstem (81). This effect was not produced by a single injection of LSD, nor by repeated injections of brom-LSD. In addition, there was no significant change in dopamine antagonist binding. These receptor binding data therefore support the hypothesis that tolerance to at

least some behavioral effects of LSD are mediated by an alteration in sensitivity of postsynaptic serotonin receptors (as discussed above, it is still unclear at what receptor sites (^{3}H)-LSD binding occurs.)

Several years ago Savage et al. (81a) reported that chronic administration of monoamine oxidase inhibitors (MAOIs) to rats for 4-16 days produced a significant decrease in the number of binding sites for (^{3}H)-serotonin. This decrease in receptor sites was not seen after a single injection of a MAOI. The effect was assumed to be due to the increased long-term build-up of synaptic levels of serotonin that are known to be produced by MAOIs, since the effect was blocked by the co-administration of a serotonin-depleting agent. This conclusion regarding serotonin is also supported by the fact that inhibitors of MAO-B, which have little effect on brain serotonin, did not have this effect on serotonin receptor binding. Chronic administration of tricyclic antidepressants also failed to reduce (^{3}H)-serotonin binding. These results were confirmed and extended by experiments from another laboratory. Peroutka and Snyder (82) reported that MAOIs decreased the availability of both serotonin agonist and antagonist binding sites, whereas tricyclic antidepressants selectively decreased the availability of serotonin antagonist binding sites.

In a recent follow-up of these results, Lucki and Frazer (83) have reported that the serotonin syndrome normally elicited by the hallucinogens 5-MeODMT and LSD was completely blocked by the chronic administration of a MAOI, but not by chronic administration of tricyclic antidepressants. These results are therefore also consistent with the hypothesis that the behavioral effects of these compounds are mediated by a direct postsynaptic serotonergic effect. Furthermore, Lucki and Frazer suggest that the important action may be occurring at the serotonin agonist binding site. In the following section, I shall describe experiments from my laboratory which have confirmed and extended these results by examining the effects of hallucinogens on the behavior of cats.

Up to this point we have exclusively been discussing the serotonin agonist effects of LSD. There is also evidence that under some conditions LSD can act as a serotonin antagonist. As we shall see in a later section, at the cellular level, serotonin can be shown to exert excitatory and inhibitory, as well as modulatory, synaptic effects. Under these conditions, LSD displays an antagonist action exclusively on serotonin's excitatory neuronal effect. This same antagonistic effect of LSD on serotonin has also been demonstrated at a physiological level. Anderson (84) has reviewed experiments on spinal reflexes conducted in acute spinal cats. Stimulation of the dorsal roots elicits monosynaptic, polysynaptic, and dorsal root reflexes. Increases in CNS levels of serotonin increased the size of the monosynaptic reflex and decreased the size of the polysynaptic and dorsal root reflexes. The increase in magnitude of the monosynaptic reflex induced by serotonin was blocked by a variety of classical serotonin antagonist drugs, and, in addition, it was blocked by the systemic administration of LSD. Decreases in the other two types of spinal reflexes were unaffected by LSD and the serotonin antagonists.

Another simple behavioral model in rats has been used to examine any direct or indirect dopamine agonist effects of hallucinogenic drugs. Pieri et al. (85) and Trulson et al. (86) reported that LSD exerted a potent direct dopamine agonist

action when examined in the unilateral dopamine lesion rotational model, whereas brom-LSD, psilocin, DMT, and 5-MeODMT were without effect. Interestingly, DOM and mescaline exerted mild amphetamine-like dopamine-releasing effects.

Finally, a presynaptic model of the action of hallucinogens predicts that these compounds should decrease the level of serotonin neurotransmission. There is an electrophysiological model available to assess this hypothesis. A variety of manipulations that decrease serotonin neurotransmission cause the release of large monophasic potentials recorded in the pons, lateral geniculate, and occipital cortex (PGO waves) of cats (86a). Therefore, if the overall effect of hallucinogens such as LSD is to produce decreased serotonergic neurotransmission in the CNS, they should cause release of PGO waves. In a careful analysis of this issue Brooks (87) reported that LSD, in a wide variety of doses, completely failed to do so. We have found similar results with 5-MeODMT (Jacobs and Heym, unpublished results). In a related series of studies, Ruch-Monachon et al. (88) reported that intravenous administration of LSD *decreased* the frequency of occurrence of PGO waves in cats previously treated with serotonin-depleting drugs. They also reported similar results for DMT and psilocybine.

There are several conclusions that we can draw in summary of the last portion of this section. (1) A good deal of data indicates that LSD and the other hallucinogens appear to exert a direct postsynaptic serotonergic effect. (2) The behavioral effects of these drugs can be blocked potently by classical serotonin antagonist drugs. (3) Gross electrophysiological studies do not support the concept that the hallucinogens produce an overall depression of serotonergic neurotransmission. (4) Although behavioral studies indicate that LSD may exert dopamine agonist effects, this is not a property universally shared by all hallucinogens.

BEHAVIOR

A large number of studies, employing a variety of different paradigms, have examined the behavioral effects of hallucinogens. We shall be selective in this chapter and discuss only those that bear on the issue of the mechanism of action of these drugs. The effects of hallucinogens are difficult to study in animals because they are often manifested most prominently in the psychological domain, and are therefore most accessible through verbal report. Hallucinogens do produce some overt behavioral effects in animals which, however, are often not obvious. Although no available animal behavior model is completely specific to hallucinogens, we shall still be able to draw some strong conclusions about these drugs because a large amount of convergent evidence exists. To strengthen several of the arguments that will be made in this section, we shall include, where appropriate, descriptions of experiments in humans.

Although experimental studies often do not fit neatly into specific categories, I have attempted, for the sake of exposition, to provide some groupings for the experiments described in this section. First, we shall discuss studies that manipulate brain levels of serotonin; then experiments which examine the effects of hallucinogenic drugs upon operant responding; next, we shall describe studies that

employ drug discrimination techniques to study hallucinogens; and finally, studies that have attempted to develop animal behavior models for the actions of hallucinogens by examining changes in spontaneously occurring behavior.

One of the simplest approaches to examining the role of serotonin in the behavioral effects of hallucinogens involves comparing the effects of these drugs with the effects of decreasing brain serotonin levels. Destruction of serotonergic neurons in the midbrain of rats produces an augmentation of the acoustic startle response (89), which is similar to that produced by LSD (90) and DMT (91). The augmented startle response produced by 5-MeODMT is blocked by pretreatment with the serotonin antagonists cinanserin and cyproheptadine (92).

Another approach involves the direct manipulation of CNS serotonin and examination of the effect on the actions of hallucinogenic drugs. Stoff et al. (93) have reported that inhibition of serotonin synthesis potentiated mescaline's facilitation of shuttlebox escape/avoidance in rats. A number of studies by Appel and his colleagues have shown that prior serotonin depletion, either by means of destruction of serotonin-containing neurons (94), or by pharmacological means (95–97) potentiates LSD's effectiveness in suppressing a bar press response for food in rats. Similarly, the suppressant effects of DOM, mescaline, and psilocybine were also potentiated by prior serotonin depletion (98, 99). We shall discuss this 'pause'-inducing effect of hallucinogens more fully later in this section. However, it is evident, as with most other effects of hallucinogens, that this change is not specific to this class of drugs. For example, it is produced by amphetamine and phenobarbital (98, 100). In addition, a variety of drugs might be expected non-specifically to block or potentiate the effects of hallucinogens on dependent variables such as bar pressing. Nonetheless, these data are valuable when considered in conjunction with other convergent evidence.

Experiments on the role of serotonin in the action of LSD which were conducted on human subjects may be more easily interpreted because they directly examined the hallucinogenic effects of LSD. Prior depletion of brain serotonin with reserpine accentuated the effects of LSD (44, 101), while prior treatment with a MAOI, which increases the synaptic activity of serotonin, attenuated the effects of LSD (102, 103) and DMT (104). One of these studies deserves further comment. Grof and Dytrych (102) reported that chronic treatment of patients with the MAOI nialamide resulted in either a minimal reaction or *no response to LSD* in doses as high as 400–500 μg. Another extraordinary aspect of this study was the fact that such a blockade of LSD's effect persisted for at least two weeks after nialamide was withdrawn. With this in mind, it is worth recalling our description, in the preceding section, of the effects of chronic MAOI administration on decreasing serotonin receptor binding as well as on decreasing behavioral response to hallucinogenic drugs in rats. We shall return to discuss this type of paradigm again later in this section.

Other studies in humans also lend support to the concept that hallucinogens act by means of an effect upon the brain serotonin system, and further suggest that the drugs may act specifically on postsynaptic serotonergic receptors. There are a number of reports that methysergide, a drug with serotonin antagonist actions, can elicit mildly hallucinogenic effects (105–108). Furthermore, Sai-Halasz has reported that the effects of DMT were potentiated by methysergide (109). In this context it is

important to recall the receptor binding data regarding methysergide described in the preceding section. Unlike other serotonin antagonists, methysergide also has a reasonably strong affinity for the serotonin agonist receptor that is labelled by (^{3}H)-serotonin. As mentioned above, this combined serotonin agonist-antagonist action may be crucial for hallucinogenesis.

As briefly discussed earlier in this section, one of the characteristic effects of hallucinogenic drugs is to produce a 'pause' in the responding of a rat trained to press a bar either for a food or water reward, or to avoid a shock (96, 110, 111). Rats given a drug such as LSD will abruptly stop bar pressing for a period of 10–20 minutes and will then abruptly resume responding again at the predrug rate. The early studies in this field demonstrated that the depressant effects of hallucinogens on response rate were potentiated by serotonin depletion (94–98). Such enhanced disruptiveness is difficult to interpret with any degree of specificity since it may occur as a result of non-specific factors. On the other hand, manipulations which block the disruptive effects of hallucinogens would provide more powerful information, since an increase in a specific behavior is less likely to be attributable to non-specific drug actions. A series of such studies has recently been completed. Commissaris et al. (112) have reported that the responding of rats trained to press a bar 40 times in order to obtain a small food pellet was disrupted for long periods by DOM. This effect of DOM was blocked by pretreatment with the serotonin antagonist cinanserin, but not by the dopamine antagonists haloperidol and chlorpromazine. In a subsequent study employing the same paradigm, Commissaris et al. (100) reported that the response suppressant effects of LSD, DOM, DMT, and mescaline were blocked by pretreatment with the serotonin antagonist metergoline. In control studies, they also demonstrated that the suppressant effects of amphetamine and phenobarbital were not blocked by metergoline, a finding which adds strength to the argument that the effect of the hallucinogens is mediated by an action on serotonergic receptors.

Another experimental paradigm that has proven to be useful in the study of hallucinogenic drugs is drug discrimination. This approach has become increasingly popular in recent years. Basically, a rat is deprived of food (or water) and is then trained that pressing one of two bars will produce food if it has been previously administered a particular drug (e.g. LSD), while pressing the other bar will produce food if it has been previously administered another compound (e.g. saline or amphetamine). When rats have been highly trained on such a discrimination, i.e. if injected with LSD, choose the left bar, if injected with amphetamine, choose the right bar, they can be used in a variety of interesting ways. For example, the rat can be given a third compound, such as DMT or cocaine, and then observed for its choice of a bar. If the drug has properties that make it 'LSD-like', the rat would choose the left bar, if the drug was 'amphetamine-like', it would choose the right bar, and if the drug had none of these properties or both of them equally, the choice would be somewhat random. The blocking effects of one drug upon another drug's actions can also effectively be tested in this paradigm, a positive feature of which is that it is often sensitive to very low drug doses (e.g. 5 μg/kg LSD) (113). A limitation that this paradigm shares with other behavioral approaches to studying drug action is its lack of complete specificity. For example, Winter (114) has reported that rats

trained to discriminate mescaline generalized to 2,3,4-trimethoxyphenylethylamine, a non-hallucinogen, and in a subsequent study, he has demonstrated that rats trained to discriminate LSD generalized to 2,5-dimethoxy-4-methyl-α-ethylphenethylamine, a non-hallucinogen (115).

This area of research began with the demonstration, by Hirschhorn and Winter (116), that the systemic administration of either LSD or mescaline to rats could function as a discriminative stimulus. Several studies have reported that animals trained to discriminate a high dose of a hallucinogen, such as mescaline or LSD, will show a moderate degree of generalization to a low dose of the same drug (117–119). When this experiment is repeated in animals whose CNS stores of serotonin are depleted, the amount of generalization is increased, implying that at least some aspect of the hallucinogenic drug's effect is mimicked by decreased serotonergic neurotransmission. This approach has also been used to demonstrate that the cue properties across hallucinogenic drugs are similar. For example, rats trained to discriminate 5-MeODMT generalized to DOM, DMT, and mescaline (120); those trained to discriminate mescaline generalized to DOM (121); rats trained on LSD transfer to mescaline and psilocybine, but not amphetamine (122); and those trained on DOM generalized to mescaline but not to amphetamine or cocaine (123). In one of the most interesting studies in this series, Colpaert et al. (124) have reported that rats trained to discriminate LSD showed partial generalization to the serotonin antagonists cyproheptadine, methysergide, and mianserin. This may imply that some aspect of LSD's effect is mimicked by serotonin receptor blockade.

Most important for the present discussion are those studies that have attempted to block the discriminative properties of the hallucinogens. Several studies have examined one or more of the classical serotonin antagonist drugs (cinanserin, cyproheptadine, methysergide, and/or metitepine) and found them to be effective in blocking the discriminative stimulus properties of one or more of the hallucinogens (mescaline, DOM and/or LSD) (117, 121, 125–127). Silverman and Ho (121) further reported that although cinanserin and methysergide, but not haloperidol, blocked the cue properties of DOM, they did not block those of methylphenidate or amphetamine, implying some degree of specificity of action. Furthermore, Kuhn et al. (127) have reported that although several serotonin antagonists blocked the discriminative stimulus properties of LSD, a variety of other drugs, such as antagonists of dopamine, acetylcholine, histamine, and α- and β-adrenergic receptors, did not exert a blocking action on LSD's cue properties.

For the remainder of this chapter, we shall examine the effects of hallucinogenic drugs upon spontaneously occurring behavior in animals. Several years ago, in a comprehensive study investigating the behavioral effects in cats of a wide range of doses of LSD, we observed the emergence of several behaviors that were rarely, if ever, seen in saline-injected animals (128,129). These responses were elicited in cats housed in their home cages, and included limb flicking (shaking the paw as if to remove some foreign substance), abortive grooming (failure to consummate the grooming act, for example, licking or scratching in mid-air), investigatory behavior, and hallucinatory-like behavior. The peak behavioral response occurred at a dose of 50 μg/kg, where 40-50 limb flicks/hour were elicited, but significant effects were produced by doses as low as 2.5 and 10 μg/kg. Other hallucinogens, such as psilocin,

mescaline, DMT and DOM, also produced these responses, but they were not elicited by a variety of non-hallucinogens: saline, Δ^9-tetrahydrocannabinol, amphetamine, chlorpheniramine, caffeine, and atropine (129,130). Brom-LSD and methysergide, both of which produce mildly hallucinogenic effects in humans, produced small, but significant, increases in responses such as the limb flick. These results may also be of more general interest since similar behavioral effects have been reported to be produced by various hallucinogens in rats (131) and monkeys (132–134).

On the basis of these data, we proposed that emergence of this cluster of behaviors, but especially the limb flick and abortive groom responses (the two that were most reliable and robust), could be used as an animal behavior model for the actions of hallucinogenic drugs (128,129). There is now reason to question this conclusion since we, and others, have found that several drugs not typically assumed to be hallucinogens also evoke these responses, for example lisuride, quipazine, apomorphine, and pilocarpine (135–139). However, the doses of these drugs that are necessary to produce these effects in cats are far in excess of those that are administered to humans. Therefore, these drugs might well be 'LSD-like' if given to human subjects at these high dose levels. We also found that serotonin depletion, either by means of synthesis inhibition or nerve terminal destruction, could elicit these responses (140; Jacobs and Trulson, unpublished observations). Since the hallucinogens were also hypothesized to act by decreasing serotonergic neurotransmission, via a depression of serotonergic unit activity, we hypothesized that the emergence of these behaviors was dependent on decreased activity at serotonin-mediated synapses (129,140). We now know that this is no longer tenable since, as discussed above, these responses can be elicited by apomorphine, lisuride, and pilocarpine, none of which are known to decrease serotonergic neurotransmission. More recently, we have proposed that the primary CNS action necessary to elicit these responses is increased dopaminergic neurotransmission mediated either directly or indirectly by means of decreased serotonergic neurotransmission (141).

Despite our incomplete understanding of the neurochemical basis of these responses, and the presumed lack of complete specificity of these effects for hallucinogenic drugs, they have nonetheless been helpful in the study of this class of drugs. For example, measurement of these responses proved very useful in the study of the development of tolerance to LSD. If cats are given an initial LSD injection of either 10 or 50 μg/kg i.p. and then given a subsequent injection of 50 μg/kg 24 hours later, they show virtually no behavioral response to this second injection (142). Such single dose tolerance begins to develop within hours and lasts for several days. As we shall describe in the next section of this review, we have also utilized these measures as a behavioral indicator of the action of hallucinogenic drugs in conjunction with single unit recordings of monoamine-containing neurons in awake, unrestrained cats.

In keeping with the basic theme of this section, we now turn to a discussion of experiments that have utilized this cat behavioral model to study the mechanism of action of hallucinogenic drugs. As mentioned above, brain serotonin depletion itself elicits limb flicking and abortive grooming, and it potentiates the effects of LSD (140; Jacobs and Trulson, unpublished observations). This suggests that at least part

of the action of hallucinogens is mediated by decreased serotonergic neurotransmission. Such an effect may be *necessary* for hallucinogenesis, but it does not appear to be *sufficient*, since we have found that administration of a variety of serotonin antagonist drugs fails to elicit these responses (Jacobs, Heym and Rasmussen, unpublished observations). Recall that both brom-LSD and methysergide elicit these responses (129), but that both also possess mild serotonin agonist activity in addition to their serotonin antagonist effects. In higher doses, the serotonin antagonist actions of methysergide may predominate, since it can block the effects of LSD (143). Schlemmer et al. (134) have reported that pretreatment of Stumptail monkeys with cinanserin blocked LSD's ability to elicit limb jerks. Similarly, we have recently found that mianserin, a potent serotonin antagonist drug, exerts a dose-dependent blocking effect (0.25–5.0 mg/kg i.p.) on the behavioral effects of LSD (50 μg/kg i.p.) in the cat (Heym, Rasmussen and Jacobs, unpublished observations). This occurs in the absence of any obvious behavioral effects such as catalepsy or sedation produced by mianserin itself. Further evidence that this blockade is not a non-specific effect is provided by the fact that mianserin had no depressant effect on the same behaviors (e.g. limb flicking) when produced by the dopamine agonist apomorphine (4 mg/kg i.p.), but it did block the behavioral effects of DOM (250 μg/kg i.p.). Although mianserin has pharmacological effects other than its serotonin antagonist action, this latter effect is more than likely responsible for the blockade of the LSD-elicited behaviors, since a similar blockade was produced by cyproheptadine. If mianserin exerts its blocking action on the behavioral effects of LSD by means of a serotonin antagonist action, it could do so either postsynaptically (i.e. on serotonergic target neurons) or presynaptically (i.e. on serotonergic neurons themselves). Preliminary evidence from our laboratory, to be described more fully in the following section, strongly argues in favor of a postsynaptic blockade, since mianserin failed to block the depressant effects of LSD upon serotonergic neurons localized in the midbrain of the cat.

In another experiment from my laboratory, we followed up on the studies employing chronic administration of MAOIs, described in the preceding section (Heym and Jacobs, unpublished observations). Cats were given a daily injection of nialamide (5 mg/kg i.p.) for one week and then tested with LSD, DOM, or apomorphine at various times after the drug was withdrawn. The behavioral response to LSD (50 μg/kg i.p.) and DOM (250 μg/kg i.p.) was almost totally blocked for the first week, showed a small amount of recovery during the second week, and returned approximately to baseline levels around the third or fourth week. To examine whether this suppression was due to any non-specific factors, such as general malaise or debilitation, animals were tested with a high dose of apomorphine (4 mg/kg i.p.) which also elicits limb flicking and abortive grooming. At no time following nialamide withdrawal was there any significant depression of the response to apomorphine. These data, in conjunction with the rat behavioral and receptor binding data described above, suggest that LSD and DOM may exert their primary action on serotonergic receptors. Furthermore, these results directly parallel the findings of Grof and Dytrych (102), who studied the effects of LSD in humans who had been withdrawn from nialamide.

Finally, we should mention that several investigators have noted that a variety of

hallucinogens elicit retropulsion or backward walking in rats, and have proposed that this can be used as a behavioral model for hallucinogenesis (144–146). Curzon et al. (147) further proposed that this behavioral effect may be attributable to both serotonergic and dopaminergic activation. Consistent with an important role of serotonin in this response, Yamamoto and Ueki (146) reported that DOM-induced backward locomotion in rats is blocked by pretreatment with methysergide.

In conclusion, the material presented in this section strongly suggests that the behavioral effects of a variety of hallucinogenic drugs, in both animals and humans, are heavily dependent upon an action on the brain serotonin system. The exact nature of this interaction between hallucinogen and the serotonin system is not completely understood, but it seems to involve a combined agonist-antagonist action, and one which may be exerted primarily upon postsynaptic serotonergic receptors. We shall examine this issue of presynaptic versus postsynaptic action of hallucinogens in greater detail in the next section. However, it is worth pointing out here, that in a number of the studies described above, the serotonergic presynaptic action of the hallucinogen was precluded or at least strongly compromised, either by synthesis inhibition or nerve terminal destruction; yet the behavioral effectiveness of the drug was either undiminished or enhanced.

ELECTROPHYSIOLOGY

In the final section of this review we shall discuss studies that have employed electrophysiological methods in attempting to analyze the mechanism of action of hallucinogenic drugs. First, we focus on studies that have recorded single-unit activity in anesthetized and/or immobilized animals. In doing so, we shall discuss the presynaptic serotonergic model of hallucinogenic drug action (i.e. the concept that these drugs exert their effects specifically by depressing the activity of serotonergic neurons). This will be followed by a discussion of the evidence that is contradictory to this hypothesis. In the second part of this section, we focus upon studies that have examined single unit activity recorded in awake, freely moving animals. As we shall see, much of these latter data are also inconsistent with a strictly presynaptic serotonergic model of hallucinogenic drug action.

Based on previous neurochemical data which indicated that LSD decreased serotonin turnover, Aghajanian and his coworkers reasoned that this might be mediated by a decrease in the unit activity of serotonergic neurons (148). They therefore set out to test this directly by examining the effects of systemic administration of LSD on unit activity of serotonergic neurons in the midbrain of the rat. This study was made feasible by the pioneering fluorescence histochemical work of Dahlstrom and Fuxe (149), who described the localization of the cell bodies of all monoamine-containing neurons, including serotonin, within the brainstem of the rat. Most serotonergic neurons were found within, or near, the various midline raphe nuclei. Equipped with this information, Aghajanian et al. (148) lowered tungsten microelectrodes into the area of the midbrain dorsal and median raphe nuclei of chloral hydrate anesthetized rats and observed the slow (1–2 spikes/sec)

and regular discharge pattern that appears to characterize all serotonergic neurons in brain. When LSD was then administered intravenously, a dose of 25–50 μg/kg was sufficient to cause a complete suppression of activity. By contrast, none of the neurons outside of the raphe ceased firing in response to the drug.

In an extension of this study, the same group of investigators (150) reported that an LSD dose of 12.5 μg/kg i.v. produced a complete suppression of activity in 50% of the serotonergic cells tested. Units in a variety of control areas were typically unaffected or slightly accelerated in rate by the drug dose. An important control experiment in this series demonstrated that, unlike LSD, brom-LSD exerted virtually no effect on serotonergic neurons in doses of 25-50 μg/kg. These investigators went on to test the effects of a variety of systemically administered psychoactive drugs, including several hallucinogens. They reported that DMT produced an effect very similar to that of LSD, but at significantly higher doses (approximately 700 μg/kg). Interestingly, mescaline and DOM depressed the activity of only a subgroup of midbrain raphe neurons, those in the ventral portion of the dorsal nucleus. Atropine, scopolamine, phencyclidine, and chlorpromazine were essentially without effect on serotonergic unit activity. In separate studies, Aghajanian's group also showed that psilocin was effective in depressing serotonergic unit activity (14), whereas amphetamine consistently increased the activity of these cells (151). Finally, an experiment from my laboratory indicated that low doses (20 μg/kg i.v.) of the hallucinogen 5-MeODMT also exerted a potent depressant effect on the activity of serotonergic neurons (152).

The next issue was to determine whether LSD and related hallucinogens exerted their depressant effects directly on serotonergic neurons, or whether this action was mediated by some type of feedback loop. Since serotonergic neurons in the dorsal and median raphe nuclei send their axons primarily rostrally, into the forebrain, it seemed reasonable to assume that the hallucinogens might act on target neurons in the forebrain that would then feed back to serotonergic neurons, causing them to decrease their activity. This concept was tested in two different ways. LSD (153) and 5-MeODMT (152) were administered systemically to animals that had complete transactions of the neuraxis, immediately rostral to the dorsal and median raphe nuclei, thus precluding any significant feedback influence from the forebrain. In both studies, the compounds were equally effective in depressing the activity of serotonergic neurons in the intact and transected groups of animals. A second approach involved the direct application of LSD, psilocin, DMT, 5-MeODMT, and mescaline onto neurons in the area of the dorsal raphe nucleus by means of microiontophoresis (14, 154, 155). In all cases, excluding the experiments with mescaline, the iontophoretic application of the hallucinogenic drugs produced a profound suppression of serotonergic unit activity at low ejection currents. This supported the hypothesis that the effect of hallucinogenic drugs is mediated by a direct action upon serotonergic neurons, possibly one mediated by serotonin receptors. This latter concept is compatible with data indicating that serotonergic neurons receive inputs from other serotonergic neurons, and thus, presumably, contain serotonin receptors on their perikarya and/or dendrites (156). Since the iontophoretic application of mescaline failed to depress serotonergic unit activity, even in the subset of those cells that were affected by systemic administration, it was

concluded that unlike the other hallucinogens, mescaline's effect on serotonergic neurons is mediated indirectly.

A final, very important, issue remained to be resolved. If the action of hallucinogenic drugs is mediated by a depressant action on serotonin-containing neurons, why then are not compounds such as l-5-hydroxytryptophan (l-5-HTP) and l-tryptophan, both of which depress raphe unit activity (157, 158), hallucinogenic? The answer, at least in the context of this theoretical framework, is contained in two elegant experiments by Haigler and Aghajanian (153, 154). When serotonin is iontophoretically applied onto serotonergic neurons in the raphe nuclei and onto their postsynaptic target neurons in the ventral lateral geniculate or amygdala, it is approximately equipotent in depressing unit activity at these various sites. Contrary to this, when LSD or psilocin are tested in the same manner, they have a much more profound effect on the serotonergic cells than on their target neurons. In other words, hallucinogenic drugs have an action that appears to be *preferential* for serotonin-containing neurons. Thus, it is reasoned, when brain levels of serotonin are elevated by administration of its precursors l-5-HTP or l-tryptophan (or any of a variety of other pharmacological means), serotonergic unit activity is depressed, but so is the activity of target neurons receiving serotonergic inputs. On the other hand, when LSD is administered systemically, it acts to depress serotonergic unit activity, while having little direct effect on target neurons. Because much of serotonin's action on target neurons in the forebrain is inhibitory (153), it is hypothesized that the ultimate effect of LSD's preferentially depressant action on serotonergic neurons is to produce a disinhibition of target neurons, which is precisely the opposite of the depression produced by elevated synaptic levels of serotonin.

Since this disinhibition will be manifested most impressively in those areas with the densest aggregation of serotonin axon terminals, i.e. portions of the visual and limbic systems, an obvious neuronal model is available to account for two of the major aspects of hallucinogenic drug action: visual hallucinations and alterations of affect. This, then, is the presynaptic serotonergic model of hallucinogenic drug action. It is based on several assumptions: (1) All hallucinogenic drugs strongly depress the activity of at least some group of serotonergic neurons, (2) serotonin's synaptic action in the forebrain is strictly inhibitory, and (3) hallucinogenic drugs exert little direct effect on postsynaptic serotonergic receptors.

We shall examine the first assumption later in this section, when we describe the effects of these drugs upon serotonergic neurons in freely moving cats. The second assumption of this model, that serotonin's action in the forebrain is inhibitory, is based on studies of subcortical sites in the rat brain that receive a dense and uniform serotonergic input. Thus, in areas such as the ventral lateral geniculate and amygdala, the iontophoretic application of serotonin exerts an exclusively depressant effect (153). However, there is also a good deal of evidence to indicate that in other brain regions, some of which receive a dense and uniform serotonergic input, such as the cerebral cortex, serotonin may exert excitatory effects on postsynaptic neurons. For example, Bradley and Wolstencroft (159) reported that 40% of brainstem neurons were excited by iontophoretic application of serotonin, and Roberts and Straughan (160) found that serotonin produced excitation in 30%

of the cortical neurons on which it was tested in acute decerebrate cats. More recently, in light of anatomical evidence that serotonergic input to the cortex of the rat is dense and fairly uniform throughout all cortical layers (161), Olpe has reported that in some cortical areas at least 20% of the cells were excited by serotonin applied iontophoretically (162).

With the concept that serotonin can exert excitatory effects in some brain areas firmly in mind, we can now re-examine the third assumption that hallucinogens exert little direct effect on postsynaptic serotonergic receptors. Before doing so, it is important to realize that, even in those subcortical brain areas where serotonin's action is strictly inhibitory, these drugs do exert some direct effect. It is not as strong as that exerted directly on serotonergic neurons, but it is nonetheless a significant effect. For example, Aghajanian and Haigler (14) reported that the amount of iontophoretically applied LSD necessary to produce a complete suppression of serotonergic unit activity produced a 30–40% suppression of activity in the geniculate and amygdala. Similarly, the amount of psilocin needed to completely suppress the activity of serotonergic neurons produced a 40–50% suppression of activity in these latter two subcortical sites.

Let us now return to an examination of the effects of hallucinogenic drugs at those sites where serotonin exerts excitatory actions. Roberts and Straughan (160) reported that the excitatory effects of iontophoretically applied serotonin on cortical neurons in acute decerebrate cats were strongly blocked by LSD in over 60% of the cells tested. Boakes et al. (163) reported that LSD exerted similar blocking effects on the excitatory action of serotonin on brainstem reticular formation neurons. In this same study LSD did not block the excitatory effects of either l-norepinephrine or acetylcholine, nor did it block the inhibitory effects of serotonin. In an important extension of these results, Boakes et al. (164) reported that brom-LSD was considerably less effective than LSD in blocking serotonergic excitation. Finally, Bradley and Briggs (165) demonstrated the generality of these effects when they reported that both DMT and 5-MeODMT antagonized the excitatory neuronal effects of serotonin in the brainstem of anesthetized rats and cats, but that 5-methoxytryptamine, a structurally related non-hallucinogen, showed no antagonism.

Roberts and Straughan (160) also tested several classical serotonin antagonists and found them to be effective in blocking these excitatory effects of serotonin. This has since been confirmed by a number of other investigators (162, 164, 166). This is interesting since both Roberts and Straughan (160) and Haigler and Aghajanian (166) reported that these antagonists failed to block the inhibitory effects of serotonin on neurons in cortical and subcortical sites. Thus, there appears to be some internal consistency in these data. Where serotonin exerts inhibitory effects, neither the hallucinogens nor the classical antagonists block these actions, whereas, where serotonin exerts excitatory effects, both the hallucinogens and the serotonin antagonists block these actions. However, it should be mentioned that Segal (167) and Olpe (162) have reported that the classical antagonists are effective in blocking the inhibitory effects of serotonin in the hippocampus and cortex, respectively.

More recently, Aghajanian has described another synaptic action for serotonin, and another related neuronal effect of the hallucinogens. Serotonin's actions on

brainstem motoneurons in the facial nucleus appear to be facilitatory (168). Thus, the iontophoretic application of serotonin produced neither excitation nor inhibition of the unit activity of facial nucleus neurons, but when applied in combination with an excitatory input, it greatly *facilitated* that excitatory effect. A similar facilitatory effect was observed for norepinephrine. The serotonin antagonist methysergide blocked the facilitatory effects of serotonin, but not those of norepinephrine. In a continuation of this line of investigation, McCall and Aghajanian (169) reported that LSD, mescaline, and psilocin had no effect themselves on facial nucleus motoneurons, but potentiated the response of these neurons to serotonin and norepinephrine. In a sense, then, the hallucinogens appear to facilitate the excitatory effects of serotonin and norepinephrine in this brainstem site. The serotonin antagonist metergoline blocked the facilitatory effect of mescaline on the action of serotonin, but not of norepinephrine.

Let us now review the various known CNS synaptic actions of serotonin, the serotonin antagonists, and the hallucinogens. (1) Both serotonin and the hallucinogens depress the activity of serotonergic neurons, and these effects are not blocked by serotonin antagonists (166; Heym, Rasmussen, and Jacobs, unpublished observations – see below). This is the so-called presynaptic action of the hallucinogens. (2) Serotonin exerts inhibitory effects on postsynaptic neurons in a variety of brain areas, especially those in forebrain subcortical regions. These effects may or may not be blocked by the classical serotonin antagonists. The hallucinogens display a moderate serotonin agonist effect at these sites. (3) Serotonin exerts excitatory effects on postsynaptic neurons in a variety of brain areas, especially those in the cerebral cortex and brainstem. These effects are strongly blocked by both the serotonin antagonists and the hallucinogens. (4) In brainstem and also spinal cord (170) areas receiving a direct serotonergic input, serotonin exerts a facilitatory effect on excitatory inputs to these target cells. This facilitation is potentiated (or facilitated) by the hallucinogens and blocked by the serotonin antagonists. It is presumably this action of serotonin that is responsible for the 'serotonin syndrome' described above. Consistent with this, recall that the hallucinogens produce this syndrome and the serotonin antagonists block it (76). Considering, as a whole, the variety of sites where serotonin acts, it is clear that the hallucinogens exert a mixed serotonin agonist-antagonist effect, which is not paralleled either by serotonin or its antagonists.

Although not extensively investigated, several single unit studies have examined the effects of hallucinogenic drugs on monoamine-containing neurons other than serotonin. As mentioned above, mescaline, LSD, and psilocin potentiate the facilitatory effects of norepinephrine on neurons in the facial nucleus. Aghajanian (171) has reported that parenteral administration of both LSD and mescaline depressed the spontaneous activity of noradrenergic neurons localized in the locus coeruleus of the rat, but potentiated the response of these neurons to a peripheral input. We have studied the effects of LSD on identified dopamine-containing neurons in the pars compacta of the substantia nigra (A-9) and on cells in the adjacent A-10 area, in chloral hydrate-anesthetized rats (172). Intravenous injections of LSD (20–50 μg/kg) produced significant decreases in the discharge rate of these cells, an effect attributable to a dopamine agonist action of LSD. This

dopamine agonist action of LSD is probably not critical for its hallucinogenic properties, however, because 5-MeODMT, another potent hallucinogen, was devoid of dopamine agonist action. Instead 5-MeODMT increased the activity of A-9 and A-10 cells through a disinhibition mediated by a depression of midbrain serotonergic unit activity. Qualitatively similar effects of LSD on dopaminergic neurons, but of a lesser magnitude, have been reported by Bunney (173). This picture has become complicated by the results of our more recent experiments examining the effects of LSD on the activity of A-9 cells in freely moving cats. Under these conditions, LSD (50 μg/kg i.p.) increases the activity of dopaminergic neurons (Steinfels and Jacobs, unpublished observations).

In summary, we do not have a sufficient amount of consistent electrophysiological data to draw any definitive conclusions concerning the effects of hallucinogenic drugs upon either noradrenergic or dopaminergic neurons.

Since the electrophysiological studies described in the preceding portion of this section were all conducted in anesthetized and/or immobilized animals, it is obviously impossible to relate changes in unit activity produced by hallucinogenic drugs directly to changes in behavior. Such analyses are imperative if our ultimate goal is to draw conclusions about functional relationships. For example, as we shall see below, a combined behavioral-electrophysiological approach is one of the ways to begin sorting out the relative importance of the four or more different effects that the hallucinogens exert upon the brain serotonin system.

In order to analyze the behavioral effects of the hallucinogens, we employed an observational method, described in the preceding section, of scoring changes in the spontaneous occurrence of specific response categories in the cat (128, 129, 174). In order to record the activity of single units in freely moving cats, we developed a technique that employs bundles of flexible large-tipped microwires (32 or 64 μm in diameter) rather than the traditional small-tipped high-impedance metal or glass microelectrodes (175, 176). These bundles of microwires can be advanced through the brain by means of an attached mechanical microdrive. Using this technique, we have had great success in isolating serotonergic units in various raphe nuclei of the cat brainstem (e.g. dorsalis, centralis superior, and pallidus). This technique also allows us to 'hold' cells for long periods of time (from several hours up to several days) and in spite of vigorous movements on the part of the cat.

We shall first describe our experiments with 5-MeODMT, which has a molecularly more simple structure than LSD and, as we shall see, produced more clear-cut data. We were particularly interested in the temporal correlations between the onset, peak, and offset of the behavioral and unit data, and whether or not the behavioral and unit data would have a correlated dose dependency. In order to examine these issues, we administered 5-MeODMT in doses of 10, 25, 50, 100, or 250 μg/kg (i.m.) and monitored the activity of serotonin-containing neurons in the dorsal raphe nucleus in conjunction with any gross behavioral effects (177). Under baseline conditions, serotonergic neurons in the awake freely moving cat discharge with the same characteristic slow rhythmic activity seen in the anesthetized rat. Following injections of 5-MeODMT, serotonergic unit activity was rapidly depressed in a dose-dependent manner, and dose-dependent increases were observed in the rate of limb flicking and abortive grooming. Furthermore, the onset, peak, and offset of the

behavioral effects were temporally correlated with the onset, peak, and offset of changes in unit activity. By directly correlating behavioral changes with changes in the activity of serotonin-containing neurons, we felt, at the time, that this study provided perhaps the strongest direct evidence for the presynaptic serotonin hypothesis of hallucinogenic drug action.

When this approach was extended to the study of LSD, the results were generally similar to those seen with 5-MeODMT, but with two critical differences (80). First, a 50 μg/kg dose of LSD produced a depression of serotonergic unit activity lasting, on the average, 3–4 hours, while the behavioral effects lasted for at least 6–8 hours. Second, when the 50 μg/kg dose was readministered 24 hours later, it produced little or no behavioral effect (tolerance), but the effect on serotonergic unit activity was as large as that seen on the previous day. Based upon those two dissociations of unit activity and behavior, we began to question the validity of the presynaptic serotonergic hypothesis.

This skepticism has been bolstered by our more recent experiments with DOM, mescaline, and psilocin (178). With all three drugs we observed the same temporal dissociations of serotonergic unit activity and behavior as observed with LSD. In addition, a low dose of psilocin (25 μg/kg i.p.) produced no significant decrease in serotonergic unit activity in any of the cells tested. However, it did produce significant behavioral effects. Mescaline (5 mg/kg i.p.) produced no overall significant change in unit activity (the discharge of three cells increased, three decreased, and two showed no change), but did produce large behavioral effects. Similarly, a low dose of DOM (50 μg/kg i.p.) did not significantly affect any of the serotonergic units tested, but did have a significant behavioral effect. The highest dose of DOM (1 mg/kg), produced only increases in serotonergic unit activity, but nonetheless elicited significant behavioral changes. Furthermore, cells in the ventral portion of the dorsal raphe nucleus did not appear to be preferentially sensitive to either mescaline or DOM. Finally, although not extensively examined, we have observed similar results, with various hallucinogens, in experiments on serotonergic neurons in nucleus centralis superior (Rasmussen, Heym, and Jacobs, unpublished observations).

We have also examined the effects of LSD upon unit activity of neurons in nucleus raphe pallidus, the most caudal group of serotonergic neurons in the cat brainstem. Somewhat surprisingly, the majority of neurons examined were almost completely unresponsive to doses of LSD (50 μg/kg i.p.) and 5-MeODMT (50 μg/kg i.m.) that produced potent behavioral effects (179; Heym, Rasmussen and Jacobs, unpublished observations).

Finally, I shall describe a recent study from my laboratory which provides perhaps the most damaging evidence against the presynaptic serotonergic hypothesis of hallucinogenic drug action. As mentioned in a preceding section, when cats are administered the serotonin antagonist mianserin prior to LSD or DOM, it blocks their behavioral effects in a dose-dependent manner. This did not appear to be due to non-specific effects, since the animals did not appear to be sedated or cataleptic. Furthermore, mianserin exerted no blocking action on the behavioral effects of the dopamine agonist apomorphine. When we pretreated animals with mianserin (1 mg/kg i.p.) and then administered LSD (50 μg/kg i.p.) 30 minutes later, we

observed an almost complete blockade of the behavioral effects of LSD, but no alteration of the 40–60% depression of serotonergic unit activity that LSD typically produces in neurons in nucleus raphe dorsalis (Heym, Rasmussen, and Jacobs, unpublished observations).

SUMMARY

Hallucinogens, such as LSD, psilocin, mescaline, DMT and DOM, produce similar phenomenological effects in humans and also display cross-tolerance of action. The most parsimonious explanation for these similarities is that these drugs share, at least to some extent, a common biological action. In this chapter, I have reviewed evidence from a variety of disciplines which indicates that this common action is exerted upon the brain serotonin system. Although various hallucinogens may interact with neurotransmitter systems other than serotonin, they do not do so universally. This action of hallucinogens upon the brain serotonin system is complex, with the critical effect probably being exerted directly upon cells postsynaptic to brain serotonin-containing neurons.

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