Electrophysiological Studies on the Actions of Hallucinogenic Drugs at 5=HT_2 Receptors in Rat Brain

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INTRODUCTION

There has been a longstanding interest in the role of the brain serotonin (5-hydroxytryptamine [5-HT]) system in the electrophysiological actions of psychedelic hallucinogenic drugs such as d-lysergic acid diethylamide (LSD) and mescaline. Early studies focused on the actions of LSD on serotonin-containing (serotonergic) neurons in the raphe nuclei of the brain stem. LSD and other indoleamine hallucinogens were found to have potent *direct* inhibitory effects upon serotonergic raphe neurons (Aghajanian et al. 1972). However, it was soon discovered that mescaline and other phenethylamine hallucinogens failed to share this action (Haigler and Aghajanian 1973). Later, it was shown that the direct inhibitory effect of LSD and other indoleamine hallucinogens on serotonergic neurons is mediated by 5-HT_{1A} receptors, and that this action is shared by a number of selective 5-HT_{1A} agonists that are not hallucinogenic (Sprouse and Aghajanian 1987, 1988). Thus, there appears to be no correlation between the activity of various drugs at 5-HT_{1A} receptors in the raphe nuclei and the presence or absence of hallucinogenic properties.

In contrast, a good correlation exists between the affinity of both indoleamine and phenethylamine hallucinogens for 5-HT_2 receptors and the potency of these drugs as hallucinogens in humans (Glennon et al. 1984; Titeler et al. 1988) As described below, electrophysiological studies in a number of brain regions show that indoleamine and phenethylamine hallucinogens have common electrophysiological action at 5-HT_2 receptors. There has, however, been some debate on whether the hallucinogens act as agonists, partial agonists (Glennon 1990; Sanders-Bush et al. 1988; Sheldon and Aghajanian 1990) or antagonists (Pierce and Peroutka 1990) at 5-HT_2 receptors. Recent electrophysiological studies bearing on this issue are described in this chapter.

The discovery of the structural and functional similarities between the 5-HT_2 and 5-HT_{1C} receptors (Hartig 1989) has also led to studies examining the effect of the hallucinogens at 5-HT_{1C} sites. Recent data from studies in the choroid plexus showed that the hallucinogens act as partial agonists at 5-HT_{1C} receptors that mediate an activation of phosphoinositide turnover (Burris et al 1991; Sanders-Bush and Breeding 1991). The electrophysiological studies are reviewed from the standpoint of how they may distinguish between actions at 5-HT_2 and 5-HT_{1C} receptors.

Quantitative autoradiographic studies show high concentrations of 5-HT_2 sites in the forebrain including the neocortex (layers IV/V), piriform cortex, claustrum, nucleus accumbens (NACC), and olfactory tubercle (OT) (Pazos et al. 1985). In contrast, with the exception of a few areas (e.g., facial nucleus and the n. tractus solitarius), relatively low concentrations of 5-HT_2 receptors are found in the brain stem. Single-cell studies on the physiological properties of 5-HT_2 receptors in several representative brain regions are described in the following sections.

PHYSIOLOGICAL ACTIONS OF HALLUCINOGENS

Locus Coeruleus

The systemic administration of indoleamine and phenethylamine hallucinogens (e.g., LSD and mescaline) results in decreased spontaneous activity of noradrenergic cells in the locus coeruleus (LC) of anesthetized rats but, paradoxically, a facilitation of the activation of these cells by sensory stimuli (Aghajanian 1980; Rasmussen and Aghajanian 1986). These effects in the LC are of theoretical interest since, in contrast to the raphe nuclei (see introduction), they are shared by the two major classes of psychedelic hallucinogens. Mediation by 5-HT_2 receptors is suggested by the fact that effects of the hallucinogens on LC neurons can be reversed by low intravenous (IV) doses of selective 5-HT_2 antagonists such as ritanserin, LY-53857 (figure 1) (Rasmussen and Aghajanian 1986), and ketanserin (Gorea and Adrien 1988). Antipsychotic drugs with affinity for 5-HT_2 binding sites are also able to reverse the actions of hallucinogens in the LC independently of their actions at dopamine (DA) and adrenergic receptors (Rasmussen and Aghajanian 1988). The relative potencies of antipsychotic drugs in blocking the actions of hallucinogens in LC neurons correlates highly with their affinity for 5-HT_2 receptors (Rasmussen and Aghajanian 1988). Of particular note is the fact that at

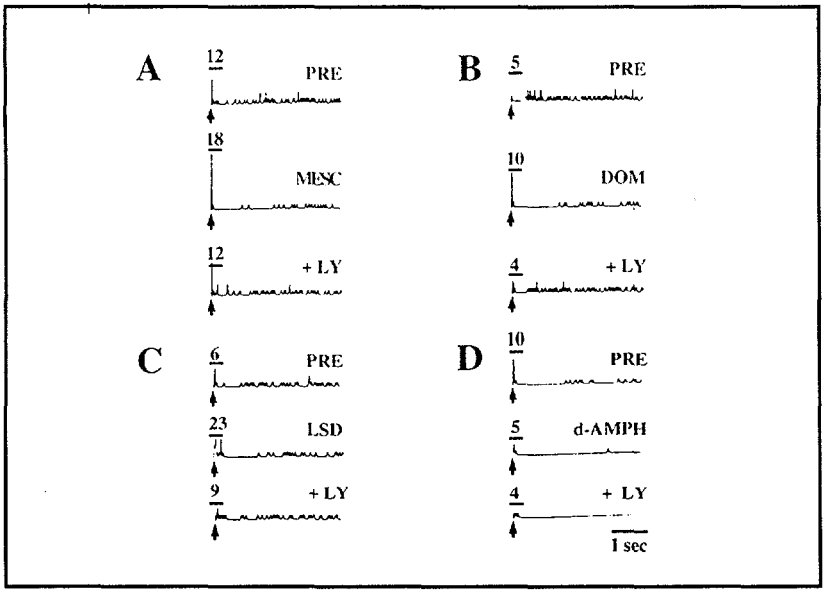

FIGURE 1. *Poststimulus time histograms during locus coeruleus cell recordings in vivo before and after administration of A, mescaline (MESC); B, DOM; C, LSD; or D, (+)-amphetamine (D-AMPH); and again after the administration of LY 53857 (LY).*

Each histogram was generated from 10 sweeps initiated by electrical stimulation of the sciatic nerve (arrows). Evoked spikes occurred during the first 250 milliseconds of each histogram (bars). The total number of evoked spikes occurring during this period is given above the bars. Note both the increased number of spikes evoked by sciatic nerve stimulation (initial 1.50 milliseconds of histogram) and the decrease in spontaneous activity (remainder of histogram) after LSD, DOM, and mescaline administration. In addition, following hallucinogen ddministration, the increased number of spikes evoked by sciatic nerve stimulation, combined with the decrease in spontaneous activity, leads to a prolonged period of postactivation inhibition. Also, note the reversal of these effects after LY 53857 administration. After (+)-amphetamine administration, both the spontaneous activity and the number of evoked spikes are decreased; however, the subsequent administration of LY 53857 does not reverse either of these effects. From Rasmussen and Aghajanian 1986.

extremely low doses spiperone, which has almost a thousandfold greater affinity for 5-HT_2 than 5-HT_{1C} receptors, completely blocks the effects of the hallucinogens. Thus, the effects of hallucinogens on the LC appear to be mediated by 5-HT_2 rather than 5-HT_{1C} receptors.

It should be noted that the effects of hallucinogens in the LC are not direct since they are not mimicked by local iontophoretic application of the drugs onto LC cell bodies (Aghajanian, unpublished observations). Moreover, the systemic administration of mescaline or LSD does not enhance the excitation of LC neurons evoked by microiontophoretically applied acetylcholine, glutamate, or substance P (Aghajanian 1980). These results imply that the hallucinogens are acting indirectly, perhaps via afferents to the LC. Thus, the LC is not useful as a model for studying the *direct* cellular actions of hallucinogens. Nevertheless, the effects of the hallucinogens upon the LC are of interest because of the unique role of this nucleus as a nodal point in processing a convergence of sensory information, both somatosensory and visceral, and relaying this information to virtually all parts of the central nervous system (CNS).

Facial Nucleus

In contrast to LC neurons, facial motoneurons have a high density of 5-HT_2 receptor binding sites, and they also express a high level of 5-HT_2 receptor messenger ribonucleic acid (mRNA) (Mengod et al. 1990*b*). The microiontophoretic application of 5-HT or norepinephrine (NE), while not by itself inducing firing in quiescent facial motoneurons, facilities the excitatory effects of iontdphoretically applied glutamate (McCall and Aghajanian 1979). Intracellular recordings in vivo (VanderMaelen and Aghajanian 1980, 1982) and in brain slices (Aghajanian and Rasmussen 1989; Larkman et al. 1989) reveal that 5-HT induces a slow depolarization in facial motoneurons by decreasing a resting potassium conductance. Similar effects of 5-HT on potassium conductance have been described in spinal motoneurons (White and Fung 1989) and in the NACC (North and Uchimura 1989).

The action of iontophoretically applied 5-HT in the facial nucleus can be blocked by the classical 5-HT antagonists metergoline, methysergide, cyproheptadine, and cinanserin (McCall and Aghajanian 1980*b*), which have varying degrees of selectivity for the 5-HT_2 receptor. More recent studies show that the selective 5-HT_2 antagonist ritanserin blocks the excitatory effects of 5-HT in facial motoneurons (Rasmussen and

Aghajanian 1990). The selective 5-HT_{1A} agonist 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) increases facial motoneuron excitability when given in vivo by the systemic route (Rasmussen and Aghajanian 1990). However, this effect is presumably due to an indirect action, since 8-OH-DPAT has no effect when applied locally either by microiontophoresis or bath application in brain slices (Garratt et al. 1993; Rasmussen and Aghajanian 1990). These results suggest that 5-HT_{1A} receptors are probably not directly involved in the excitatory actions of 5-HT on facial motoneurons.

Since behavioral as well as binding techniques have shown that both indoleamine and phenethylamine hallucinogens interact with 5-HT_2 receptors (Glennon et al. 1983, 1984; Heym et al. 1984; Mokler et al. 1985), it is not surprising that members of both classes of hallucinogens have direct effects in the facial motor nucleus. The iontophoretic administration of LSD, mescaline, or psilocin, although at low doses having relatively little effect by themselves, enhance the facilitiation of facial motoneuron excitation produced by ionophoretically applied 5-HT and NE (McCall and Aghajanian 1980*a*). Curiously, the enhancement can persist for several hours after only a single brief application. Intracellular studies in brain slices show that LSD produces an increase in the electrical excitability of facial motoneurons; however, even at maximal concentrations, this is associated with only a small depolarization of facial motoneurons compared to that produced by 5-HT itself (figure 2) (Garratt et al. 1993).

The phenethylamine hallucinogen l-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) produces effects similar to those of LSD, but with a slightly greater maximal depolarization. Since the depolarizing effect of 5-HT is mainly due to a decrease in potassium conductance, LSD and DOI would appear to have low intrinsic activity relative to 5-HT in this transduction pathway. This observation parallels studies of the effects of hallucinogens on phosphoinositide hydrolysis (Sanders-Bush et al. 1988; Barker et al. 1991). In those studies, 5-HT caused the greatest increase in phosphoinositide hydrolysis, whereas 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), 2,5-dimethoxy-4-methylamphetamine (DOM), and LSD acted as partial agonists with LSD having the least intrinsic activity.

Recently, it was found that in addition to producing a decrease in resting potassium conductance, 5-HT produces an enhancement of the non-

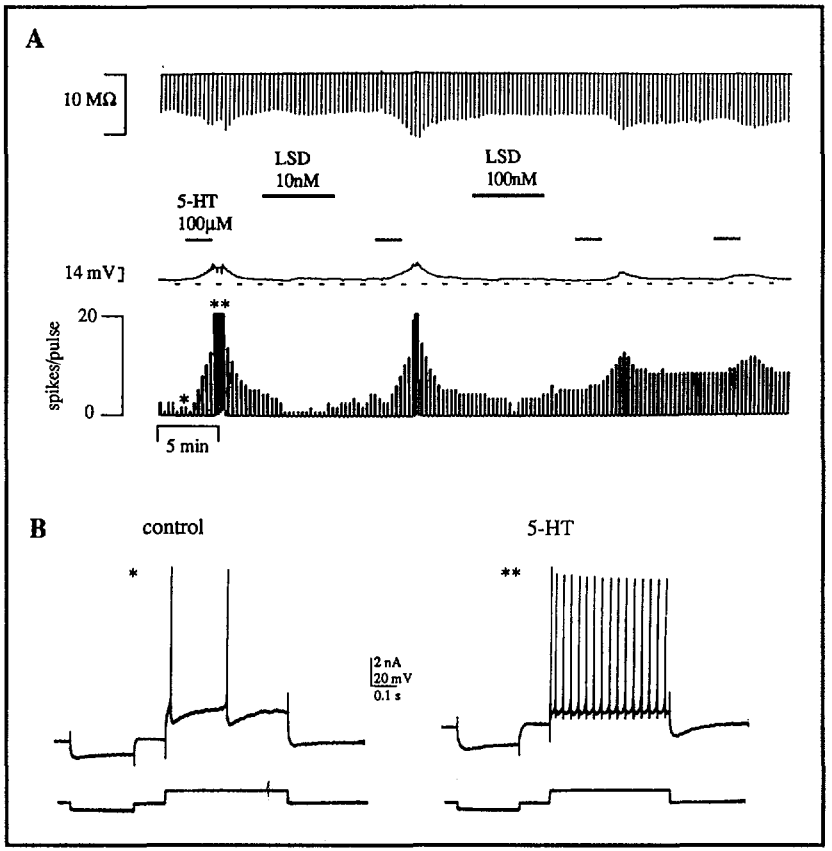

FIGURE 2. *A. Effects of bath application of 5-HT and LSD on input resistance (upper trace), membrane potential (middle trace) and electrical excitability (lower trace) recorded simultaneously in a rat facial motoneuron from an in vitro brain slice preparation.*

Bath application of 5-HT (100μM) produces an increase in apparent input resistance, a depolarization (14 mV), and an increase in electrical excitability of the cell (i.e., an increase in spikes induced by a constant current pulse); note that the ratemeter trace goes off scale at the peak of the response. Application of LSD (10 nM) produces little change in apparent input resistance or membrane potential; however, there is a clear increase in electrical excitability, which has a slow onset of action. Interestingly, LSD at this dose slightly suppressed the response of the cell to 5-HT.

FIGURE 2. (cont.) *A. Effects of bath application of 5-HT and LSD on input resistance (upper trace), membrane potential (middle trace) and electrical excitability (lower trace) recorded simultaneously in a rat facial motoneuron from an in vitro brain slice preparation.*

A higher concentration of LSD (100 nM) again produces little change in apparent input resistance or membrane potential. There is, however, a further increase in the electrical excitability which also has a slow onset of action and very long duration (>2 hrs., not shown). At this dose there is further suppression of the response of the cell to 5-HT. Electrical excitability is measured by injecting the cell with a depolarizing pulse (+1.5 nA, 400 ms duration) which elicits one or two spikes under control conditions. Periods of drug application are indicated by horizontal bars.

B . Oscilloscope traces showing the effect of 5-HT on the electrical excitability of the facial motoneuron shown in A.

The spikes were evoked by a depolarizing pulse (+1.5 nA); the cell is otherwise silent (resting potential, -72 mV). The left hand panel shows that under control conditions two spikes are elicited by the depolarizing pulse. Single asterisk denotes time point that sweep was taken in (A). In the presence of 5-HT (100 μM) (in the right hand panel), the same pulse elicits 16 spikes (double asterisk in A), thus indicating that 5-HT increases the electrical excitability of the cell. Also, note the increase in input resistance (i.e., greater voltage deflection in response to the hyperpolarizing pulse) following 5-HT.Prom Garratt et al. 1993

specific hyperpolarizing activated cationic current (I_h) which also increases the excitability of facial motoneurons (Garratt et al. 1993).

Surprisingly, both LSD (figure 3) and DOI produce a greater maximal enhancement of I_h than does 5-HT (LSD > DOI > 5-HT). Moreover, in contrast to 5-HT, DOI and LSD have a slow onset and very long duration

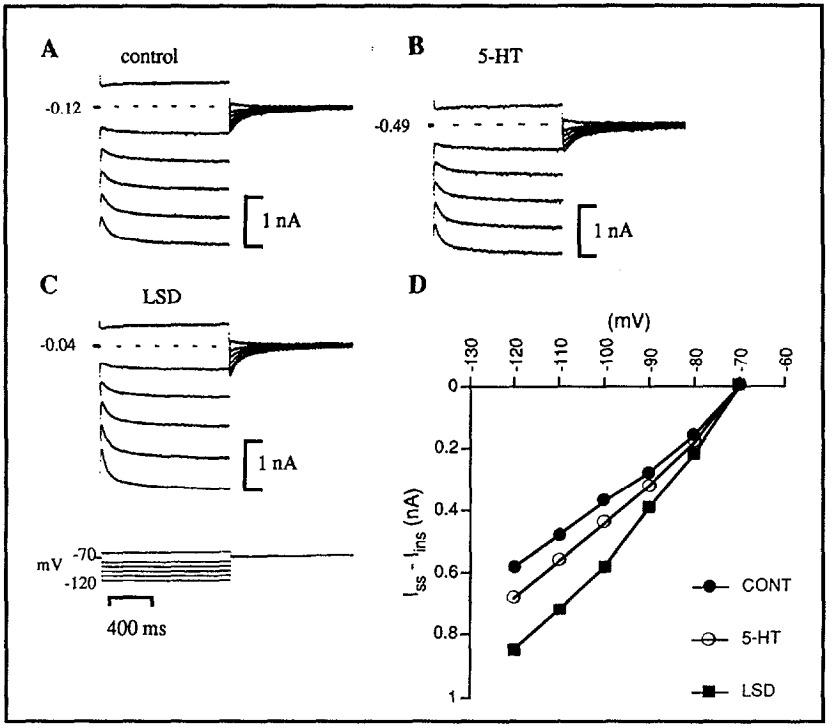

FIGURE 3. *Effects of bath application of 5-HT and LSD on the hyperpolarization-activated cation current (I_h) in facial motoneurons.*

A, B, C are oscilloscope traces showing intracellular voltage-clamp recordings from facial motoneuron. (A) shows a progressing increase in the size of the hyperpolarization-activated cation current (I_h) in response to increased hyperpolarizing steps from -70 mV to -120 mV. (B) shows the enhancement of I_h in the presence of 5-HT (100 µM).(C) shows that LSD (100 nM) produces a greater increase in I_h than 5-HT. (D) is a current-voltage plot obtained from A, B, and C showing the difference between steady state and instantaneous currents in response to voltage clamp commands in 10 mV steps from a holding potential of -70 mV to -120 mV. Note that LSD produces a greater increase than 5-HT in I_h at all voltage steps. From Garratt et al. 1993.

of action (> 2 hours). The enhancement of I_h by LSD and DOI is reversed by application of both the 5-HT_2/5-HT_{1A}/5-HT_{1A} antagonist spiperone and the 5-HT_2/5-HT_{1C} antagonist ritanserin, suggesting that the increase in I_h is mediated by receptors. This appears to be the first example of a direct 5-HT_2-mediated electrophysiological response in the brain in which hallucinogens have greater efficacy than 5-HT (Pierce and Peroutka 1990).

The finding that LSD has high efficacy in increasing I_h and low efficacy in decreasing resting potassium conductance could be explained most simply by supposing that the 5-HT_2 receptor couples to the two different channels via two different guanosine triphosphate binding proteins (G proteins). Thus, the same type of 5-HT_2 receptor could couple to potassium channels via one type of G protein and to I_h channels via another type of G protein, yielding two different receptor/G-protein complexes that would have differential intrinsic activity with respect to the different agonists. A second possibility is that there are two or more different 5-HT_2 receptor subtypes that independently confer differential intrinsic activity to 5-HT and the hallucinogens.

Regardless of the mechanism, the high efficacy of LSD relative to, 5-HT on the I_h current in rat facial motoneurons raises the interesting possibility that such an action elsewhere in the brain could be involved in mediating hallucinogenic processes. Neurons in several brain regions have been shown to have an I_h current that is enhanced by 5-HT (Bobker and Williams 1989; McCormick and Pape 1990; Nedergaard et al. 1991; Takahashi and Berger 1990). It would be interesting to see if LSD produces a greater enhancement of I_h relative to 5-HT in these or other brain regions, especially in cases when the effect on I_h may be mediated by a 5-HT_2 receptor.

Cerebral Cortex

The electrophysiological effects of 5-HT at 5-HT_2 receptors have been studied in several cortical regions. In vivo, the 5-HT_2 agonist DOI has been reported to have an overall inhibitory effect on the firing of unidentified neurons in the prefrontal cortex (Ashby et al. 1989). Curiously, the inhibitions produced by DOI but not by 5-HT itself are blocked by 5-HT_2 antagonists (Lakoski and Aghajanian 1985). In brain slices, pyramidal cells in various regions of the cerebral cortex have been found to respond to 5-HT by a small hyperpolatization, depolarization, or no change in potential (Davies et al. 1987). It was suggested that the

depolarizations are mediated by 5-HT_2 receptors since they can be blocked by 5-HT_2 antagonists.

Recently, the author and coworkers have observed a novel effect of 5-HT in pyramidal cells of the piriform cortex: the enhancement of spontaneous inhibitory postsynaptic potentials (IPSPs) (Sheldon and Aghajanian 1990). The IPSPs are blocked by the gamma-aminobutyric acid (GABA) antagonist bicuculline, suggesting that GABAergic interneurons are excited by 5-HT, giving rise to the increase in IPSPs in the pyramidal cells. In accord with this expectation, a subpopulation of interneurons at the border of layers II and III were found that are excited by 5-HT. The 5-HT_2/5-HT_{1C} antagonist ritanserin blocks both the 5-HT-induced activation of interneurons and the associated IPSPs in pyramidal cells (Sheldon and Aghajanian 1990). Interestingly, the hallucinogens LSD and DOM behave as partial agonists in this system, producing a modest activation by themselves but occluding the full effect of 5-HT (figure 4).

Another effect of 5-HT in the piriform cortex is a direct depolarization of pyramidal cells that is also blocked by ritanserin. However, blockade of the 5-HT-induced activation of interneurons by ritanserin occurs much more readily than the blockade of pyramidal cell depolarization (Sheldon and Aghajanian 1990). Since ritanserin has a nearly tenfold higher affinity for the 5-HT_2 receptor than for the 5-HT_{1C} receptor (Hoyer 1988), it is possible that the action of 5-HT on these interneurons might be through 5-HT_2 receptors, and that the action of 5-HT on the pyramidal cells might be through 5-HT_{1C} receptors. This hypothesis is consistent with recent in situ hybridization studies that show that mRNA for the 5-HT_2 receptor is expressed in cortical interneurons (Mengod et al. 1990*b*), while that for the 5-HT_{1C} receptor is expressed in pyramidal cells (Mengod et al. 1990*a*).

To test this hypothesis further, the author and coworkers studied the effects of the 5-HT antagonist spiperone on the actions of 5-HT in both interneurons and pyramidal cells (Sheldon and Aghajanian 1991). The activating effect of 5-HT on interneurons is blocked by bath application of low concentrations of spiperone (100 nanomolars [nM]), while in pyramidal cells the direct excitatory effects of 5-HT are unaffected by 100 nM to 1 micromolar (μM) spiperone but are blocked by 10 μM ritanserin. These findings support the hypothesis that in the piriform cortex the excitatory action of 5-HT on interneurons is mediated by 5-HT_2 receptors while the excitatory action of 5-HT on pyramidal cells is

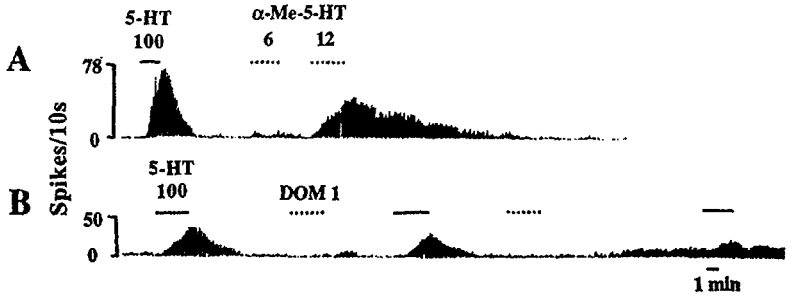

FIGURE 4. *Note the prolonged action of DOM following the second application. Concentrations in mM. Agonist actions of 5-HT, α-Me-5-HT, and DOM on putative interneurons in piriform cortex. (A) The 5-HT_2 agonist α-Me-5-HT mimics the action of 5-HT in a dose-dependent manner. (B) The 5-HT_2 agonist DOM acts as a partial agonist, having a small activating effect of its own and blunting the efect of 5-HT. From Sheldon and Aghajanian 1990*

mediated by 5-HT_{1C} receptors. Thus, the effects of 5-HT and hallucinogens in the cerebral cortex are likely to be complex, involving actions at multiple 5-HT receptors differentially expressed by interneurons and pyramidal cells.

5-HT RECEPTORS: SIGNAL TRANSDUCTION MECHANISMS

The role of G proteins in mediating the 5-HT_2-induced slow inward current in facial motoneurons was evaluated by using the hydrolysis-resistant guanine nucleotide analogs GTPγS and GDPßS (Aghajanian 1990). Due to a persistent activation of G protein, the 5-HT-induced inward current becomes largely irreversible in the presence of intracellular GTPγS. The inward current is reduced by intracellular GDPßS, suggesting mediation by G proteins since the binding of GDPßS to the G protein renders it resistant to activation by agonist. These electrophysiological results are consistent with binding studies which show that guanosine triphosphate (GTP) analogs induced a downward shift in the affinity of a radiolabeled 5-HT_2, agonist for brain membranes (Lyon et al. 1986). This GTP dependency is consistent with the structural analysis of a cloned 5-HT_2 receptor from a rat brain carrier deoxyribonucleic acid (cDNA) library, demonstrating seven transmembrane regions

typical of G protein coupled receptors (Pritchett et al. 1988). The identity of the G proteins that couple to the 5-HT_2 receptor remains to be determined.

Serotonin stimulates phosphatidylinositol hydrolysis in the brain through 5-HT_2 and 5-HT_{1C} receptors (Conn and Sanders-Bush 1986). LSD and DOM act as partial agonists of this effect (Sanders-Bush et al. 1988). Phosphatidylinositol hydrolysis yields at least two major second messengers: inositol trisphosphate (IP_3) and diacylglycerol. The latter activates protein kinase C (PKC), thereby potentially affecting many long-term cellular responses through protein phosphorylation. The author and coworkers have tested the effect of protein kinase inhibitors on the response of facial motoneurons to serotonin (Aghajanian 1990). In concentrations that have no effect of their own (100 and 10µM, respectively), two protein kinase inhibitors with different mechanisms of action, 1-(5-isoquinolylsulfonyl)-2-methylpiperazine (H7), a nonselective protein kinase inhibitor, and sphingosine, a selective PKC inhibitor, both markedly enhance and prolong the excitation of facial motoneurons induced by 5-HT. Conversely, phorbol esters that are known to activate PKC reduce the excitatory effect of serotonin. These results suggest that activation of phosphatidylinositol turnover, perhaps through PKC-induced receptor phosphorylation, has a negative feedback effect on 5-HT-induced excitations in the facial nucleus. These observations are consistent with studies on 5-HT_2 receptor-mediated responses in rat aorta, which indicate that the activation of PKC desensitizes 5-HT_2 receptors (Roth et al. 1986).

An interesting implication of the negative feedback model is the possibility that the partial agonist (Sanders-Bush et al. 1988) or even antagonist (Pierce and Peroutka 1988) properties of hallucinogens with respect to 5-HT-stimulated phosphatidylinositol hydrolysis may contribute to, rather than interfere with, their electrophysiological actions. Thus, the greater enhancement of $I_h$in facial motoneurons by hallucinogens relative to 5-HT could be explained by a combination of two factors: LSD has high efficacy in this transduction system, and by not markedly activating phosphatidylinositol hydrolysis, LSD does not provoke a large negative feedback reduction in response.

SUMMARY AND CONCLUSIONS

Receptor Specificity

This review has considered the electrophysiological effects of hallucinogens in three different brain regions: the LC, the facial motor nucleus, and the cerebral cortex. The results of those studies, together with findings from earlier studies in the raphe nuclei, make it clear that the indoleamine and phenethylamine hallucinogens have common electrophysiological actions on 5-HT_2 but not 5-HT_{1A}, receptors. Furthermore, in each of these three regions, the effects of the hallucinogens are blocked by spiperone, which has almost a thousandfold higher affinity for 5-HT_2 than 5-HT_{1C} receptors. Thus, it may be concluded that the electrophysiological effects of hallucinogens, at least those examined to date, are likely to be mediated primarily by 5-HT_2 rather than 5-HT_{1C} receptors, although the latter may have a contributory role.

Signal Transduction Mechanisms

The net effect of 5-HT_2 receptor stimulation is to produce an increase in neuronal excitability through a G protein-coupled mechanism. The ionic mechanism underlying increased excitability involves a reduction in resting potassium conductance and/or enhancement of the hyper-polarizing-activated cationic current I,. In addition, biochemical studies show that both 5-HT_2 and 5-HT_{1C} receptors are coupled to PKC and IP_3 mechanisms through the phosphoinositide signal transduction pathway. Altogether it would appear that 5-HT_2 receptors are coupled to at least three different transduction systems: potassium channels, cationic I_h channels, and phosphoinositide hydrolysis. The coupling could be through a single G protein or through multiple G proteins and multiple 5-HT_2 receptor subtypes, one for each transduction pathway. Several hypothetical models for 5-HT_2-receptor/G protein coupling mechanisms are presented in figure 5.

It might be supposed that the electrophysiological effects of 5-HT and hallucinogens acting upon 5-HT_2 receptors are mediated through the phosphoinositide pathway. However, it has been found, mainly from studies in the facial motor nucleus, that activators of PKC suppress, while inhibitors of PKC enhance, 5-HT_2-induced increases in neuronal excitability. Thus, the phosphoinositide second messenger system may

serve as a negative feedback system with respect to the electrophysiological effects produced by 5-HT_2 receptor activation. The fact that hallucinogens are only partial agonists at stimulating phosphoinositide turnover may enhance rather than diminish their electrophysiological effects.

Behavioral Correlations

As yet, the interrelationships between electrophysiological and behavioral actions of hallucinogenic drugs have not been examined in detail. Nevertheless, certain intriguing links are emerging. For example, the enhancement of sensory responsivity in LC neurons may contribute to the characteristic intensification of certain kinds of sensory experience produced by hallucinogens in humans. The increase in motoneuronal excitability producted by hallucinogens could explain the hyperreflexia induced by these drugs. Finally, the persistent activation of a subpopulation of 5-HT_2-expressing interneurons in the cerebral cortex may underlie the various cognitive and perceptual distortions produced by the hallucinogenic drugs.

FIGURE 5. *(facing page) Hypothetical models for the coupling of 5-HT_2 receptors to three different effector mechanisms: decreased K^+ conduc-tance, increased phosphoinositide (PI) turnover, and increased I_h. (A) A single class of 5-HT_2 receptors couples via one type of G protein to the three different effectors. (B) A single class of 5-HT_2 receptors couples to three different G proteins (G, G', and G"), one for each effector system. (C) Three 5-HT_2 receptor variants (5-HT_2, 5-HT_2', 5-HT_2") couple separately to the three effectors, each via a different G protein.*

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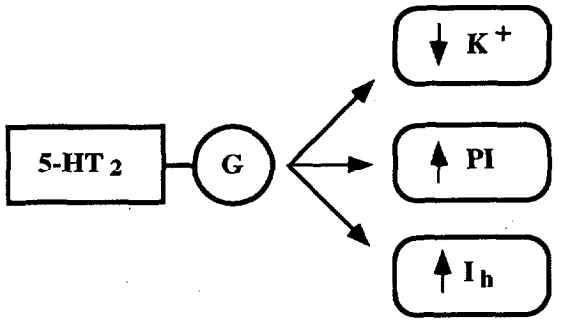

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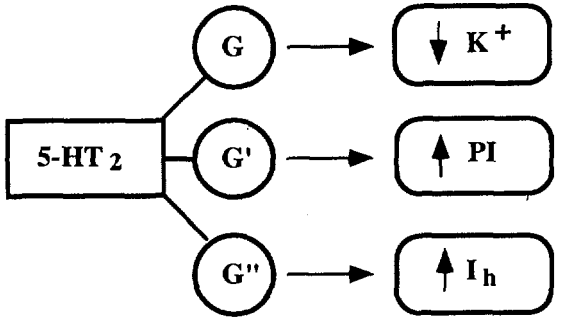

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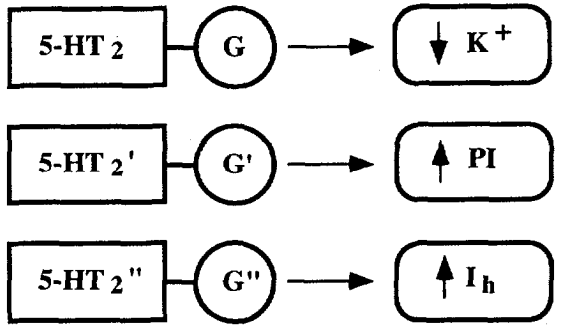

ACKNOWLEDGMENTS

This chapter was prepared with support from National Institute of Mental Health grant MH-17871, the State of Connecticut, and a gift from Bristol-Myers Squibb.

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