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Indoleamine and the phenethylamine hallucinogens: mechanisms of psychotomimetic action

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1. Introduction

The psychedelic hallucinogens are comprised of three different groups of compounds according to their chemical structure (Fig. 1): (1) the ergolines which contain an indole moiety (e.g. lysergic acid diethylamide, LSD); (2) simple indoleamine hallucinogens (e.g. *N*,*N*-dimethyltryptamine, DMT and psilocybin) which share an indoleamine structure with the endogenous neurotransmitter 5-hydroxytryptamine (5-HT, serotonin); and (3) the ring-substituted phenethylamine hallucinogens (e.g. mescaline). One of the outstanding features of ergoline, indoleamine, and phenethylamine hallucinogens is that they alter all cortical functions including cognition, perception, and mood. This implies that the sites mediating the psychotomimetic effects of these hallucinogens are located in the neocortex or in subcortical areas with efferent projections throughout the neocortex. This review will consider evidence suggesting that both the indoleamine and phenethylamine hallucinogens bind to a common neurotransmitter receptor in the brain, the 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor, and that subsequent activation of this serotonin receptor mediates the psychotomimetic effects of these hallucinogens. We will also discuss potential site(s) in the brain at which the hallucinogens exert their psychotomimetic effects.

2. Hallucinogens and 5-HT receptors

LSD has have been known to interact with the serotonergic system since the 1950s. Early studies in simple preparations (e.g. carotid arteries and uteri) had found that LSD antagonized the effects of 5-HT and this was advanced as the mechanism underlying the hallucinogenic effects of LSD (Gaddum, 1953; Woolley and Shaw, 1954). Later, LSD was found to have a 5-HT agonist action in other systems and this was then advanced as an alternate mechanism to account for the hallucinogenic effects of 5-HT (Shaw and Woolley, 1956). Since their psychotomimetic effects are similar, these three classes of hallucinogenic drugs may share a similar mechanism of action at the receptor level. A prediction derived from this assumption is that ergoline, simple indoleamine, and phenethylamine hallucinogens should act similarly at a candidate site for hallucinogenic activity. Early electrophysiological studies had shown that LSD potently suppressed the firing rate of 5-HT-containing neurons in the midbrain dorsal raphe nucleus (Aghajanian et al., 1968). However, this effect was later shown to be dependent upon activation of somatodendritic 5-HT$_{1A}$ autoreceptors (Sprouse and Aghajanian, 1987). Later studies showed that mescaline, a phenethylamine hallucinogen, did not inhibit the firing rate of 5-HT-containing neurons through 5-HT$_{1A}$ receptors (Haigler and Aghajanian, 1973). These results indicated that agonist activity at the 5-HT$_{1A}$ autoreceptor on 5-HT-containing neurons could not provide a shared mechanism of action for all classes of psychedelic hallucinogens.

Currently, there are upwards of 14 5-HT receptor subtypes based on pharmacological, physiological and molecular cloning data (Hoyer et al., 1994). The promiscuity of LSD for most of the 5-HT receptor subtypes is a not surprising given the historical linkage of LSD to the serotonergic system. LSD potently binds to 5-HT$_{1A/1B/1D/1E/1F}$ receptors, although its affinity for the 5-HT$_{1B}$ receptor is comparatively low (Hoyer, 1988; Lovenberg et al., 1993). In contrast, the phenethylamine hallucinogens do not bind potently to the 5-HT$_1$ family of receptors (Titeler et al., 1988;

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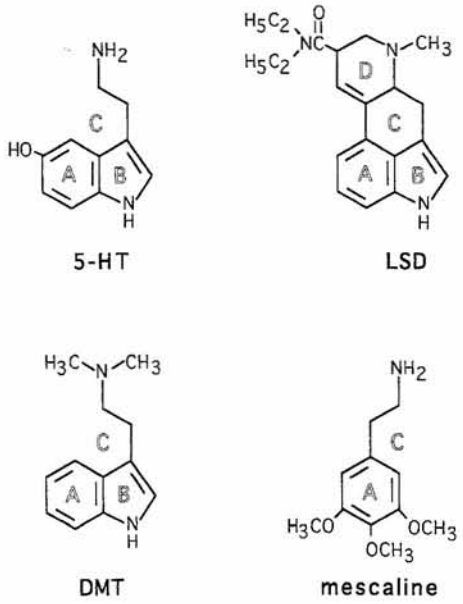

Fig. 1. Chemical structure of the endogenous neurotransmitter 5-hydroxytryptamine (5-HT, serotonin); the ergoline hallucinogen lysergic acid diethylamide (LSD); the simple indoleamine hallucinogen *N*,*N*-dimethyltryptamine (DMT); and the phenethylamine hallucinogen mescaline. The letters A–D in the outline font correspond to shared chemical similarities between the four different compounds.

Pierce and Peroutka, 1989; Zgombick et al., 1992; Adham et al., 1993). LSD does not bind potently to either the 5-HT_3 or the 5-HT_4 receptor (Peroutka and Hamik, 1988; Gerald et al., 1995). While LSD has relatively high affinity for the 5-$HT_{5A/5B/6/7}$ receptors (Matthes et al., 1993; Monsma et al., 1993; Ruat et al., 1993), phenethylamine hallucinogens do not bind potently or act as an agonist at the 5-HT_5 or the 5-HT_7 receptors (Erlander et al., 1993; Lovenberg et al., 1993). However, thus far, no binding data for phenethylamine hallucinogens has been reported at the 5-HT_6 receptor. The one class of 5-HT receptors to which ergoline, simple indoleamine, and phenethylamine hallucinogens all potently bind to is the 5-HT_2 class which includes the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors. The 5-HT_{2B} receptor has a restricted CNS expression (Duxon et al., 1997). Thus, the 5-HT_{2A} and 5-HT_{2C} receptors remain as the most likely shared targets of action for the ergoline, simple indoleamine, and phenethylamine hallucinogens. Given the predominance of 5-HT_{2A} receptors over 5-HT_{2C} receptors in most areas of the neocortex (Pompeiano et al., 1994; Wright et al., 1995), the 5-HT_{2A} receptor appears to be the most likely candidate to mediate the major hallucinogenic effects of indoleamine and phenethylamine hallucinogens.

Correlations between 5-HT_2 receptor binding affinity and the hallucinogenic potency of lysergic acid diethylamide (LSD) and phenethylamine hallucinogens in humans have suggested that 5-HT_2 receptors mediate the hallucinogenic effects of indoleamine and phenethylamine hallucinogens (Glennon et al., 1984). LSD has a similar affinity for the 5-HT_{2A} receptor (K_d: 0.5–2.5 nM) and for the 5-HT_{2C} receptor (K_d: 3.8–12 nM; Titeler et al., 1988; Hoyer, 1988). The K_d of LSD for 5-HT_2 receptors is near the peak plasma levels (10–20 nM) measured following both i.v. and oral LSD administration (Aghajanian and Bing, 1964; Hawks and Chiang, 1986). However, agreement does not exist regarding whether LSD and other hallucinogens act as full or partial agonists (Sanders-Bush et al., 1988; Glennon, 1990; Sheldon and Aghajanian, 1990) or antagonists (Pierce and Peroutka, 1988, 1990) at cortical 5-HT_2 receptors.

This issue has been examined recently in the piriform cortex (Marek and Aghajanian, 1996) using γ-amino butyric acid (GABA)-ergic neurons excited by 5-HT via 5-HT_{2A} receptors (Sheldon and Aghajanian, 1990; Marek and Aghajanian, 1994) as a model system to study the effects of both ergoline and phenethylamine hallucinogens. Both LSD and the phenethylamine hallucinogen 1-(2,5-dimethoxy-4-iodophenyl)-2-aminoproprane (DOI) excited a subpopulation of interneurons; both drugs were blocked by the selective 5-HT_{2A} antagonist MDL 100,907. The maximal excitation induced by LSD and DOI was 39% and 55% of the effect of a near-maximal 5-HT concentration (Fig. 2). Furthermore, high concentrations of LSD (100 nM; Figs. 3 and 4) and DOI (3 and 10 μM), which excited the interneurons decreased the excitatory effect of a near-maximal 5-HT concentration. Thus, both the indoleamine LSD and the phenethylamine DOI act as potent partial agonists at least for one subset of cortical 5-HT_{2A} receptors (Figs. 5 and 6).

3. Hallucinogens and potential CNS site(s) of action

The highest density of 5-HT_{2A} receptors exists in the neocortex (layer Va) and the piriform cortex. High concentrations of the 5-HT_{2A} receptor are also present in the olfactory bulb and subcortical areas such as the claustrum, nucleus accumbens, the cranial motor nuclei and the nucleus tractus solitarius. The psychotomimetic effects of the hallucinogens may be mediated by a single site or multiple sites. The manner in which the hallucinogens exert profound effects on cognition, perception and mood suggests that either the neocortex or an area with widespread projections throughout the neocortex mediates the psychotomimetic effects of the hallucinogens via 5-HT_{2A} receptor activation.

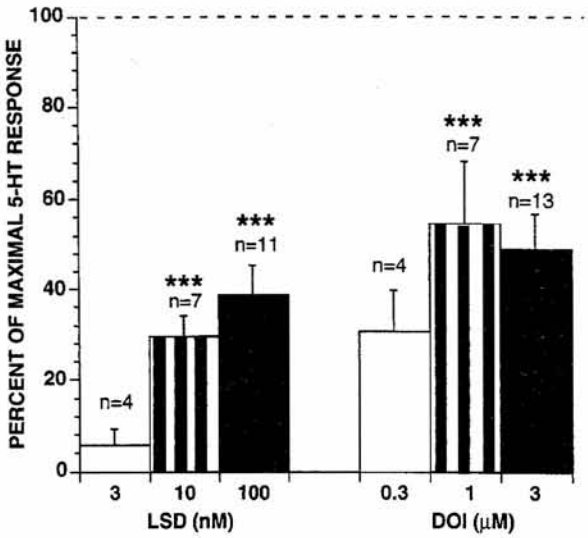

Fig. 2. Efficacy of LSD and DOI with respect to 5-HT for excitation of piriform cortical interneurons. LSD (3–100 nM) and DOI (0.3–3 μM) were applied for 10 min to a rat piriform cortical slice preparation and the resulting excitation of piriform cortical interneurons was compared to the near maximal excitation induced by 100-μM 5-HT. Significantly different from the base line, $^{***}P < 0.001$ (from Marek and Aghajanian, 1996).

3.1. Locus coeruleus

One subcortical area upon which hallucinogens exert an effect and which projects throughout the entire neocortex and virtually all regions of the brain is the locus coeruleus (LC). The LC is the major cluster of noradrenergic-containing cells that is present bilaterally in the upper pons at the lateral border of the fourth ventricle. The actions of hallucinogens on the LC could play a profound role in perceptual changes since the LC receives a convergence of somatic, visceral and other sensory inputs from all regions of the body and has been described as a novelty detector.

The systemic administration of the indoleamine LSD and the phenethylamines mescaline and DOB in anesthetized rats decreases spontaneous activity of the LC but facilitates the activation of LC neurons by sensory inputs (Aghajanian, 1980; Rasmussen and Aghajanian, 1986). These effects of the hallucinogens are mediated via the 5-HT_{2A} receptor because they are blocked by a number of 5-HT_2 antagonists, including several which possess 30–1000-fold selectivity at the 5-HT_{2A} vs. the 5-HT_{2C} receptor (Rasmussen and Aghajanian, 1988). The hallucinogens are not acting directly upon the LC neurons because microiontophoresis of the hallucinogens onto LC cells does not mimic the effects of systemic administration. Furthermore, systemic administration of the hallucinogens does not enhance the effects of microiontophoresis of neurotransmitters with widespread excitatory effects such as glutamate, acetylcholine and substance P (Aghajanian, 1980). Thus, the hallucinogens act indirectly, apparently through afferents to the LC. The relevance for this discussion, however, is that the LC has long been noted to enhance the 'signal to noise' ratio in modulating post-synaptic activity in the forebrain (Woodward et al., 1979). The action of the hallucinogens on the LC, i.e. suppression of basal activity together with increased responses to sensory afferents, can be viewed as enhancing the 'signal to noise' ratio of sensory inputs to the LC itself. Thus, the hallucinogens could alter sensory processing throughout the brain via the LC.

3.2. Facial nucleus

LSD and other hallucinogens also have effects on motor function in addition to their widely recognized effects on perception, cognition and mood. Hallucinogens are known to enhance motor reflexes in humans. Animal studies have also demonstrated that hallucinogens enhance reflexes via 5-HT_2 receptors (Maj et al., 1976, 1977; Skarsfeldt et al., 1990). These effects might be mediated by direct effects of hallucinogens on motor nuclei themselves. Facial motoneurons, like other cranial motor nuclei, possess an especially high level of 5-HT_{2A} binding sites (Pazos and Palacios, 1985) and also express a high level of 5-HT_{2A} receptor mRNA (Pompeiano et al., 1994; Wright et al., 1995). Thus, the facial motor nucleus has been used as a model system to study the electrophysiological effects of hallucinogens since this motor nucleus does not contain any interneurons.

5-HT, by itself, does not excite facial motoneurons to the point of firing, but does depolarize facial motoneurons and enhance the excitation observed after microiontophoretic application of glutamate or stimulation of the motor cortex (McCall and Aghajanian, 1979). The increased excitability of facial motoneurons induced by glutamate was associated with a decreased resting potassium conductance (Vander-Maelen and Aghajanian, 1982). The ergoline hallucinogen LSD, the simple indoleamine hallucinogen psilocybin, and the phenethylamine hallucinogen mescaline were all found to enhance the facilitating effect of iontophoretically applied 5-HT or norepinephrine (NE) on glutamate-induced excitation (McCall and Aghajanian, 1980). This facilitating effect of 5-HT and the phenethylamine hallucinogen DOM were found to be mediated by a 5-HT_2 receptor (Rasmussen and Aghajanian, 1990). The 5-HT_{2A} receptor was found to mediate, at least in part, increases in motoneuron excitability induced by both 5-HT and LSD (Garratt et al., 1993). Furthermore, 5-HT, LSD and DOI were also found to increase the excitability of facial motoneurons through a second ionic mechanism; the opening of a non-specific

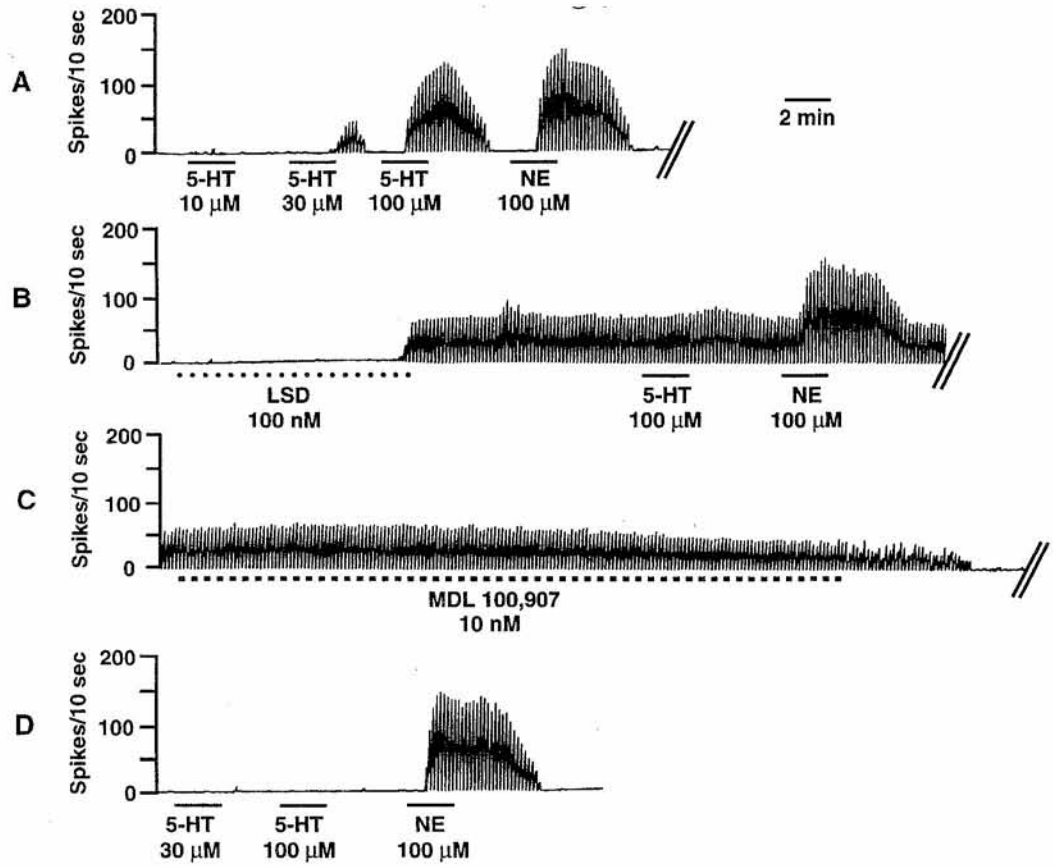

Fig. 3. Firing rate histogram of a piriform cortical interneuron showing that LSD is a partial agonist with respect to 5-HT-induced excitation. The top panel (A) shows the firing rate in response to 2-min bath application of 5-HT (10, 30 and 100 μM) and NE (100 μM). The second panel (B) shows that the quiescent interneuron begins to fire shortly before the end of the 10-min application with LSD (100 nM) and the cell maintains a steady firing rate. Now, the maximal amplitude of the firing rate for this cell compared to the quiescent baseline is reduced in response to 100-μM 5-HT, but is unchanged in response to 100-μM NE. A 30-min application of the selective 5-HT_{2A} antagonist MDL 100,907 suppresses the LSD-induced response (C). The last panel (D) shows that following the MDL 100,907 application, 5-HT (30 and 100 μM) does not induce the cell to fire while the response to NE is unchanged (modified from Marek and Aghajanian, 1996).

cationic current I_h (Garratt et al., 1993). Taken together, these studies suggest that the effects of hallucinogens on motor function in humans, could be mediated in part, through increasing the excitability of lower motoneurons.

3.3. Neocortex

As discussed above, the profound effects of hallucinogens on cognition, perception and mood suggest involvement of the neocortex. Certain features of the effects of hallucinogens such as synesthesias (when sounds are 'seen', etc.) seem difficult to explain unless the neocortex is involved in the effects of the hallucinogens. As discussed above, the hallucinogenic effects of all the ergolines, simple indoleamines and the phenethylamine hallucinogens have been linked to the 5-HT_{2A} receptor. Localization of 5-HT_{2A} receptors by autoradiographic, immunohistochemical, and in situ mRNA hybridization studies all point to the neocortex as having the most prominent expression of 5-HT_{2A} receptors (Pazos and Palacios, 1985; Hoyer et al., 1986; Pompeiano et al., 1994; Wright et al., 1995; Lopez-Gimenez et al., 1997; Willins et al., 1997). The distribution of 5-HT_{2A} receptor binding has a precise laminar pattern in the rat where it is heavy in layer I and especially in layer Va (Blue et al., 1988). Recent immunohistochemical studies (Willins et al., 1997; Jakab and Goldman-Rakic, 1998) agree that 5-HT_{2A} receptors are found both in GABAergic interneurons and prominently in the apical dendrites of pyramidal cells.

Since 5-HT_{2A} receptors have been linked to depolarization and the closing of potassium conductances in a number of brain areas including piriform cortex (Sheldon and Aghajanian, 1990) and the neocortex (Araneda and Andrade, 1991; Tanaka and North, 1993), the presence of 5-HT_{2A} receptors on both interneurons and pyramidal cells might appear incongruent. However, excitation of several subtypes of GABAergic interneurons might have interesting excitatory or modulatory action on pyramidal cells

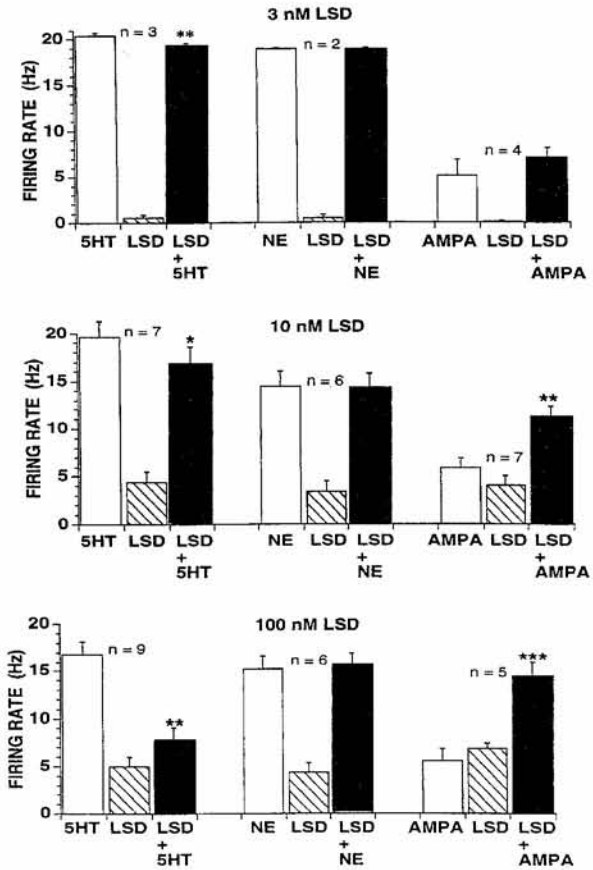

Fig. 4. LSD (3–100 nM) exerts partial agonist properties. The maximal response to 5-HT (100 μM), NE (100 μM) and the excitatory amino acid agonists AMPA (5 μM) both before and after a 10-min perfusion with 3 nM (top panel), 10 nM (middle panel) and 100 nM (bottom panel) LSD. The open bars show the effect of 5-HT, NE or AMPA before LSD application. The hatched bars demonstrate the effects of LSD on the firing rate for the minute immediately preceding application of 5-HT, NE or AMPA. The shaded bars present the maximal response to 5-HT, NE or AMPA when tested after the LSD application and thus demonstrate the combined effects of LSD and either 5-HT, NE or AMPA. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (from Marek and Aghajanian, 1996).

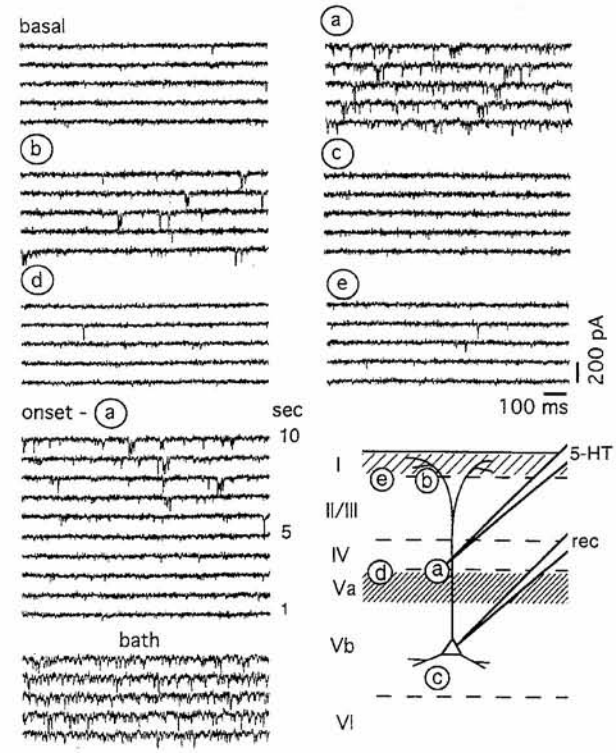

Fig. 5. Microiontophoretically applied 5-HT induces EPSCs in the apical dendritic field of a frontoparietal layer V pyramidal cell. At site a, near the border of layer IV/Va, 5-HT (20 mM ejected at +100 nA from a patch pipette for 30 s) induced a brisk response which began within 6 s (see onset a). At site b, near the border of layer I/II, there was a clear but less pronounced response to 5-HT microiontophoresis. In contrast, at sites lateral (> 100–200 μm) to a radial corridor extending perpendicularly from the recording site to the pial surface (sites e and d), there were virtually no EPSCs induced by 5-HT. Microiontophoresis of 5-HT into the basilar dendritic field (site c) also was not effective. The response of this cell to bath applied 5-HT is shown at the lower left. At the lower right is a schematic diagram indicating the relative positions of the recording (rec) and microiontophoretic (5-HT) micropipettes relative to cortical layers I-VI; the shaded zones indicate bands of high-density 5-HT_{2A} receptor binding (Blue et al., 1988). Intracellular recording was performed with sharp micropipettes containing a 1-M K^{+}-acetate solution.

depending upon the nature of the relationship between the interneuron and the pyramidal cells. For example, excitation of an interneuron which inhibits another actively firing GABAergic interneuron that in turn inhibits a pyramidal cell would result in an increase in the excitability or firing rate of that pyramidal cell, i.e. disinhibition. Another unique type of anatomical relationship to pyramidal cells is seen with a subpopulation of parvabumin-containing GABAergic interneurons that are known as Chandelier cells based on an impressive array of synaptic terminals that surround the initial axon segment of nearby pyramidal cells. The initial axon segment is the portion of the cell from which action potentials are generated generally. Hyperpolarization of the cell together with activation of synaptic inputs that open

cation non-selective I_h currents (e.g. 5-HT_{2A} receptors; Garratt et al., 1993) can lead to a dramatic sculpturing of cell firing such that cells tend to fire in bursts (McCormick and Pape, 1990).

A second effect of 5-HT_{2A} receptor activation in the neocortex is an increase in the excitability that occurs with a depolarization, the appearance of depolarizing afterpotentials following cell firing, and a decrease in spike frequency accommodation (Araneda and Andrade, 1991). Such effects are observed in roughly one-third of layer V pyramidal cells while another one-third of the cells are observed to have a biphasic response to 5-HT, involving a transient hyperpolarization (mediated via activation of 5-HT_{1A} receptors) followed by a depolarization (Araneda and

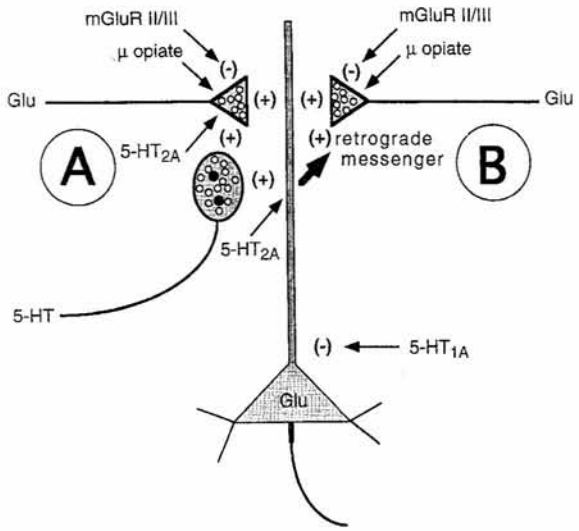

Fig. 6. Alternative models to account for the modulation by μ-opiate agonists and metabotropic glutamate agonists on 5-HT-induced EPSCs in the apical dendritic field of layer V neocortical pyramidal cells. The left side (A) assumes that 5-HT_{2A} receptors are present in the same afferents to the layer V pyramidal cells from which 5-HT induces glutamate release. The right side (B) assumes that 5-HT_{2A} receptors are present on the apical dendrites of layer V pyramidals and they have a *presynaptic* effect on glutamatergic afferents to layer V pyramidals through release of a diffusible 'retrograde messenger' that acts upon the glutamatergic afferents. With both models, μ-receptors and group II/III metabotropic glutamate receptors are present on the afferents on which 5-HT induces to release glutamate.

Andrade, 1991). We have recently discovered a third effect of 5-HT_{2A} receptor activation in the neocortex that may be instrumental in the mechanism of the psychotomimetic effects of ergoline, simple indoleamine and phenylethylamine hallucinogens. Most of the synaptic potentials induced by 5-HT in layer V pyramidal cells were excitatory rather than inhibitory (Aghajanian and Marek, 1997). This finding was surprising since in earlier studies we had found that 5-HT induces inhibitory post-synaptic potentials (IPSPs) in layer II pyramidal cells of rat piriform cortex (paleocortex) via excitation of GABAergic interneurons (Sheldon and Aghajanian, 1990, 1991; Gellman and Aghajanian, 1993). Thus, while only ~ 15% of 5-HT-induced synaptic potentials in neocortex are blocked by the $GABA_A$ antagonist bicuculline, the great majority of synaptic potentials are blocked by the AMPA glutamatergic receptor antagonist LY293558, indicating that they represent largely excitatory post-synaptic potentials (EPSPs) rather than IPSPs (Aghajanian and Marek, 1997). Nevertheless, as with IPSPs in the piriform cortex, the excitatory post-synaptic currents (EPSCs) induced by 5-HT in neocortex are mediated by 5-HT_{2A} receptors as they are blocked by low concentrations of two drugs with a 30–100-fold selectivity at the 5-HT_{2A} vs. the 5-HT_{2C} receptor, MDL100,907 and SR46349B. While we have observed that 5-HT increases EPSCs throughout the neocortex, this effect is most pronounced in the medial prefrontal cortex where there is an increased density of 5-HT_{2A} receptors compared to more posterior regions.

Whole-cell patch clamp recordings have demonstrated that 5-HT induces a small but significant increase in the amplitude of EPSCs, an effect which may involve a post-synaptic amplification mechanism (Aghajanian and Marek, 1997). Such a post-synaptic effect is consistent with the finding of a high density of 5-HT_{2A} receptor immunoreactivity in the apical dendrites of cortical pyramidal cells (Willins et al., 1997; Jakab and Goldman-Rakic, 1998). However, the most pronounced effect of 5-HT in neocortex is to increase the *frequency* of EPSCs (Aghajanian and Marek, 1997). Classically, changes in the frequency of synaptic currents or potentials are considered presumptive evidence for modulation of presynaptic function. Consistent with this model, activation of μ-opiate receptors (Marek and Aghajanian, 1997) and group II/III metabotropic glutamate receptors (Aghajanian and Marek, 1997) both appear to block 5-HT-induced EPSCs through a presynaptic rather than post-synaptic action upon layer V pyramidal cells. Together, these findings suggest that activation of 5-HT_{2A} receptors increases the release of glutamate onto layer V pyramidal cells through a presynaptic mechanism.

A novel mechanism independent of impulse flow appears to be involved in the increase in glutamate release induced by 5-HT_{2A} receptor activation. Blockade of 5-HT-induced EPSCs by bath application of the fast sodium channel blocker tetrodotoxin (TTX) or perfusion of the slice with a solution containing no added calcium ('0' calcium) would generally suggest that 5-HT had activated glutamatergic cells in the slice, leading to an impulse-flow-dependent release of glutamate. Several lines of evidence argue against this conventional interpretation. First, we rarely found any neurons induced to fire by bath application of 5-HT which is markedly unlike our experience in the piriform cortex where we readily find GABAergic interneurons excited by 5-HT. Second, none of the pyramidal cells (a potential source of intracortical excitatory inputs) in our sample were depolarized by 5-HT sufficiently to reach threshold for firing. Third, microiontophoresis of 5-HT in the apical dendrites of layer V pyramidal cells also elicited EPSCs, but even when these focal 5-HT applications induced EPSCs with a latency of a few seconds, we never detected any cells firing while recording extracellularly with the *microiontophoretic electrode* (Fig. 5, Aghajanian and Marek, 1997). Together, these experiments support the conclusion that 5-HT-induces EPSCs in neocorti-

cal cells via a focal mechanism that does not require impulse flow (Fig. 6).

Since the microiontophoretic experiments indicate that 5-HT-induced EPSCs do not result from an increase in impulse flow in excitatory afferents, we were prompted to explore alternative mechanisms of transmitter release. Classically, two major types of vesicular neurotransmitter release have been characterized in experiments analyzing electrically-evoked synaptic potentials (Katz and Miledi, 1965; Goda and Stevens, 1994). The first type of neurotransmitter release, termed *synchronous* release, is closely coupled in an almost immediate fashion to the action potential invasion of the nerve terminals with a subsequent flooding of Ca^{2+} into the terminal through voltage-gated Ca^{2+} channels. This is the form of neurotransmitter release that we typically envision. However, analysis of 'synaptic noise' shows that there is also a slow, *asynchronous* phase of transmitter release, characterized by the presence of small EPSCs with a slightly longer latency ($\sim$ 50 ms) than the synchronous EPSC which can persist for $\sim$ 500–1000 ms following the evoked synchronous EPSC. This form of release is sustained by low levels of residual Ca^{2+} remaining within the terminal following the initial wave of Ca^{2+} influx.

One of several distinguishing characteristics for these alternative mechanism of transmitter release is that Sr^{2+} is able to substitute for Ca^{2+} for the asynchronous, but not synchronous release (Goda and Stevens, 1994). This feature appears to be a result of two different isoforms of synaptotagmin, being differentially involved in the two alternative release mechanisms (Li et al., 1995). We are now investigating the possibility that the 5-HT-induced EPSCs result from an activation of the asynchronous release pathway. In preliminary experiments we have found that Sr^{+} is highly effective in enabling 5-HT to induce EPSCs in the absence of Ca^{2+} (Aghajanian and Marek, 1998).

Recently we have found that hallucinogenic drugs, via 5-HT_{2A} receptors, also promote the asynchronous release of glutamate, particularly in conjunction with electrically-evoked EPSPs (Aghajanian and Marek, 1998). (5-HT itself is less effective than the hallucinogens in promoting electrically-evoked asynchronous release except during the washout phase, presumably due to opposing actions at 5-HT_1 or other non-5-HT_{2A} receptors.) An enhancement of asynchronous evoked EPSPs via 5-HT_{2A}-receptors provides a possible synaptic mechanism for the hallucinogenic effects of these drugs.

3.4. Hallucinogenic drugs and schizophrenia

While at first glance, this wide spectrum of psychotomimetic effects induced by the LSD-like hallucinogens could suggest that LSD and other hallucinogens may have relatively non-specific effects, this constellation of activity might be related to the presence of 5-HT_{2A} receptors throughout most of the human neocortex (Hoyer et al., 1986). Furthermore, the neocortex is organized into columns in which the cells have similar functional properties (Powell and Mountcastle, 1959; Hubel and Wiesel, 1977). Each of 50–100 cytoarchetectonic areas of the neocortex is made of up a multitude of columns. Obviously, higher order perceptual, affective and cognitive processes rely on the mode of intercommunication between neighboring columns as well as different areas. Thus, by altering excitatory transmission, 5-HT_{2A} receptors in the neocortex would be expected to influence a multitude of higher order functions.

3.5. Psychiatric manifestations of hallucinogen use

The psychotomimetic effects of hallucinogenic drugs (e.g. LSD, psilocybin, and mescaline) have been suggested to resemble more closely the symptoms of acute, rather than chronic schizophrenia (Vollenweider et al., 1997b). The indoleamine psilocybin and the phenethylamine mescaline both produce a global increase (somewhat larger in prefrontal cortex) in regional cerebral glucose metabolism (Hermle et al., 1992; Vollenweider et al., 1997). This is of interest since some SPECT and PET imaging studies have found a significantly increased resting frontal to parietal ratio of cerebral glucose metabolism in acute, unmedicated first-episode schizophrenics (Cleghorn et al., 1989; Ebmeier et al., 1993; Kaplan et al., 1993; Parellada et al., 1994). A hyperfrontal metabolic pattern also occurs following administration of the noncompetitive NMDA antagonist ketamine to normal humans at subanesthetic doses (Vollenweider et al., 1997a). Ketamine is known to exert psychotomimetic effects in normal humans (Krystal et al., 1994) and to exacerbate psychotic symptoms of stable, but actively psychotic schizophrenics (Lahti et al., 1995).

The suggestion that the LSD-like hallucinogens may model some of the acute symptoms of schizophrenia may be relevant to the long-standing anecdotal observations of a relationship between the onset of schizophrenia and hallucinogen use in a vulnerable population (Glass and Bowers, 1970; Bowers, 1977; Vardy and Kay, 1983). The characteristics of the Post-Hallucinogen Perceptual Disorder (PHPD) suggests that the LSD-like hallucinogens may exert long-lasting physiological changes in the CNS (Abraham, 1983a). Recent preclinical work showing that the phenethylamine hallucinogen DOI increases the expression of brain-derived neurotrophic factor (BDNF)

could provide a clue to the mechanism by which hallucinogens might exert long-lasting changes in synaptic connections in the brain (Vaidya et al., 1997).

3.6. Summary and future directions

The psychotomimetic effects of ergoline, simple indoleamine and phenethylamine hallucinogens appears to be associated with activation of 5-HT_{2A} receptors. While 5-HT_{2A} receptor activation in multiple areas of the brain is probably involved in explaining these psychotomimetic effects, certainly cortical 5-HT_{2A} receptors are a critical site involved in the wide ranging effects on perception, cognition and mood. However, in order to fully explain the mechanism of action of these hallucinogens, one question remains unanswered. Why does not 5-HT itself induce psychotomimetic effects? In particular, psychotomimetic effects are not observed after administration of selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs). Both of these treatments enhance the synaptic availability of 5-HT and increase 5-HT_{2A} receptor activation (along with activation of non-5-HT_{2A} receptors). Even more striking, co-administration of these drugs causes a profound elevation of 5-HT throughout the brain resulting in the 5-HT syndrome, yet psychotomimetic effects are not observed. In this context, an anecdotal report that the 5-HT precursor 5-hydroxytryptophan (5-HTP) reversed the LSD-induced psychotic symptoms is of interest (Abraham, 1983b). These clinical correlations suggest that in order to explain the mechanism of action for the three different classes of LSD-like hallucinogens is really a two-stage process. The first stage requires that a site at which all three classes of drugs share a common action must be elucidated. The 5-HT_{2A} receptor appears to be the most likely candidate. The second stage requires a site at which all three different classes of hallucinogens are inactive, but which 5-HT is active and is able to suppress the effects of the hallucinogens at the 5-HT_{2A} receptor. Research directed to this latter goal might result in the discovery of novel classes of antipsychotic drugs, which may of be particular benefit for patients with LSD-induced psychosis which generally tend to be treatment refractory.

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