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Serotonin–Glutamate Interactions: A New Target for Antipsychotic Drugs

George K. Aghajanian, M.D., and Gerard J. Marek, M.D., Ph.D.

Interest in the role of serotonin (5-HT) in the therapeutic effects of atypical antipsychotic drugs originated from the observations that: (1) clozapine and other atypical drugs have a high affinity for 5-HT_{2A} relative to D_2 receptors; and (2) 5-HT_{2A} receptors mediate the central effects of psychedelic hallucinogens. Recently, we found that 5-HT evokes a focal release of glutamate in the apical dendritic field of layer V pyramidal cells in prefrontal cortex, measured electrophysiologically by an increased frequency of spontaneous excitatory postsynaptic potentials/currents (EPSPs/EPSCs). An atypical mode of transmitter release (termed asynchronous *release) seems to be involved because EPSC induction is tetrodotoxin (TTX)-sensitive but is not dependent on impulse flow and is supported by Sr^{2+} in the absence of external Ca^{2+}. The 5-HT-induced increase in spontaneous EPSCs is blocked completely by the selective 5-HT_{2A} antagonist M100907 (MDL 100,907). M100907 also blocks the enhancement by hallucinogens of a late,* asynchronous *component of electrically evoked EPSPs/EPSCs. Group II/III metabotropic glutamate agonists, which act downstream from 5-HT_{2A} receptors at presynaptic inhibitory autoreceptors, markedly suppress the 5-HT-induced release of glutamate. Subtype-selective group II/III agonists, such as the group II metabotropic agonist LY354740, are particularly interesting in terms of therapeutic potential, because they are able to suppress the 5-HT_{2A}-induced EPSCs while sparing overall glutamatergic transmission. An analysis of the mechanisms by which 5-HT_{2A} receptors induce glutamate release suggests new targets for the design of novel treatments for schizophrenia.* ***[Neuropsychopharmacology 21:S122–S133]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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In the late 1970s, using radioligand binding techniques, it was discovered that antipsychotic drugs interacted not only with dopamine receptors but also with serotonin (5-HT) receptors, particularly in the frontal cortex (Leysen et al. 1978). Shortly thereafter, using radiolabeled 5-HT and the hallucinogen LSD (d-lysergic acid diethylamide) as ligands, at least two distinct populations of 5-HT receptors, termed 5-HT_1 and 5-HT_2, were described in the brain (Peroutka and Snyder 1979). Based on this classification, it was determined that some antipsychotic drugs, such as clozapine, interacted more potently with the 5-HT_2 than D_2 receptor; however, clinical potency appeared to correlate only with affinity for the D_2 receptor (Peroutka and Snyder 1980). Only later, when antipsychotic drugs were grouped separately according to whether they had "typical" or "atypical" characteristics, did a high affinity for 5-HT_2 relative to D_2 receptors emerge as a distinguishing feature of the drugs in the atypical category (Altar et al. 1986; Meltzer et al. 1989).

Antipsychotic drugs are generally classified as atypical if they have reduced extrapyramidal side effects

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and/or an enhanced spectrum of antipsychotic efficacy, particularly with regard to negative symptoms. An early clinical study suggested that a drug, setoperone, with high affinity for 5-HT_2 relative to D_2 receptors, in addition to having relatively low extrapyramidal side effects, may have enhanced efficacy in the treatment of negative symptoms (e.g., emotional withdrawal, blunted affect) (Ceulemans et al. 1985). It is noteworthy that part of the rationale given in the latter study for testing the antipsychotic properties of 5-HT_2-antagonist drugs was their ability to block certain effects of LSD in animal model systems (Colpaert and Janssen 1983). The hypothesis that 5-HT_2 receptor blockade contributes to the favorable profile of atypical antipsychotic drugs led to the development of a new generation of agents with a high 5-HT_{2A} to D_2 ratio, some of which (e.g., risperidone) have now become accepted for clinical use in the treatment of schizophrenia (for reviews, see: Breier et al. 1997; Lieberman et al. 1998; Meltzer and Nash 1991).

Meanwhile, a large body of evidence has accumulated that 5-HT_2 receptors may be involved in the mechanism of action of psychedelic hallucinogens. Originally, this idea was based on the demonstration of a high correlation between hallucinogenic potency in humans and the affinity of both phenethylamine (e.g., mescaline) and indoleamine (e.g. LSD and psilocybin) hallucinogens for 5-HT_2 receptors (Glennon et al. 1984; Titeler et al. 1988). Indeed, among all known 5-HT receptor subtypes, affinity for 5-HT_2 receptors is the only one shared by both the indoleamine and phenethylamine classes of hallucinogens. There is now abundant evidence from biochemical (Sanders-Bush et al. 1988), electrophysiological (Marek and Aghajanian 1996), and animal behavioral (Glennon 1990) studies that the effects of hallucinogens involve a partial agonist action at 5-HT_2 receptors, particularly of the 5-HT_{2A} subtype. Very recently, studies on the role of 5-HT_2 receptors in the action of hallucinogens have been extended to human subjects. As predicted by the preclinical studies, the psychotomimetic effects of the indoleamine hallucinogen psilocybin have now been shown to be blocked completely by the preferential 5-HT_{2A} antagonist ketanserin, the atypical antipsychotic risperidone, but not the typical antipsychotic haloperidol (Vollenweider et al. 1998). However, it remains to be determined whether 5-HT_{2A} antagonism alone is sufficient for the treatment of schizophrenia or whether a threshold level of D_2 antagonism may be required for full antipsychotic efficacy (Farde et al. 1992; Kapur et al. 1999). The resolution of these issues will require the completion of clinical testing with highly selective 5-HT_{2A} antagonists such as M100907 (also referred to as MDL 100,907).

Because of their possible involvement in the action of psychedelic hallucinogens and atypical antipsychotics there has been much interest in the location and function of 5-HT_{2A} receptors in the central nervous system. Autoradiographic studies show 5-HT_{2A} receptor binding in several regions of the brain, but the bulk of these receptors are found in the cerebral cortex (Lopez-Gimenez et al. 1997; Pazos and Palacios 1985). A correspondingly high density of 5-HT_{2A} receptor mRNA has been found by in situ hybridization in the cerebral cortex (Mengod et al. 1990; Wright et al. 1995). Recent immunocytochemical studies have demonstrated a particularly high density of 5-HT_{2A} receptors within the apical dendrites of cortical pyramidal cells (Hamada et al. 1998; Jakab and Goldman-Rakic 1998; Willins et al. 1997). This postsynaptic localization is consistent with electrophysiological studies on cortical pyramidal cells showing direct depolarizing effects mediated by 5-HT_2 receptors (Aghajanian and Marek 1997; Araneda and Andrade 1991; Sheldon and Aghajanian 1990; Tanaka and North 1993).

The focus of this review is on the physiological role of 5-HT_{2A} receptors in the medial prefrontal and anterior cingulate regions of the cerebral cortex, particularly in relation to their ability to enhance certain kinds of glutamatergic transmission by indoleamine and the phenethylamine hallucinogens. These electrophysiological effects are discussed in relation to the NMDA antagonist class of psychotomimetics, which, surprisingly, have now been reported to induce an increase in glutamate release in the cerebral cortex. Finally, potential new targets for antipsychotic drug design based on a hyperglutamatergic model of psychotomimetic drug action are discussed.

5-HT_{2A} RECEPTORS ENHANCE GLUTAMATE RELEASE IN NEOCORTEX

Electrophysiological actions of hallucinogens, acting via 5-HT_2 receptors, have been described in several subcortical regions of the rat (Aghajanian 1980; Garratt et al. 1993; McCall and Aghajanian 1980; Rasmussen and Aghajanian 1986). However, because hallucinogens characteristically alter higher-level processes, such as cognition, perception, and mood, studies on their effects in the cerebral cortex are receiving increasing attention. One of the most striking effects of 5-HT is an increase in spontaneous postsynaptic potentials (PSPs) in various cortical regions. Originally, recordings from pyramidal cells in brain slices from rat piriform cortex, a paleocortical region, showed that 5-HT induces mostly inhibitory postsynaptic potentials (IPSPs) (Sheldon and Aghajanian 1990). However, more recent studies have shown that in layer V pyramidal cells of the neocortex, 5-HT-induced synaptic events consist mostly of excitatory postsynaptic potentials/currents (EPSPs/EPSCs) (Figure 1), shown in part by the fact that they are blocked by the AMPA/kainate glutamate receptor antagonist LY293558 but not the $GABA_A$ antagonist

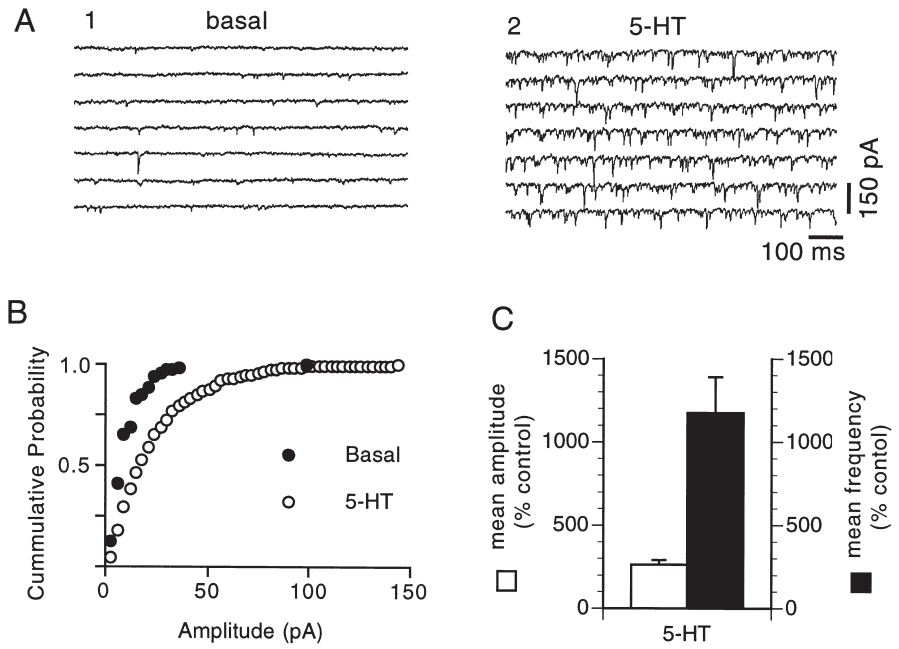

Figure 1. 5-HT-induced increases in the frequency and amplitude of EPSCs in neocortical pyramidal cells. *A* shows a whole cell recording of the effect produced by bath applied 5-HT (100 μM, 1 min) on spontaneous EPSCs in a layer V pyramidal cell in medial prefrontal cortex; seven consecutive 1-s episodes are shown. *B* shows a plot of the normalized cumulative distribution of EPSC amplitudes before and during the application of 5-HT for the cell illustrated in *A* (data taken from 10 1-s episodes; 2 pA cutoff). The shift in distribution to higher amplitudes was significant at $p < .001$ (Kolmogorov–Smirnov test). *C* shows the change in mean frequency and amplitude (±SEM) in response to 5-HT (100 μM, 1 min) for the entire sample of cells tested ($n = 9$). Mean basal frequency, 12.6 ± 2.2 Hz; mean basal amplitude, 7.9 ± 0.9 pA. The increase in frequency was significant at $p < .001$ (paired t- test) (Aghajanian and Marek 1997).

bicuculline (Aghajanian and Marek 1997). The 5-HT-induced EPSCs are antagonized by low concentrations of the highly selective 5-HT_{2A} antagonist M100907 (Figure 2), indicating that they are mediated by 5-HT_{2A} receptors (Aghajanian and Marek 1997; Marek and Aghajanian 1999). The 5-HT-induced increase in EPSCs is most pronounced in frontal regions such as the medial prefrontal cortex (Aghajanian and Marek 1997), where the density of 5-HT_{2A} receptors is increased relative to more posterior regions (Lopez-Gimenez et al. 1997; Pazos and Palacios 1985). Norepinephrine (NE), via α_1 adrenoceptors, also induces an increase in EPSPs in layer V pyramidal cells, but, at least in the rat, to only a fraction of that produced by 5-HT (Marek and Aghajanian 1999).

Quantitatively, the most pronounced effect of 5-HT in prefrontal cortex is to increase the *frequency* of EPSCs (Figure 1). Changes in the frequency of synaptic currents or potentials are generally regarded as being indicative of a modulation of presynaptic function. Accordingly, the relatively nonspecific group II/III metabotropic glutamate receptor agonist (1S, 3S)-ACPD (Aghajanian and Marek 1997) (Figure 3) or the selective group II metabotropic agonist LY354740 (Marek et al. 1999), acting at presynaptic inhibitory autoreceptors located on glutamatergic nerve terminals, suppresses the 5-HT-induced increase in the frequency of EPSCs in prefrontal cortex. These findings are consistent with the idea that activation of 5-HT_{2A} receptors increases the release of glutamate onto layer V pyramidal cells through a presynaptic mechanism. However, this presynaptic effect might be mediated indirectly through a retrograde messenger, because, as discussed below, 5-HT_{2A} receptors appear predominantly to have a postsynaptic localization (Hamada et al. 1998; Jakab and Goldman-Rakic 1998). 5-HT also produces a small but significant increase in the *amplitude* of spontaneous EPSCs, an effect that may involve a postsynaptic amplification mechanism (Aghajanian and Marek 1997). Such a postsynaptic effect is consistent with the finding of a high density of 5-HT_{2A} receptor immunoreactivity in the apical dendrites of cortical pyramidal cells (Jakab and Goldman-Rakic 1998; Willins et al. 1997).

The 5-HT-induced EPSCs are blocked 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) (Aghajanian and Marek 1997). Ordinarily, TTX sensitivity or Ca^{2+} dependence would suggest that 5-HT had activated glutamatergic cells located within the slice, leading to an

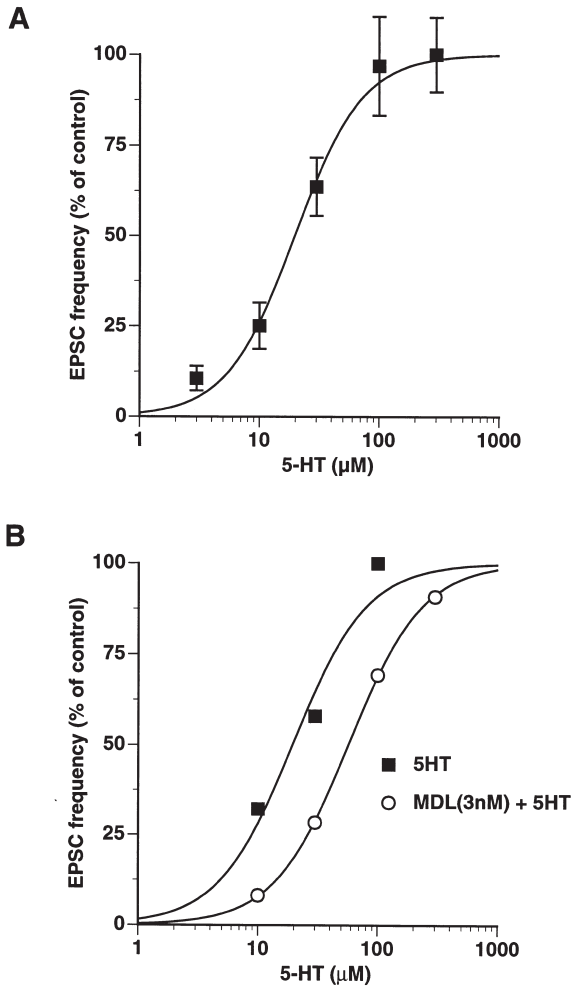

Figure 2. Concentration-response curve for 5-HT-induced EPSCs in neocortical layer V pyramidal cells and blockade by the 5-HT_{2A} antagonist M100907 (MDL). *A* shows a normalized concentration-response curve for randomly selected layer V pyramidal cells (n = 6, 4 medial prefrontal cortex and 2 frontoparietal cortex) where the 5-HT-induced increase in EPSC frequency at each concentration (3, 10, 30, 100, and 300 μM) is expressed as the percentage of the 300 μM 5-HT response for each cell (mean ± SEM). The EC_{50} was 19.7 μM, and the maximal EPSC frequency was 36.5 Hz. *B* shows the 5-HT concentration-response curve for a frontoparietal layer V pyramidal cell both before (closed squares) (EC_{50} = 19.4 μM) and after (open circles) (EC_{50} = 57.0) a 27-min treatment with 3 nm M100907 (M100907 perfusion continued in between the 1-min 5-HT applications). The pA_2 in this cell calculated by the Schild equation was 8.8. Note that M100907 treatment resulted in a rightward parallel shift of the concentration-response curve and that the antagonism by M100907 was surmountable by a higher 5-HT concentration (300 μM) (Aghajanian and Marek 1997).

impulse-flow dependent release of glutamate. However, several lines of evidence argue against this conventional interpretation. First, rarely were neurons within the confines of the brain slice induced to fire by bath application of 5-HT. Second, none of the recorded pyramidal cells (a potential source of intracortical excitatory inputs) was depolarized sufficiently by 5-HT to reach threshold for firing. Third, EPSCs could be induced by the microiontophoresis of 5-HT onto "hotspots" along the apical dendrites of layer V pyramidal cells, but no cell firing could be detected in the same locations while recording extracellularly through the microiontophoretic electrode (Aghajanian and Marek 1997). Together, these experiments suggest that 5-HT induces EPSCs in neocortical cells through a focal action involving a Ca^{2+}-dependent mechanism that does not require impulse flow.

5-HT_{2A} RECEPTORS AND ASYNCHRONOUS TRANSMISSION IN THE CEREBRAL CORTEX

Recently, we have begun to investigate possible atypical mechanisms by which 5-HT, in the absence of an increase in afferent impulse flow, could induce a focal, TTX-sensitive/Ca^{2+}-dependent release of glutamate. Previously, it has been reported that mildly depolarizing agents, such as the K^+ channel blocker 4-aminopyridine (4-AP), can induce a TTX-sensitive release of glutamate from isolated cortical synaptosomes; whereas, the increase in glutamate release produced by strongly depolarizing concentrations of KCl (sufficient to activate voltage-gated Ca^{2+} channels) is not TTX-sensitive (Tibbs et al. 1989). Notably, 4-AP preferentially enhances the "slow" rather than the "fast" component of glutamate release from cortical synaptosomes; this slow component has been hypothesized to represent the asynchronous mode of release, because it is supported by Sr^{2+} in the absence of Ca^{2+} (Herrero et al. 1996). Sr^{2+} substitutes for Ca^{2+} at the high-affinity Ca^{2+} sensor synaptotagmin III, which is believed to be responsible for slow, asynchronous transmitter release; in contrast, Sr^{2+} is ineffective at the low-affinity Ca^{2+} sensor synaptotagmin I thought to be essential for fast, synchronous transmitter release (Figure 4) (Geppert et al. 1994; Goda and Stevens 1994; Li et al. 1995). It has been proposed that the formation of a multi-molecular complex, consisting of synaptotagmin I together with synaptic core complex proteins, interacts with the segment II/III intracellular loop of Ca^{2+} channels (Tobi et al. 1998), forming the basis for rapid Ca^{2+}-triggered transmitter release (for review, see Stanley 1997). Thus, if coupling to the synaptic protein interaction site of Ca^{2+} channels is prevented, fast synchronous transmitter release is impaired; whereas, late asynchronous release remains intact (Mochida et al. 1996).

In various regions of brain, including cerebral cortex (Araneda and Andrade 1991; Sheldon and Aghajanian 1990; Tanaka and North 1993), the effects of 5-HT_{2A}-receptor activation resemble those of 4-AP in producing

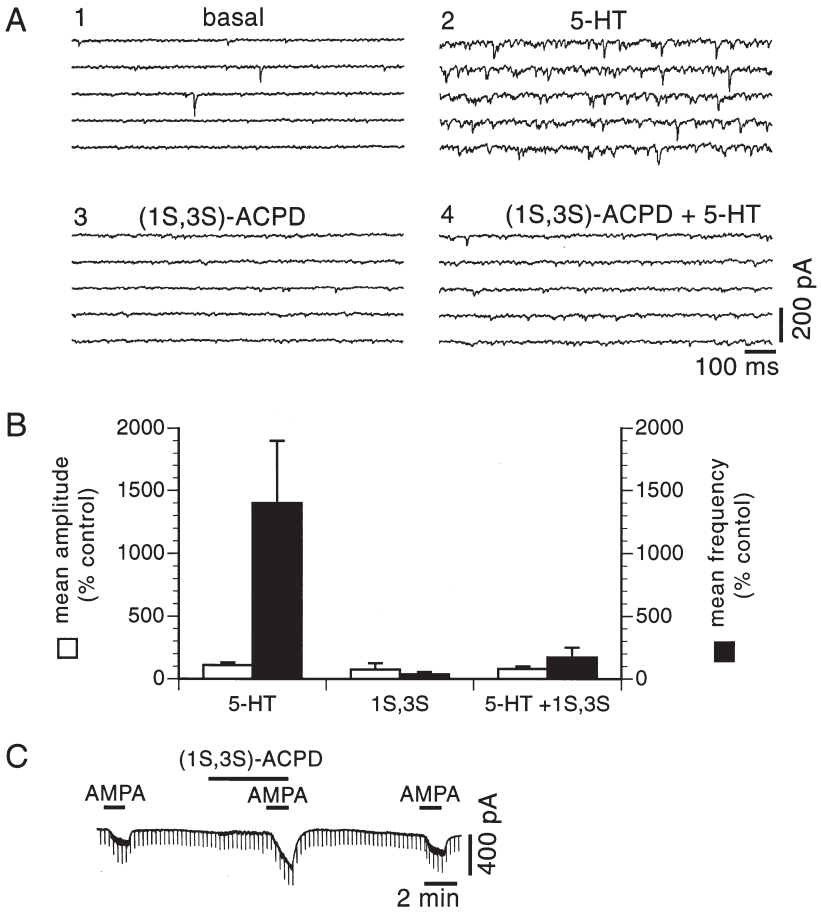

Figure 3. The effect of the group II/III metabotropic agonist (1S, 3S)-ACPD on 5-HT-induced EPSCs. *A* shows a whole-cell recording from a layer V cell in medial prefrontal cortex in which the prior (4 min) and concurrent application of (1S, 3S)-ACPD (200 μM) largely blocks the 5-HT-induced increase in EPSCs; the effect of (1S, 3S)-ACPD reversed rapidly during 4 to 5 min of washout (not shown). *B* gives normalized mean EPSC amplitude and frequency data for five cells; basal amplitude was 31 ± 4 pA, and basal frequency was 2 ± 0.7 Hz. The predominant effect of (1S, 3S)-ACPD was to reduce the 5-HT-induced increase in EPSC frequency ($p < .05$, two-tailed t-test). *C* represents a voltage-clamp recording (K acetate electrode) of inward AMPA currents measured before and during the application of (1S, 3S)-ACPD (200 μM). Note that the inward current produced by bath applied AMPA (5 μM) is not reduced during the application of (1S, 3S)-ACPD. In all five cells tested, (1S, 3S)-ACPD caused an increase rather than a reduction in postsynaptic AMPA currents. Inward currents are downward in direction; input conductance was monitored by periodic (20 s) 1-s negative current pulse, giving rise to brief downward deflections (Aghajanian and Marek 1997).

a slow depolarization through a reduction in K^+ channel conductance. By analogy with 4-AP, it is possible that 5-HT induces an a TTX/Ca^{2+}-sensitive focal increase in spontaneous EPSCs through an increase in the Sr^{2+}-supported asynchronous mode of glutamate release. To test this possibility, we have examined the ability of Sr^{2+} to substitute for Ca^{2+} in supporting 5-HT-induced *spontaneous* EPSCs. We have found that the 5-HT-induced increase in the *frequency* of spontaneous EPSCs is fully supported by Sr^{2+} in the absence of added Ca^{2+}, suggesting mediation by the asynchronous rather than synchronous mode of transmitter release (Figure 5). In contrast, the *amplitude* of spontaneous EPSCs is not fully supported by Sr^{2+} in the absence of Ca^{2+}, consistent with the importance of Ca^{2+} in the postsynaptic amplification of glutamatergic inputs to apical dendrites of layer V pyramidal cells (Schiller et al. 1997).

In layer V pyramidal cells of medial prefrontal cortex, when extracellular Ca^{2+} is removed, there is a loss of synchronous electrically evoked EPSCs; the subsequent addition of Sr^{2+} leads to the appearance of late asynchronous EPSCs in the continued absence of synchronous EPSCs (Figure 6) (Aghajanian and Marek 1999). A similar increase in late, nonsynchronous component electrically evoked EPSCs was observed during 5-HT washout (when 5-HT_{2A} receptors are unopposed by non-5-HT_{2A} actions of 5-HT) or application of the 5-$HT_{2A/2C}$ partial agonist DOI (Figure 7). M100907 is highly effective in reversing the DOI enhancement of the late component of the evoked EPSC, confirming that this effect is mediated by 5-HT_{2A} receptors (Figure 8). The conventional interpretation of this late component would be that it represents polysynaptic or epileptiform activity. However, in several respects (e.g., refractory period) this late component of the evoked response is distinct from conventional polysynaptic evoked EPSCs that occur, for example, in the presence of the $GABA_A$ antagonist bicuculline (Aghajanian and Marek 1999). Therefore, we hypothesize that the late component of the EPSC enhanced by 5-HT_{2A} receptors is mediated by the asynchronous mode of glutamate release at the nerve terminal rather than through a polysynaptic pathway.

PROPOSED MECHANISMS FOR 5-HT_{2A} RECEPTOR-INDUCED ASYNCHRONOUS GLUTAMATE RELEASE

A mechanism by which 5-HT_{2A} receptors, either directly or indirectly, could promote asynchronous EPSCs in

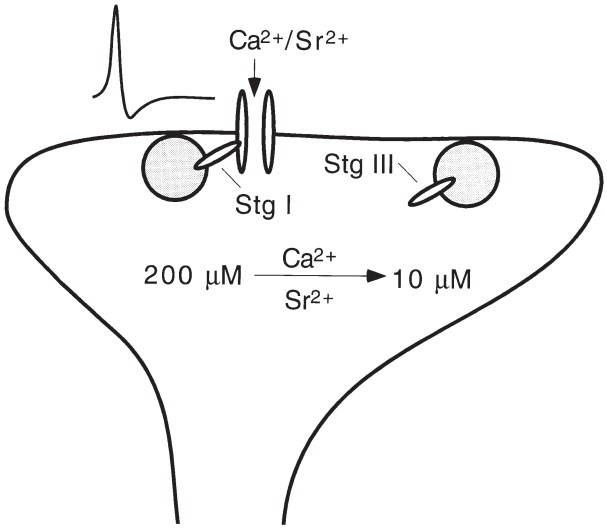

Figure 4. A schematic of how a synaptic vesicle associated with the low-affinity Ca^{2+} sensor synaptotagmin I (Stg I) is coupled to a voltage-gated Ca^{2+} channel (arrow), while a synaptic vesicle associated with synaptotagmin III (Stg III) is at a distance from the Ca^{2+} channel. With the arrival of a nerve impulse, the entry of Ca^{2+} is able to trigger rapid, synchronous release of transmitter via Stg I, because there is a high, localized concentration of this ion (~200 μm); Sr^{2+} can also enter but cannot trigger transmitter release via Stg I. As Ca^{2+} or Sr^{2+} diffuse away from the Ca^{2+} channel, their concentration declines (e.g., to ~10 μm), but both ions can trigger late or asynchronous release via the high-affinity Ca^{2+} sensor Stg III.

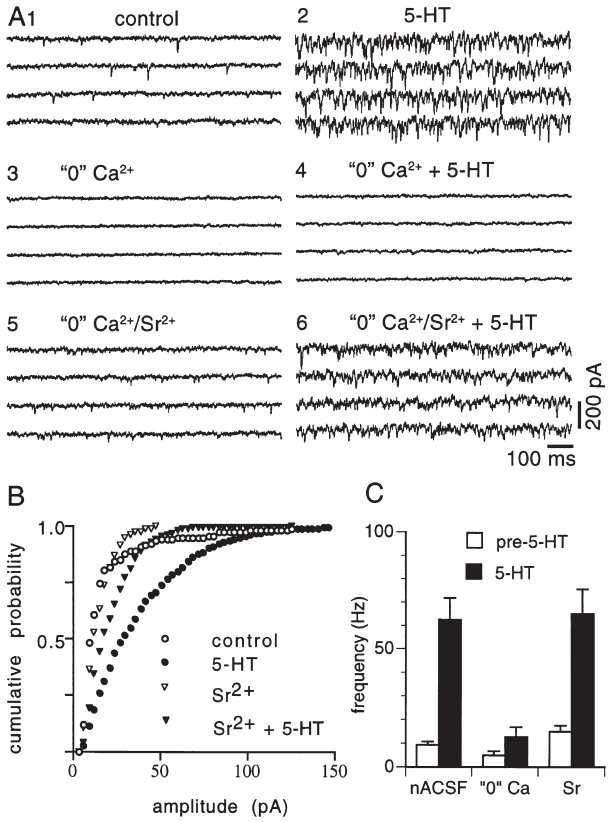

Figure 5. Effect of Sr^{2+} on 5-HT-induced spontaneous EPSCs in layer V pyramidal cells of medial prefrontal cortex. **($A_{1\text{-}6}$)** Whole cell patch-clamp recording showing responses of an individual pyramidal cell to a 1-min application of 5-HT (100 μM) in normal ACSF, after 9 to 10 minutes of ACSF with "0" added Ca^{2+} (2 mM Mg^{2+} substituted for Ca^{2+}), or after 9 to 10 min in Sr^{2+} (1 mM) substituted for Ca^{2+}. **(B)** Cumulative probability plot for the amplitude distribution of spontaneous EPSCs for the cell illustrated in (A); 5-HT induces a significant shift to higher amplitudes both in the normal ACSF and Sr^{2+} conditions ($p < .001$, Kolmogorov–Smirnov test). **(C)** Summary of results for five cells showing increased frequency of spontaneous EPSCs induced by 5-HT in normal ACSF or Sr^{2+}/"0" Ca^{2+} conditions ($p < .004$, paired t-test); spontaneous EPSCs were not increased over the normal ACSF baseline by 5-HT in the "0" Ca^{2+} condition (Aghajanian and Marek 1999).

layer V pyramidal cells would be by increasing residual Ca^{2+} in excitatory nerve terminals; thereby activating of synaptotagmin III (see Figure 4). There are a number of possible mechanisms through which the activation of 5-HT_{2A} receptors could augment levels of residual Ca^{2+} (Figure 9). It is known that 5-HT_{2A} receptors are coupled via the G_q family of G proteins to the phospholipase C/phosphoinositide second messenger pathway, one limb of which leads to the formation of inositol trisphosphate (IP_3), a releasor of Ca^{2+} from intracellular stores (Conn and Sanders-Bush 1986). This has been demonstrated directly in C6 glioma cells where a 5-HT_{2A}-receptor mediated release of intracellular Ca^{2+} has been shown to be mimicked by an increase in intracellular IP_3 (Bartrup and Newberry 1994). Nevertheless, although an elevation of intraterminal Ca^{2+} levels may contribute to residual Ca^{2+} levels, the observed dependence on extracellular Ca^{2+} (or Sr^{2+}) indicates that entry of extracellular Ca^{2+} is required for 5-HT_{2A}-induced asynchronous EPSCs. In the case of electrically evoked EPSCs, Ca^{2+} entry through voltage-gated Ca^{2+} channels could synergize with Ca^{2+} released from intracellular stores. However, in the case of *spontaneous* EPSCs, it is more difficult to account for the entry of extracellular Ca^{2+} because, in the absence of an increase in impulse flow, voltage-gated Ca^{2+} channels would not be activated. Earlier, we reported that 5-HT enhances a subtheshold, TTX-sensitive persistent Na^+ current in layer V pyramidal cells (Aghajanian and Marek 1997). We have proposed elsewhere, that, if 5-HT acts to induce an increase in a persistent subthreshold Na^+ current in excitatory nerve terminals, the resulting increase in intracellular Na^+ could activate reverse Na^+/Ca^{2+} exchange (NCX_r), resulting in increased Ca^{2+} influx (Marek and Aghajanian 1998). Figure 9 depicts how Ca^{2+} entry through voltage-gated channels, in conjunc-

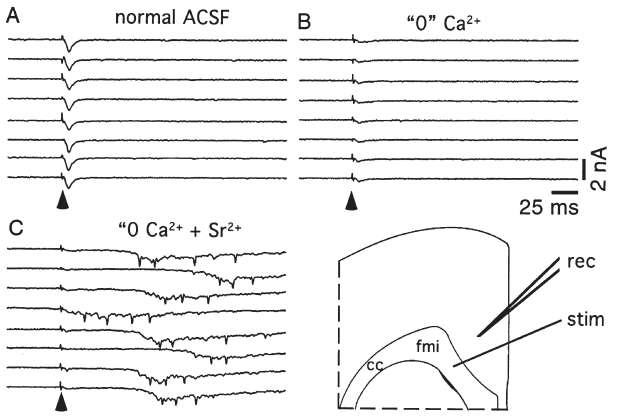

Figure 6. Evoked EPSCs in a layer V pyramidal cell of medial prefrontal cortex: effects of Sr^{2+} substitution for Ca^{2+}. Electrical stimuli (0.2 ms; arrowheads) were applied at 10-s intervals to the underlying white matter of the forceps minor (fmi), medial to the corpus callosum (cc; see inset). **(A)** shows 10 consecutive responses in normal ACSF where only a short latency (~2 ms) synchronous EPSCs were evoked. **(B)** All EPSCs, both synchronous and asynchronous, are suppressed markedly in ACSF with "0" added Ca^{2+} applied for 6 to 7 min. **(C)** The inclusion of Sr^{2+} in "0" Ca^{2+} ACSF results in sweeps of asynchronous evoked EPSCs following each stimulus in the absence of synchronous EPSCs. Downward deflections indicate inward currents (Aghajanian and Marek 1999).

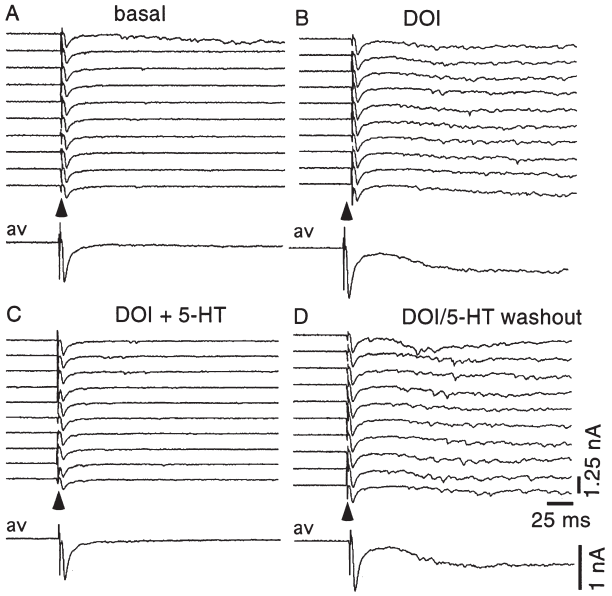

Figure 7. DOI increases the occurrence of late components of evoked EPSCs in a layer V pyramidal cell. **(A)** Under basal conditions, there is an all-or-none sweep of a late component of the evoked EPSC only after the first in a series of 10 stimuli. **(B)** Following DOI (3 μM) applied for 10 to 12 minutes, there is a progressive increase in the proportion of sweeps with a persistent late component of EPSCs; at the time point shown (~10 min following the end of DOI application), all sweeps show a late component following the synchronous response. Note that DOI, because of its partial agonist properties relative to 5-HT, induces only a minor increase in spontaneous EPSC (Aghajanian and Marek 1999). **(C–D)** During the application of 5-HT (100 μM) for 1 min, there is a suppression of this late component; the latter return after approximately 10 min of washout (Aghajanian and Marek 1999).

tion with reverse Na^+/Ca^{2+} exchange and IP_3-induced release from internal stores, may increase residual Ca^{2+} levels thereby, enhancing asynchronous release.

The fact that 5-HT produces a marked increase in the frequency of spontaneous EPSCs points to the involvement of a presynaptic site of action. However, a recent electron immunocytochemical study has shown only a scattering of 5-HT_{2A}-labeled nerve terminals in prefrontal cortex; whereas, the bulk of these receptors are located postsynaptically on pyramidal cell apical dendrites (Jakab and Goldman-Rakic 1998). Thus, although postsynaptic 5-HT_{2A} receptors may serve to increase the amplitude of spontaneous EPSCs (Aghajanian and Marek 1997), there is no simple way to explain how such a postsynaptic action could result in a marked increase in the *frequency* of EPSCs. Given the evidence for a predominantly postsynaptic location of 5-HT_{2A} receptors, there is a need to explain how interactions with presynaptic modulators may occur. One possibility would be that a retrograde messenger is generated through the action of 5-HT on postsynaptic 5-HT_{2A} receptors, which then could have a presynaptic effect on excitatory nerve terminals. Inhibitory modulators could then suppress this retrograde effect through their separate presynaptic site of action. Nevertheless, it is still possible that the effect of 5-HT on asynchronous EPSCs is mediated through a direct presynaptic action upon the apparently small subset of 5-HT_{2A}-positive terminals that have been demonstrated to exist by electron immunocytochemistry (Jakab and Goldman-Rakic 1998).

EFFECTS OF PSYCHOTOMIMETIC NMDA ANTAGONISTS ON GLUTAMATE RELEASE: COMPARISON WITH PSYCHEDELIC HALLUCINOGENS

Recently, it has been reported that many effects of psychotomimetic NMDA antagonists, such as phencyclidine and ketamine, may be mediated through excess glutamate acting at non-NMDA (i.e., AMPA/kainate) receptors. Microdialysis techniques show that systemic administration of ketamine enhances the release of glutamate in prefrontal cortex (Moghaddam et al. 1997). Parallel behavioral studies have shown that the systemically active AMPA/kainate antagonist LY293558 ame-

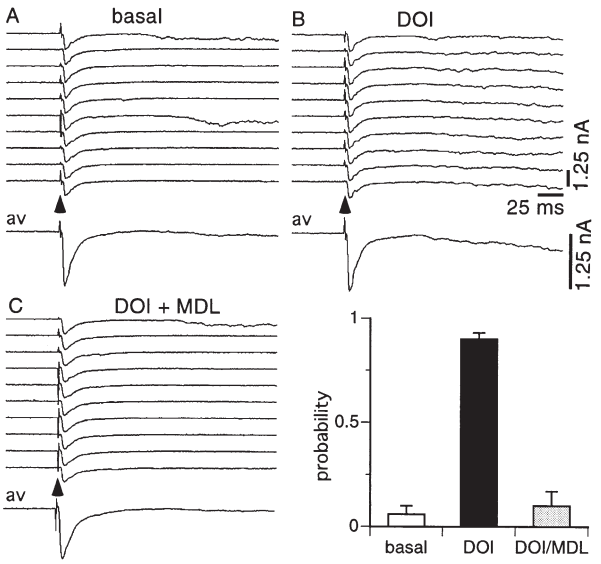

Figure 8. The 5-HT_{2A} antagonist M100907 (MDL) reverses the increase in evoked EPSCs by DOI. **(A–C)** Illustrate in a single layer V pyramidal cell the increase in evoked EPSCs induced by DOI (3 μm) and the reversal of this effect ($p <$ .001 compared to basal or DOI/M100907) after a 35-min application of M100907 (100 nm). **(B)** Bar graph shows a summary of data for five cells (Aghajanian and Marek 1999).

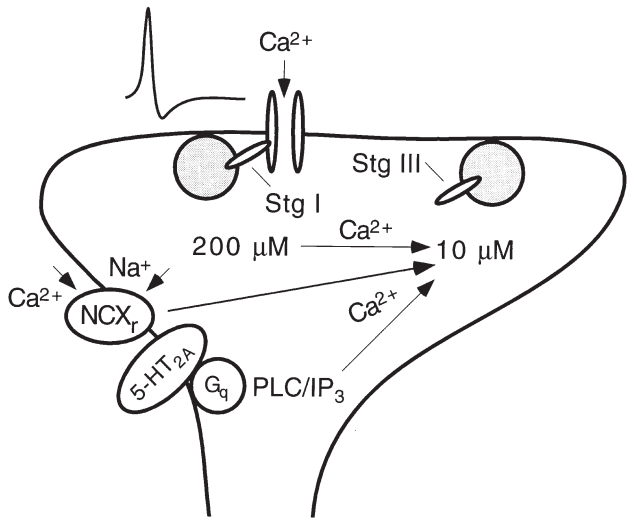

Figure 9. Schematic representation of how Ca^{2+} entry through voltage-gated channels, combined with reverse Na^+/Ca^{2+} exchange (NCXr) and inositol trisphosphate (IP_3)-induced release from internal stores, may synergize to increase residual Ca^{2+} levels, thereby enhancing asynchronous release via synaptotagmin III (Stg III). Activation of the 5-HT_{2A} receptor is shown as increasing the formation of IP_3 via the G protein G_q coupled to phospholipase C (PLC) hydrolysis.

liorates the cognitive deficits produced by ketamine, suggesting that NMDA antagonists may disrupt cognitive function by increasing the release of glutamate thereby, stimulating non-NMDA receptors (Moghaddam and Adams 1998). Moreover, a group II metabotropic glutamate agonist, LY354740, which prevented excessive release of glutamate, reduced the cognitive and motor effects of phencyclidine. The mechanism by which NMDA antagonists induce an increase in glutamate release appears to be distinct from that of 5-HT_{2A} agonists, because bath application of phencyclidine to brain slices does not result in an increase in EPSCs in layer V pyramidal cells of prefrontal cortex (Marek and Aghajanian unpublished data). This lack of a direct effect suggests a requirement for the activation of intact afferent systems for NMDA antagonists to induce an increase in glutamate release. In any case, the precise mechanisms by which psychedelic hallucinogens and NMDA antagonists cause an increase in glutamate release are likely to differ. The evidence for an increase in glutamate transmission for both the psychedelic hallucinogens and the NMDA antagonists raises the possibility that there is a convergent or common final glutamatergic pathway that may account for overlapping aspects of their psychotomimetic effects. On the other hand, the effects of the two classes of drugs would not be expected to be identical, because the psychedelic hallucinogens do not block NMDA receptors.

Brain-imaging studies in human subjects also reveal similarities in the effects of psychedelic hallucinogens and NMDA antagonists. Representatives of the two major classes of psychedelic hallucinogens, the indoleamine psilocybin (Vollenweider et al. 1997b) and the phenethylamine mescaline (Hermle et al. 1992), have been shown to produce metabolic hyperfrontality in the anterior cingulate and other frontal regions. Interestingly, psychotomimetic doses of ketamine have been shown to produce a similar pattern of hyperfrontality, both in healthy volunteers (Breier et al. 1997; Vollenweider et al. 1997a) and schizophrenic patients (Lahti et al. 1995). In rat studies, the metabolic activation produced by ketamine in prefrontal cortex and other regions is blocked by clozapine but not haloperidol, perhaps because of the 5-HT_{2A} antagonist properties of clozapine, which are not shared by haloperidol (Duncan et al. 1998). Regardless of differences in specific mechanisms, it is possible that an increased release of glutamate underlies the hyperfrontality seen with both psychedelic hallucinogens and ketamine.

In contrast to the hyperfrontality seen in the drug studies, the results of brain-imaging studies in schizophrenic patients have been mixed. Some studies, particularly in acutely psychotic, unmedicated, or drug-naive patients, have reported a hyperfrontal pattern similar to that produced by psychotomimetic drugs (Cleghorn et al. 1989; Ebmeier et al. 1993; Parellada et al. 1994). However, other studies, even those conducted in unmedi-

cated or drug-naive schizophrenic patients (Andreasen et al. 1997; Haznedar et al. 1997), did not find a hyperfrontal pattern. A more consistent finding in schizophrenic subjects, regardless of whether they display hypofrontality (Andreasen et al. 1992; Buchsbaum et al. 1992; Weinberger et al. 1986) or hyperfrontality (Parellada et al. 1994) under resting conditions, is a diminished ability to respond with prefrontal activation when challenged with cognitive tasks. Interestingly, this deficit in task-related prefrontal activation is mimicked by the administration of psilocybin to normal human volunteers (Gouzoulis-Mayfrank et al. 1999).

NEW TARGETS FOR ANTIPSYCHOTIC DRUGS BASED ON PSYCHOTOMIMETIC DRUG MODELS

If hyperglutamatergic states play a role in the pathogenesis of schizophrenia, as they do in the psychotomimetic drug models, then treatments that limit or suppress glutamate release may be therapeutic or prophylactic in this disease. However, because glutamate is the main excitatory transmitter in the central nervous system, a generalized block of glutamatergic transmission would not be useful. Our studies on 5-HT_{2A}-receptor mediated glutamate release in the cerebral cortex reveal the highly localized nature of this process, which involves only a subset of glutamatergic afferents innervating the apical dendrites of layer V pyramidal cells. Thus, the selective 5-HT_{2A} antagonist M100907 is able to achieve a high degree of specificity by blocking glutamate release at a restricted set of glutamatergic terminals regulated by this receptor. We also have found an increased release of glutamate mediated by α_1 receptors, which, like 5-HT_{2A} receptors, are coupled through the $G_{q/11}$/phosphoinositide pathway. It is possible that antagonists of other receptors that are coupled through the $G_{q/11}$/phosphoinositide pathway also have therapeutic potential.

An alternative way to normalize glutamatergic transmission would be to suppress glutamate release at sites downstream from the initial 5-HT_{2A} or other G_q-coupled receptor. Such an approach would allow for the possibility that the site of pathology in naturally occurring psychoses may not be at the initial receptor but may be at one or more of the steps involved in the complex process of regulating glutamate release. The hallucinogen model suggests that one such target is the regulation of residual Ca^{2+} levels, which underlie the process of asynchronous release. Residual Ca^{2+} can be regulated both positively (e.g., through release from internal stores via the phosphoinositide/inositol trisphosphate pathway and reversal of Na^+/Ca^{2+} exchange) and negatively (e.g., by presynaptic autoreceptors). In preliminary studies, we have shown that low concentrations of the group II metabotropic agonist LY354740 can reduce the late asynchronous EPSP while sparing the early synchronous EPSP (Marek et al. 1999). One possible basis for this selectivity is that metabotropic subtypes are differentially expressed in different afferents to layer V pyramidal cells. For example, mGluR2 receptor mRNA is expressed strongly by relay cells in the anterior and midline nuclei of thalamus (Ohishi et al. 1993), possibly contributing to the band of mGluR2 receptor protein corresponding to the terminal regions of the thalamocortical pathway, which can be seen in the mid-layer of the cerebral cortex (Ohishi et al. 1998). Interestingly, this is the same layer that has been implicated in 5-HT_{2A}-induced EPSCs (Marek and Aghajanian 1998).

As described above, pharmacological manipulations of glutamate transmission provide unexpected parallels between the hallucinogen and NMDA antagonists drug models of psychosis. Thus, the group II/III metabotropic agonist (1S, 3S)-ACPD and the preferential group II metabotropic agonist LY354740, which reduce the release of glutamate by acting upon presynaptic inhibitory autoreceptors, are able to block EPSCs induced by activation of 5-HT_{2A} receptors in vitro (Aghajanian and Marek 1997; Marek et al. 1999). Similarly, LY354740 (which is active by the systemic route of administration [Schoepp et al. 1997]) has been shown to ameliorate certain cognitive deficits in rats produced by the NMDA antagonist phencyclidine in vivo (Moghaddam and Adams 1998). Taken together, these results suggest that metabotropic agonists would be useful in normalizing excesses in glutamate release, regardless of the cause. The availability of orally active metabotropic glutamate receptor agonists makes it feasible to test the hypothesis that excessive glutamate release, particularly in such critical sites as the prefrontal cortex, plays a role in the positive and/or negative symptoms of schizophrenia.

Clearly, there is need to explore new treatment approaches in schizophrenia, because even the best of therapeutic responses obtained with existing typical or atypical antipsychotic drugs are often delayed and not fully restorative (Tamminga 1998). As suggested above, a possible reason for this lack of full efficacy may be that the primary site of pathology in schizophrenia may lie downstream from the receptors (D_2, 5-HT_{2A}, etc.) that are targeted by currently available drugs.

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REFERENCES

Aghajanian GK (1980): Mescaline and LSD facilitate the activation of locus coeruleus neurons by peripheral stimuli. Brain Res 186:492–498

Aghajanian GK, Marek GJ (1997): Serotonin induces excitatory postsynaptic potentials in apical dendrites of neocortical pyramidal cells. Neuropharmacology 36:589–599

Aghajanian GK, Marek GJ (1999): Serotonin, via 5-HT_{2A} receptors, increases EPSCs in layer V pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Res 825:1–2, 161–171

Altar CA, Wasley AM, Neale RF, Stone GA (1986): Typical and atypical antipsychotic occupancy of D2 and S2 receptors: An autoradiographic analysis in rat brain. Brain Res Bull 16:517–525

Andreasen HC, Rezai K, Alliger R, Swayze VW, Flaum M, Kirchner P, Cohen G, O'Leary DS (1992): Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia: Assessment with xenon-133 single-photon emission computed tomography and the Tower of London. Arch Gen Psychiat 49:943–958

Andreasen NC, O'Leary DS, Flaun M, Nopoulos P, Watkins GL, Boles Ponto LL (1997): Hypofrontality in schizophrenia: Distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 349:1730–1734

Araneda R, Andrade R (1991): 5-Hydroxytryptamine$_2$ and 5-Hydroxytryptamine$_{1A}$ receptors mediate opposing responses on membrane excitability in rat association cortex. Neuroscience 40:399–412

Bartrup J, Newberry NR (1994): 5-HT_{2A} receptor-mediated outward current in C6 glioma cells is mimicked by intracellular IP_3 release. NeuroReport 5:1245–1248

Breier A, Malhotra AK, Pinals DA, Weisenfeld NI, Pickar D (1997): Association of ketamine-induced psychosis with focal activation of the prefrontal cortex in healthy volunteers. Am J Psychiat 154:805–811

Buchsbaum MS, Haier RJ, Potkin SG, Nuechterlein K, Bracha HS, Katz M, Lohr J, Wu J, Lottenberg S, Jerabek PA, Trenary M, Tafalla R, Reynolds C, Bunney WE (1992): Frontostriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch Gen Psychiat 49:935–942

Ceulemans DLS, Gelders YG, Hoppenbrouwers M-LJA, Reyntjens AJM, Janssen PAJ (1985): Effect of serotonin antagonism in schizophrenia: A pilot study with setoperone. Psychopharmacology 85:329–32

Cleghorn JM, Garnett ES, Nahmias C, Firnau G, Brown GM, Kaplan R, Szechtman H, Szechtman B (1989): Increased frontal and reduced parietal glucose metabolism in acute untreated schizophrenia. Psychiat Res 28:119–133

Colpaert FC, Janssen PAJ (1983): A characterization of LSD-antagonist effects of pirenperone in the rat. Neuropharmacology 22:1001–1005

Conn PJ, Sanders-Bush E (1986): Regulation of serotonin-stimulated phosphoinositide hydrolysis: relation to the serotonin 5-HT2 binding site. J Neuroscience 6:3669–3675

Duncan GE, Leipzig JN, Mailman RB, Lieberman JA (1998): Differential effects of clozapine and haloperidol on ketamine-induced metabolic activation. Brain Res 812:65–75

Ebmeier KP, Blackwood HR, Murray C, Souza V, Walker M, Dougall N, Moffoot APR, O'Carroll RE, Goodwin GM (1993): Single-photon emission computed tomography with ^{99m}Tc-exametazime in unmedicated schizophrenic patients. Biol Psychiat 33:487–495

Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G (1992): Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extrapyramidal side effects. Arch Gen Psychiat 49:538–544

Garratt JC, Alreja M, Aghajanian GK (1993): LSD has high efficacy relative to serotonin in enhancing the cationic current I_h: intracellular studies in rat facial motoneurons. Synapse 13:123–134

Geppert M, Goda Y, Hammer RE, Li C, Rosahl TW, Stevens CF, Sudhof TC (1994): Synaptotagmin I: A major Ca^{2+} sensor for transmitter release at a central synapse. Cell 79:717–727

Glennon RA (1990): Do classical hallucinogens act as 5-HT_2 agonists or antagonists? Neuropsychopharmacology 3:509–517

Glennon RA, Titeler M, McKenney JD (1984): Evidence for 5-HT_2 involvement in the mechanism of action of hallucinogenic agents. Life Sci 35:2502–2511

Goda Y, Stevens CF (1994): Two components of transmitter release at a central synapse. Proc Nat Acad Sci USA 91:12942–12946

Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, Arning C, Thelen B, Spitzer M, Kovar K-A, Hermle L, Bull U, Sass H (1999): Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. Neuropsychopharmacology 20:565–581

Hamada S, Senzaki K, Hamaguchi-Hamada K, Tabuchi K, Yamamoto H, Yamamoto T, Yoshikawa S, Okano H, Okado N (1998): Localization of 5-HT2A receptor in rat cerebral cortex and olfactory system revealed by immunohistochemistry using two antibodies raised in rabbit and chicken. Mol Brain Res 54:199–211

Haznedar MM, Buchsbaum MS, Luu C, Hazlett EA, Siegel BV, Lohr J, Wu J, Haier RJ, Bunney WEJ (1997): Decreased anterior cingulate gyrus metabolic rate in schizophrenia. Am J Psychiat 154:682–684

Hermle L, Funfgeld M, Oepen G, Botsch H, Borchardt D, Gouzoulis E, Fehrenbach RA, Spitzer M (1992): Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: Experimental psychosis as a tool for psychiatric research. Biol Psychiat 32:976–991

Herrero I, Castro E, Miras-Portugal MT, Sanchez-Prieto J (1996): Two components of glutamate exocytosis differentially affected by presynaptic modulation. J Neurochem 67:2346–2354

Jakab RL, Goldman-Rakic PS (1998): 5-Hydroxytryptamine$_{2A}$ serotonin receptors in the primate cerebral cortex: Possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Nat Acad Sci USA 95:735–740

Kapur S, Zipursky RB, Remington G (1999): Clinical and theoretical implications of 5-HT_2 and D_2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiat 156:286–293

Lahti AC, Holcomb HH, Medoff DR, Tamminga CA (1995): Ketamine activates psychosis and alters limbic blood flow in schizophrenia. NeuroReport 6:869–872

Leysen JE, Niemegeers CJE, Tollemaere JP, Lauduron PM (1978): Serotonergic component of neuroleptic receptors. Nature 272:168–171

Li C, Bazbek CL, Davletov A, Sudhof TC (1995): Distinct Ca^{2+} and Sr^{2+} binding properties of synaptotagmins. J Biol Chem 270:24898–24902

Lieberman JA, Mailman RB, Duncan G, Sikich L, Chakos M, Nichols DE, Kraus JE (1998): Serotonergic basis of antipsychotic drug effects in schizophrenia. Biol Psychiat 44:1099–1117

Lopez-Gimenez JF, Mengod G, Palacios JM, Vilaro MT (1997): Selective visualization of rat brain 5-HT_{2A} receptors by autoradiography with [3H]MDL 100,907. Naunyn-Schmiedeberg's Arch Pharmacol 356:446–454

Marek GJ, Aghajanian GK (1996): LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT_{2A} receptors on neurons in the rat piriform cortex. J Pharmacol Exp Ther 278:1373–1382

Marek GJ, Aghajanian GK (1998): 5-HT-induced EPSCs in neocortical layer V pyramidal cell of prefrontal cortex: Suppression by m opiate receptor activation. Neuroscience 86:485–497

Marek GJ, Wright RA, Schoepp DD, Monn JA, Aghajanian GK (1999): Physiological antagonism between 5-hydroxytryptamine$_{2A}$ and group II metabotropic glutamate receptors in prefrontal cortex. J Pharmacol Exp Ther, in press.

Marek GJ, Aghajanian GK (1999): 5-HT_{2A} receptor or α_1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. Eur J Pharmacol 367:197–206

McCall RB, Aghajanian GK (1980): Hallucinogens potentiate responses to serotonin and norepinephrine in the facial motor nucleus. Life Sci 26:1149–1156

Meltzer HY, Matsubara S, Lee JC (1989): Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2, and serotonin-2 pKi values. J Pharmacol Exp Ther 251:238–246

Meltzer HY, Nash JF (1991): Effects of antipsychotic drugs on serotonin receptors. Pharmacol Rev 43:587–604

Mengod G, Pompeiano M, Martinez-Mir MI, Palacios JM (1990): Localization of the mRNA for the 5-HT_2 receptor by in situ hybridization histochemistry: Correlation with the distribution of receptor binding sites. Brain Res 524:139–143

Mochida S, Sheng S-H, Baker C, Kobaysashi H, Catterall WA (1996): Inhibition of neurotransmission by peptides containing the synaptic protein interaction site of N-type Ca^{2+} channels. Neuron 17:781–788

Moghaddam B, Adams B (1998): Stimulation of group II metabotropic glutamate receptors normalizes the cognitive and motoric effects of phencylidine. Science 281:1349–1352

Moghaddam B, Adams B, Verma A, Daly D (1997): Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with prefrontal cortex. J Neurosci 17:2921–2927

Ohishi H, Neki A, Mizuno N (1998): Distribution of a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat and mouse: An immunohistochemical study with a monoclonal antibody. Neurosci Res 30:65–82

Ohishi H, Shigemoto R, Nakanishi S, Mizuno N (1993): Distribution of the messenger RNA for a metabotropic glutamate receptor, mGluR2, in the central nervous system of the rat. Neuroscience 53:1009–1018

Parellada E, Catafau AM, Bernardo M, Lomena F, Gonzalez-Monclus E, Setoain J (1994): Prefrontal dysfunction in young acute neuroleptic-naive schizophrenic patients: A resting and activation SPECT study. Psychiat Res Neuroimaging 55:131–139

Pazos A, Palacios JM (1985): Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 346:205–230

Peroutka SJ, Snyder SH (1979): Multiple serotonin receptors: differential binding of ^{3}H-serotonin, ^{3}H-lysergic acid diethylamide and ^{3}H-spiroperidol. Mol Pharmacol 16:687–699

Peroutka SJ, Snyder SH (1980): Relationship of neuroleptic drug effects at brain dopamine, serotonin, α-adrenergic, and histamine receptors to clinical potency. Am J Psychiat 137:1518–1522

Rasmussen K, Aghajanian GK (1986): Effects of hallucinogens on spontaneous and sensory-evoked locus coeruleus unit activity in the rat: Reversal by selective 5-HT_2 antagonists. Brain Res 385:395–400

Sanders-Bush E, Burris KD, Knoth K (1988): Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. J Pharmacol Exp Ther 246:924–928

Schiller J, Schiller Y, Stuart G, Sakmann B (1997): Calcium action potentials restricted to distal apical dendrites of rat neocortical pyramidal neurons. J Physiol Lond 505:605–616

Schoepp DD, Johnson BG, Wright RA, Salhoff CR, Mayne NG, Wu S, Cockerham SL, Burnett JP, Belegaje R, Bleakman D, Monn JA (1997): LY354740 is a potent and highly selective group II metabotropic glutamate receptor agonist in cells expressing human glutamate receptors. Neuropharmacology 36:1–11

Sheldon PW, Aghajanian GK (1990): Serotonin (5-HT) induces IPSPs in pyramidal layer cells of rat piriform cortex: Evidence for the involvement of a 5-HT_2-activated interneuron. Brain Res 506:62–69

Stanley EF (1997): The calcium channel and the organization of the presynaptic transmitter release face. TINS 20:404–409

Tamminga CA (1998): Sertotonin and schizophrenia. Biol Psychiat 44:1079–1080

Tanaka E, North RA (1993): Actions of 5-hydroxytryptamine on neurons of the rat cingulate cortex. J Neurophys 69:1749–1757

Tibbs GR, Barrie AP, Van Mieghem FJE, McMahon HT, Nicholls DG (1989): Repetitive action potentials in isolated nerve terminals in the presence of 4-aminopyridine: Effects on cytosolic free Ca^{2+} and glutamate release. J Neurochem 53:1693–1699

Titeler M, Lyon RA, Glennon RA (1988): Radioligand binding evidence implicates the brain 5-HT_2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. Psychopharmacology 94:213–216

Tobi D, Wiser O, Trus M, Atlas D (1998): N-type voltage-sensitive calcium interacts with syntaxin, synaptobrevin and SNAP-25 in a multiprotein complex. Receptors Channels 6:89–98

Vollenweider FX, Leenders KL, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J (1997a): Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG). Eur Neuropsychopharmacology 7:9–24

Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J (1997b): Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16:357–372

Vollenweider FX, Vollenweider-Scherpenhuyzen MFI, Babler A, Vogel H, Hell D (1998): Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. NeuroReport 9:3897–3902

Weinberger DR, Berman KF, Zec RF (1986): Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow (rCBF) evidence. Arch Gen Psychiat 43:114–125

Willins DL, Deutch AY, Roth BL (1997): Serotonin 5-HT_{2A} receptors are expressed on pyramidal cells and interneurons in the rat cortex. Synapse 27:79–82

Wright DE, Seroogy KB, Lundgren KH, Davis BM, Jennes L (1995): Comparative localization of serotonin$_{1A, 1C,}$ and $_2$ receptor subtype mRNAs in rat brain. J Comp Neurol 351:357–373