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Contribution of serotonin neurotoxins to understanding psychiatric disorders: the role of 5-HT_2 receptors in schizophrenia and antipsychotic activity

C.J. Schmidt, J.H. Kehne, A.A. Carr, G.M. Fadayel, T.M. Humphreys, H.J. Kettler, T.C. McCloskey, R.A. Padich, V.L. Taylor and S.M. Sorensen

CNS Research, Marion Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, Ohio, OH 45215, USA

Correspondence to: C.J. Schmidt at above address

INTRODUCTION

Neurotoxins, particularly those agents selective for specific transmitter systems, have been instrumental in increasing our understanding of the structure and function of the central nervous system. In this review we will describe how studies aimed at elucidating the mechanism of serotonergic neurotoxicity of one such agent lead to the identification of a novel function of 5-HT in the brain and provided new insight into the possible role of the serotonergic system in schizophrenia.

MDMA AND 5-HT_2 RECEPTORS

3,4-Methylenedioxymethamphetamine (MDMA) is a popular drug of abuse known among users as "XTC" or simply "X". MDMA is a structural analog of amphetamine which shares a number of neurochemical and behavioral characteristics with the parent drug. Pharmacologically, MDMA is an indirect monoaminergic agonist producing a potent, carrier-mediated release of both dopamine and serotonin (Schmidt *et al.*, 1987). As predicted by these activities, MDMA is a mild central stimulant and sympathomimetic. The unique subjective effects of MDMA in humans include a heightened sense of awareness as well as a feeling of increased empathy or emotional closeness to others. This unique constellation of behavioral effects has contributed to its popularity as a "party drug".

Our interest in MDMA arose out of its structural similarity to methamphetamine and the established ability of high doses of methamphetamine to produce long-term depletions of 5-HT and dopamine in laboratory animals (for a review see Gibb *et al.*, 1990). Given the rising popularity of MDMA as a recreational agent, we were interested in determining its potential to produce similar long-term neurochemical alterations.

The results of a number of independent studies indicate that MDMA does indeed produce long-term neurochemical alterations in the brains of laboratory animals including primates (Schmidt *et al.*, 1986; Stone *et al.*, 1986; Battaglia *et al.*, 1987; Commins *et al.*, 1987; O'Hearn *et al.*, 1988; Ricaurte *et al.*, 1988; Kleven *et al.*, 1989). However, in contrast to the effects of methamphetamine, these changes appear to be limited to the serotonergic system. The time course of some of the neurochemical changes produced by a single high dose of MDMA in rats is shown in Fig. 1. In our laboratory, we have divided these changes into an acute (< 24 h) and long-term phase (≥ 7 days). Although the acute effects of MDMA on the serotonergic system are dramatic and very interesting, it is the long-term changes which have become the focus of most MDMA studies. The decrease in 5-HT concentrations and the loss of tryptophan hydroxylase (TPH) activity measured at one week can be correlated with a decrease in the number of functional serotonergic nerve terminals by both biochemical and immunohistological methods (Schmidt, 1987; Commins *et al.*, 1987). This has been interpreted as a degeneration or pruning of serotonergic axons and nerve terminals. Although this effect of MDMA appears to be restricted to the cell processes, the loss of the efferent limb of a serotonergic neuron can be regarded as a neurotoxic response to the drug. We have routinely used the MDMA-induced reduction in forebrain 5-HT concentrations at one week as a marker of this neurotoxic effect in our mechanistic studies.

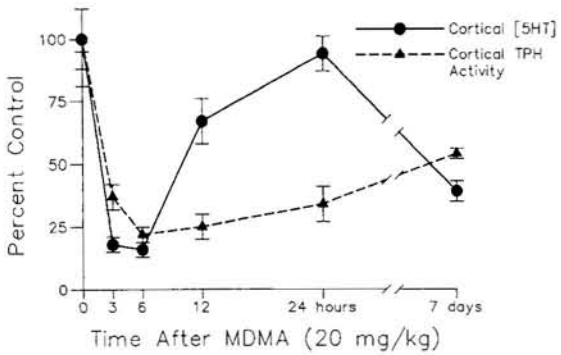

FIG. 1. Time course of the changes in tissue concentrations of 5-HT and tryptophan hydroxylase activity (TPH) following the s.c. administration of a single, high dose of MDMA to rats (from Schmidt, 1989). The decrease in 5-HT concentrations and in enzyme activity at 7 days correlates with a loss in functional 5-HT terminals.

Work from several groups has demonstrated that the long-term deficits in forebrain concentrations of dopamine and 5-HT produced by methamphetamine are somehow dependent on methamphetamine-induced dopamine release. Studies by Stone *et al.* (1988) and our own work, indicated a similar requirement for an intact dopaminergic system in the production of MDMA-induced serotonergic neurotoxicity. A number of manipulations of the dopamine system were found to prevent the neurotoxic effects of MDMA. Permanent mesencephalic lesions of the dopamine system with 6-hydroxydopamine or temporary dopamine depletion with the tyrosine hydroxylase inhibitor, α-methyl-*p*-tyrosine, were both effective at preventing the long-term effects of MDMA (Schmidt *et al.*, 1990a). Blockade of MDMA-induced dopamine release with inhibitors of the dopamine uptake carrier such as GBR 12909 was also protective (Stone *et al.*, 1988). Consequently, although *in vitro* studies showed MDMA to be much less potent than methamphetamine for inducing dopamine release, it appears the long-term effects of MDMA on the serotonergic system *in vivo* still occur as a result of MDMA-induced dopamine release. Interestingly, more recent microdialysis studies have demonstrated that MDMA and methamphetamine are equipotent at releasing dopamine *in vivo* (Nash and Yamamoto, 1992). We now believe that this discrepancy between the drug's *in vitro* and *in vivo* potency for producing dopamine release is related to its effects on 5-HT release. Some of the earliest *in vitro* work with MDMA indicated that the drug preferentially released 5-HT over dopamine (Johnson *et al.*, 1986; Schmidt *et al.*, 1987). Given this "serotonergic selectivity", we decided to determine if 5-HT release also played a role in the neurotoxic effects of the drug. Much to our surprise, we observed that 5-HT receptor antagonists, specifically those blocking 5-HT_2 receptors, could prevent the long-term serotonergic deficits produced by MDMA (Schmidt and Kehne, 1990). This observation was confirmed through the use of several selective 5-HT_2 receptor antagonists as well as in studies comparing the protective effects of the active and inactive stereoisomers of the 5-HT_2 antagonist, MDL 11,939 (Schmidt *et al.*, 1990a,b, 1991, 1992a).

Although the mechanism underlying the dopamine dependence of the neurotoxicity produced by the amphetamine analogs is unknown, a number of reasonable hypotheses have been offered (Seiden and Vosmer, 1984; Schmidt and Lovenberg, 1985). Most of these relate to the well-known instability of dopamine and its tendency to undergo auto-oxidation. Cytotoxic active oxygen species and quinones are all potential products of such reactions. Given the apparent role for dopamine release in the neurotoxic effects of MDMA, it was difficult at the time to understand why 5-HT_2 receptor antagonists should prevent this neurotoxic response.

Work by Nash and colleagues examining the effects of MDMA on dopamine synthesis identified the link between these phenomena. Indirect agonists such as amphetamine and MDMA increase dopamine synthesis by releasing the newly synthesized pool of dopamine which normally exerts feedback inhibition on tyrosine hydroxylase (Connor and Kuczenski, 1986). This stimulation of synthesis can be observed *in vivo* as an increase in the accumulation of dopa following decarboxylase inhibition. Nash *et al.* (1990) demonstrated that this effect of MDMA on synthesis was blocked by the 5-$HT_{2/1C}$ antagonist, ketanserin. These results suggested that 5-HT_2 antagonism might prevent the neurotoxic effects of MDMA by blocking the dopamine synthesis necessary for transmitter release. Nash (1990) later confirmed that ketanserin reduced MDMA-induced dopamine release using *in vivo* microdialysis. We subsequently designed experiments to verify that this effect on synthesis and release was indeed the mechanism through which the 5-HT_2 antagonists interfered with the long-term effects of MDMA. These studies demonstrated that the protective effects of 5-HT_2 antagonists such as MDL 11,939, ritanserin and MDL 28,133A were prevented if dopamine synthesis was artificially maintained by coadministration of the dopamine precursor, L-dopa (Schmidt *et al.*, 1991). The ability of L-dopa to negate the protective effects of the 5-HT_2 antagonists supported the proposal that 5-HT_2 receptor stimulation was required for the enhanced dopamine synthesis and release produced by agents such as MDMA. The results were also consistent with a dopaminergic mechanism underlying MDMA-induced neurotoxicity.

To determine if this phenomenon was of broader significance we examined the amphetamine- and MDMA-induced slowing of dopaminergic neurons as an electro-

physiological response to dopamine release. The slowing of cell firing following amphetamine administration has been well-characterized as a consequence of drug-induced dopamine release and the subsequent activation of both somatodendritic autoreceptors and polysynaptic feedback loops (Bunney and Aghajanian, 1976; Wang, 1981). Because haloperidol and other clinically effective antipsychotic agents reverse this effect of amphetamine, antagonism in this model is considered to be predictive of antipsychotic activity (Bunney and Aghajanian, 1975). Goldstein *et al.* (1989) had previously demonstrated that the amphetamine-induced slowing of mesolimbic A10 dopaminergic neurons was unexpectedly sensitive to 5-HT_2 antagonists. We have repeated and extended these studies to include the slowing of nigrostriatal A9 dopaminergic neurons by MDMA. The effects of either amphetamine or MDMA on the firing rate of dopamine neurons in anesthetized rats could be completely prevented by pretreatment with a 5-HT_2 antagonist such as ritanserin or the more selective compound MDL 28,133A (Sorensen *et al.*, 1992; Schmidt *et al.*, 1992a). D2 dopamine antagonists such as haloperidol have also been shown to block this effect of amphetamine on dopamine neurons. However, these antagonists also increase the basal firing rate of the dopamine neurons whereas 5-HT_2 antagonists have little or no effect on basal firing rate. Figure 2 shows the results obtained from individual A9 neurons following exposure to MDMA alone and in the presence of MDL 28,133A. In complete agreement with the results of the neurotoxicity studies, pretreatment with L-dopa circumvents the effects of the 5-HT_2 antagonist and restores the ability of MDMA to produce a reduction in cell firing rate.

The results of the neurotoxicity and electrophysiology experiments suggested the existence of a previously undescribed interaction between the serotonergic and midbrain dopaminergic systems. Although the serotonergic system is generally considered to exert an inhibitory influence on the activity of the dopaminergic system, our results indicated that under some conditions, serotonergic activity, particularly 5-HT_2 receptor stimulation, is necessary to support elevated dopamine release. Mechanistically, the results of work by Nash *et al.* (1990) and our own experiments indicate that 5-HT_2 receptor stimulation is required for the activation of dopamine synthesis necessary to support enhanced transmitter release.

SCHIZOPHRENIA

The ability of selective 5-HT_2 antagonists to interfere with heightened states of dopaminergic activity without altering basal dopaminergic tone suggests such compounds may be useful antipsychotic agents. All current antipsychotics are thought to act primarily through the blockade of D2 dopamine receptors. This common action of antipsychotics was key to the development of the hypothesis that excessive dopaminergic activity is responsible for the symptoms of schizophrenia (Carlsson, 1988). The pharmacological evidence from which the dopamine hypothesis developed 25 years ago still affords this model considerable validity despite the subsequent failure to pro-

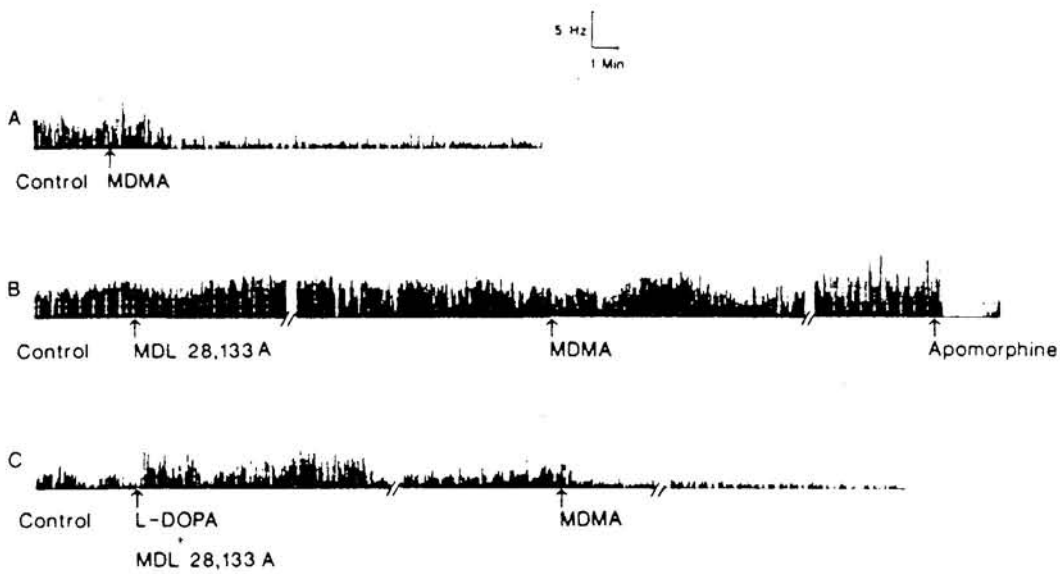

FIG. 2. Effect of 5-HT_2 receptor blockade on the MDMA-induced slowing of A9 dopaminergic neurons in the chloral hydrate anesthetized rat. Each panel shows the strip chart recording for an individual A9 cell. (A) Effect of MDMA (15 mg/kg, i.v.) on the firing rate of a control neuron. (B) Pretreatment with the selective 5-HT_2 antagonists MDL 28,133A, prevents the slowing of cell firing by MDMA but not the effect of a high dose of apormorphine (25 μg/kg, i.v.). (C) Administration of the dopamine precursor L-dopa, with MDL 28,133A restores the rate effect of MDMA (from Schmidt *et al.*, 1992a).

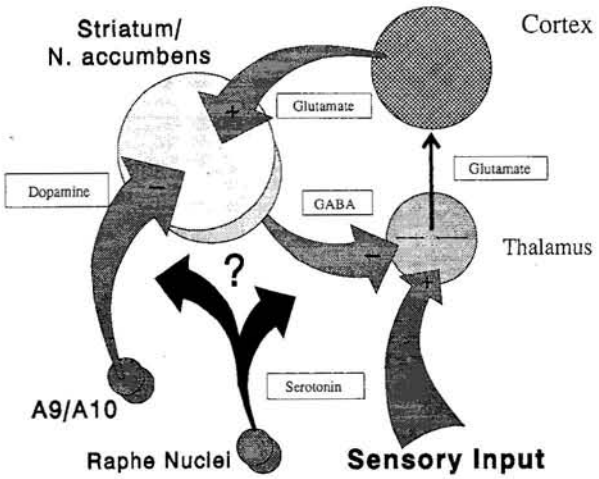

FIG. 3. Schematic representation of the corticostriatothalamic feedback loop controlling thalamic sensorimotor gating. Only the major pathways of the circuit are shown. Activation of the striatum by glutamatergic input from the cortex ultimately results in the inhibition of thalamic activity and a reduction in sensory input to the cortex. The activation of this inhibitory pathway is opposed at the level of the striatum by inputs from the midbrain dopaminergic nuclei. This model predicts that either excessive dopaminergic activity or hypoglutamatergic activity could produce the sensory overload believed to exist in schizophrenia. Although the neurochemical anatomy and many of the transmitter interactions of this circuit have been defined, the role of serotonin in the regulation of sensorimotor gating is almost completely unknown.

vide convincing evidence of dopaminergic hyperactivity in schizophrenia.

The original dopamine hypothesis has been expanded in recent years to incorporate newly acquired knowledge of basal ganglia neuroanatomy, sensorimotor processing and the pathophysiology of schizophrenia (for review see Carlsson and Carlsson, 1990). An absolute excess of dopaminergic activity is no longer required to explain the disorder or the ability of D2 antagonist to reduce the severity of its symptoms. A review of some of this new information and how it relates to schizophrenia will provide the background for some of our preclinical observations on the antipsychotic potential of 5-HT_2 antagonists.

At its simplest, schizophrenia can be considered to be the result of a disruption of the normal processes regulating the flow of sensory input to the brain. The inability to correctly assimilate or ignore both internal and external sensory cues leads to the formal thought disorders, cognitive fragmentation and bizarre behavior characteristic of schizophrenia. The "gating" or "filtering" of sensory input to the cortex is believed to be regulated in the brain at the level of the thalamus. The cortex itself controls information flow through this gate via a complex corticostriatothalamic circuit (Fig. 3). Activation of the striatum by a massive glutamatergic input from the cortex results in the stimulation of a polysynaptic GABAergic outflow to the thalamus. Thus, glutamatergic excitation of the striatum increases sensorimotor filtering by inhibiting thalamic activity. Opposing the actions of glutamate in the striatum are the mesolimbic (A10) and mesostriatal (A9) dopamine systems. The mesolimbic dopamine system, which projects primarily to the nucleus accumbens or ventral striatum, plays a significant role in the integration of cognitive information. The mesostriatal system projects most heavily to the dorsal striatum which is considered primarily a motor nucleus. By inhibiting striatal outflow, the dopaminergic input to the striatum reduces the amount of filtering occurring at the level of the thalamus and increases sensorimotor input. Given that it is a balance between the striatal dopaminergic and glutamatergic systems which ultimately determines the magnitude of sensory input, it is apparent that a loss of gating could be produced by either an increase in dopaminergic activity or a decrease in glutamatergic activity. Modern anatomical and neuroimaging methods have provided evidence that it is the latter which occurs in schizophrenia (for reviews see Buchsbaum, 1990; Roberts, 1990). This reduction in glutamatergic input from the cortex, or "hypofrontality", unbalances the system to the extent that any increase in dopamine release, such as that known to occur during stress (Dunn, 1988), results in a behaviorally relevant excess of dopaminergic activity. This model remains compatible with the therapeutic utility of the D2 dopamine receptor antagonists in psychosis.

Current theory holds that it is the blockade of the dopamine receptors in the nucleus accumbens which is primarily responsible for the therapeutic efficacy of these agents. Unfortunately, antipsychotic agents typically produce a 65 to 85% blockade of all striatal D2 receptors (Farde *et al.*, 1989) including those involved primarily in motor function. The result is the extrapyramidal side-effects (EPS) or drug-induced parkinsonism characteristic of typical antipsychotic therapy. The development of antipsychotic agents without the serious EPS liability of current D2 antagonists would be a major advance in the treatment of schizophrenia.

If the blockade of 5-HT_2 receptors can prevent the activation of the dopamine system and enhanced dopaminergic transmission, it follows that 5-HT_2 receptor antagonists may have antipsychotic activity. Furthermore, such agents should have low extrapyramidal side-effect liability based upon their apparent lack of effect on basal dopaminergic tone.

PRECLINICAL TESTING OF THE HYPOTHESIS

The 5-HT_2 receptor antagonist MDL 100,907 (R-(+)-α (2,3 - dimethoxyphenyl) - 1 - [2 (4 - fluorophenethyl)] - 4 -

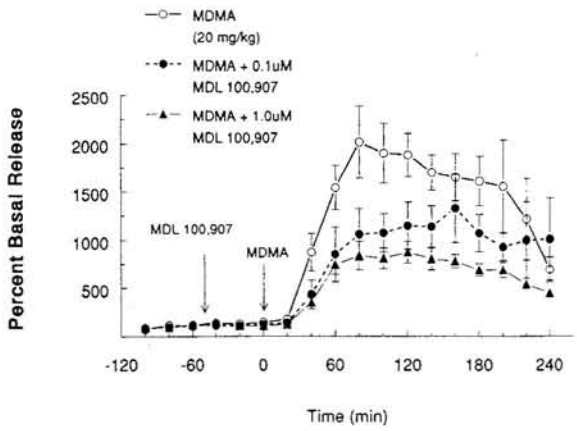

FIG. 4. Effect of intrastriatal infusion of MDL 100,907 on the increase in extracellular concentrations of dopamine produced by MDMA in awake, freely moving rats. The 5-HT_2 antagonist was infused through the microdialysis probe at the time indicated by the first arrow. The second arrow indicates the administration of MDMA (20 mg/kg, s.c.). Both concentrations of MDL 100,907 produced a significant attenuation of MDMA-induced transmitter release (from Schmidt *et al.*, 1993).

piperidinemethanol) was selected as the lead compound for study in preclinical tests of antipsychotic activity. MDL 100,907 possesses subnanomolar affinity for the 5-HT_2 receptor with a minimum 300-fold selectivity for the 5-HT_2 site over all other receptors examined including the 5-HT_{1C}, dopamine D2, and α_1 adrenergic receptors (Dudley *et al.*, 1990). The compound also has the advantage of being a single resolved optical isomer.

In vivo neurochemical studies demonstrated MDL 100,907 was a potent antagonist of both the acute stimulation of dopamine synthesis and the long-term serotonergic deficits produced by the administration of high doses of MDMA. Dopamine synthesis was examined *in vivo* by measuring the accumulation of dopa in rats treated with the decarboxylase inhibitor, NSD 1015. The stimulation of synthesis produced by MDMA (20 mg/kg) was antagonized by doses of MDL 100,907 as low as 10 μg/kg (Schmidt *et al.*, 1992b). The same dose of the antagonist significantly attenuated the serotonergic deficits measured in rat brain one week after MDMA administration with higher doses of MDL 100,907 providing complete protection (Schmidt *et al.*, 1992b). These results indicate that 5-HT_2 antagonists can inhibit both stimulated dopamine synthesis and the neurochemical response to increased dopamine release.

Microdialysis studies in awake, freely moving rats were performed to determine directly the effect of MDL 100,907 on MDMA-stimulated dopamine release. In these studies, a "neurotoxic" dose of MDMA typically produced a 15- to 20-fold increase in extracellular concentrations of striatal dopamine. Systemic administration of MDL 100,907 (1 mg/kg, s.c.) only 20 min prior to MDMA reduced the subsequent rise in extracellular transmitter concentrations by greater than 40% (Schmidt *et al.*, 1992b). As shown in Fig. 4, this effect of systemic MDL 100,907 could be reproduced by directly infusing concentrations of the drug at low as 0.1 μM into the striatum via the microdialysis probe (Schmidt *et al.*, 1993). Infusion of the antagonist into the midbrain regions containing the dopamine cell bodies did not alter MDMA-induced transmitter efflux in the striatum. It is important to note that MDL 100,907 was without effect on either basal dopamine synthesis or release in all these studies.

These neurochemical results are consistent with the hypothesis that 5-HT_2 receptors are involved in the augmentation of MDMA-stimulated release. Furthermore, based on the results from the infusion experiments, these receptors appear to be located in the terminal field of the dopamine system, i.e. the striatum. Their precise neuronal location within the striatum remains to be determined.

Behavioral studies with MDL 100,907 also indicate that the blockade of 5-HT_2 receptors can selectively interfere with elevated dopaminergic activity. The stimulation of locomotor activity in mice by amphetamine has been attributed to dopamine release in the nucleus accumbens and is often used as a test system for the evaluation of potential antipsychotics (Cole, 1978; Costall *et al.*, 1977). Table I provides the ED_{50} values for the antagonism of this behavior by haloperidol, MDL 100,907 and clozapine. The ED_{50} of each agent for the inhibition of spontaneous motor activity is also included. MDL 100,907 is equipotent with haloperidol at antagonizing amphetamine-stimulated activity and more potent than clozapine. However, the dose of haloperidol required to inhibit amphetamine-induced locomotion is similar to that which reduces spontaneous activity. In contrast, MDL 100,907 has no effect on spontaneous motor activity at doses several-fold higher than its ED_{50} for antagonism of amphetamine stimulation (Sorensen *et al.*, 1993).

TABLE I. ED_{50} values for the antagonism of amphetamine-induced locomotor activity and inhibition of spontaneous motor activity (SMA) in mice

	ED_{50} (mg kg, i.p.)	
	Amphetamine-induced locomotion	Inhibition of SMA
MDL 100,907	0.3	> 8.0
Haloperidol	0.2	0.1
Clozapine	1.4	4.8

(a) data were collected for 90 min following drug administration using 16 mice per dose at 7-10 dose levels (Sorensen *et al.*, 1993). (b) data were collected for 30 min following drug administration using 6 mice per dose at 7 dose levels (Sorensen *et al.*, 1993).

MDL 100,907 was also tested in a chronic electrophysiological animal model believed to be predictive of antipsychotic activity. The effects of chronic antipsychotic drug administration on the number of spontaneously active dopaminergic neurons in both the A9 and A10 nuclei have been well described (Chiodo and Bunney, 1983; White and Wang, 1986; Goldstein *et al.*, 1989; Skarsfeldt, 1992). Typical antipsychotics with significant EPS liability such as haloperidol reduce the number of spontaneously active cells recorded in both regions. The reduction in mesolimbic dopaminergic activity has been suggested to contribute to the antipsychotic efficacy of haloperidol. However, the concurrent reduction in mesostriatal dopaminergic tone may well aggravate the extrapyramidal effects of such agents. In contrast, chronic administration of the atypical antipsychotic clozapine results in a reduction in A10 activity without producing a significant alteration in the A9 nucleus. This "limbic" selectivity of clozapine has been suggested to be responsible for its low incidence of EPS and its classification as an atypical antipsychotic agent. Like clozapine, chronic administration of MDL 100,907 produced a selective reduction in the number of active A10 neurons without producing a similar effect in the A9 mesostriatal system (Sorensen *et al.*, 1993). These results are therefore consistent with the prediction that MDL 100,907 has antipsychotic potential with low EPS liability.

The final data to be reviewed examined the activity of MDL 100,907 in a model of sensorimotor gating known as prepulse inhibition (PPI). PPI is a behavioral phenomenon in which the presentation of a subthreshold stimulus inhibits the response to a subsequent suprathreshold stimulus. Reflexes such as the startle or eye blink which occur in response to a sharp tone (acoustic stimulus) or air puff (tactile stimulus) are most frequently measured. One of the most attractive features of PPI as a model of sensorimotor gating is that it can be measured in humans as well as laboratory animals. Studies in humans indicate that schizophrenic patients have reduced PPI consistent with a deficit in sensorimotor filtering (Braff *et al.*, 1978, 1992). As predicted by the corticostriatothalamic model of sensorimotor gating, PPI is sensitive to manipulations of both the dopaminergic or glutamatergic systems. Administration of a direct dopamine agonist such as apomorphine (Swerdlow *et al.*, 1986) or an indirect agonist such as amphetamine (Swerdlow *et al.*, 1990) reduces PPI of the acoustic startle response in rats. This effect is reversed by the administration of haloperidol (Mansbach *et al.*, 1988) or by lesions of the nucleus accumbens in the case of amphetamine (Swerdlow *et al.*, 1990). Antagonists of the NMDA-subtype of the glutamate receptor such as MK-801 or phencyclidine (PCP) also disrupt PPI in rats presumably by decreasing glutamatergic activity (Mansbach and Geyer, 1989; Mansbach, 1991).

Our own studies of the acoustic startle response in rats have demonstrated that the administration of MDMA also reduces PPI (Padich *et al.*, 1993). Surprisingly, we were unable to reverse the effect of MDMA with haloperidol. In contrast to this finding, MDL 100,907 restored sound-induced PPI in MDMA-treated rats to control levels. These results indicate that the effect of MDMA on PPI is secondary to its effects on 5-HT release and not due to dopamine release. Perhaps more importantly, it is apparent that 5-HT_2 receptor stimulation must now be added to the list of transmitter systems which can alter PPI and by extension, sensorimotor gating. This conclusion was confirmed in studies using the direct 5-$HT_{2/1C}$ agonist, 2,5-dimethoxy-4-iodo-phenylisopropylamine (DOI) to disrupt PPI of the acoustic startle response in rats. This effect was also insensitive to haloperidol but was reversed by MDL 100,907.

It is important to stress that this effect of 5-HT_2 receptor stimulation on sensorimotor gating in the rat is independent of the dopamine system and must occur in parallel to the effects of 5-HT_2 receptor stimulation on dopamine synthesis and release. The lack of effect of haloperidol on 5-HT_2 receptor-mediated disruption of PPI indicated that these receptors regulate sensorimotor gating at some point downstream from the dopamine system.

An interesting speculation derived from these observations may relate to that subpopulation of schizophrenic patients resistant to typical antipsychotics such as haloperidol but who do respond to clozapine. It is well recognized that the affinity of clozapine for 5-HT_2 receptors is greater than its affinity for D2 receptors (Meltzer *et al.*, 1989). Is it possible that a disruption of sensorimotor gating in this population of patients is due to excessive activity in the serotonergic system? If this is the case, agents such as MDL 100,907 may be particularly useful in these patients.

In summary, studies on the mechanism of neurotoxicity of the amphetamine analog, MDMA, revealed a previously undescribed interaction between the serotonergic and dopaminergic systems of the forebrain. 5-HT_2 receptor stimulation appears to be permissive for the stimulation of dopamine synthesis necessary to support elevated levels of dopamine release such as occur in the presence of MDMA or amphetamine. It is possible that this function of 5-HT_2 receptors may underlie the contribution of 5-HT_2 receptor antagonism to the unique antipsychotic profile of mixed D2/5-HT_2 agents such as clozapine. Follow-up studies examining sensorimotor gating in rats indicate there are also non-dopaminergic mechanisms through which 5-HT_2 blockade could influence the antipsychotic activity of a drug. The results of these neurochemical, electrophysiological and behavioral tests of antipsychotic activity indicate that 5-HT_2 receptor antagonism alone may be sufficient for antipsychotic activity particularly in some populations of patients.

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