Pergamon

Life Sciences, Vol. 56, No. 25, pp. 2209-2222, 1995

0024-3205/95 $29.00 + .00

0024-3205(95)00210-3

MINIREVIEW

THE ROLE OF 5-HT$_{2A}$ RECEPTORS IN ANTIPSYCHOTIC ACTIVITY

Christopher J. Schmidt*, Stephen M. Sorensen, John H. Kehne, Albert A. Carr, and Michael G. Palfreyman

Marion Merrell Dow Research Institute, 2110 E. Galbraith Rd. Cincinnati, Ohio, 45215

(Received in final form March 13, 1995)

Summary

The correlation between the clinical activity of antipsychotic agents and their affinity for the D_2 dopamine receptor has been the mainstay of the hypothesis that schizophrenia is due to excessive dopaminergic function. More recently, the unique clinical profile of the atypical antipsychotic clozapine has been proposed to involve actions on additional receptor systems. In particular, the high affinity of clozapine for the 5HT$_{2A}$ receptor subtype has been suggested to contribute to its reduced side-effect liability, greater efficacy and its activity in therapy-resistant schizophrenia. We have used the highly selective 5-HT$_{2A}$ antagonist MDL 100,907 to explore the contribution of 5-HT$_{2A}$ receptor blockade to antipsychotic activity. Biochemical, electrophysiological and behavioral studies reveal that selective 5HT$_{2A}$ receptor antagonists have the preclinical profile of an atypical antipsychotic. The limited clinical evidence available also suggests that compounds producing 5-HT$_{2A}$ receptor blockade are effective, in particular, against the negative symptoms of schizophrenia.

Key Words: schizophrenia, serotonin-2 receptors, serotonin-dopamine interactions

The proposal that serotonin might be implicated in the pathophysiology of schizophrenia dates back to suggestions made by Woolley and Shaw in the early 1960s (1). Their discovery that lysergic acid diethylamide (LSD) could act as a potent serotonin antagonist gave credence to the suggestion that hallucinations, common in schizophrenia, were linked to a derangement of the serotonergic system. These early theories were largely discounted when it became clear that LSD-induced hallucinations are qualitatively different from those experienced by schizophrenics. The serotonin theory of schizophrenia was superceded by the pharmacologically based dopamine theory of Carlsson (2).

In this review, we will provide evidence for an important role for 5-HT and the 5-HT$_{2A}$ receptor in the regulation of the physiological processes compromised in schizophrenia. Although these effects of 5-HT are likely to be mediated by a variety of 5-HT receptor subtypes, we will limit our discussion to those actions involving the 5-HT$_{2A}$ receptor subtype. In some cases, these actions of 5-HT are mediated indirectly via effects on the dopaminergic system. However, direct effects of 5-HT on basal ganglia function can also be demonstrated. The data support the claim that 5-HT$_{2A}$ receptor blockade is an important contributor to the clinical activity of atypical

* Author for correspondence

antipsychotics such as clozapine and further suggests that 5-HT_{2A} antagonism alone may be sufficient for antipsychotic activity.

5-HT_2 receptor subtypes

Serotonin receptors have been classified using a wide variety of different nomenclatures starting with the "M" and "D" classification of Gaddum and Picarelli (3). The most recent classification is based on the molecular biology of the receptors. Humphreys et al. (4) have proposed a classification which renames the $5HT_2$ receptor, the receptor of the rat stomach fundus and the $5HT_{1C}$ receptor as the $5HT_{2A}$, $5HT_{2B}$ and $5HT_{2C}$ receptor, respectively. The $5HT_{2A}$ and $5HT_{2C}$ subtypes have received considerable attention due to their potential roles in the action of atypical antipsychotics (5-10) and contribution to the etiology of schizophrenia (11-13)

Anatomical evidence for 5-HT_{2A}/ dopamine interactions

The dopaminergic cell bodies in the A9 and A10 nuclei of the midbrain are innervated by serotonergic projections from both the medial and dorsal raphe, whereas the dopamine terminal fields of the striatum and nucleus accumbens are predominantly innervated by serotonergic projections from the dorsal raphe (14-19). Although serotonergic terminals have been reported to make direct synapses on dopaminergic cell bodies (14,20,21), the relationship between serotonergic and dopaminergic terminals within the forebrain is unknown. The distribution of serotonin receptor subtypes throughout the brain is heterogeneous, but low to intermediate densities of $5HT_{2A}$ receptors have been identified in both the midbrain and terminal regions of the nigrostriatal and ventral tegmental-limbic dopamine systems (22-24). The highest levels of 5-HT_{2A} receptors are located in the frontal cortex (25).

Biochemical evidence for 5-HT_{2A} receptor/dopamine interactions

Neurochemical studies with the amphetamine analogue, 3,4-methylenedioxymethamphetamine (MDMA): MDMA, like other amphetamines, induces the carrier-mediated release of monoaminergic neurotransmitters to produce the majority of its pharmacological effects (26-28). In addition to the myriad of acute neurochemical and behavioral effects resulting from such release, the administration of high doses of MDMA to rats results in a long-term depletion of brain 5-HT concentrations (29-34). The correlation between these transmitter deficits and the loss of functional serotonergic nerve terminals has lead to the suggestion that these long-term changes are a neurotoxic effect of MDMA. Numerous groups have now demonstrated that this neurotoxic effect of MDMA and several related amphetamine analogues is somehow dependent upon the release of dopamine (35-37). For example, pretreatment of rats with the dopamine synthesis inhibitor α-methyl-ρ-tyrosine or prior lesioning of midbrain dopaminergic neurons with 6-hydroxydopamine will prevent the subsequent neurotoxic response to MDMA (37).

In the course of our investigations of MDMA-induced neurotoxicity, we and others made the unexpected observation that serotonin antagonists and specifically selective $5HT_{2A}$ antagonists would prevent the long-term serotonergic deficits produced by MDMA (37-41). Experiments demonstrating that the 5-HT_{2A} antagonist, MDL 11,939 could stereoselectively prevent MDMA-induced serotonin depletion were among the approaches used to confirm that this protection was mediated by 5-HT_{2A} receptor blockade (41).

Subsequent studies revealed that 5-HT_{2A} antagonists prevent the neurotoxic effects of MDMA by reducing the supply of newly-synthesized dopamine available for carrier-mediated release. The rate-limiting enzyme for dopamine synthesis, tyrosine hydroxylase, is subject to a host of regulatory mechanisms including direct feedback inhibition by newly synthesized (non-vesicular) transmitter. Discharge of dopamine from this pool disinhibits tyrosine hydroxylase (28) and accelerates synthesis to maintain carrier-mediated release. Several studies have demonstrated that the MDMA-induced increase in dopamine synthesis is prevented by agents blocking 5-HT_{2A} receptors (38,40,42). It is also significant that selective antagonists such as MDL 100,907 [R-(+)-α-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol] accomplish this inhibition of activated synthesis without altering basal dopamine synthesis (Table 1). The use of L-DOPA pretreatment to abolish the protective effects of antagonists such as MDL 11,939, ritanserin (41) and MDL 28,133A (40) on MDMA-induced neurotoxicity confirmed the imporance of this effect on synthesis. Ultimately, *in vivo* microdialysis studies established that 5-HT_{2A} antagonists such as ritanserin or MDL 100,907 were very effective at attenuating MDMA-induced dopamine release *in vivo*. We concluded from these findings that 5-HT_{2A} receptor stimulation is required for the enhanced dopamine synthesis and release produced by agents such as MDMA. This activity of 5-HT_{2A} receptors also explains the blunting effect of 5-HT_{2A} antagonists on the slowing of dopamine cell firing following the administration of amphetamine or MDMA (see below). In contrast to its effects on MDMA-induced stimulation of dopamine release, MDL 100,907 did not alter the increase in dopamine release or turnover produced by haloperidol or reserpine (38).

Table 1: Selective blockade of the MDMA-induced increase in striatal dopamine synthesis *in vivo* by MDL 100,907 following decarboxylase inhibition with NSD 1015. The antagonist was given 30 min prior to MDMA and 90 min prior to sacrifice (31).
** P<0.01.

	DOPA (ng/g)	
MDL 100, 907 mg/kg, s.c.	Saline	MDMA (20 mg/kg)
Control	1291±73 (100 ±5.7)	1972±232** (153± 18)
0.01	1271±46 (99 3.6)	1257±175 (97±14)
0.10	1184±36 (92±3)	1379±249 (107±19)
1.0	1103 ±129 (85±10)	1092±120 (85±9.3)

Effect of MDL 100,907 on dopamine efflux in the medial prefrontal cortex (mPFC): The ability of 5-HT_{2A} receptor antagonists to selectively dampen excessive dopaminergic activity without altering basal activity provided our initial rationale for their evaluation as atypical antipsychotic agents. However, further investigation of these compounds has revealed additional

activities which may bear on their potential as antipsychotic or more properly *antischizophrenic* agents. One such activity is the effect of 5-HT_{2A} receptor blockade on dopamine release in the prefrontal cortex. Although 5-HT_{2A} receptor blockade has no effect on extracellular dopamine concentrations in either the striatum or nucleus accumbens, systemic administration or direct infusions of MDL 100,907 produces marked increases in dopamine efflux in the rat mPFC (43).

The mPFC is frequently identified as a region likely to be involved in the pathogenesis of schizophrenia. Interest in this region was originally based on clinical observations such as the poor performance of schizophrenics in neuropsychological tests of prefrontal function and the similarities between the enduring sequela of prefrontal lesions and deficits symptoms of schizophrenia (44). Modern neuroimaging techniques have also provided evidence of reduced metabolic function in the frontal cortex of schizophrenic patients (45).

The mesocortical dopamine system has assumed a prominent position in the study of prefrontal function. Animal studies indicate that deficiencies in this system may actually result in excessive activity or responsivity of the subcortical dopaminergic systems such as that of the nucleus accumbens (46-50). Such a condition would be consistent with early suggestions that schizophrenia involves both excesses and deficiencies in dopaminergic function and the ability of dopaminergic agonists to exacerbate psychotic symptoms but alleviate negative symptoms (51).

Given these considerations, it is significant that the atypical antipsychotic clozapine, unlike typical agents such as haloperidol, preferentially increases dopamine efflux in the rat mPFC (52). Such an effect may well explain the unique antipsychotic profile of clozapine including its activity against the negative symptoms of schizophrenia. Indeed, Meltzer and his colleagues have championed the view that the unique clinical profile of clozapine is a function of its affinity for both D2 dopamine and 5-HT_{2A} receptors (53). In light of the fact that the affinity of clozapine for the 5-HT_{2A} receptor is higher than for any of the dopamine receptor subtypes (54) we examined the effects of MDL 100,907 on cortical dopamine release. Microdialysis studies in awake, freely moving rats confirmed that 5-HT_{2A} receptor blockade increases dopamine release in the mPFC. This effect was observed following either systemic administration or direct infusion of MDL 100,907 into the mPFC. These results indicate that the effect of clozapine on mesocortical dopamine release can be attributed to 5-HT_{2A} receptor blockade. In addition, the activity of MDL 100,907 within the mPFC lends further support to the claim that a selective 5-HT_{2A} antagonist may have antipsychotic activity similar to that of clozapine.

It may be useful to consider the potential relationship between the effect of MDL 100,907 on prefrontal dopamine release and its effects on the subcortical dopamine pathways. Just as decreases in mPFC dopaminergic activity have been linked to increased subcortical dopaminergic function, increases in mPFC dopaminergic activity have been reported to decrease subcortical dopaminergic function (see ref. 43). It is therefore not unreasonable to speculate that the increase in mesocortical dopamine release produced by MDL 100,907 may play a role in the reduced response of the subcortical systems to agents such as amphetamine. This hypothesis awaits experimental testing.

Electrophysiological evidence for 5-HT_{2A} receptor/dopamine interactions.

Serotonin is generally considered to have an inhibitory effect on the firing rate of dopaminergic neurons (14,17). Results from a limited number of antagonist studies suggest that this effect may be mediated by the 5-HT_{2A} or 5-HT_{2C} receptor (55). However, the effect of 5-HT_{2A} antagonists on the response of dopaminergic neurons to amphetamines suggests that the interaction of serotonin with the dopaminergic system is much more complex (40, 56-58). In our

studies, the administration of amphetamine (1mg/kg i.v.) reduced the firing rate of rat A10 neurons by 50-60%. This response to released dopamine was prevented by pretreatment with the selective 5-HT$_{2A}$ antagonists, MDL 28,133A or MDL 100,907 (58). The role of serotonin in this phenomenon was confirmed by demonstrating that the A10 cells of rats pretreated with the tryptophan hydroxylase inhibitor, p-chlorophenylalanine, were also resistant to this action of amphetamine (57). Consistent with the neurochemical results showing that 5-HT$_{2A}$ receptor blockade may interfere with stimulated dopamine synthesis, the effect of 5-HT$_{2A}$ antagonists could be completely abolished by pretreatment with L-DOPA plus carbidopa (57). Similar results were demonstrated with the amphetamine analogue MDMA for A9 dopamine neurons (40, 59). These data corroborate the results from neurochemical studies which indicate that under certain conditions, serotonergic input acting via the 5-HT$_{2A}$ receptor can regulate the availability or response to an amphetamine releasable pool of dopamine.

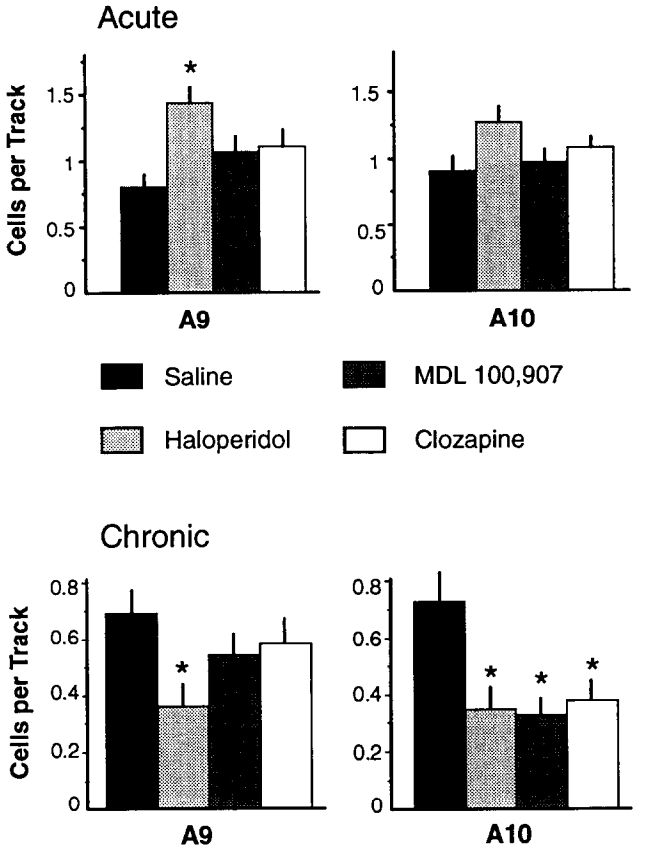

Figure 1 Effect of acute or chronic (once daily for 21 days) treatment with saline (CTL), haloperidol (HAL, 0.5 mg/kg, i.p.), clozapine (CLOZ, 20 mg/kg, i.p.) or MDL 100,907 (1mg/kg, i.p.) on the number of spontaneously active dopamine neurons in the A9 or A10 nucleus. Values are the means with S.E.M. for 10 to 15 rats. * $P < 0.05$ vs. saline. Reprinted with permission from (58).

It is also possible to demonstrate serotonin/dopamine interactions following chronic administration of selective 5-HT$_{2A}$ antagonists. The acute effect of haloperidol and other typical

neuroleptics is to increase the activity of A9 and A10 dopaminergic activity. Bunney and Grace (60) first demonstrated that chronic treatment with the D_2 dopamine antagonist haloperidol paradoxically decreased the number of active dopamine neurons in both regions presumably due to depolarization-induced blockade. Although a decrease in the activity of A10 dopaminergic neurons can be viewed as beneficial in reducing psychotic behavior, a similar reduction in A9 activity would be predicted to have consequences consistent with the extrapyramidal symptoms (EPS) of typical antipsychotic therapy. In contrast, clozapine has no effect on dopamine cell firing following acute administration and selectively decreases the activity of A10 neurons on chronic administration (61-64). This electrophysiological profile is therefore in agreement with the clinical profile of clozapine as an effective antipsychotic agent with low EPS liability. As already described, clozapine is a potent antagonist of 5-HT_{2A} receptors (54) and it has been suggested that its atypical electrophysiological profile may be a reflection of this activity. Numerous studies have shown that 5-HT_{2A} receptor antagonists such as MDL 100,907 (58), ICI 169,369 (56) and sertindole (65) produce a pattern of electrophysiological changes after both acute and chronic administration that closely resemble the effects of clozapine (see Fig. 1). These data are also consistent with a modulatory role for the 5-HT_{2A} receptor on dopaminergic activity and further suggest that selective 5-HT_{2A} antagonists possess atypical antipsychotic activity.

Behavioral evidence of 5-HT_{2A} receptor/dopamine interactions

Effect of 5-HT_{2A} antagonists on amphetamine-stimulated locomotor activity: Low doses of amphetamine produce locomotor hyperactivity mediated by dopamine release from mesolimbic dopamine neurons. Amphetamine hyperactivity is blocked by both typical and atypical antipsychotics, an effect that is assumed to result from the D_2 antagonism that is shared, to a certain extent, by these compounds. However, selective 5-HT_{2A} antagonists, such as amperozide and MDL 100,907, which are virtually devoid of D_2 antagonist activity also reduce amphetamine hyperactivity in mice (58, also Figure 2). These results are consistent with the concept that 5-HT_{2A} antagonists may be effective antipsychotic agents. More generally, they support the idea that 5-HT_{2A} antagonists can dampen behavioral states associated with excessive dopaminergic activity, a concept that was established in neurochemical studies of MDMA neurotoxicity (see previous section).

In animal models, the doses of many antipsychotics required to antagonize amphetamine-stimulated locomotion are very close to those which produce more general depressant effects on behavior, perhaps due to additional antagonism of D_2, $alpha_1$ adrenergic, and/or histamine receptors. Notably, the 5-HT_{2A} antagonists, MDL 100,907 and amperozide were superior to haloperidol and clozapine in that they demonstrated a greater separation between doses that blocked amphetamine hyperlocomotion and those that reduced spontaneous motor activity (58, Fig. 2).

In addition to blocking mesolimbic D_2 receptors, typical antipsychotics also block striatal D_2 receptors and this effect is thought to result in EPS. The exploratory locomotor activity that is produced by low doses of amphetamine in rats is replaced by more focused, repetitive behaviors when high doses are administered. These "stereotyped" behaviors, are also produced by the direct dopamine agonist, apomorphine. Typical but not atypical antipsychotics block such stereotypic behavior suggesting this antagonism is predictive of the EPS liability of a compound. In contrast to haloperidol, MDL 100,907 does not antagonize amphetamine or apomorphine-induced stereotypies in rats (58). MDL 100,907 was also without effect on apomorphine climbing in mice, another striatally mediated behavior only weakly affected by clozapine. Taken together with the findings that MDL 100,907, amperozide and other 5-HT_{2A} antagonists do not produce

catalepsy (58), these results suggest that 5-HT$_{2A}$ antagonists will be devoid of extrapyramidal liability. In light of the demonstrated antagonism of mesolimbic mediated behaviors, they also indicate that 5-HT$_{2A}$ receptors may be more important in regulating mesolimbic versus nigrostriatal functions. The latter speculation is consistent with studies demonstrating a relative enrichment of 5-HT$_{2A}$ receptors in the nucleus accumbens when compared to the dorsal striatum (66).

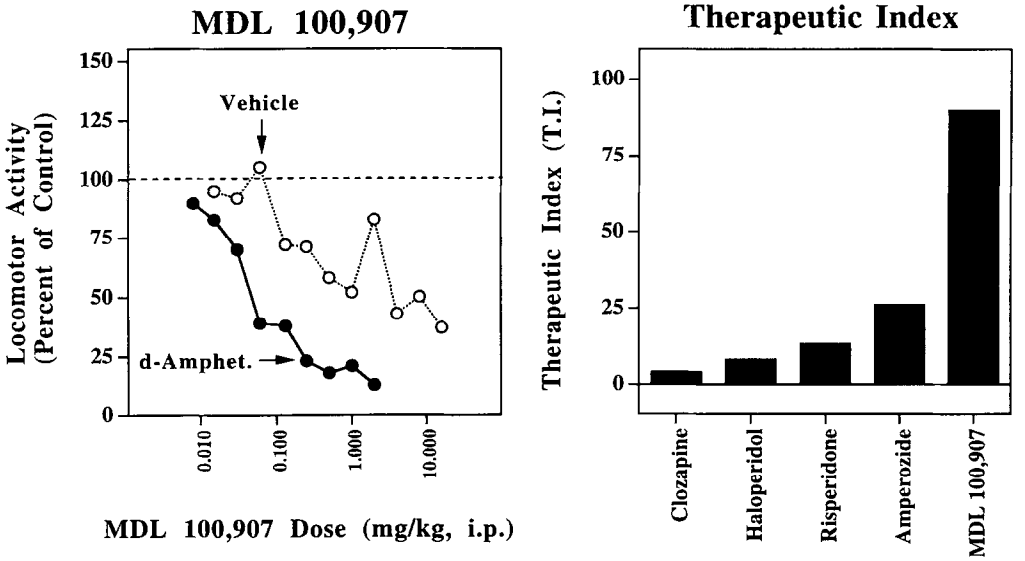

Figure 2 *Left panel:* The effects of MDL 100,907 (0.01 - 16 m/kg, i.p., 0.5 h pretreat) on locomotor activity in mice injected with saline (open circles) or 2.0 mg/kg d-amphetamine (closed circles). Data are expressed as a percent of the appropriate control group. *Right panel:* The "therapeutic index" (T.I. defined as the estimated ED$_{50}$ for depressing locomotion in vehicle injected mice / ED$_{50}$ for reducing d-amphetamine stimulated locomotion) of MDL 100,907 and selected reference compounds. ED$_{50}$s for both conditions were calculated using 90 min test means. Estimated ED$_{50}$s (mg/kg) for amphetamine reduction and for baseline reduction, respectively and calculated T.I.s were: *MDL 100,907:* 0.08, 7.2, 90; *Amperozide:* 0.26, 6.7, 26; *Risperidone:* 0.04, 0.5, 13; *Haloperidol:* 0.09, 0.7, 8; *Clozapine:* 0.6, 2.5, 4. ED$_{50}$s are based on recalculations of published data corrected for baseline activity (58) and additional unpublished data.

Effect of 5-HT$_{2A}$ antagonists on prepulse inhibition: Prepulse inhibition (PPI) is a behavioral phenomenon in which the presentation of a subthreshold stimulus inhibits the response to a subsequent suprathreshold stimulus. Examples of reflexes that can easily be measured are the whole body startle or eye blink response which occurs following an acoustic stimulus such as a

loud tone or a tactile stimulus such as an air puff. This model of sensorimotor gating can be measured in man as well as in laboratory animals. Experiments in schizophrenics show that these patients have a reduced PPI consistent with a deficit in sensorimotor gating (67,68). PPI is sensitive to both dopaminergic and glutamatergic manipulation. The direct dopamine agonist apomorphine (69) or the indirect agonist amphetamine (70) reduce PPI of the acoustic startle response in rats and these effects are reversed by haloperidol (71) or, in the case of amphetamine, by 6-hydroxydopamine lesions of the nucleus accumbens. Work in our laboratory indicates that MDMA also reduces PPI but this effect is not sensitive to haloperidol. The MDMA effect is however sensitive to blockade by MDL 100,907 thereby implicating the 5-HT_{2A} receptor (72). To confirm that PPI was sensitive to 5-HT_2 receptor manipulation we demonstrated that the disruption of acoustic PPI by the direct 5-HT_{2A}/5-HT_{2C} agonist ,2,5-dimethoxy-4-iodo-phenylisopropylamine (DOI) was sensitive to MDL 100,907 but not haloperidol (72). It is interesting to speculate that this effect of 5-HT agonists and antagonists may relate to the subpopulation of schizophrenics who do not respond to typical antipsychotics but who are sensitive to the therapeutic benefits of clozapine. Kahn et al., 1993 (73) have provide data that increased 5-HT receptor function may in fact predict the therapeutic response to clozapine in patients unresponsive to typical antipsychotics. Given the high affinity of clozapine for 5-HT_{2A} receptors and relatively low affinity for most dopamine receptor subtypes, it will be interesting to see if selective 5-HT_{2A} antagonists are effective in this subpopulation of patients.

Evidence for 5-HT_{2A} antagonist activity of atypical antipsychotic agents

Clozapine has some therapeutic efficacy in otherwise resistant patients and is largely devoid of EPS liability (74-77). However, the complex pharmacological profile of clozapine has made the task of determining its mechanism of action extremely difficult. Clozapine has reasonable affinity for a large number of receptors including several histaminergic, serotonergic, adrenergic, dopaminergic, and cholinergic subtypes (54, 78-82). Nonetheless, Meltzer and colleagues (82-84) have argued cogently that the best predictor of atypical antipsychotic activity is the ratio of 5-HT_{2A} to dopamine D_2 affinity. However, it should be noted that "atypicality" is defined in these studies by a lack of EPS rather than by activity against negative symptoms. Hence the ratio of 5-HT_{2A} to D_2 activity has been considered to be more relevant to predicting a reduced side-effect liability than improved efficacy. However, developments linking the 5-HT_{2A} antagonist activity of clozapine with mesocortical dopamine release and the pathogenesis of negative symptoms may change this situation.

Several new antipsychotic agents are being developed based on the prediction that combining the known antipsychotic effects of dopamine D_2 antagonism with blockade of 5-HT_{2A} receptors will produce clinically effective compounds with reduced extrapyramidal effects (85-87). This concept has been validated by the results achieved with risperidone, an antipsychotic that is as effective as haloperidol but which is reported to have a much reduced propensity to produce EPS (88).

Clinical evidence for an antipsychotic effect of 5-HT_{2A} antagonists

Most clinical studies of 5-HT_{2A} receptor antagonists have used the mixed 5-HT_{2A}/5-HT_{2C} antagonist, ritanserin. The effectiveness of ritanserin has been investigated both as a monotherapy and as an add-on to existing neuroleptic treatment. Two placebo-controlled, double-blind studies have demonstrated an effect of ritanserin predominantly on the negative symptom cluster in schizophrenic patients that had been poorly controlled by ongoing therapy with a classical antipsychotic agent (89, 90). A recent open trial of ritanserin in acute psychotic

patients yielded significant clinical improvements in both negative and positive symptoms (91). Ritanserin treatment has also been shown to reduce the EPS associated with antipsychotic therapy (89, 92). A double blind trial comparing ritanserin to orphenadrine or placebo in neuroleptic treated schizophrenic patients found ritanserin to be superior to both orphenadrine and placebo (93). As previously mentioned, several mixed 5-HT_{2A}/D_2 antagonists undergoing clinical evaluation have shown effective antipsychotic activity with a reduced EPS liability (85-87, 94, 95).

Evidence for altered 5-HT_{2A} function in schizophrenics

Direct evidence for abnormal neurotransmission at 5-HT_{2A} receptors in schizophrenia comes primarily from post-mortem ligand binding studies. The majority of these investigations have found a decrease in receptor number in the frontal cortex with no change in receptor affinity (96-99). Predictably, several studies have also reported no change in 5-HT_2 receptor density in the frontal cortex of schizophrenics (100, 101). It is controversial as to whether these differences could be the result of prior antipsychotic treatment as preclinical studies have shown no effect, decreased, or enhanced binding of 5-HT_{2A} ligands following exposure to antipsychotic agents (99, 102, 103). Joyce et al., (101) recently used autoradiography to simultaneously determine the post-mortem regional density of 5-HT uptake sites and 5-HT_2 receptors in the brains of schizophrenics. They observed an increase in both the number of uptake sites and 5-HT_2 receptors in the striatum and nucleus accumbens. However, 5-HT_2 receptor density was also increased in limbic cortex while 5-HT uptake sites were reduced in number. Investigations using platelets to examine the activity of 5-HT_2 receptors have likewise given equivocal data. Some studies have shown an increase in 5-HT_2 receptors, some a decrease and others, no change (104-106). Future studies will undoubtedly rely upon positron emission tomography (PET) to measure 5-HT_2 activity *in vivo* using a ligand such as [^{11}C]N-methylspiperone (107, 108).

Conclusions

Typical antipsychotics are thought to act primarily through blockade of D_2 dopamine receptors and this common action was a key to the development of the hypothesis that excessive dopaminergic activity is responsible for the symptoms of schizophrenia. This theory still has considerable validity in spite of the relative paucity of *in vivo* evidence of abnormal dopaminergic function. The ability of selective 5-HT_{2A} antagonists to interfere with the heightened state of dopamine activity without altering basal tone suggests that such compounds also possess antipsychotic activity. Potent 5-HT_{2A} receptor antagonism has been postulated to contribute to the therapeutic action of several clinically effective atypical antipsychotic drugs such as clozapine and risperidone. The primary features of these atypical antipsychotics are their effects on the negative symptoms of schizophrenia and their relative lack of EPS in both animals and humans.

More recently, the original dopamine hypothesis has been expanded to incorporate new knowledge of basal ganglia neuroanatomy, sensory processing and the pathophysiology of schizophrenia (109). This modified hypothesis considers that schizophrenia is due to a disruption of the normal processes regulating the flow of sensory input to the brain. The inability to ignore or correctly process the internal and external sensory information leads to the formal thought disorder, cognitive fragmentation and bizarre behavior which are the hallmarks of schizophrenia. Sensory input to the cortex is regulated by a complex corticostriatal-thalamic circuit which is shown diagramatically in 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. The thalamus functions as the final filter or gate to control sensory input to the cortex. Glutamatergic excitation in the striatum increases sensorimotor gating by inhibiting thalamic activity while increased mesolimbic and mesostriatal dopaminergic activity acts in opposition and increases sensory input.

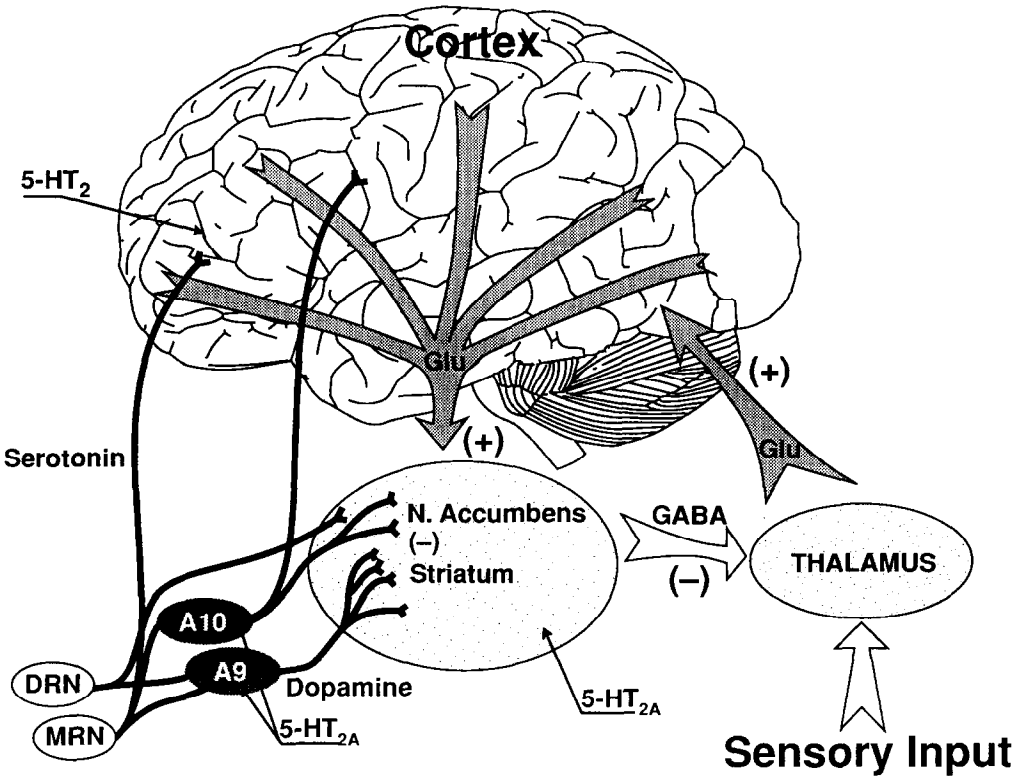

Figure 3: Schematic diagram of the corticostriatothalamic pathway illustrating the primary sites of neurotransmitter interaction. Serotonergic input is ubiquitous throughout the circuit and likely modifies sensory-motor gating at a variety of sites. Although their exact cellular location is unknown, 5-HT$_{2A}$ receptors have been shown to influence neuronal activity in the indicated regions of the pathway.

Given that a balance between glutamatergic and dopaminergic activity is essential for maintaining the correct flow of sensory information, it is apparent that aberrations would occur if dopamine function was excessive or glutamatergic activity decreased. Clinical, biochemical and modern imaging methods have provided evidence that decreased glutamatergic activity could be central to the schizophrenic process (110-113). Excessive dopaminergic activity as could occur in stress (49, 114,115) would result in an unopposed, behaviorally-relevant excess of dopaminergic activity. It is proposed that such excess dopaminergic activity may be susceptible to modulation by 5-HT$_{2A}$ receptor antagonists and because such agents have little action on basal dopaminergic activity it is postulated that they will have little propensity to cause EPS. Agents such as MDL 100,907 should allow this hypothesis to be tested in patients.

Acknowledgements

The authors wish to thank the numerous colleagues from Marion Merrell Dow who contributed to this work. In particular, Gina Fadayel, Vicki Taylor, Christine Sullivan, Herbert Ketteler, Tim McCloskey, Teresa Humphreys and Robert Padich contributed significant technical expertise. We also thank Dorothy Reed for her help in compiling the literature searches. Mark Dudley was instrumental in the early development of MDL 100,907 and we thank him for his continuing advice.

REFERENCES

1. D.W. WOOLEY, The Biochemical Basis of Psychosis. Wiley, New York. (1962)
2. A. CARLSSON, Neuropharmacol. 1 179-186 (1988)
3. J.H. GADDUM and Z.P.PICARELLI, Br. J. Pharmacol. 12 323-328 (1957)
4. P.A.A. HUMPHREY, P. HARTIG and D. HOYER, Trends.Pharmacol. Sci. 14 233-236 (1993)
5. J.E. LEYSON, P.M.F. JANSSEN, W. GOMMEREN, J. WYNANTS, P.J. PAULWELS and P.A.J. JANSSEN, Mole. Pharmacol. 41 494-508 (1991)
6. H.Y. MELTZER , S.MATSUBARA and J.C.LEE, J.Pharmacol. Exp. Ther. 251 238-246 (1989)
7. H.Y. MELTZER and J.F. NASH, Pharmacol. Rev. 43 587-604 (1991)
8. H. CANTON, L. VERIELE and F.C. COLPAERT, Eur. J. Pharmacol. 191 93-96 (1990)
9. H. FINK, R.MORGENSTERN and W.OELSSNER, Pharmacol. Biochem. Behav. 20 513-517 (1984)
10. H.Y. MELTZER, Psychopharmacol. 99 S18-S27 (1989)
11. J.P. BENNETT, S.J.ENNA, D.B.BYLUND, J.C.GILLIN, R.J. WYATT and S.H.SNYDER, Arch. Gen. Psychiat. 36 927-934 (1979)
12. T. MITA, S.HANADA, N.NISHINO, T.KUNO, H.NAKAI, T.YAMADORI, Y.MIZOI and C.TANAKA, Biol. Psychiat. 21 1407-1414 (1986)
13. A. BLEICH, S.L. BROWN, R. KAHN and H.M. VAN PRAAG, Schizo. Bull. 14 297-315 (1988)
14. A. DRAY, J.DAVIES, N.R.OAKLEY, P.TONGROACH and S.VELLUCCI, Brain Res. 151 431-442 (1978)
15. P. BOBILLIER, S.SEGUIN, F.PETITJEAN, D.SALVERT, M.TOURET and M.JOUVET, Brain Res. 113 449-486 (1976)
16. A. DRAY, T.J.GOUYE, N.R.OAKLEY and T.TANNER, Brain Res. 113 45-57 (1976)
17. H.C. FIBIGER and J.J. MILLER, Neuroscience 2 975-987 (1977)
18. H. IMAI, D.A. STEINDLER and S.T. KITAI, J.Comp. Neurol. 243 363-380 (1986)
19. A. PARENT, L. DESCARRIES and A. BEAUDET, Neuroscience 6 115-138 (1981)
20. C.T. GIAMBALVO and S.R.SNODGRASS, Brain Res. 152 555-566 (1978)
21. A. PAZOS, R.CORTES and J.PALACIOS, Brain Res. 346 231-249 (1985)
22. S.J. PEROUTKA and S.H. SNYDER, Mol. Pharmacol. 16 687-699 (1978)
23. G.P. REYNOLDS, M.N. ROSSER and L.L. IVERSEN, J. Neural Transm. [Suppl.] 18 273-277 (1983)
24. R.L. GELLMAN and G.K. AGHAJANIAN, Brain Res. 600 63-73 (1993)
25. A. PAZOS, A. PROBST and J. PALACIOS, Neurosci. 21 123-139 (1987)
26. C.J. SCHMIDT, J.A. LEVIN and W. LOVENBERG, Biochem. Pharmacol. 36 747-755 (1987)
27 C.J. SCHMIDT, Amphetamine and its analogs, A.K. Cho and D. Segal (eds.) pp 151-175 Academic Press, Inc. San Diego (1994)

28. C.E. CONNOR, & R. KUCZENSKI, Biochem. Pharmacol. 35 3123-3130 (1986)
29. J.W. GIBB, M. JOHNSON, D.STONE and G.R. HANSON, The Neuropharmacology of Serotonin, S.M. Whitaker-Azvaitia and S.J. Peroutka (eds) Ann. N.Y. Acad. Sci. 600 601-612 (1990)
30. D.M. STONE, D.C. STAHL, G.R. HANSON and J.W. GIBB, Eur. J. Pharmacol. 128 41-48 (1986)
31. C.J. SCHMIDT, J. Pharmacol. Exp. Ther. 240 1-7 (1987)
32. C.J. SCHMIDT and J.H. KEHNE, The Neuropharmacology of Serotonin. S.M. Whitaker-Azmitia and S.J.Peroutka (eds) Ann. N.Y. Acad. Sci. 600 665-681 (1990)
33. C.J. SCHMIDT, L. WU and W. LOVENBERG, Eur. J. Pharmacol. 124 175-178 (1986)
34. G. BATTAGLIA, S.Y. YEH, E. O'HEARN, M.E. MOLLIVER, M.J. KUHAR and E.B. DE SOUZA, J. Pharmacol. Exp. Ther. 242 911-916 (1987)
35. D.M. STONE, M. JOHNSON, G.R. HANSON and J.W. GIBB, J.Pharmacol. Exp. Ther. 247 79-87 (1988)
36. M.S. KLEVEN, W.L. WOOLVERTON and L.S. SEIDEN, Brain Res. 488 121-125 (1989)
37. C.J. SCHMIDT, C.K. BLACK and V.L. TAYLOR, Eur. J. Pharmacol. 181 59-70 (1990)
38. C.J. SCHMIDT, G.M. FADAYEL, C.K. SULLIVAN and V.L. TAYLOR, Eur. J. Pharmacol. 223 65-74 (1992)
39. C.J. SCHMIDT, G.M. ABBATE, C.K. BLACK and V.L. TAYLOR, J. Pharmacol. Exp. Ther. 255 478-483 (1990)
40. C.J. SCHMIDT, C.K. BLACK, V.L. TAYLOR, G.M. FADAYEL, T.M. HUMPHREYS, T.R. NIEDUZAK and S.M. SORENSEN, Eur. J. Pharmacol. 220 151-159 (1992)
41. C.J. SCHMIDT, V.L. TAYLOR, G.M. ABBATE and T.R. NIEDUZAK, J. Pharmacol. Exp. Ther. 256 230-235 (1991)
42. J.F. NASH, H.Y. MELTZER and G.A. GUDELSKY, J. Neurochem. 54 1062-1067 (1990)
43. C.J. SCHMIDT and G.M. FADAYEL, Eur. J. Pharmacol. 273 273-279 (1995)
44. W.W. BEATTY, Z. JOCIC, N. MUNSON and R.D. STANTON, J. Nervous and Mental Diseases 181 448-453 (1993)
45. D.R. WEINBERGER, Trends Neurosci. 11 367-370 (1988)
46. C.J. PYCOCK, R.W. KERWIN and C.J. CARTER, Nature 286 74-77 (1980)
47. A.P. LECCESE and W.H. LYNESS, Neuropharmacol. 26 1303-1308 (1987)
48. V. HAROUTUNIAN, P. KNOTT and K.L. DAVIS, Psychopharmacol. Bull. 24 341-344 (1988)
49. A.Y. DEUTCH, W.A. CLARK and R.H. ROTH, Brain Res. 521 311-315 (1990)
50. D.L. ROSIN, W.A. CLARK, M. GOLDSTEIN, R.H. ROTH and A.Y. DEUTCH, Neurosci. 48 831-839 (1992)
51. B.M. ANGRIST, J. ROTROSEN and S. GERSHON, Psychopharmacol. 72 17-19 (1980)
52. B. MOGHADDAM and B.B. BUNNEY, J. Neurochem. 54 1755-1760 (1990)
53. H.Y. MELTZER, British J. Psychiatry 160 22-29 (1992)
54. J.E. LEYSEN, P.M.F. JANSSEN, A. SCHOTTE, W.H.L.M. LUYTEN and A.A.H.P. MEGENS, Psychopharmacol. 112 s40-54 (1993)
55. L. UGEDO, J. GRENHOFF and T.H. SVENSSON, Psychopharmacol. 98 45-50 (1989)
56. J.M. GOLDSTEIN, L.C. LITWIN, E.B. SUTTON and J.B. MALICK, J. Pharmacol. Exp. Ther. 249 673-680 (1989)
57. S.M. SORENSEN, T.M. HUMPHREYS, V.L. TAYLOR and C.J. SCHMIDT, J. Pharmacol. Exp. Ther. 260 872-878 (1992)

58. S.M. SORENSEN, J.H. KEHNE, G.M. FADAYEL, T.M. HUMPHREYS, H.J. KETTELER, C.K. SULLIVAN, V.L. TAYLOR and C.J. SCHMIDT, J. Pharmacol. Exp. Ther. 266 684-691 (1993)
59. C.J. SCHMIDT, J.H. KEHNE, A.A.CARR, G.M. FADAYEL, T.M.HUMPHREYS, H.J. KETTELER, T.C. McCLOSKEY, R.A. PADICH, V.L. TAYLOR and S.M. SORENSEN, Int. Clin. Psychopharmacol. 8 Suppl. 2 25-32 (1993)
60. B.S. BUNNEY and A.A.GRACE, Life Sci. 23 1715-1728 (1978)
61. L.A. CHIODO and B.S. BUNNEY, J. Neurosci. 3 1607-1619 (1983)
62. L.A. CHIODO and B.S. BUNNEY, J. Neurosci 5 2539-2544 (1985)
63. F.J. WHITE and R.Y. WANG, Life Sci. 42 983-993 (1993)
64. F.J. WHITE and R.Y. WANG, Neuropharmacol. 25 995-1001 (1986)
65. T. SKARSFELDT, Synapse 10 25-33 (1992)
66. J.N. JOYCE, Psychopharmacol. 112 s16-34 (1993)
67. D.L. BRAFF, C. STONE, W. CALLAWAY, M.A. GEYER, I.D. GLICK and L. BALI, Psychopharmacol. 15 339-343 (1978)
68. D.L. BRAFF, C. GRILLON and M.A.GEYER, Arch. Gen. Psychiat. 49 206-215 (1992)
69. N.R. SWERDLOW, M.GEYER, D. BRAFF and G.F. KOOB, Biol. Psychiatry 21 23-33 (1986)
70. N.R. SWERDLOW, R.S. MANSBACH, M.A. GEYER, L. PULVIRENTI, G.F. KOOB and D.L. BRAFF, Psychopharmacol. 100 413-416 (1990)
71. R.S. MANSBACH, M.A. GEYER and D.L. BRAFF, Psychopharmacol. 94 507-514 (1988)
72. R.A. PADICH, T.C. McCLOSKEY and J.H. KEHNE, (submitted)
73. R.S. KAHN, M. DAVIDSON, L. SIEVER, S. GABRIEL, S. APTER and K.L. DAVIS, Am J. Psychiatry 150 1337-1342 (1993)
74 J. KANE, G. HONIGFELD, J. SINGER and H.Y. MELTZER, Arch. Gen. Psychiat. 45 789-796 (1988)
75. D. PICKAR, R.R. OWEN, R.E. LITMAN, E. KONICKI, R. GUTIERREZ and M.H. RAPAPORT, Arch. Gen. Psychiat. 49 345-353 (1992)
76. H.Y. MELTZER, Psychopharmacol. 99 S18-S27 (1989)
77. J.H. FRIEDMAN and M.C. LANNON, Neurology 39 1219-1221 (1989)
78. H. FINK, R. MORGENSTERN and W. OELSSNER, Pharmacol. Biochem. Behav. 20 513-517 (1984)
79. C.A. ALTAR, W.C. BOYER, A WASLEY, J.M. LIEBMAN, P.L. WOOD and S.G. GERHARDT, Naunyn. Schmied. Arch . Pharmacol. 338 162-168 (1988)
80. R.J. MILLER and C.R. HILLEY, Nature 248 546-547 (1974)
81. B.M. COHEN and J.F. LIPINSKI, Life Sci. 39 2571-2586 (1986)
82. B.L. ROTH, S.C. CRAIGO, S.M. CHOUDHARY, A. ULUER, F.J. MONSMA, Y. SHEN, H.Y. MELTZER and D.R. SIBLEY, J. Pharmacol. Exp. Ther. 268 1403-1410 (1994)
83. H.Y. MELTZER, S. METSUBARA and J.C. LEE, J. Pharmacol. Exp Ther. 251 238-246 (1989)
84. H.Y. MELTZER, Schizo. Bull. 17 263-287 (1991)
85. T. SKARSFELDT, Synapse 10 25-33, (1992)
86. N.A. MOORE, N.C. TYE, M.S. AXTON and F.C. RISIUS, J. Pharmacol. Exp. Ther. 262 545-551 (1992)
87. J.E. LEYSEN, W. GOMMEREN, A. EENS, D. DeCHAFFOY DeCOURCELLES, J.C. STOOF and P.A.J. JANSSEN, J. Pharmacol. Exp Ther. 247 661-670 (1988)
88. G. BERSANI, G. MECO, S. MARINI and F. POZZI, Human Psychopharmacol. 5 225-231 (1990)

89. A. REYNETJENS, M.L. GELDERS, J.A. HOPPENBROUWERS and G.V. BUSSCHE, Drug Development Res. 8 205-211, (1986)
90. S.J. DUINKERKE, P.A. BOTTER, A.A. JANSEN, P.A. VAN DONGEN, A.J. VAN HAAFTEN, A.J. BOOM, J.H. VAN LAARHOVEN and H.L. BUSARD, Br. J. Psychiat. 163 451-455 (1993)
91. F-A. WIESEL, A-L. NORDSTROM, L. FARDE and B. ERIKSSON, Psychopharmacol. 114 31-38 (1994)
92. C.H. MILLER, W.W. FLEISCHHACKER, H. EHRMANN and J.M. KANE, Psychopharmacol. Bull, 26 373-376 (1990)
93. G. BERSANI, A. GRISPINI, S. MARINI, A. PASINI, M. VALDUCCI and N. CIANI, Clin. Neuropharmacol. 13 500-506 (1990)
94. S.K. MIN, C.S. RHEE, C.E. KIM and O.Y. KANG, Yonsei Med. J. 34 179-190 (1993)
95. C. BARNAS, C.H. STUPPACK, C. MILLER, C. HARING, B. SPERNER-UNTERWEGER and W.W. FLEISCHHAKER, Int. Clin. Psychopharmacol. 7 23-27 (1992)
96. R.C. ARORA and H.Y. MELTZER, J. Neural Transm. Gen. Sect. 85 19-29 (1991)
97. P.M. WHITAKER, T.J. CROW and N. FERRIER, Arch. Gen. Psychiat. 38 278-280 (1981)
98. T. MITA, S. HANADA, N. NISHINO, T. KUNO, H.NAKAI, T. YAMADORI, Y. MIZOI and C. TANAKA, Biol. Psychiat. 21 1407-1414 (1986)
99. J.P. BENNETT, S.J. ENNA, D.B. BYLUND, J.C. GILLIN, R.J. WYATT and S.H. SNYDER, Arch. Gen. Psychiat. 36 927-934 (1979)
100. F. OWEN, A.J. CROSS, T.J. CROW, R. LOFTHOUSE and M.POULTER, Acta. Psychiat. Scand. 63 20-28 (1981)
101. J.N. JOYCE, A. SHANE, N. LEXOW, A. WINOKUR, M.F. CASANOVA and J.E. KLEINMAN, Neuropsychopharmacol. 8 315-336 (1993)
102. S. MATSURBARA and H.Y. MELTZER, Life Sci. 45 1397-1406 (1989)
103. T.H. ANDREE, M. MIKUNI, C.Y. TONG, J.I. KOENIG and H.Y. MELTZER, J. Neurochem. 46 191-197 (1986)
104. R.C. ARORA and H.Y. MELTZER, Neuropsychopharmacol. 10 109-114 (1994)
105. R.C. ARORA and H.Y. MELTZER, Psychiatry Res. 47 111-120 (1993)
106. M. SCHACHTER, D.P. GEANCY, D.G. GRAHAME-SMITH, P.J. COWEN and J.M. ELLIOTT, J. Clin. Pharmacol. 19 453-457 (1985)
107. A-L. NORDSTROM, L. FARDE and C. HALLDIN, Psychopharmacol. 110 365-367 (1993)
108. S. NYBERG, L. FARDE, L. ERIKSSON, C. HALLDIN and B. ERIKSSON, Psychopharmacol. 110 265-272 (1993)
109. M. CARLSSON and A. CARLSSON, Trends Neurosci. 13 272-276 (1990)
110. D.C. JAVITT and S.R. ZUKIN, Am. J. Psychiatry 148 1301-1308 (1991)
111. M.D.C. SIMPSON, P. SLATER, M.C. ROYSTON and J.F. W. DEAKIN, Psychiatry Res. 42 273-282 (1992)
112. G.W. ROBERTS, Trends in Neurosci. 13 207-211 (1990)
113. M.S. BUSHCBAUM, Schizophr. Bull. 16 379-389 (1990)
114. A.J. DUNN, Ann. N.Y. Acad. Sci. 537 188-205 (1988)
115. B.A. MORROW, W. A. CLARK and R.H. ROTH, Eur. J. Pharmacol. 238 255-262 (1993)