

# Serotonergic Agents That Activate 5HT<sub>2A</sub> Receptors Prevent NMDA Antagonist Neurotoxicity

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*Phencyclidine, ketamine, and other agents that block NMDA glutamate receptors trigger a schizophrenia-like psychosis in humans and induce pathomorphological changes in cerebrocortical neurons in rat brain.*

*Accumulating evidence suggests that a complex network disturbance involving multiple transmitter receptor systems is responsible for the neuronal injury, and it is proposed that a similar network disturbance is responsible for the psychotomimetic effects of NMDA antagonists, and might also be involved in the pathophysiology of schizophrenia. In the present study we present evidence that serotonergic agents possessing 5HT<sub>2A</sub> agonist activity prevent NMDA antagonist neurotoxicity in rat brain. It is*

*proposed that 5HT<sub>2A</sub> agonists may also prevent the psychotomimetic effects of NMDA antagonists. Among the 5HT<sub>2A</sub> agonists examined and found to be neuroprotective are LSD and related hallucinogens. The apparent contradiction in proposing that these agents might have antipsychotic properties is resolved by evidence linking their hallucinogenic activity to agonist action at 5HT<sub>2C</sub> receptors, whereas antipsychotic activity would be attributable to agonist action at 5HT<sub>2A</sub> receptors.*

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Phencyclidine (PCP) and ketamine cause a schizophrenia-like psychosis and cognitive impairments in normal humans (Luby et al. 1959; Rosenbaum et al. 1959; Cohen et al. 1962; Krystal et al. 1994; Newcomer et al. 1996), and a return to the acute exacerbated state in patients with chronic stabilized schizophrenia (Ban et al. 1961; Luby et al. 1962; Lahti et al. 1995). The discovery that

these agents are noncompetitive antagonists of the NMDA subtype of glutamate receptor (Lodge and Anis 1982; Lodge et al. 1987) has led to the hypothesis that suppression or disruption of NMDA receptor activity is psychotogenic, and to the proposal that NMDA receptor hypofunction (NRH) is a candidate mechanism to explain symptom formation in schizophrenia (Olney 1988; Javitt and Zukin 1991; Olney and Farber 1995b). More recently it has been found that PCP and various other NMDA receptor antagonists, which trigger psychotic reactions in humans, also induce cytopathological changes in cerebrocortical neurons in the adult rat brain (Olney et al. 1989; Ellison and Switzer 1993; Ellison 1994; Fix et al. 1993; Fix et al. 1995; Corso et al. 1997). Based upon several lines of evidence we have hypothesized (Olney and Farber 1995b) that a common mechanism may underlie both the neurotoxic and psychotogenic actions of NMDA antagonists, and that this

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may be a complex mechanism involving not only a primary disruption of a major excitatory transmitter system (NMDA glutamate system), but a secondary impairment in at least one other major transmitter system (GABA<sub>A</sub> inhibitory system). If a common mechanism underlies the neurotoxic and psychotogenic actions of NMDA antagonists in rats and humans respectively, and the human psychosis induced by these agents has a schizophrenia-like quality, further elucidation of the specific transmitter receptor disturbances, that contribute to the NMDA antagonist neurotoxic syndrome in rats, may provide valuable clues to the complex transmitter disturbances that contribute to symptom formation in schizophrenia. With this prospect in mind, we have evaluated various neuroactive agents, including known and putative antipsychotic agents, for their ability to protect against NRH-induced neurotoxicity in rats. We have found that both traditional (for example, loxapine, haloperidol, and thioridazine) and novel (for example, clozapine and olanzapine) antipsychotics protect against NRH-induced neurotoxicity. However, the novel agents are approximately an order of magnitude more effective than the traditional agents in preventing the neurotoxic reaction (Farber et al. 1993; Farber et al. 1996). This is of considerable interest since the novel agents, through unknown mechanisms, appear to have a superior clinical profile in the treatment of schizophrenia.

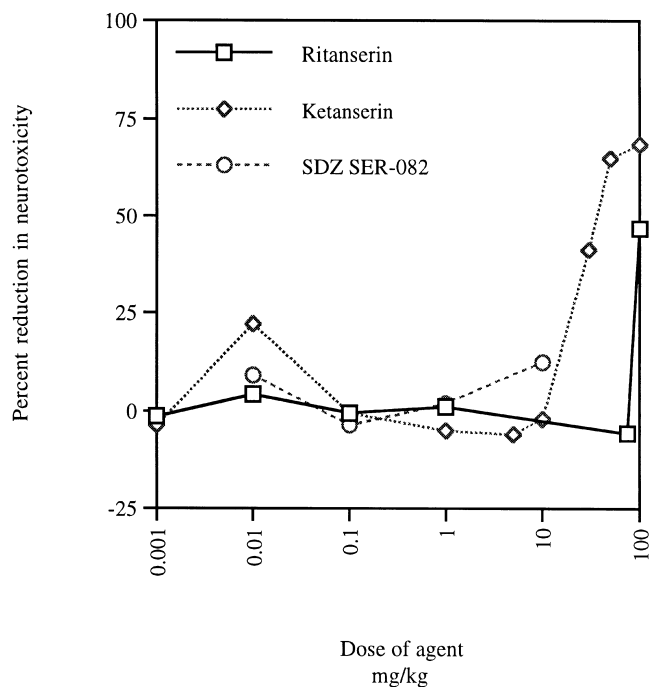
Several mechanisms, including antagonism of serotonin (5HT) receptors, have been proposed to explain clozapine's unique clinical profile. Recent advances in molecular pharmacology have led to the reclassification of the serotonergic system into several distinct receptor types (Martin and Humphrey 1994). The 5HT<sub>2</sub> receptor is now recognized to be a family containing three separate molecular subtypes of receptors, two of which (5HT<sub>2A</sub> [previously named 5HT<sub>2</sub>] and 5HT<sub>2C</sub> [previously named 5HT<sub>1C</sub>]) are considered potentially relevant to clozapine's efficacy in treating schizophrenia (Hoenicke et al. 1992; Schmidt et al. 1995). Given the potential involvement of 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors in schizophrenia, and in the therapeutic actions of clozapine, we undertook the present study to explore the role of 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors in NRH-induced neurotoxicity.

## METHODS

Adult female Sprague Dawley rats were injected intraperitoneally (ip) with a test agent followed, 15 minutes later, by an injection of MK-801 (0.5 mg/kg) subcutaneously (sc). Control animals ( $n = 88$ ) received either dimethyl sulfoxide or saline, the vehicles used to dissolve the test agents, and MK-801 (0.5 mg/kg sc). For each test agent, at least 20 rats were used and at least 4 doses tested. The animals were sacrificed 4 hours after exposure to MK-801 and the severity of damage assessed by

previously described methods (Olney et al. 1989; Farber et al. 1995). In a second set of experiments designed to further clarify the receptor site of action of the neuroprotective drugs, adult female rats ( $n = 70$ ) received MK-801 (0.5 mg/kg sc) plus the 5HT<sub>2A/2C</sub> agonist DOI (ip) at one of several doses, and a fixed dose of either the 5HT<sub>2A/2C</sub> antagonist ritanserin (0.03 mg/kg ip) or the selective 5HT<sub>2C</sub> antagonist SDZ SER-082 (0.1 mg/kg ip). Results were analyzed by ANCOVA using the dose of DOI as the covariate and the treatment condition (ritanserin or SDZ SER-082) as the between subjects factor.

The Research Technology Branch of the National Institute on Drug Abuse provided ( $\pm$ )-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), ( $\pm$ )-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), and d-lysergic acid diethylamide (LSD). Research Biochemical International was the source of ( $\pm$ )-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), R(+)-lisuride, and ketanserin. Ritanserin and SDZ SER-082 were gener-



**Figure 1.** Inability of various 5HT<sub>2</sub> antagonists to prevent MK-801 neurotoxicity. Data points represent the percent reduction in neurotoxicity for ritanserin, ketanserin, and SDZ SER-082. Neither ritanserin nor ketanserin show consistent protection in the dose range (0.01–1 mg/kg) where their serotonergic activity predominates. Supra-serotonergic doses of ketanserin are effective at blocking MK-801 neurotoxicity with an ED<sub>50</sub> of approximately 40 mg/kg. Ritanserin at extremely high doses also provides some mild but fleeting protection. SDZ SER-082, a more selective 5HT<sub>2C</sub> antagonist, provides little or no protection over the dose range tested (0.01–10 mg/kg).

**Table 1.** Efficacy of 5HT<sub>2A</sub> Agonists in Blocking MK-801 Neurotoxicity

Test Compound	ED <sub>50</sub> (mg/kg ip)	Confidence Limits (25th & 75th Percentiles)
Lisuride	0.17	(0.03–0.85)
DOB	0.36	(0.17–0.79)
LSD	0.67	(0.13–3.46)
DOM	0.81	(0.27–2.39)
DOI	0.98	(0.37–2.57)

ously provided by Janssen Pharmaceuticals and San-  
doz, respectively.

**RESULTS**

**Combined 5HT<sub>2A/2C</sub> Antagonists**

Ritanserin, a nonspecific 5HT<sub>2A/2C</sub> antagonist, administered at several doses between 0.001 mg/kg and 100 mg/kg (*n* = 34), showed no consistent evidence for protection against NRH-induced neurotoxicity (Fig. 1). However, at the extreme dose of 100 mg/kg it did show a moderate degree of protection (approximately 50%) while

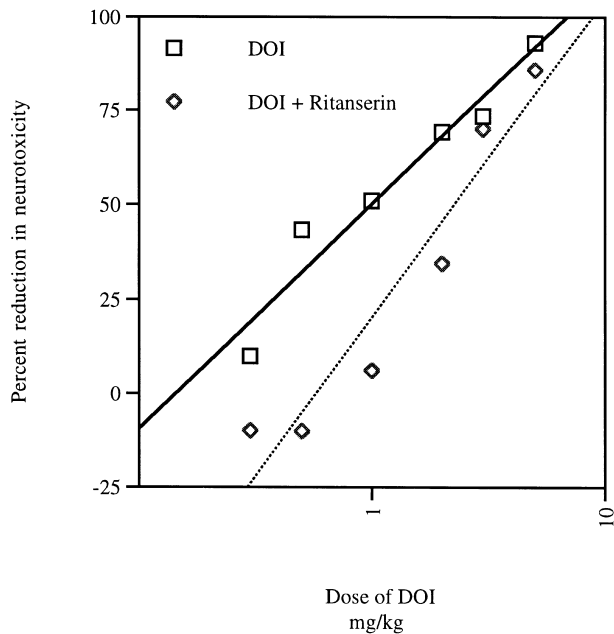
even higher doses were less effective (data not shown). The nonspecific 5HT<sub>2A/2C</sub> antagonist ketanserin (*n* = 33) also provided minimal to no protection over a broad range of dosages (0.001–10 mg/kg). At substantially higher doses ( $\geq 30$  mg/kg; *n* = 18), where it would be binding to other receptors, possibly muscarinic (Leysen et al. 1981), it did consistently protect against MK-801 neurotoxicity with an ED<sub>50</sub> of approximately 40 mg/kg (Fig. 1).

**Combined 5HT<sub>2A/2C</sub> Agonists**

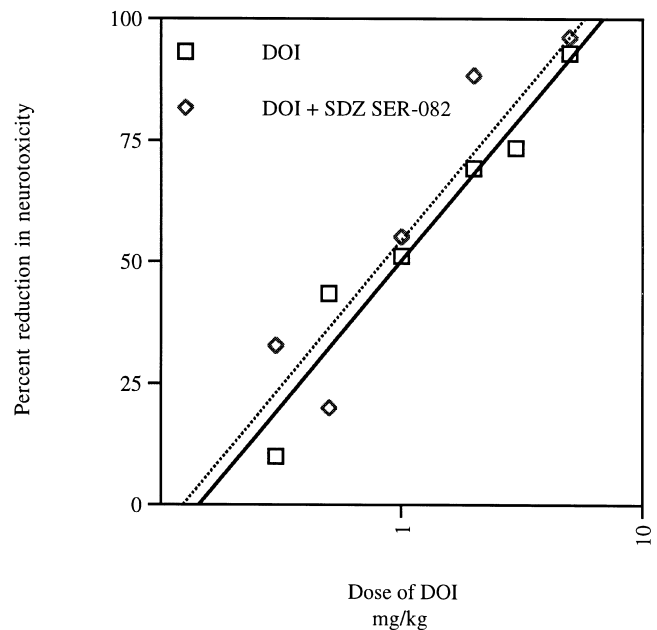
DOI (*n* = 73), DOB (*n* = 48), DOM (*n* = 28) and LSD (*n* = 55), all 5HT<sub>2A/2C</sub> agonists, dose dependently prevented MK-801 neurotoxicity. DOB was the most potent with an ED<sub>50</sub> of 0.36 mg/kg (Table 1). LSD, DOM, and DOI were also effective but slightly less potent with ED<sub>50</sub>s of 0.67 mg/kg, 0.81 mg/kg, and 0.98 mg/kg, respectively (Table 1).

**Reversal of DOI's Protection by Ritanserin**

To further confirm the involvement of the 5HT<sub>2A/2C</sub> receptor system, a fixed dose of ritanserin (0.03 mg/kg ip) was administered together with various doses of DOI to MK-801-treated rats (*n* = 36) to see if ritanserin would



**Figure 2.** Inhibition by ritanserin of DOI's protection against MK-801 neurotoxicity. Data points represent the percent reduction in neurotoxicity. DOI, a 5HT<sub>2A/2C</sub> agonist, dose-dependently prevents the neurotoxic effect of MK-801. Ritanserin, a 5HT<sub>2A/2C</sub> antagonist, significantly interferes with DOI's protection [*F*(1,100) = 25.95, *p* < 0.0005] as is indicated by shifting of the dose-response curve to the right. *Squares*: MK-801 (0.5 mg/kg) plus DOI. *Diamonds*: MK-801 (0.5 mg/kg) plus DOI plus ritanserin (0.03 mg/kg).



**Figure 3.** Inability of SDZ SER-082 to inhibit DOI's protection against MK-801 neurotoxicity. Data points represent the percent reduction in neurotoxicity. DOI, a 5HT<sub>2A/2C</sub> agonist, dose-dependently prevents the neurotoxic effect of MK-801. SDZ SER-082, a 5HT<sub>2C</sub> antagonist, is unable to interfere with DOI's protection [*F*(1,98) = 0.43, *p* = 0.5] as is indicated by the two curves being superimposed. *Squares*: MK-801 (0.5 mg/kg) plus DOI. *Diamonds*: MK-801 (0.5 mg/kg) plus DOI plus SDZ SER-082 (0.1 mg/kg).

reverse DOI's protection. Consistent with the hypothesis that the 5HT<sub>2A/2C</sub> system is the site of DOI's protective action, ritanserin significantly ( $p < 0.0005$ ) shifted DOI's protection curve to the right in a manner consistent with a competitive interaction (Fig. 2). Similar findings were seen with ritanserin + LSD ( $n = 4$ ) and ketanserin + DOI ( $n = 5$ ), but full dose response data were not generated (data not shown). Confirming our impression that ketanserin's protective action against MK-801 neurotoxicity is not due to its 5HT<sub>2A/2C</sub> activity, the dose of ketanserin (0.03 mg/kg ip) that reversed DOI's protection is 3 orders of magnitude lower than the dose of ketanserin ( $\geq 30$  mg/kg) required to appreciably block MK-801's neurotoxic effect.

### 5HT<sub>2A</sub> vs. 5HT<sub>2C</sub> Receptor

To explore initially whether the protection provided by LSD, DOI, DOB, and DOM can be attributed to activity at the 5HT<sub>2A</sub> receptor, the 5HT<sub>2C</sub> receptor, or both, we tested the LSD analog lisuride, which has been reported to be a 5HT<sub>2A</sub> agonist, but a 5HT<sub>2C</sub> antagonist (Burriss et al. 1991). Lisuride ( $n = 45$ ) also potentially protected against MK-801's neurotoxic action (Table 1), indicating that the 5HT<sub>2A</sub> receptor might be the site of action for lisuride and the several 5HT<sub>2A/2C</sub> agonists as well. To determine if agonism at 5HT<sub>2C</sub> receptors could contribute also to the protection against the neurotoxic effects of MK-801, we tested whether SDZ SER-802, a selective 5HT<sub>2C</sub> antagonist, could inhibit DOI's blocking action. Consistent with the hypothesis that 5HT<sub>2A</sub> receptor interaction is solely responsible for the neuroprotective action of these agents, SDZ SER-082 (0.1 mg/kg ip;  $n = 34$ ) was ineffective ( $p = 0.5$ ) in reversing DOI's blocking action (Fig. 3). When used alone and across a wide dose range, SDZ SER-082 ( $n = 22$ ) did not affect MK-801 neurotoxicity (Fig. 1).

## DISCUSSION

Accumulating evidence (reviewed in Olney and Farber 1995a and b; Farber et al. 1997; Kim et al. 1997) suggests that NMDA antagonist neurotoxicity is mediated by an indirect mechanism involving disturbances in multiple transmitter receptor systems subserving a complex neural network in which major excitatory pathways are ordinarily held under inhibitory restraint by glutamate acting tonically at NMDA receptors on inhibitory (GABAergic or noradrenergic) neurons. Blockade of these NMDA receptors inactivates the inhibitory mechanism thereby disinhibiting the excitatory pathways, and unleashing excitotoxic activity that serves as the proximal cause of neuronal injury. Given evidence for serotonergic innervation of GABAergic interneurons via 5HT<sub>2A</sub> receptors (Mengod et al. 1990; Sheldon and Aghajanian 1990; Cor-

nea-Hebert et al. 1996; Mathews et al. 1996; Shen and Andrade 1996), we postulate that a 5HT<sub>2A</sub> receptor is located on one or more of the GABAergic neurons in the NRH neurotoxicity circuit, and that activation of this receptor by the 5HT<sub>2A</sub> agonist restores inhibition to the network and prevents neuronal injury. A potentially important implication of our findings is that 5HT<sub>2A</sub> agonists could be used to prevent the neurotoxic side effects of NMDA antagonists, thus improving the safety of NMDA antagonists for the treatment of nervous system conditions such as stroke, trauma, and neuropathic pain. In addition, if a common mechanism does underlie the neurotoxic and psychotomimetic effects of NMDA antagonists, then coadministration of a selective 5HT<sub>2A</sub> agonist with an NMDA antagonist could also prevent the psychotomimetic effects of NMDA antagonists.

It seems contradictory to propose that drugs such as LSD and its analogs, which are notorious hallucinogens, might possess properties that could counteract the psychosis induced by PCP and other NMDA antagonists. However, this is a reasonable proposal when viewed in light of the findings of Burriss et al. (1991) that agonist action at 5HT<sub>2C</sub> receptors is responsible for the hallucinogenic effects of LSD. Our evidence, when taken together with the findings of Burriss et al. (1991), suggests that stimulation of 5HT<sub>2C</sub> receptors may promote one type of psychotic activity (LSD hallucinosis), and stimulation of 5HT<sub>2A</sub> receptors may suppress another type (PCP psychosis). Perhaps this might explain the findings that PCP exacerbates a schizophrenic psychosis, and LSD does not (Erard et al. 1980; Domino and Luby 1981). For further clarification it will be important to evaluate drugs that are selective 5HT<sub>2A</sub> antagonists or agonists. Similar studies of agonists and antagonists specific for the 5HT<sub>2C</sub> receptor would also be of benefit. Since LSD has significant affinity not only for 5HT<sub>2A</sub> and 5HT<sub>2C</sub> receptors but for the recently described 5ht<sub>5A</sub>, 5ht<sub>5B</sub>, 5ht<sub>6</sub> and 5ht<sub>7</sub> receptors (Martin and Humphrey 1994), the potential involvement of all such receptors should be explored once selective ligands become available.

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