Effects of dextromethorphan on dopamine dependent behaviours in rats

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Dextromethorphan, a noncompetitive blocker of N-methyl-D-aspartate (NMDA) type of glutamate receptor, at 7.5-75 mg/kg, ip did not induce oral stereotypes or catalepsy and did not antagonize apomorphine stereotype in rats. These results indicate that dextromethorphan at 7.5-75 mg/kg does not stimulate or block postsynaptic striatal D2 and D1 dopamine (DA) receptors. Pretreatment with 15 and 30 mg/kg dextromethorphan potentiated dexamphetamine stereotype and antagonised haloperidol catalepsy. Pretreatment with 45, 60 and 75 mg/kg dextromethorphan, which release 5-hydroxytryptamine (5-HT), however, antagonised dexamphetamine stereotype and potentiated haloperidol catalepsy. Apomorphine stereotype was not potentiated or antagonised by pretreatment with 7.5-75 mg/kg dextromethorphan. This respectively indicates that at 7.5-75 mg/kg dextromethorphan does not exert facilitatory or inhibitory effect at or beyond the postsynaptic striatal D2 and D1 DA receptors. The results are explained on the basis of dextromethorphan (15-75 mg/kg) – induced blockade of NMDA receptors in striatum and substantia nigra pars compacta. Dextromethorphan at 15 and 30 mg/kg, by blocking NMDA receptors, activates nigrostriatal dopaminergic neurons and thereby potentiates dexamphetamine stereotype and antagonizes haloperidol catalepsy. Dextromethorphan at 45, 60 and 75 mg/kg, by blocking NMDA receptors, releases 5-HT and through the released 5-HT exerts an inhibitory influence on the nigrostriatal dopaminergic neurons with resultant antagonism of dexamphetamine stereotype and potentiation of haloperidol catalepsy.

Keywords: Apomorphine, Catalepsy, Dexamphetamine, Dextromethorphan, Haloperidol, Rat, Stereotypy

The antitussive drug dextromethorphan is a noncompetitive blocker of the N-methyl-D-aspartate (NMDA) type of glutamate receptor1,2. In rats, high doses of dextromethorphan (45-90 mg/kg, ip) cause a rapid release of 5-hydroxytryptamine (5-HT, serotonin) from central serotonergic neurons and induce a dose–dependent degree of the postsynaptic 5-HT1A receptor mediated behavioural syndrome characterized by reciprocal forepaw treading, lateral head-weaving, hind-limb abduction and flat body posture3. Further, based on these findings and the reports of Becquet et al.4 and Whitton et al.5, it was suggested that dextromethorphan may be releasing 5-HT by blocking the NMDA receptors and thereby counteracting the inhibitory influence of glutamate on 5-HT release.

The corpus striatum and the substantia nigra receive glutamatergic innervation from the cerebral cortex6,7 and serotonergic innervation from the midbrain raphe nuclei8. Glutamate, via activation of the NMDA receptors, inhibits the synthesis and release of dopamine (DA) from the nigrostriatal dopaminergic neurons9-11 while 5-HT, by stimulating the 5-HT2C receptors, decreases the synthesis and release of DA from the nigrostriatal dopaminergic neurons12,13.

Behavioural studies in animals indicate a functional interaction between the central glutamatergic and nigrostriatal dopaminergic systems6,7 and between the central serotonergic and nigrostriatal dopaminergic systems8. Drugs enhancing or reducing central glutamatergic and central serotonergic neurotransmission modulate the intensity of behaviours dependent on the functional status of the nigrostriatal dopaminergic system viz neuroleptic-induced catalepsy and DA agonist-induced stereotyped behaviour (SB). Haloperidol-induced catalepsy was potentiated by subconvulsant doses of NMDA administered ip14 and was antagonised by the noncompetitive NMDA receptor antagonist dizocilpine (MK-801)14-17. Haloperidol-induced catalepsy was enhanced by clomipramine, a 5-HT uptake inhibitor, quipazine, a directly acting 5-HT agonist and dexfenfluramine, a 5-HT releaser18,19 and was reduced by the 5-HT2A/2C receptor antagonists methysergide18 and trazodone20. Amphetamine

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induced SB was potentiated by trazodone and methysergide and was antagonised by dexfenfluramine and l-tryptophan, a precursor of 5-HT.

The observations that, dextromethorphan is a noncompetitive NMDA receptor antagonist and at high doses releases 5-HT, prompted us to investigate in rats the effects of pretreatment with a wide dose range of dextromethorphan on haloperidol-induced catalepsy and on dexamphetamine and apomorphine induced oral stereotypies characterized by biting, gnawing or licking behaviour. Furthermore, we have investigated whether dextromethorphan induces catalepsy in rats.

Materials and Methods

Animals — Male Wistar rats (weighing 100-180 g), bred in Central Animal House facility of the Institute, were used. The animals were housed under standard conditions, maintained on a 12 hr light/dark cycle and had free access to food and water up to the time of experimentation. The animals were brought to the department and kept in a noiseless diffusely illuminated laboratory, at least 1 hr before the experiments for acclimatization to the laboratory environment. Animals were randomly distributed into groups of 10 animals each. Each animal was used only once. For observation of SB, the rats were placed in individual cages made of wire netting, measuring 30×20×20 cm. For observation and measurement of catalepsy the rats were placed in individual Perspex cages (30×20×20 cm). The rats were placed in the cages 30 min before drug treatment for adaptation to their new environment. All observations were made between 1000 and 1600 hrs at 27°-30°C. Observations were made blind with respect to the treatments used. The experimental protocols were approved by the Institutional Animal Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals.

Drugs — Drugs used were dextromethorphan hydrobromide (Nicholas Piramal, India), dexamphetamine sulfate (Koch-light, UK), apomorphine hydrochloride (Sigma, USA), and haloperidol (‘Senorm’ injection, Sun Pharmaceuticals, India). Dextromethorphan and dexamphetamine were dissolved in distilled water while apomorphine was dissolved in distilled water containing 0.2 mg/ml ascorbic acid. Haloperidol injection solution was diluted to required strength with distilled water. All drug solutions were prepared immediately before use and were injected ip in a volume of 2 ml/kg body weight except dextromethorphan which was injected in a volume of 5 ml/kg body weight. Doses refer to the forms mentioned. Drug doses and the testing time intervals were selected based on previous studies conducted in the laboratory and those reported in literature.

Dexamphetamine and apomorphine-induced SB in rats — Following administration of dexamphetamine (5 and 10 mg/kg) or apomorphine (1.5 and 3 mg/kg), the intensity of SB was assessed over a 30 sec observation period at 10 min intervals, using the scoring system of Costall and Naylor where periodic sniffing = score 1, continuous sniffing = 2, periodic biting, gnawing or licking = 3 and continuous biting, gnawing or licking = 4. Inter-rater reliability was calculated from those simultaneous ratings made by two of the authors using the Pearson product-moment correlation (r). Inter-rater correlation coefficient r was found to be 0.96, indicating a high degree of inter-rater agreement. The cumulative stereotyped rating for each animal was determined as the sum of each 10 min score for 180 min for dexamphetamine-induced SB or 90 min for apomorphine-induced SB. The cumulative stereotypy score of each rat in the group was taken to compute the median value of the group. Dextromethorphan (7.5-75 mg/kg) or haloperidol (0.5 mg/kg) was injected 1 hr before dexamphetamine or apomorphine. Control groups for dextromethorphan and haloperidol received 5 and 2 ml/kg body weight of distilled water ip respectively, 1 hr before receiving the DA agonists.

Catalepsy testing in rats — Animals were tested for catalepsy according to the method of Costall and Naylor by placing both front paws of the animal over an 8 cm high horizontal bar. The time elapsing between paw placement and the first movement of either paw (descent latency) was measured in sec. Animals were tested and evaluated for catalepsy 1, 2, 3 and 4 hr after ip injection of dextromethorphan (7.5-75 mg/kg), haloperidol (1 mg/kg) or distilled water (5 ml/kg body weight, control group). Catalepsy score (descent latency) in sec of each animal in the group, at the respective testing time interval, was taken to compute the mean value of the group for that particular timing. Furthermore, the animals whose catalepsy score was more than 10 sec were considered to be cataleptic.
Haloperidol-induced catalepsy in rats—Dextromethorphan (7.5–75 mg/kg) was injected 1 hr before haloperidol (0.5 and 1 mg/kg). Control groups received 5 ml/kg body weight of distilled water ip 1 hr before receiving haloperidol. Animals were tested and evaluated for catalepsy 1 and 2 hr after haloperidol treatment in the same manner as stated in the section “Catalepsy testing in rats”. Catalepsy score (descent latency) in sec of each animal in the group, at the respective testing time interval, was taken to compute the mean value of the group for that particular timing.

Statistical analysis — The results of stereotypy studies were evaluated statistically by the two-tailed Mann-Whitney U-test for non-parametric data using the individual cumulative stereotypy score. The results of catalepsy studies were analysed by the two-tailed Student’s unpaired t-test. The level of statistical significance chosen was \( P < 0.05 \).

Results

During preliminary studies it was observed that animals treated with 7.5, 15 and 30 mg/kg ip doses of dextromethorphan did not exhibit oral stereotypies or any feature of the postsynaptic 5-HT1A receptor mediated behavioural syndrome and appeared the same as distilled water (5 ml/kg body weight, ip) treated control animals. Animals receiving 45, 60, 75 and 90 mg/kg, ip doses of dextromethorphan did not exhibit oral stereotypies. The animals, however, as reported earlier, did exhibit the postsynaptic 5-HT1A receptor mediated behaviours in a dose-dependent manner. The behaviours usually manifested about 15 min after drug administration and wore off by 1 hr. As at 90 mg/kg dose dextromethorphan had produced ataxia, muscular hypotonia, motor incoordination and 20 % mortality (n = 10), for subsequent interaction studies dextromethorphan was used in the dose range of 7.5 to 75 mg/kg, ip.

Effect of dextromethorphan and haloperidol pretreatment on dexamphetamine and apomorphine induced SB in rats (Table 1) — Dexamphetamine (5 and 10 mg/kg) induced dose-dependent SB. Pretreatment with 7.5 mg/kg dextromethorphan did not significantly affect dexamphetamine (5 and 10 mg/kg) induced SB. Pretreatment with 15 and 30 mg/kg dextromethorphan significantly increased the intensity of the SB induced by 5 and 10 mg/kg dexamphetamine. However, pretreatment with 45, 60 and 75 mg/kg dextromethorphan significantly decreased the intensity of dexamphetamine (5 and 10 mg/kg) induced SB. Pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 5 mg/kg dexamphetamine and significantly decreased the intensity of the SB induced by 10 mg/kg dexamphetamine.

Apomorphine (1.5 and 3 mg/kg) induced dose-dependent SB. Pretreatment with dextromethorphan (7.5 to 75 mg/kg) did not significantly influence apomorphine (1.5 and 3 mg/kg)-induced SB. However, pretreatment with 0.5 mg/kg haloperidol abolished the SB induced by 5 mg/kg dexamphetamine and significantly decreased the intensity of the SB induced by 10 mg/kg dexamphetamine.

Table 1 — Effect of dextromethorphan and haloperidol pretreatment on the intensity of stereotyped behaviour induced by dexamphetamine and apomorphine in rats

<table>
<thead>
<tr>
<th>Pretreatment (mg/kg, ip)</th>
<th>Dexamphetamine (mg/kg, ip)</th>
<th>Apomorphine (mg/kg, ip)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Distilled water</td>
<td>20.5 (18–22)</td>
<td>37.0 (34–39)</td>
</tr>
<tr>
<td>Dextromethorphan (7.5)</td>
<td>21.5 (17–23)</td>
<td>38.0 (33–40)</td>
</tr>
<tr>
<td>Dextromethorphan (15)</td>
<td>24.0 (22–26)</td>
<td>40.5 (38–43)</td>
</tr>
<tr>
<td>Dextromethorphan (30)</td>
<td>28.0 (26–30)</td>
<td>44.5 (42–47)</td>
</tr>
<tr>
<td>Dextromethorphan (45)</td>
<td>17.5 (15–19)</td>
<td>34.0 (31–36)</td>
</tr>
<tr>
<td>Dextromethorphan (60)</td>
<td>13.5 (11–15)</td>
<td>30.0 (27–32)</td>
</tr>
<tr>
<td>Dextromethorphan (75)</td>
<td>10.5 (8–12)</td>
<td>27.0 (24–29)</td>
</tr>
<tr>
<td>Distilled water</td>
<td>21.0 (18–23)</td>
<td>37.5 (34–40)</td>
</tr>
<tr>
<td>Haloperidol (0.5)</td>
<td>0.0</td>
<td>14.5 (11–17)</td>
</tr>
</tbody>
</table>

P values: \( ^a < 0.05 \); \( ^b < 0.02 \); \( ^c < 0.01 \); \( ^d < 0.001 \) as compared to respective distilled water pretreated control dexamphetamine group by Mann-Whitney’s U-test.

Note: Results of dextromethorphan pretreatment on apomorphine-induced stereotyped behaviour were analysed for statistical significance and found to be non-significant (\( P > 0.05 \) as compared to respective distilled water pretreated control apomorphine group by Mann-Whitney’s U-test).
Induction of catalepsy in rats —

Dextromethorphan (7.5 to 75 mg/kg) and distilled water (5 ml/kg) treated rats were considered not to exhibit catalepsy as the catalepsy score of these animals did not exceed 3 sec at any of the testing time intervals. The mean values with SE of these groups ranged from 2.1±0.10 to 2.3±0.15 sec and did not differ significantly from one another at any of the testing time intervals (data not shown). However, all animals (n=10) treated with 1 mg/kg haloperidol had a catalepsy score of more than 10 sec at each testing time interval and hence were considered to be cataleptic.

Effect of dextromethorphan pretreatment on haloperidol – induced catalepsy in rats (Table 2) —

Pretreatment with 7.5 mg/kg dextromethorphan did not significantly affect the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2 hr testing time intervals, while pretreatment with 15 and 30 mg/kg dextromethorphan significantly decreased the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2 hr testing time intervals. However, pretreatment with 45, 60 and 75 mg/kg dextromethorphan significantly increased the cataleptic effect of 0.5 and 1 mg/kg haloperidol at both 1 and 2 hr testing time intervals.

Table 2 — Effect of dextromethorphan (DMP) pretreatment on haloperidol (HAL) induced catalepsy in rats

<table>
<thead>
<tr>
<th>Treatment (mg/kg, ip)</th>
<th>Catalepsy score (descent latency in seconds)</th>
<th>at 1 hr</th>
<th>at 2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>DW + HAL (0.5)</td>
<td></td>
<td>35.1 ± 1.39</td>
<td>29.0 ± 1.28</td>
</tr>
<tr>
<td>DMP (7.5) + HAL (0.5)</td>
<td></td>
<td>33.0 ± 1.35</td>
<td>26.9 ± 1.25</td>
</tr>
<tr>
<td>DMP (15) + HAL (0.5)</td>
<td></td>
<td>29.4 ± 1.26</td>
<td>23.3 ± 1.23</td>
</tr>
<tr>
<td>DMP (30) + HAL (0.5)</td>
<td></td>
<td>23.6 ± 1.22c</td>
<td>17.5 ± 1.19c</td>
</tr>
<tr>
<td>DMP (45) + HAL (0.5)</td>
<td></td>
<td>40.7 ± 1.40c</td>
<td>34.6 ± 1.36c</td>
</tr>
<tr>
<td>DMP (60) + HAL (0.5)</td>
<td></td>
<td>43.2 ± 1.44b</td>
<td>37.1 ± 1.38b</td>
</tr>
<tr>
<td>DMP (75) + HAL (0.5)</td>
<td></td>
<td>46.5 ± 1.48c</td>
<td>40.4 ± 1.42c</td>
</tr>
<tr>
<td>DW + HAL (1)</td>
<td></td>
<td>58.7 ± 1.59</td>
<td>52.5 ± 1.53</td>
</tr>
<tr>
<td>DMP (7.5) + HAL (1)</td>
<td></td>
<td>56.6 ± 1.55</td>
<td>50.4 ± 1.49</td>
</tr>
<tr>
<td>DMP (15) + HAL (1)</td>
<td></td>
<td>53.0 ± 1.51b</td>
<td>46.8 ± 1.47a</td>
</tr>
<tr>
<td>DMP (30) + HAL (1)</td>
<td></td>
<td>47.2 ± 1.42c</td>
<td>41.0 ± 1.43c</td>
</tr>
<tr>
<td>DMP (45) + HAL (1)</td>
<td></td>
<td>64.3 ± 1.61a</td>
<td>58.1 ± 1.56a</td>
</tr>
<tr>
<td>DMP (60) + HAL (1)</td>
<td></td>
<td>66.8 ± 1.64b</td>
<td>60.6 ± 1.60b</td>
</tr>
<tr>
<td>DMP (75) + HAL (1)</td>
<td></td>
<td>70.1 ± 1.73c</td>
<td>63.9 ± 1.62c</td>
</tr>
</tbody>
</table>

P values: ^a<0.05; ^b<0.01; ^c<0.001 as compared to the respective distilled water pretreated control haloperidol group, at the respective testing time interval, by Student’s unpaired t-test.

DW = Distilled water (5 ml/kg, ip).

Discussion

Apomorphine in high doses elicits oral stereotypies in rats by directly stimulating the postsynaptic striatal D2 and D1 DA receptors. The intensity of apomorphine stereotypy therefore depends on the functional status of the postsynaptic striatal D2 and D1 DA receptors. High doses of dexamphetamine induce oral stereotypies in rats by releasing DA from the nigrostriatal dopaminergic neurons with resultant activation by the released DA of postsynaptic striatal D2 and D1 DA receptors. The intensity of dexamphetamine stereotypy therefore depends on the synthesis of DA and the intraneuronal stores of DA available for release by dexamphetamine, in addition to the functional status of the postsynaptic striatal D2 and D1 DA receptors.

In the present study, treatment with dextromethorphan (7.5 to 75 mg/kg) did not induce oral stereotypies in rats. This indicates that dextromethorphan at 7.5 to 75 mg/kg does not stimulate the postsynaptic striatal D2 and D1 DA receptors either directly or indirectly by releasing DA from the nigrostriatal dopaminergic neurons. Further, treatment with 7.5 to 75 mg/kg dextromethorphan did not induce catalepsy, and pretreatment with these doses of dextromethorphan failed to antagonize apomorphine–induced oral stereotypy in rats. This indicates that at 7.5 to 75 mg/kg dextromethorphan does not exert postsynaptic striatal D2 and D1 DA receptor blocking activity.

Pretreatment with dextromethorphan (15 to 75 mg/kg) however, did significantly influence dexamphetamine stereotypy and haloperidol catalepsy in rats. Dextromethorphan, at 15 and 30 mg/kg doses, which do not release 5-HT as evident by their failure to induce the postsynaptic 5-HT1A receptor mediated behaviours in rats, potentiated dexamphetamine stereotypy and antagonised haloperidol catalepsy in rats.
rats. Dextromethorphan, at 45, 60 and 75 mg/kg doses, which release 5-HT and induce the postsynaptic 5-HT1A receptor mediated behaviours in rats, antagonised dexamphetamine stereotypy and potentiated haloperidol catalepsy in rats. Since pretreatment with 15 and 30 mg/kg dextromethorphan had not potentiated apomorphine stereotypy, it suggests that potentiation of dexamphetamine stereotypy and antagonism of haloperidol catalepsy by 15 and 30 mg/kg dextromethorphan is not due to any facilitatory effect of these doses of dextromethorphan at or beyond the postsynaptic striatal D2 and D1 DA receptor sites. Similarly, since pretreatment with 5-HT releasing doses of dextromethorphan viz, 45, 60 and 75 mg/kg had not antagonised apomorphine stereotypy it suggests that antagonism of dexamphetamine stereotypy and potentiation of haloperidol catalepsy by 5-HT releasing doses of dextromethorphan is not due to any inhibitory effect of these doses of dextromethorphan or the released 5-HT at or beyond the postsynaptic striatal D2 and D1 DA receptor sites.

Potentiation of dexamphetamine stereotypy and antagonism of haloperidol catalepsy by pretreatment with 15 and 30 mg/kg doses of dextromethorphan is explained on the basis of dextromethorphan being a noncompetitive NMDA receptor antagonist. In vivo biochemical studies have demonstrated that the noncompetitive NMDA receptor antagonist MK-801, by blocking the NMDA receptors in the striatum and substantia nigra pars compacta (SNc), causes activation of the nigrostriatal dopaminergic neurons with resultant increase in the synthesis and release of DA in the striatum. It is postulated that dextromethorphan, like the noncompetitive NMDA receptor antagonist MK-801, by blocking the NMDA receptors in the striatum and SNc causes activation of the nigrostriatal dopaminergic neurons. As a result, there is an increase in the synthesis of DA and hence in the intraneuronal stores of DA. As more intraneuronal stores of DA are available for release by dexamphetamine, there is a resultant potentiation of dexamphetamine stereotypy. Further, as more DA is available for release during the haloperidol-induced compensatory ‘feedback’ increase of nigrostriatal dopaminergic neuronal activity, the haloperidol-induced blockade of the postsynaptic striatal D2 and D1 DA receptors is counteracted to a greater extent, with the resultant antagonism of haloperidol catalepsy.

Antagonism of dexamphetamine stereotypy and potentiation of haloperidol catalepsy by the 5-HT releasing doses of dextromethorphan viz, 45, 60 and 75 mg/kg is explained as follows:

Glutamate exerts an inhibitory control on 5-HT release via stimulation of NMDA receptors. At higher doses (45, 60 and 75 mg/kg) dextromethorphan releases 5-HT by blocking the NMDA receptors and thereby counteracting the inhibitory influence of glutamate on 5-HT release.

In vivo microdialysis and electrophysiological studies have shown that 5-HT, via activation of 5-HT2C receptors, decreases the synthesis and release of DA from the nigrostriatal dopaminergic neurons. It is contended that 45, 60 and 75 mg/kg doses of dextromethorphan, through the released 5-HT, stimulate the 5-HT2C receptors and thereby decrease the synthesis of DA in the nigrostriatal dopaminergic neurons. Consequently, the stores of DA in the nigrostriatal dopaminergic neurons are decreased. As less DA is now available for release by dexamphetamine, there is antagonism of dexamphetamine stereotypy. Further, as less DA is available for release during the haloperidol-induced compensatory ‘feedback’ increase of nigrostriatal dopaminergic neuronal activity, the haloperidol-induced blockade of the postsynaptic striatal D2 and D1 DA receptors is counteracted to a lesser extent with resultant potentiation of haloperidol catalepsy.

The observation that pretreatment with 15 and 30 mg/kg dextromethorphan had antagonised haloperidol catalepsy concurs with the finding of Scotti de Carolis et al. that 15 and 30 mg/kg, ip doses of dextromethorphan, administered 15 min after injection of 1 mg/kg, ip haloperidol antagonised haloperidol-induced catalepsy. These authors however, had not studied on haloperidol-induced catalepsy the effect of treatment with higher doses of dextromethorphan which we did. In the present study the effect of pretreatment with higher 5-HT releasing doses of dextromethorphan viz, 45, 60 and 75 mg/kg has also been investigated on haloperidol catalepsy and observed that pretreatment with these doses of dextromethorphan had potentiated haloperidol catalepsy. This observation is in agreement with the finding of Thorat et al., that haloperidol catalepsy was potentiated by pretreatment with 5-HT releasing doses of dexfenfluramine.

Haloperidol-induced catalepsy is considered an experimental model of idiopathic Parkinson’s disease.
and drugs antagonizing haloperidol catalepsy relieve symptoms of Parkinson’s disease while drugs potentiating haloperidol catalepsy aggravate Parkinson’s disease. The present result demonstrates that dextromethorphan exerts dose-dependent opposite effects on haloperidol catalepsy. At lower 15 and 30 mg/kg ip doses dextromethorphan antagonizes haloperidol catalepsy and may therefore prove beneficial in the treatment of idiopathic Parkinson’s disease, while at higher 5-HT releasing doses (45, 60 and 75 mg/kg) it potentiates haloperidol catalepsy and may aggravate Parkinson’s disease. Findings of the present study indicate that the doses of dextromethorphan used for treatment of Parkinson’s disease will determine the outcome of treatment and may account for the conflicting clinical reports regarding the utility of dextromethorphan in the treatment of Parkinson’s disease. Though Bonuccelli et al. and Saenz et al., in open-label trials with small groups of idiopathic parkinsonian patients, found that dextromethorphan alone and as add-on therapy with l-dopa caused improvement in the symptoms of their patients and enhanced the motor improvement obtained with l-dopa, Montastruc et al. however, could not corroborate these findings. Montastruc et al. subsequently reviewed the literature to determine the effect of dextromethorphan treatment in parkinsonian patients. The authors have reported that controlled trials with dextromethorphan in small groups of parkinsonian volunteers failed to demonstrate conclusive symptomatic improvement.

Amphetamine-induced stereotyped behaviour in animals, because of its similarity to abnormal behaviour observed during amphetamine psychosis in humans and in schizophrenics, is considered to be one of the DA related animal models of paranoid schizophrenia. In the present study dextromethorphan had exerted dose-dependent opposite effects on dexamphetamine stereotypy. Pretreatment with lower doses of dextromethorphan viz, 15 and 30 mg/kg had potentiated dexamphetamine stereotypy while pretreatment with higher 5-HT releasing doses of dextromethorphan viz, 45, 60 and 75 mg/kg had antagonised dexamphetamine-induced stereotyped behaviour.

The NMDA hypofunction hypothesis of schizophrenia suggests that schizophrenia is due to excessive stimulation of striatal D2 DA receptors associated with deficient activity within the corticostriatal glutamatergic pathway with resultant deficiency of glutamate at NMDA receptors in striatum. Thus according to the NMDA hypofunction hypothesis of schizophrenia NMDA receptor agonists may prove beneficial in the treatment of schizophrenia, whereas NMDA receptor antagonists are likely to aggravate schizophrenia. The present finding, that pretreatment with lower doses of dextromethorphan viz 15 and 30 mg/kg, which by blocking NMDA receptors, activate nigrostriatal dopaminergic neurons and potentiate dexamphetamine stereotypy is supportive to the NMDA hypofunction hypothesis of schizophrenia. Further, the present observation that pretreatment with higher doses (45, 60 and 75 mg/kg) of dextromethorphan, which release 5-HT by blocking NMDA receptors and through the released 5-HT antagonise dexamphetamine stereotypy is in agreement with the finding of Thorat et al. that dexamphetamine stereotypy was antagonised by pretreatment with 5-HT releasing doses of dexfenfluramine. The present study indicates that, since dextromethorphan pretreatment exerts dose-dependent opposite effects on dexamphetamine stereotypy the effects of its administration in schizophrenic patients i.e. aggravation or amelioration of schizophrenic symptoms will depend on the doses of dextromethorphan which are administered to the schizophrenic patient.

Based on the present observations it is concluded that dextromethorphan at 7.5-75 mg/kg, ip doses neither stimulates nor blocks the postsynaptic striatal D2 and D1 DA receptors. The present study however, demonstrates that dextromethorphan exerts a dose-dependent opposite modulatory effect on the functioning of the nigrostriatal dopaminergic neurons. Dextromethorphan at lower doses (15 and 30 mg/kg, ip), by blocking NMDA receptors, activates the nigrostriatal dopaminergic neurons and thereby potentiates dexamphetamine stereotypy and antagonizes haloperidol catalepsy. Dextromethorphan however, at higher doses (45, 60 and 75 mg/kg, ip), by blocking NMDA receptors, releases 5-HT and through the released 5-HT exerts an inhibitory influence on the nigrostriatal dopaminergic neurons with resultant antagonism of dexamphetamine stereotypy and potentiation of haloperidol catalepsy. The present observations thus lend support to the reports stating that the corticoglutamatergic and the central serotonergic systems regulate the functioning of the nigrostriatal dopaminergic system and thereby
modulate the intensity of the behaviours dependent on the functional status of the nigrostriatal dopaminergic system.

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