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Stimulation of rat striatal tyrosine hydroxylase activity following intranigral administration of σ receptor ligands

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Abstract

The effects of σ ligands on turning behavior and striatal tyrosine hydroxylase activity were determined following microinjection of two chemically dissimilar σ ligands into the rat substantia nigra. Striatal tyrosine hydroxylase activty was monitored by measuring the amount of 3,4-dihydroxyphenylalanine (DOPA) formed following inhibition of DOPA decarboxylase activity with *m*-hydroxybenzylhydrazine (NSD-1015). The σ ligands, 1,3-di-*o*-tolylguanidine (DTG) and (−)-deoxy-*N*-benzylnormetazocine, produced a significant increase both in contralateral turning and in tyrosine hydroxylase activity. The DTG-induced increase in tyrosine hydroxylase activity was not antagonized by intranigral injection of the NMDA receptor antagonist, 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP). CPP alone produced significant contralateral turning that was not accompanied by an increase in striatal tyrosine hydroxylase activity, indicating that turning per se is not sufficient to activate striatal tyrosine hydroxylase. The DTG-induced increase in tyrosine hydroxylase activity was antagonized by general anesthetics such as halothane and chloral hydrate. These results indicate that occupancy of σ receptors in the substantia nigra is associated with an activation of dopamine formation in dopaminergic terminals in the striatum and support the concept that σ activity in the substantia nigra produces an activation of dopamine-mediated responses in the striatum.

Keywords: σ Receptor ligand; Tyrosine hydroxylase; Turning; Dopamine; DTG (1,3-di-*o*-tolylguanidine)

1. Introduction

Several lines of evidence suggest that occupancy of σ receptors in the rat substantia nigra produces an increase in dopamine-mediated responses in the striatum: (1) microinjection of σ ligands such as 1,3-di-*o*-tolylguanidine (DTG) into the rat substantia nigra produces contralateral turning (Walker et al., 1988, 1992), a motor behavior shown to be produced by activation of dopamine receptors in the striatum (Ungerstedt, 1971), (2) the turning produced by σ ligands is prevented when the nigrostriatal dopamine neurons are destroyed by prior treatment with the neurotoxic agent, 6-hydroxydopamine (Goldstein et al., 1989), and (3) microdialysis experiments have shown an increase in extracellular dopamine in the striatum following intraperitoneal injections of σ ligands such as DTG and (+)-pentazocine (Patrick et al., 1993; Gudelsky, 1993). Taken together, these data support the concept that σ receptor occupancy in the central nervous system can modulate dopaminergic control of motor activity.

Alterations in the above parameters can be viewed as useful indices of possible σ-induced functional changes occurring within the striatal dopaminergic nerve terminals. In order to obtain more direct evidence for a σ-induced change in the biochemistry of dopaminergic terminals we have measured the effects of intranigral σ ligand administration on the activity of tyrosine hydroxylase in the striatum. This activity was measured by determination of the accumulation of the tyrosine hydroxylase product, 3,4-dihydroxyphenylalanine (DOPA), following inhibition of DOPA decarboxylase activity with *m*-hydroxybenzylhydrazine

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(NSD-1015; Carlsson et al., 1972). Using this technique, it has been shown that an increase in nigrostriatal dopaminergic firing rate produces an increase in dopamine terminal tyrosine hydroxylase activity in the striatum (Murrin and Roth, 1976).

Previous electrophysiological studies of nigrostriatal firing rates have found either a very modest, or no increase in firing rate following acute peripheral administration of σ ligands such as (+)-pentazocine and DTG (Meltzer et al., 1992; Zhang et al., 1992). Since most electrophysiological studies use general anesthetics, we have examined the effects of several anesthetics on σ ligand-induced biochemical alterations to determine if anesthetics might alter the neuronal responsiveness to σ ligands. In addition, in light of previous studies suggesting a potentiation of *N*-methyl-D-aspartate (NMDA)-mediated neuronal activation by DTG (Monnet et al., 1990), we have analyzed the interactions between DTG and the NMDA receptor antagonist, 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid (CPP), following microinjections of these two compounds into the substantia nigra.

2. Materials and methods

2.1. Surgery

Male Sprague-Dawley rats (250–350 g) were used for cannulae implantation under deep sodium pentobarbital anesthesia (50 mg/kg i.p.). Guide cannulae constructed of 24 gauge thin wall stainless steel tubing were implanted 4 mm above either the left or right substantia nigra using the following coordinates: AP +3.2 mm from lambda, LAT 2.2 mm from the midline suture and DV −8.7 mm from the skull surface according to the atlas of Paxinos and Watson (1982). Cannulae were secured with stainless steel screws and dental acrylic. Animals were allowed to recover 3–5 days before testing.

2.2. Drug administration

Rats were injected with NSD-1015, 100 mg/kg i.p., in isotonic saline at time zero to inhibit DOPA decarboxylase activity (Carlsson et al., 1972). At 5 min the rat received a microinjection of test drug (0.5 μl in isotonic saline) in the substantia nigra using a 31 gauge stainless steel microneedle connected to a motor driven infusion pump. The drug was administered over a period of 72 s, and, following an additional 10 s post-injection, the microneedle was removed. Since the DTG was used as the acetate salt, control injections were carried out with similar concentrations of acetate and similar pH to those used for the DTG studies (27.9 mM sodium acetate in isotonic saline, pH adjusted to 5.2 with 0.1 N HCl). No significant effect on turning or DOPA production was observed with these control injections. When more than one drug was administered into the substantia nigra, the drugs were administered together in the same solution. Anesthetics were administered as follows: chloral hydrate, 400 mg/kg i.p., ketamine, 100 mg/kg i.p. and halothane, 2% v/v in air.

2.3. Rotational behavior

Immediately after intranigral injection (7 min after NSD-1015 administration) rats were fitted with an elastic harness that was connected by a metal cable to an optical position transducer interfaced to a computer that recorded the number and direction of half turns for a 12 min period. Rotational behavior was monitored in a 25 cm diameter bowl that served as the test chamber. Net contralateral half turns were calculated as contralateral half turns minus ipsilateral half turns. Animals were killed by decapitation 20 min after NSD-1015 administration (1 min after cessation of behavioral testing).

2.4. Tissue preparation

After killing, the brain was rapidly dissected on ice. The left and right striata were frozen on dry ice and stored at −20°C until preparation for neurochemical analyses. The remainder of the posterior brain was stored in 30% sucrose/10% formalin overnight, sliced, fixed with formaldehyde vapor and stained with cresyl violet for histological verification of the microinjection site.

Each striatal side was separately weighed and homogenized in 1.5 ml of 0.2 N perchloric acid containing 0.1 mM ascorbic acid. After centrifugation at 4000 × *g* for 10 min, the supernatants were filtered through a 0.2 μm syringe filter (Nalge Company, Rochester, NY, USA) before high-performance liquid chromatography (HPLC)-electrochemical analyses.

2.5. Neurochemical analyses

Tissues were analyzed for DOPA and dopamine content using HPLC-electrochemical detection (ESA Coulochem Detector, Bedford, MA, USA) as previously described (Patrick et al., 1991). The mobile phase contained 0.1 M monosodium phosphate, 0.13 mM octyl sodium sulfate, 0.1 mM EDTA, 4% methanol, pH 3.4. At a flow rate of 1.5 ml/min the retention times were (min): DOPA (4.3), 3,4-dihydroxyphenylacetic acid (DOPAC; 4.8), dopamine (6.6) and homovanillic acid (HVA; 15.9) on an ESA HR-80 column. The retention times of DOPAC and HVA were monitored in order to assure that they did not interfere with the determi-

nations of DOPA and dopamine. The first electrode was set at +0.35 V, the second at +0.07 V and the third (recording) electrode at −0.20 V. The sensitivity of the detector was adjusted so that 60 pg of DOPA or dopamine gave a peak height of approximately 100 mm. Injection of a 1 μl aliquot of a sample from the contralateral side typically gave peaks for DOPA and DA that were 22 and 110 times the baseline, respectively. Tissue levels of DOPA and dopamine were calculated based on comparisons with known standards and the ipsilateral/contralateral (I/C) ratio calculated. None of the treatments in the present study produced any significant changes in the dopamine I/C, and the DOPA I/C value was divided by the dopamine I/C to correct for individual animal and/or dissection variability. The DOPA I/C values presented thus represent the mean ± S.E.M. of the ratio of the DOPA I/C to the dopamine I/C for each animal.

2.6. Statistics

Data are expressed as the mean ± S.E.M. and were analyzed for statistical significance using a one-way analysis of variance with Tukey-Kramer multiple comparisons test as indicated using InStat (GraphPad, San Diego, CA, USA; Dowdy and Wearden, 1983). A P value of 0.05 or smaller was considered significant.

2.7. Drugs

All drugs for both intraperitoneal and intranigral injections were dissolved in isotonic saline. NSD-1015 was obtained from Sigma Chemical Co. (St. Louis, MO, USA) and (±)-CPP from Research Biochemicals International (Natick, MA, USA). DTG_2-acetate was crystallized from a saturated acetic acid solution of the free base (Aldrich Chemicals, Milwaukee, WI, USA) as previously described (Walker et al., 1988). (−)-Deoxy-*N*-benzylnormetazocine-HCl was synthesized as described (Carroll et al., 1992).

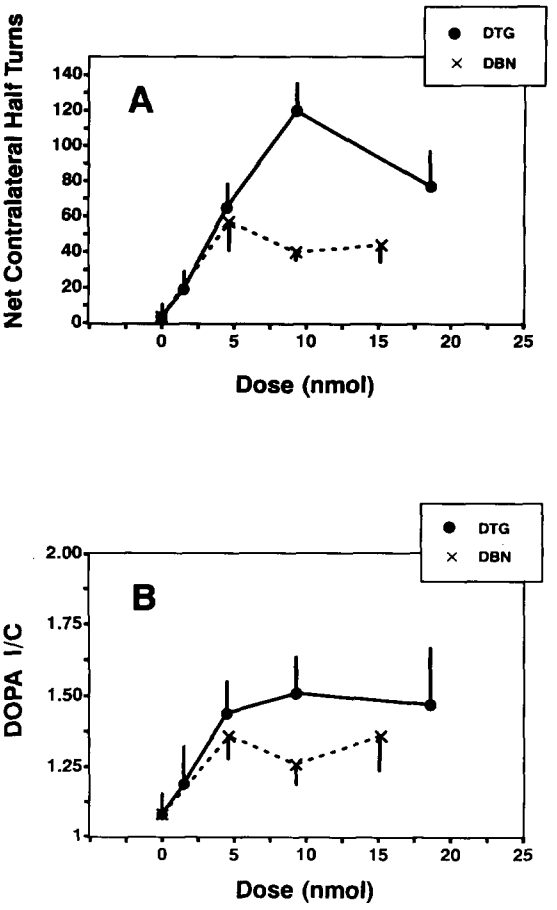

Fig. 1. Effect of intranigral DTG and (−)-deoxy-*N*-benzylnormetazocine (DBN) on turning behavior and striatal tyrosine hydroxylase activity. (A) Rats were administered either vehicle, DTG or DBN at the dosages indicated and the net number of contralateral half turns determined for a 12 min period as described in the text. Each value represents the mean ± S.E.M. of 6–15 animals. One-way analysis of variance: $P < 0.0001$ for DTG; $P = 0.0002$ for DBN. (B) Represents the same rats treated as in (A), with the striatal tissue taken separately from the ipsilateral (I) and contralateral (C) sides for catechol analyses as described in the text. One-way analysis of variance: $P = 0.026$ for DTG; $P = 0.034$ for DBN. For the vehicle-treated animals: contralateral and ipsilateral DOPA = 0.740 ± 0.074 and 0.813 ± 0.066 μg/g, respectively; contralateral and ipsilateral dopamine = 5.57 ± 0.57 and 5.67 ± 0.44 μg/g, respectively.

3. Results

3.1. Effects of DTG and (−)-deoxy-N-benzylnormetazocine on turning and striatal tyrosine hydroxylase activity

Intranigral DTG administration produced a significant increase both in contralateral turning and striatal tyrosine hydroxylase activity (Fig. 1A and B, $F(4,37) = 20.57$ for turning, $P < 0.0001$; $F(4,37) = 3.13$ for DOPA production, $P = 0.026$). Significant increases in contralateral turning produced by intranigral administration of (−)-deoxy-*N*-benzylnormetazocine were also associated with a significant increase in striatal tyrosine hydroxylase activity (Fig. 1A and B, $F(3,32) = 8.74$ for turning, $P = 0.0002$; $F(3,32) = 3.26$ for DOPA production, $P = 0.034$).

3.2. Lack of antagonism by CPP of the DTG-induced stimulation of DOPA production

CPP alone (9.3 nmol) produced substantial contralateral turning (Fig. 2): $F(3,33) = 10.91$, $P < 0.001$. Tukey-Kramer multiple comparisons test: vehicle vs. either DTG, CPP or CPP plus DTG, $P < 0.001$. In contrast to the effects of DTG, the CPP-induced increase in contralateral turning was not accompanied by an increase in striatal tyrosine hydroxylase activity (Fig.

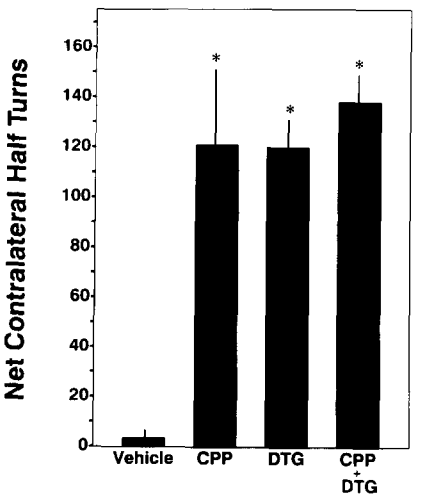

Fig. 2. Turning behavior following CPP and DTG treatment. Rats received intranigral administration of either CPP alone (9.3 nmol), DTG alone (9.3 nmol) or the combination together in one injection. Each value represents the mean ± S.E.M. of 7–15 animals. * $P < 0.001$ vs. vehicle (Tukey-Kramer multiple comparisons test).

3). In addition, this dosage of CPP did not antagonize the DTG-induced stimulation of tyrosine hydroxylase activity: $F(3,33) = 6.32$, $P = 0.0017$. Tukey-Kramer multiple comparisons test: vehicle vs. CPP, not significant; DTG vs. CPP plus DTG, not significant; vehicle vs. either DTG or CPP plus DTG, $P < 0.05$.

Lower dosages of CPP (2.5, 0.5 and 0.05 nmol) also produced significant contralateral turning (98, 88 and 38 half turns, respectively). As with 9.3 nmol of CPP, none of these treatments produced a significant increase in striatal tyrosine hydroxylase activity, showing that an increase in turning is not sufficient to produce an increase in dopamine formation. We also tested the highest dosage of CPP that did not produce turning (0.002 nmol) in combination with a reduced dosage (4.5 nmol) of DTG. No inhibition of DTG-induced turning or stimulation of tyrosine hydroxylase activity was observed (68 ± 12 turns for the combination vs. 65 ± 9 turns for 4.5 nmol DTG alone and 47 ± 12% stimulation of tyrosine hydroxylase for the combination vs. 44 ± 8% stimulation for 4.5 nmol DTG alone; $n = 11$ for the combination and $n = 7$ for DTG alone; data not shown).

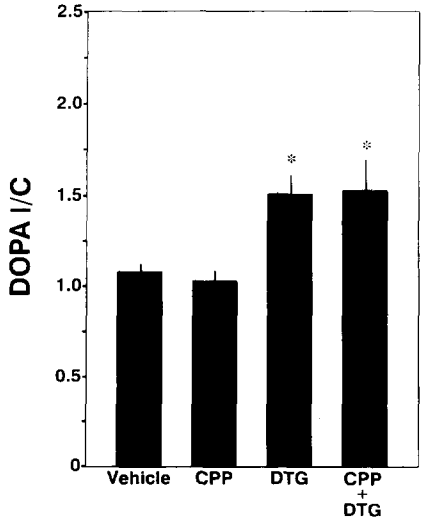

Fig. 3. Striatal tyrosine hydroxylase activity following CPP and DTG treatment. The same rats were treated as described in Fig. 2 legend, with striatal tissue taken separately from each side for catechol analyses as described in the text. Each value represents the mean ± S.E.M. of 7–15 animals. * $P < 0.05$ vs. vehicle (Tukey-Kramer multiple comparisons test).

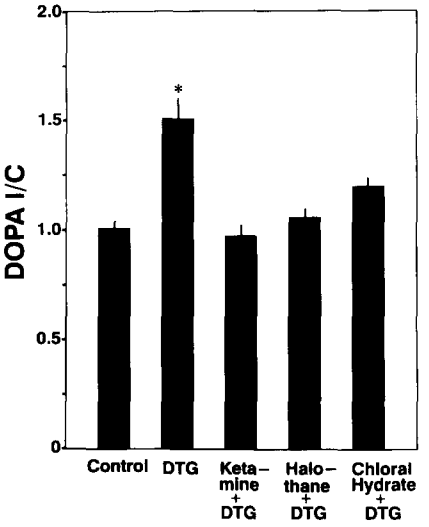

Fig. 4. Effect of general anesthetics on DTG-induced stimulation of striatal tyrosine hydroxylase activity. Rats received intranigral administration of DTG (9.3 nmol) either alone or following peripheral administration of general anesthetics as described in the text. Striatal tissue was taken separately from each side for catechol analyses. Each value represents the mean ± S.E.M. of 5–15 animals. * $P < 0.001$ vs. vehicle (Tukey-Kramer multiple comparisons test).

3.3. Effects of general anesthetics on the DTG-induced stimulation of DOPA production

Halothane, ketamine and chloral hydrate all significantly inhibited the DTG-induced increase in striatal tyrosine hydroxylase activity (Fig. 4): $F(4,36) = 8.48$, $P < 0.0001$. Tukey-Kramer multiple comparisons test: control vs. DTG, $P < 0.001$; control vs. ketamine, halothane or chloral hydrate, not significant. In order to obtain an indication of the effect of the anesthetic alone on tyrosine hydroxylase activity, the value for DOPA production in the control animals (using the average of the two separate sides) was compared to the value for the contralateral side of the animals receiving anesthetic plus DTG. This comparison indicated that halothane increased tyrosine hydroxylase activity by 42% (Tukey-Kramer multiple comparisons test, $P <$

0.05), but that the effects of chloral hydrate (18% increase) and ketamine (9% increase) were not statistically significant (data not shown).

4. Discussion

The present studies provide evidence for alterations in striatal dopamine synthesis as a result of σ receptor occupancy in the substantia nigra. The observation that two chemically dissimilar σ ligands can produce the same biochemical change argues in favor of an action at σ receptor sites. This supports the concept that σ receptor occupancy in the nigra can activate dopamine functioning in the striatum. Further studies using additional ligands with different affinities for σ_1 vs. σ_2 receptor sites will be required to determine if a specific σ subtype is responsible for the increase in striatal DOPA production (Walker et al., 1993). Our results are consistent with previous studies indicating that peripheral σ ligand administration increases dopamine formation and metabolite levels in the striatum (Berkowitz, 1974; Iyengar et al., 1990; Pugsley et al., 1992). Our studies show specifically that the tyrosine hydroxylase enzymatic step is activated following σ ligand administration. The results of our intranigral injections also help to locate the specific sites in the brain through which peripheral σ ligand administration alters dopamine production in the striatum. The finding that 6-hydroxydopamine-induced lesions of the rat nigrostriatal pathway produce a loss of about one-third of the σ receptor sites in the substantia nigra (Gundlach et al., 1986) suggests that intranigral injections of σ ligands may produce their effects directly on dopamine neurons, although an indirect action mediated through other σ receptor containing neurons in the substantia nigra cannot be ruled out.

The present studies differ from previous determinations of contralateral turning following intranigral σ ligand administration (Walker et al., 1988; Goldstein et al., 1989) in that rats were pretreated with a DOPA decarboxylase inhibitor in the present studies. While direct comparisons of the DTG dose-response curves are difficult due to differences in time-course of treatment, it appears that in animals treated with NSD-1015 the dose-response curve for turning peaks at a lower DTG concentration compared to animals not injected with NSD-1015 (cf. Walker et al., 1988). A more direct comparative study would be necessary, however, to determine the exact effect of inhibiting dopamine formation on σ ligand-induced turning behavior. Dluzen et al. (1992) have reported that NSD-1015 can stimulate dopamine release from striatal minces. If large amounts of dopamine were released on both sides of the striatum following NSD-1015 treatment in vivo, this could in theory mask a drug-induced unilateral stimulation of dopamine release. However, that does not appear to be the case in our studies since we obtained robust contralateral turning with the two σ ligands we employed, indicating a good deal of asymmetric dopamine stimulation in the striatum.

Two possible mechanisms for σ ligand-induced alterations in DOPA production are: (1) a change in striatal dopamine terminal biochemistry occurring via a change in nigrostriatal dopaminergic firing rate and/or firing pattern, or (2) a change in terminal biochemistry occurring because of changes in input to the striatum via outputs from the nigra that do not go through the dopaminergic nigrostriatal neuronal pathway.

With regard to the first possibility, two issues need to be addressed. First is the relationship between alterations in firing rate and changes in DOPA production. The fact that electrical stimulation of the nigrostriatal pathway leads to an increase in DOPA production (Murrin and Roth, 1976) suggests that an increase in firing rate will stimulate DOPA formation, possibly as a result of tyrosine hydroxylase phosphorylation and activation subsequent to an increase in Ca^{2+} influx (Murrin et al., 1976; Haycock and Haycock, 1991). However, it has been shown that conditions that decrease firing rate can also increase DOPA production. This has been demonstrated following intraperitoneal injection of γ-butyrolactone, an agent that decreases nigrostriatal firing rate but also increases DOPA formation (Roth et al., 1974). This increase in DOPA production may be due to decreased inhibitory autoreceptor occupancy as a result of the decrease in dopamine release (Roth et al., 1974). The fact that intranigral σ ligand injections are associated with contralateral turning that is blocked by 6-hydroxydopamine treatment (Goldstein et al., 1989) would argue against a σ ligand-induced decrease in dopamine release in the striatum, and would suggest that if intranigral σ ligand injections are altering dopaminergic firing rate, they are either causing it to increase or changing its pattern to produce an increase in striatal dopamine release (Grace and Bunney, 1984; Gonon, 1988).

The second issue with regard to firing rate concerns the fact that previous studies have found either a modest, or no increase in nigrostriatal firing rate following acute peripheral administration of σ ligands such as (+)-pentazocine and DTG (Meltzer et al., 1992; Zhang et al., 1992). Although more robust changes in firing have been reported with σ ligands such as 3-(3-hydroxyphenyl)-*N*-1-(propyl)piperidine (3-PPP: inhibition of firing) and BMY 14802 (increase in firing), it has been suggested that these effects may be due to action at dopamine receptor sites (for 3-PPP) or 5-HT receptor sites for BMY 14802 (Freeman, 1992; Zhang et al., 1993).

While the route of drug administration in our studies (intranigral) differs from that used in the electrophysiological studies, the electrophysiological studies do raise the possibilities that (1) the increase in striatal tyrosine hydroxylase activity that we observe occurs independently of an alteration in nigrostriatal firing rate or (2) some aspect of the methodology employed in the electrophysiological studies prevents an alteration in firing from being observed. In the former case, multisynaptic pathways from the substantia nigra to the thalamus, from thalamus to cortex and cortex to striatum could be involved (Cote and Crutcher, 1991). In the latter case, the issue of the effects of general anesthetics merits consideration.

Mereu et al. (1984) found that chloral hydrate and halothane increased nigrostriatal dopamine neuron firing rate when administered to unanesthetized paralyzed rats. In addition, choral hydrate inhibited the increase in firing rate normally produced by haloperidol and (−)-sulpiride, and halothane inhibited the increase in soluble tyrosine hydroxylase activity normally produced by haloperidol and (−)-sulpiride. Taken together with our findings of an inhibition of DTG-induced activation of striatal tyrosine hydroxylase activity by general anesthetics, these results suggest caution in interpreting electrophysiological studies employing these anesthetics. This issue could perhaps be clarified if a general anesthetic could be found that does not inhibit DTG-induced tyrosine hydroxylase activation. This anesthetic might then be preferable to use to test for σ ligand effects on dopamine firing rate and firing pattern.

In previous experiments Monnet et al. (1990) found that both intravenous and microiontophoretic administration of DTG potentiated the activation of rat CA_3 dorsal hippocampal pyramidal neurons produced by microiontophoretic application of NMDA. In light of these results, we attempted to determine if the DTG-induced activation of striatal tyrosine hydroxylase activity is inhibited by the competitive NMDA receptor antagonist, CPP. At the highest intranigral dosage of CPP tested (9.3 nmol), we did not observe antagonism of the stimulation of DOPA production produced by 9.3 nmol of DTG. At the highest dosage of CPP which did not produce turning (0.002 nmol) no antagonism of the increase in DOPA production produced by 4.5 nmol of DTG was observed. One caveat in interpreting the latter study is the possibility that lower dosages of CPP which no longer cause turning may also no longer block NMDA receptors. Further studies using additional dosages of DTG and also other NMDA antagonists will be necessary to evaluate the implication of the above studies that NMDA receptor activation is not necessary for intranigral σ ligand-induced activation of striatal tyrosine hydroxylase activity. The fact that ketamine, which can also interfere with NMDA functioning (Wong and Kemp, 1991), does block the DTG-induced increase in tyrosine hydroxylase activity may be related to the difference in route of administration (intranigral for CPP vs. intraperitoneal for ketamine) with corresponding differences in sites of action in the brain, and/or the high dosage of ketamine necessary to achieve anesthetic effect.

The results following CPP administration were of interest, in that CPP alone produced contralateral turning that was not accompanied by an increase in tyrosine hydroxylase activity. This shows that turning per se is not a sufficient stimulus to induce an increase in DOPA production, and supports the concept that the σ ligands are having a specific biochemical effect on the dopamine terminals in the striatum. The mechanism responsible for CPP-induced turning is not known, but could be due to a reduction in firing of inhibitory GABA neurons originating in the substantia nigra and leading to motor control centers in the thalamus and brainstem premotor areas (Cote and Crutcher, 1991).

In summary, the present studies indicate that occupancy of σ receptors in the rat substantia nigra is associated with an increase in tyrosine hydroxylase activity in the striatum. This effect does not appear to depend upon NMDA receptor functioning in the nigra, and may occur either through direct activation of nigrostriatal dopaminergic neurons or indirectly via multi-synaptic pathways leading from the substantia nigra to the striatum. Taken together with previous work showing an activation of tyrosine hydroxylase in striatal minces incubated with σ receptor ligands (Booth and Baldessarini, 1991), the present data suggest that occupancy of σ receptors at both the cell bodies and terminals of nigrostriatal dopamine neurons leads to an activation of dopamine formation, and support the concept that σ receptors are involved in modulating dopaminergic functioning in motor control areas in the central nervous system.

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