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Catalepsy Produced by Striatal Microinjections of the D_1 Dopamine Receptor Antagonist SCH 23390 in Neonatal Rats

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ROWLETT, J. K., N. W. PEDIGO, JR. AND M. T. BARDO. *Catalepsy produced by striatal microinjections of the D_1 dopamine receptor antagonist SCH 23390 in neonatal rats.* PHARMACOL BIOCHEM BEHAV **40**(4) 829–834, 1991.—Systemic injection of the D_1 dopamine receptor antagonist SCH 23390 produces catalepsy that is of lesser magnitude in neonatal than in adult rats. The present experiments were conducted in order to determine if SCH 23390 would produce catalepsy in neonatal rats following intrastriatal injection and if the ontogenetic pattern of catalepsy induced by intrastriatal SCH 23390 would be similar to the pattern observed with systemic injections. Rat pups (11 or 28 days of age) were microinjected unilaterally with SCH 23390 (0.2, 1, 5 or 10 μg) and tested for catalepsy using the forepaw-on-horizontal-bar test. The results demonstrated that robust catalepsy occurred at both ages following intrastriatal injection and that catalepsy induced by 5 μg SCH 23390 was of lesser magnitude in 11-day-olds than in 28-day-olds. A separate study assessed the distribution of [^{3}H]SCH 23390 (5 μg) following intrastriatal injection in 28-day-olds. Results of the distribution study indicated that [^{3}H]SCH 23390 was localized primarily within the striatum. Taken together, these results suggest that the striatal mechanisms for catalepsy produced by D_1 receptor blockade are present, but not fully mature, in preweanling rat pups.

D_1 dopamine receptor SCH 23390 Catalepsy Striatum Ontogeny Rat

DOPAMINE receptors in the central nervous system are categorized by pharmacological, physiological and biochemical criteria into at least two distinct subtypes termed D_1 and D_2 (10,36). The D_1 subtype of dopamine receptor is positively coupled to adenylyl cyclase (40), phosphoinositide hydrolysis and Ca^{2+} mobilization (22). The D_2 subtype is negatively linked to adenylyl cyclase (40), phosphoinositide hydrolysis (41), Ca^{2+} mobilization (3) and is linked to activation of K^+ channels (21). In the nigrostriatal pathway of the rat, the D_1 and D_2 subtypes of dopamine receptors appear to develop rapidly, reaching adult levels between approximately the second and third week of postnatal life (6, 16, 17, 26–28, 31, 34, 42). In general, behavioral responses to dopaminergic drugs appear to mature during this same period of development (38). One such response, antipsychotic-induced catalepsy, appears between postnatal day 10 and postnatal day 20 (2, 7, 24).

The D_1 selective antagonist SCH 23390 produces a cataleptogenic response in adult rats and mice similar to D_2-selective and mixed D_1/D_2 antagonists (1, 8, 23, 25, 29). The ontogeny of the cataleptogenic response to systemically administered SCH 23390 has been recently characterized (14). Catalepsy to SCH 23390 increased from 13 days of age to 17 days of age in male rats and the cataleptogenic response was equivalent between 17 and 20 days after birth (14). Further, muscarinic cholinergic antagonist reversal of SCH 23390-induced catalepsy occurred at 21 days after birth, but not at 13 days after birth, suggesting that D_1 antagonist-induced catalepsy depends on forebrain cholinergic system maturation (14).

The purpose of the present experiments was to determine if the ontogenetic differences in catalepsy induced by systemic SCH 23390 could be observed following microinjection into the striatum. The striatum has been proposed to mediate D_2 antagonist-induced catalepsy (9, 29, 30). Further, the ontogeny of D_1 dopamine receptor sites labelled by [^{3}H]SCH 23390 has been extensively characterized in this region by radioligand-binding studies [e.g., (16, 17, 27)], which would allow us to make correlative comparisons between the receptor system development and a putative index of receptor function.

METHOD

Animals

Animals were 11- and 28-day-old male rat pups of Harlan Sprague-Dawley descent, born and reared at the University of Kentucky. Some 28-day-old animals were purchased directly from Harlan Industries (Indianapolis, IN) at 21 days of age. The day of birth was defined as day 0. Litters were culled to 10 pups each at 3 days of age. Pups were weaned at 21 days of age and housed in group cages (three per cage) with food and water sup-

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plied continuously. The colony room was maintained at 23–25°C and kept under a 14:10 h light:dark cycle. All behavioral testing was conducted during the light phase of the cycle.

Test for Catalepsy

The forepaw-on-horizontal bar test (35) was used to assess catalepsy. The apparatus consisted of a wire mesh cage which had a metal bar placed horizontally in the corner. The bar could be adjusted vertically. Black cardboard paper was wrapped around the cage in order to minimize availability of sensory stimulation. The bar was 1 mm in diameter, and was placed 3 cm above the floor for 11-day-old pups and 6 cm above the floor for 28-day-old pups.

During behavioral testing, each rat pup was allowed to adapt to the test apparatus for approximately 30–60 s. After this time, the pup's forepaws were gently placed on the bar, and latency to remove both forepaws from the bar was recorded. If the pup immediately removed its paws (i.e., within approximately 3 s), the pup's forepaws were placed on the apparatus again. If the pup immediately removed its paws a second time, the procedure was repeated a final time. An observer timed the duration of catalepsy to the nearest second. If the rat remained on the bar for 300 s, the test was terminated and a score of 300 s was recorded.

Drug

SCH 23390 [R(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol hydrochloride, Research Biochemicals, Natick, MA] was mixed fresh daily in saline (0.9% NaCl). All dosages were calculated based on the salt form of the drug.

Peripheral Injection Procedure

In order to assess the cataleptogenic properties of SCH 23390 using our testing procedure, an initial study was carried out using peripheral injections in 28-day-old pups. Each pup was injected IP with either 0, 0.1, 0.3 or 1.0 mg/kg SCH 23390 (n = 8 per group), and then was tested for catalepsy at 15, 30, 60 and 120 minutes after injection.

Microinjection Procedure

Rat pups at 11 and 28 days after birth were anesthetized with ethyl ether. An incision was made to expose the dorsal surface of the skull, and a small hole was drilled by hand on the right side of the skull using either a 22-gauge (11-day-olds) or 18.5-gauge (28-day-olds) needle. This hole was made 2 mm lateral from the midline, approximately 1 mm anterior to bregma for 11-day-old pups or even with bregma for 28-day-old pups. The pups were then placed in a rat stereotaxic incisor bar modified in order to ensure that the head of the pup was level. A beveled tip needle attached to a 10-μl syringe was lowered into the striatum, and a 2 μl volume of drug or saline was injected. The depth was 4 mm below the surface of the dura for both 11- and 28-day-old pups. All coordinates were initially determined using a developmental stereotaxic atlas (37) and adjustments were made by pilot studies using a dye-injection procedure (see below). The needle tip was aimed slightly to the medial aspect of the striatum such that the beveled edge of the syringe needle faced the middle of the caudate-putamen.

Injections were delivered over a 60-s period and the needle tip was left in place for an additional 30 s after completion of the injection. The rat pup was then removed from the stereotaxic device. The hole was filled with saline-soaked Gel-foam, a topical antibiotic was applied (sulfathiazole), and the incision was closed with a wound-clip (9 mm). Each pup was placed on a heating pad (approximately 30°C) before behavioral testing commenced. Testing for catalepsy occurred 10, 20, 40 and 60 minutes after the injection. These test intervals were chosen based on the results of the time course of the peripheral injections in 28-day-old pups. After testing, 11-day-old pups were returned to their litters, while 28-day-old pups were returned to their home cage.

To test for potential differences in baseline catalepsy due to the anesthesia and surgery in 11-day-olds, an additional 11-day-old group was treated the same as the microinjected animals, except that no anesthesia, surgery or microinjection was given.

Verification of the microinjection into the striatum was carried out in two ways: 1) dye injection of a sample of pups and 2) histological verification of brains from pups tested behaviorally. A third, indirect method of verification was by determination of the distribution of microinjected [^{3}H]SCH 23390 in a separate group of pups (see below). For dye injections, rat pups at both ages were injected with 2 μl of Fast Blue dye (0.5 mg Fast Blue/ml saline) into the striatum using the microinjection procedure described above. Pups were euthanized with chloral hydrate (200 mg/kg, IP) immediately after the injection and the brains were removed. A coronal cut was made from the dorsal surface of the brain at the injection site in order to expose the extent of the stained tissue. This procedure was repeated intermittently on separate animals during the course of the experiments.

For histological verification of the injection site in animals tested behaviorally, pups were euthanized (chloral hydrate, 200 mg/kg) 2–4 days after the injection procedure. The brains were removed and placed in 10% formalin. Eighty μm coronal cuts were made through the brain using a cryostat (−15°C) and the approximate site of the needle point was determined. In some cases, tissue damage and glial formation were visible only in the cortex overlying the striatum. When this occurred, the placement of the syringe tip was estimated based on the depth of the angle of the cortical tract.

Distribution of Microinjected [^{3}H]SCH 23390

To determine the distribution of SCH 23390 after the striatal microinjection procedure, [^{3}H]SCH 23390 was injected into the striatum of 28-day-old rats and the distribution of the drug was quantified in the striatum and surrounding brain tissue using a method adapted from Pedigo et al. (32). [^{3}H]SCH 23390 (specific activity = 73 Ci/mmol, Amersham, Arlington Heights, IL) was warmed in a microcentrifuge tube and the solvent removed under nitrogen flow in a desiccator. The radiolabelled solute was diluted to 7.3 Ci/mmol with nonlabelled SCH 23390 mixed in saline, and injected at a concentration of 5 μg/2 μl.

Ten or 20 min following the microinjection of [^{3}H]SCH 23390, the 28-day-old pups were sacrificed by rapid decapitation. The brains were rapidly removed, placed on an ice-cold plate and the right (injection side) and left striata were dissected. In addition, unilateral tissue samples from the right (injected) side of the brain were taken from the nucleus accumbens-olfactory tubercle, hippocampus and neocortex surrounding the right striatum. Bilateral sections of the septal region and frontal cortex were also included. Each tissue sample was weighed and placed in a scintillation vial with 1 ml tissue solubilizer (Protosol, DuPont-New England Nuclear, Boston, MA). The samples were shaken for 12 hours at 37°C in a water bath. Scintillation

fluor [3 l toluene, 16 g Omnifluor (DuPont-New England Nuclear, Boston, MA) and 5 ml glacial acetic acid] was then added and the mixture cooled at least 4 hours prior to measuring radioactivity in a liquid scintillation counter (counting efficiency = 25–30%).

Data Analysis

Catalepsy latency scores were transformed using a method suggested by Kirk (20). Reciprocal transformation for data sets with zero scores was used: 1/(latency score + 1). For the peripheral and microinjection procedures, the catalepsy latency scores within each age group were analyzed after reciprocal transformation by mixed factor analysis of variance (ANOVA), with postinjection test interval as the repeated measure. Average latency scores across the 4 test intervals were analyzed after reciprocal transformation by analysis for variance and Dunnett's test (saline as control). For age comparisons, it was necessary to adjust for baseline differences, since 11-day-old pups microinjected with saline displayed catalepsy levels above noninjected animals at the earliest test intervals. For these analyses, area-under-the-curves (AUC) were computed for each rat using the trapezoidal method (39). The mean AUC values for the saline-injected controls within the age group were subtracted from each of the age group's dose mean AUC score. The statistical analyses between ages were carried out using the following F ratio:

$$F = [(Aa - C) - (Ba - D)]^2/[MS_e(1/n_{Aa} + 1/n_c + 1/n_{Ba} + 1/n_D)]$$

In the equation, the Aa represents the mean of 11-day-old pups at dose "a," the Ba represents the mean of 28-day-old pups at dose "a." The C and D represent the saline control means of 11- and 28-day-old pups, respectively. The MS_e represents the mean square error of the control, 0.2 μg, 1.0 μg and 5.0 μg groups for both ages. The n represents the number of animals in the group denoted in the subscript. The critical F value was determined using the Scheffé procedure.

Data from the [^{3}H]SCH 23390 distribution study were expressed as disintegrations/min/mg tissue. These data were analyzed by a mixed factor ANOVA with brain region as the repeated measure. In addition, planned Bonferroni *t*-tests were performed comparing all regions to the right (injection side) striatum.

The level of significance in all statistical analyses was $p<0.05$. In ANOVAs involving repeated measures, violations of homogeneity of variance were examined using the Huynh-Feldt epsilon. If the epsilon value was less than 0.75, the degrees of freedom were adjusted using the Huynh-Feldt correction factor (19).

RESULTS

Catalepsy to SCH 23390 Administered Peripherally

Following an IP injection of SCH 23390, 28-day-old rat pups displayed significant catalepsy (Fig. 1). The ANOVA revealed a significant main effect of test interval, $F(3,75)=3.19$, $p<0.05$, as well as a significant main effect of dose, $F(3,25)=5.13$, $p<0.01$. However, the test interval × drug dose interaction was not significant. Latency scores collapsed across the four test intervals are shown in the right panel of Fig. 1. Dunnett's tests revealed that only the 0.3 mg/kg dose of SCH 23390 produced reliable catalepsy above control values.

Catalepsy to SCH 23390 Administered Intrastriatally

Latency scores for 11-day-old pups following microinjection of SCH 23390 are shown in Fig. 2. The ANOVA revealed that

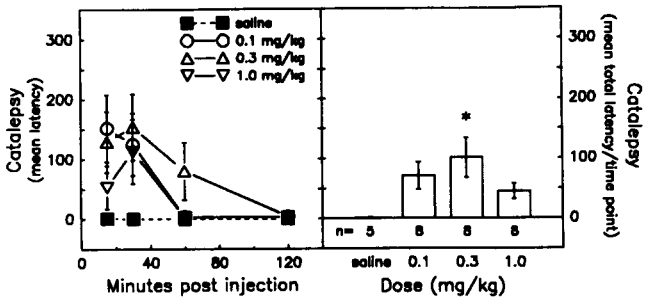

FIG. 1. Latency scores (mean ± SEM) for 28-day-old rat pups following an IP injection of SCH 23390. The right panel represents the average latencies across the four test intervals. Note that *$p<0.05$ vs. saline, Dunnett's test.

neither the test interval main effect nor test interval × drug dose interaction was significant. However, there was a main effect of dose, $F(4,25)=23.19$, $p<0.001$. Subsequent Dunnett's tests revealed that the group that received no surgery (none), as well as the groups that received the 1.0 and 5.0 μg doses, were significantly different from the 0 μg control group.

Latency scores for 28-day-old pups following striatal microinjection of SCH 23390 are shown in Fig. 3. The main effect of test interval was significant, $F(3,60)=5.78$, $p<0.01$, as was the main effect of drug dose, $F(4,20)=14.29$, $p<0.001$. In addition, the interaction of test interval and drug dose was significant, $F(12,60)=4.06$, $p<0.001$, suggesting that the time course depended on the dosage level. Dunnett's tests of the latency scores collapsed across the four test intervals revealed that all the doses tested were significantly different from the 0 μg control group ($p<0.05$).

Age Comparison

Since the 11-day-old rat pups in the 0 μg groups displayed significant catalepsy (see Fig. 2), it was necessary to adjust for baseline differences. Figure 4 shows the mean adjusted AUC scores for the two ages. The AUC values for 11-day-old pups were significantly lower than the AUC values for 28-day-old pups at the 5 μg dose (Scheffé's test, $p<0.05$). No other age comparisons were significantly different.

Distribution of [^{3}H]SCH 23390

The overall ANOVA of the concentration of radioactivity in the various rat brain regions at the 10- and 20-min time points revealed only a significant main effect of region, $F(6,24)=7.52$,

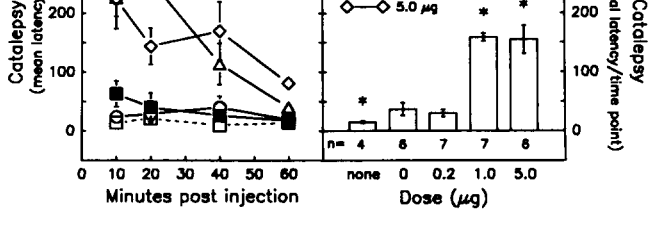

FIG. 2. Latency scores (mean ± SEM) for 11-day-old rats following a microinjection into the striatum with SCH 23390. The right panel represents the average latencies across the four test intervals. The "none" group received no anesthesia or surgery. Note that *$p<0.05$ vs. 0 μg group, Dunnett's test.

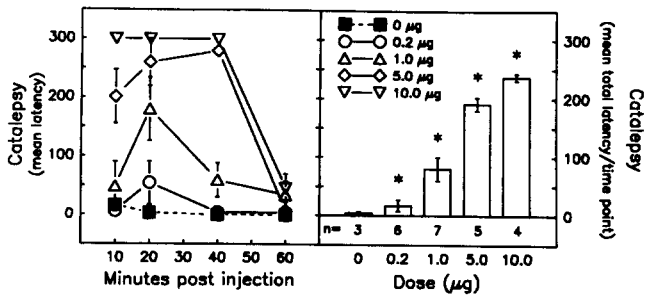

FIG. 3. Latency scores (mean ± SEM) for 28-day-old rats following a microinjection into the striatum with SCH 23390. The right panel represents the average latencies across the four test intervals. Note that *$p<0.05$ vs. 0 μg group, Dunnett's test.

$p<0.05$, Huynh-Feldt epsilon = 0.31. Bonferroni t-tests indicated that, at 10 min, the right striatum had a significantly higher concentration of radioactivity than all regions except for the septal region, which had a significantly higher concentration of radioactivity than the right striatum (Bonferroni t-tests, $p<0.05$, see Fig. 5). At 20 min, the right striatum had a significantly higher concentration of radioactivity than all the regions (Bonferroni t-test, $p<0.05$; see Fig. 5). A further ANOVA showed that the concentration of radioactivity significantly decreased between 10 and 20 min in the septum, $F(1,4) = 33.9$, $p<0.01$.

Histological Verification

Verifications in the entire 1.0 μg dose group and a sample from the 0 μg dose group for both 11- and 28-day-olds indicated that all injections were within the striatum, the majority being the medial aspect of the caudate-putamen. Two 11-day-old pups' microinjection tracts were not detected. Diagrams of the estimated syringe tip placements are shown in Fig. 6.

DISCUSSION

The primary finding of these experiments was that intrastriatal microinjections of SCH 23390, a selective antagonist for the D_1 subtype of dopamine receptor (4,18), produced marked catalepsy in rat pups. This finding suggests that the striatum may be a major site for the modulation of catalepsy by SCH 23390, similar to antipsychotics (9), and extends previous studies (15,30) which have demonstrated catalepsy to SCH 23390 microinjected

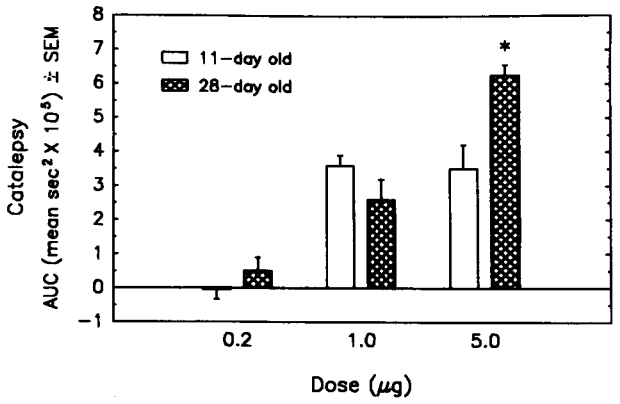

FIG. 4. Mean area-under-the-curve (AUC) ± SEM values for 11- and 28-day-old rat pups microinjected in the striatum with SCH 23390. AUC values were calculated using the trapezoidal method. The AUC values were adjusted for age-related baseline differences as described in the text. Note that *$p<0.05$, 11- vs. 28-day-olds, Scheffé's test.

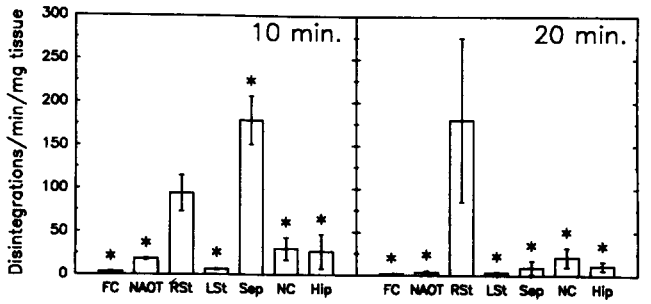

FIG. 5. Distribution of [^{3}H]SCH 23390 10 and 20 min following microinjection into the right striatum of 28-day-old rat pups. Data are expressed as concentration of radioactivity (mean disintegrations/min/mg wet tissue weight ± SEM) for 3 animals per time group. Region abbreviations are as follows: FC, frontal cortex; NAOT, nucleus accumbens-olfactory tubercle; RSt, right striatum; LSt, left striatum; Sep, septum; NC, neocortex surrounding the microinjection tract; Hip, hippocampus. Note that *$p<0.05$ vs. RStr, Bonferroni t-test.

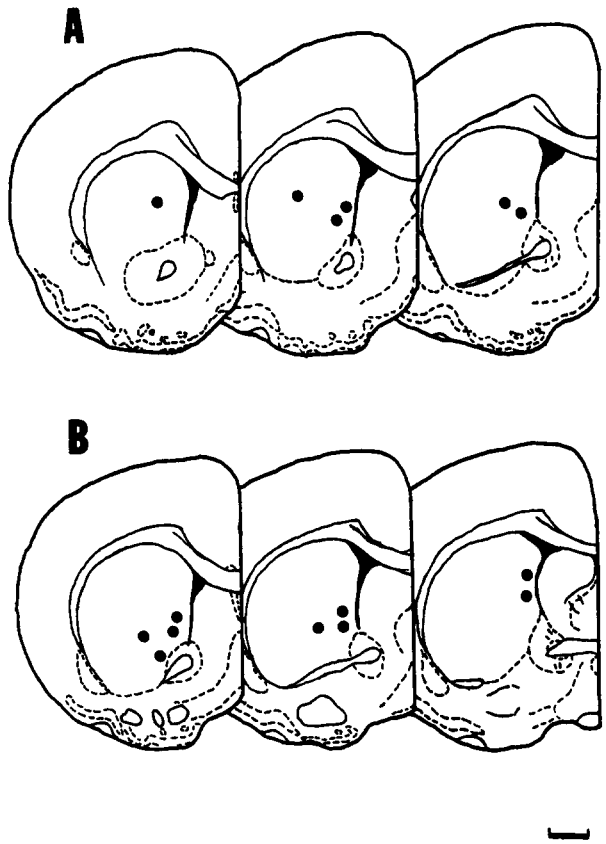

FIG. 6. Estimated syringe tips for 0 and 1 μg doses in 11-day-old pups (A) and 28-day-old pups (B). These drawings are adapted from Sherwood and Timiras (37). The bar in the lower right of the graph represents 1 mm. Distances from the interaural line are from left to right: (A) 5.9 mm, 5.6 mm, 5.3 mm; (B) 7.0 mm, 6.5 mm, 6.2 mm.

bilaterally into the striatum of adult rats.

In the present study, microinjections of SCH 23390 into the striatum of both 11- and 28-day-old rat pups produced catalepsy. However, with 5 μg SCH 23390, 11-day-old pups were less sensitive to the cataleptogenic effects of SCH 23390 than 28-day-olds. The 28-day-old pups were at a near maximum response using our criteria, while the 11-day-old pups at this dose were at approximately 50% of the maximum response shown by 28-day-old pups. Thus the striatal mechanisms responsible for the full expression of catalepsy are not mature at 11 days of age.

These behavioral results are generally consistent with findings from radioligand binding experiments, which have demonstrated that D_1 sites labelled by [^{3}H]SCH 23390 are below adult levels at approximately day 11 after birth and have reached or exceeded adult levels by day 28 after birth (17,42). Unpublished data from our laboratory have demonstrated that striatal D_1 binding site density (B_{max}) characterized by [^{3}H]SCH 23390 saturation studies in 11-day-old rats are significantly lower than 28-day-old rats (B_{max} = 1610 fmol/mg protein in 11-day-olds, B_{max} = 3290 fmol/mg protein in 28-day-olds) with no concomitant change in receptor affinity (K_d's = 0.5 nM for both ages). Thus the diminished catalepsy response to intrastriatal SCH 23390 in 11-day-old pups may be due to their deficit in D_1 binding sites relative to 28-day-old pups. However, other neurotransmitter systems postulated to influence SCH 23390-induced catalepsy, including the cholinergic, GABAergic and enkephalinergic systems, may also display ontogenetic changes which can explain our results (14,29).

A previous study by Fitzgerald and Hannigan (14) found that systemic injection of SCH 23390 produced a cataleptogenic response in 13-day-old rat pups which was of lesser magnitude than that obtained in 17- or 21-day-old pups. Further, 13-day-old pups were less sensitive to scopolamine reversal of catalepsy. Thus forebrain cholinergic system maturation may be necessary for the full expression of catalepsy. Our results extend the observations of Fitzgerald and Hannigan (14) by ruling out possible age-related differences in bioavailability of SCH 23390 following systemic injection. The results of this study and Fitzgerald and Hannigan (14) suggest that the expression of SCH 23390-induced catalepsy depends on maturation of the striatal D_1 receptor system, as well as development of the striatal cholinergic system.

In order to be able to draw conclusions about the regional specificity of SCH 23390-induced catalepsy during ontogeny, it was necessary to verify the distribution of [^{3}H]SCH 23390 throughout the rat brain following an intrastriatal injection. At both 10 and 20 minutes after the intrastriatal microinjection in the 28-day-old pups, [^{3}H]SCH 23390 was detectable in every brain region assessed. This suggests that SCH 23390 diffuses rapidly with this procedure, possibly via the lateral ventricles. Thus we cannot exclude the possible involvement of a nonstriatal system modulating catalepsy which would require blockade of a relatively small number of D_1 receptors.

Interestingly, at 10 minutes after injection, the septum contained more radioactivity than the striatum. This spread of radioactivity to the septal region most likely resulted because of the placement of injection sites at the medial portion of the caudate-putamen. In contrast to the caudate-putamen, the septum has a relatively low density of D_1 receptors, being approximately 5% of the density evident in the caudate-putamen (5, 11–13, 33). In addition, the radioactivity in the septum was considerably reduced at 20 minutes, suggesting that the drug readily diffused from this site. At 20 minutes, when the cataleptic response was maximal, the concentration of radioactivity was clearly greater in the injected striatum than in any other region examined. It is possible that the high density of D_1 sites in the striatum attenuated the diffusion process. Taken together, these results suggest that the catalepsy induced by microinjection of SCH 23390 in neonatal rats was most likely due to D_1 receptor blockade in the injection side striatum.

In conclusion, SCH 23390 microinjected into the striatum of 11- and 28-day-old rat pups produced marked catalepsy, suggesting that the D_1 receptor system responsible for catalepsy is intact by the eleventh day after birth in the rat. However, this catalepsy response was attenuated in 11-day-old rat pups compared to 28-day-old rat pups. The resistance to SCH 23390-induced catalepsy in 11-day-old rat pups is consistent with radioligand receptor binding studies which suggest that the D_1 receptor system is not fully developed at this age. In addition, previous studies suggest that the ontogeny of catalepsy to peripheral injections of SCH 23390 depends on maturation of forebrain cholinergic systems. Thus the maturation of the neural system(s) responsible for catalepsy in the rat may depend on a concomitant increase in striatal D_1 receptor and cholinergic function during the preweanling period.

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