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Effect of Nicotine Pretreatment on Striatal Dopaminergic System in Rats[1]

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FUNG, Y. K. AND Y.-S. LAU. *Effect of nicotine pretreatment on striatal dopaminergic system in rats.* PHARMACOL BIOCHEM BEHAV 32(1) 221–226, 1989.—Rats were pretreated with saline or nicotine (1.5 mg/kg/day) by subcutaneously implanting each animal with an Alzet osmotic minipump for 1 or 14 days. Short-term (1-day) administration of nicotine to rats reduced the stimulatory effect of (+)-amphetamine on locomotor activity. This was correlated with an attenuation in the ability of (+)-amphetamine to stimulate [^{3}H]dopamine formation from [^{3}H]tyrosine in rat striatal slices of these nicotine-treated animals. In long-term (14-day) nicotine-pretreated animals, both the apomorphine- and (+)-amphetamine-induced locomotor activity were potentiated. This behavioral potentiation was associated with an increase in the total number of postsynaptic dopaminergic receptor binding sites in the striatum. The development of striatal dopamine receptor supersensitivity may be caused by a decrease in the rate of dopamine turnover in the striatum.

Locomotor activity Dopamine Nicotine Striatum

SMOKING and/or chewing tobacco continually deliver nicotine to the central nervous system (4, 14, 23). Some of the central nervous system effects of nicotine are suggested to be mediated by stimulating the nicotinic receptors in the corpus striatum (12, 18, 19, 25). Activation of presynaptic nicotine receptors at the dopaminergic (DAergic) nerve terminals in striatal and mesolimbic regions has been shown to stimulate the release of dopamine (DA) (6, 12, 25). Therefore, DA may play an important role in eliciting some of the central nervous system effects in animals produced by the systemic administration of nicotine.

Acute administration of nicotine to rodents increases striatal turnover of DA (1, 2, 11). In most of these studies, nicotine was injected in high doses to laboratory animals, which may cause a rapid rise of nicotine level in the brain. Our previous studies showed that in acute (1-day) nicotine-treated rats, the stimulatory effects of apomorphine on postsynaptic DAergic receptors and locomotor activity were not affected (8). However, the stimulatory effect of (+)-amphetamine on locomotor activity was attenuated (8). The possible mechanisms underlying the above observations remain unclear. Therefore, this study was designed to evaluate in detail the behavioral and neurochemical changes following short-term (1-day) and long-term (14-day) administration of nicotine. Nicotine was continually administered to each animal by the subcutaneous implantation of an osmotic minipump containing the drug. This method of delivering nicotine will circumvent any instantaneous burst of nicotine to the brain as in the case of systemic injection (22). Consequently, changes in the neurochemistry of brain and the behavioral responses with continuous administration of nicotine can be correlated to provide important information regarding the effects of nicotine on striatal DAergic system. In these animals, the effects of short- and long-term nicotine pretreatment on locomotor activity, striatal DAergic receptor binding sites, the (+)-amphetamine-stimulated synthesis and release of DA, the concentrations and the rate of DA turnover were examined.

METHOD

Animals and Nicotine Pretreatment

Male, Sprague-Dawley rats (Sasco, Omaha, NE) weighing between 200–230 g were used. They were housed in groups of 3 per cage in a light- and temperature- (23± 1°C) controlled environment with a 12-hr light-dark cycle and free access to food (Purina Lab Chow, St. Louis, MO) and water.

Animals were anesthetized with a mixture of halo-

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thane/oxygen mixture and were implanted subcutaneously posterior to the shoulder with an Alzet osmotic minipump (Alza Corp., Palo Alto, CA, model 2001 for 1-day studies and model 2002 for 14-day experiments). These pumps were filled with either sterile physiological saline or nicotine (1.5 mg/kg/day). Before implantation, each pump was primed overnight at 37°C in physiological saline solution. The dose of nicotine administered was calculated as the free base using nicotine tartrate (Sigma Chemical Co., St. Louis, MO) dissolved in sterile physiological saline. Studies were conducted at 1 and 14 days after the pump implantation.

Assessment of Locomotor Activity

Locomotor activity of rats was measured with a motor activity cage equipped with photocells and an automatic counter (Lehigh Valley Electronics, Allentown, NJ). Each animal was allowed to adapt to the activity cage for 1 hr prior to the administration of saline, (+)-amphetamine (1 mg/kg, SC) or apomorphine (0.7 mg/kg, SC). After the drug injection, locomotor activity of each animal was determined at 10-minute intervals for a period of 90 minutes. All studies were conducted between 8 a.m. and 4 p.m.

[^{3}H]Spiperone Binding Assay

Striata from the nicotine-treated or saline-treated control animals were homogenized in 4 ml of 50 mM Tris-HCl buffer (pH 7.4, 4°C) containing 0.1% ascorbic acid, 0.01 mM pargyline, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$. The homogenate was centrifuged at 27,000×g for 20 min at 4°C. The pellet was additionally washed twice with the same buffer in the same manner. [^{3}H]Spiperone binding assay was performed according to our previous method (17) using (+)-butaclamol (1 μM) for determining the nonspecific binding sites and mianserin (1 μM) for masking [^{3}H]spiperone binding to 5-hydroxytryptamine receptors. The binding parameters (K_D and B_{max}) of the high affinity [^{3}H]spiperone binding sites were determined by using the nonlinear least-squares regression LIGAND analysis.

Determination of [^{3}H]DA Synthesis and Release

This study was conducted according to the method as described by Fung and Uretsky (10). Rats were killed and their striata were dissected, weighed and sliced into 0.25×0.25 mm square sections using a McIlwain tissue chopper. The tissue slices were dispersed in ice-cold normal medium containing 118.4 mM NaCl, 4.73 mM KCl, 1.2 mM KH_2PO_4, 1.18 mM $MgSO_4 \cdot 7H_2O$, 1.25 mM $CaCl_2 \cdot 2H_2O$ and 22 mM of 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid and 2 mg/ml dextrose. The solution was aerated with 95% O_2 and 5% CO_2 for 30 min and adjusted to pH 7.2 with 1 N NaOH. The slices were then centrifuged at 500×g for 5 min. The supernatant fluid containing amino acids released from the slices was discarded (16). The slices were then resuspended in a volume of cold normal medium such that each 0.25 ml aliquot of this suspension would contain 25 mg of the striatal tissue slices. (+)-Amphetamine (10^{-6} M) was added to the suspension in a final volume of 3 ml. The slices were aerated with 95% O_2 and 5% CO_2 and incubated in a shaking water bath at 37°C for 8 min. [^{3}H]Tyrosine was then added to a final concentration of 10 μM. The incubation was continued for an additional 20 min and the reaction was stopped by cooling the flasks on ice. Replicate slices that were kept on ice throughout the experiment served as blanks. Tissues were separated from the medium by centrifugation and both fractions were assayed for [^{3}H]DA. [^{3}H]DA was separated from [^{3}H]tyrosine by alumina absorption and ion exchange (Amberlite CG 50) chromatography. The radioactivity present was determined by liquid scintillation counting. The total [^{3}H]DA formation was obtained by adding the activity from both tissue and medium fractions. The release of newly synthesized [^{3}H]DA from the tissue was calculated by dividing the amount of [^{3}H]DA in the medium by the total amount of [^{3}H]DA formed (10).

TABLE 1

PLASMA LEVELS OF NICOTINE AND COTININE WITH NICOTINE TREATMENT

Treatment	Days	Nicotine (ng/ml)	Cotinine (ng/ml)
Saline	1	0	0
Nicotine (1.5 mg/kg)	1	14.0 ± 1.1*	119 ± 3.0*
Saline	14	0	0
Nicotine (1.5 mg/kg)	14	20.0 ± 2.0*	182 ± 21*

Animals were implanted subcutaneously with osmotic minipumps containing either physiological saline or nicotine (1.5 mg/kg/day) for 1 or 14 days. They were killed at the end of each period and plasma concentrations of nicotine and cotinine were determined by radioimmunoassays carried out by American Health Foundation, NY (13,16). Results are mean ± S.E.M. of 5 determinations.

*Significantly different from corresponding saline-treated controls ($p<0.05$, Student's t-test).

Determination of Striatal DA Concentrations

Isolated striata from nicotine-treated or saline-treated rats were suspended in 1 ml of 0.2 N perchloric acid. The sample was sonicated and centrifuged at 11,000×g for 5 min at 4°C. The supernatant was filtered through a nylon syringe filter unit (0.45 micron). An aliquot of the filtrate was injected into a high performance liquid chromatography (HPLC) (Waters, Milford, MA) in a mobile phase consisting of 100 mM sodium acetate, 20 mM citric acid, 100 mg/l sodium octyl sulfate (Eastman Organic Chemicals, Rochester, NY), 50 mg/l EDTA and 4% (v/v) methanol, pH 4.1. The sample was chromatographed by μBondapak C_{18} reversed phase column (3.9×150 mm, Waters, Milford, MA) at a constant flow rate of 2 ml/min. Dopamine concentration in each sample was determined by electrochemical detection at a potential of 0.6 V.

DA Turnover in the Striatum

The rate of DA turnover was measured as the rate at which the striatal DA level declined after intraperitoneal administration of the tyrosine hydroxylase inhibitor, alpha methyl-p-tyrosine (300 mg/kg, IP) (7). Rats were killed at 0, 1 and 2 hours after the injection of the inhibitor and their striata were used for the determination of DA contents using HPLC.

Drugs

All drugs were administered in a volume of 1 ml/kg body weight of animal. Amphetamine sulfate and alpha methyl-p-tyrosine methyl ester (Sigma Chemical Co., St. Louis, MO) were dissolved in physiological saline. Apomorphine hydro-

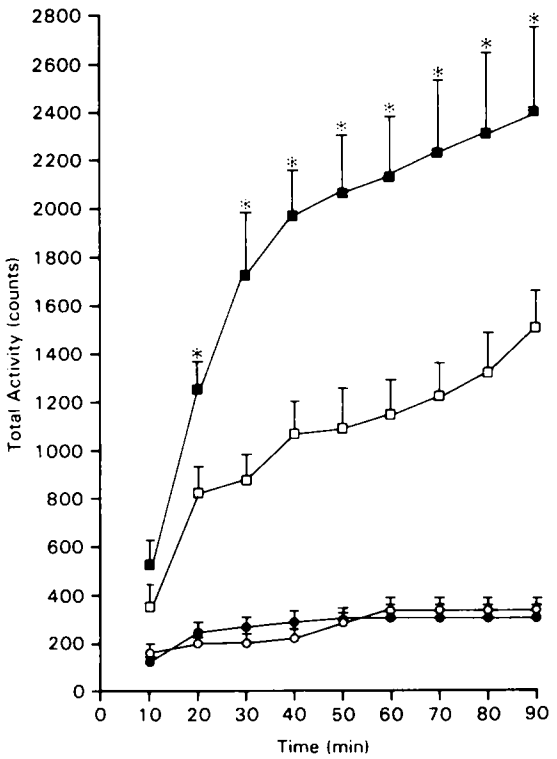

FIG. 1. Rats were implanted with osmotic minipumps containing either physiological saline or nicotine (1.5 mg/kg/day). Fourteen days later, each animal was allowed to adapt to a motor activity cage for 1 hr. Animals were injected with either saline or apomorphine (0.7 mg/kg, SC). Locomotor activities were monitored at 10-min intervals for 90 min. Data are presented as mean±S.E.M. of 5 animals. ○: Animals were implanted with saline pumps followed by saline injection, ●: animals were implanted with nicotine pumps followed by saline injection, □: animals were implanted with saline pumps followed by apomorphine injection, ■: animals were implanted with nicotine pumps followed by apomorphine injection. *Significantly different from saline-treated controls ($p<0.05$, Least significant difference test).

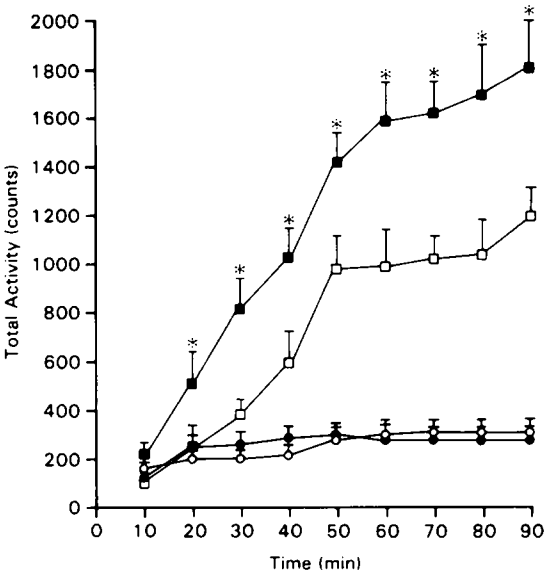

FIG. 2. Rats were implanted with osmotic minipumps containing either physiological saline or nicotine (1.5 mg/kg/day). Fourteen days later, each animal was allowed to adapt to a motor activity cage for 1 hr. Animals were injected with either saline or (+)-amphetamine (1 mg/kg, SC). Locomotor activities were monitored at 10-min intervals for 90 min. Data are presented as the mean± S.E.M. of 5 animals. ○: Animals were implanted with saline pumps followed by saline injection, ●: animals were implanted with nicotine pumps followed by saline injection, □: animals were implanted with saline pumps followed by (+)-amphetamine injection, ■: animals were implanted with nicotine pumps followed by (+)-amphetamine injection. *Significantly different from saline-treated controls ($p<0.05$, Least significant difference test).

chloride (Sigma Chemical Co.) was dissolved in 0.1% sodium metabisulfite. [^{3}H]Spiperone (23.2 Ci/mmole) was purchased from New England Nuclear (Boston, MA) and [^{3}H]tyrosine (55 Ci/mmole) was purchased from Amersham (Chicago, IL).

Statistical Analysis

For the biochemical data, differences between the means of treated groups were analyzed using the two-tail Student's *t*-test. Analysis of variance (ANOVA) was used to analyze the data on locomotor studies followed by Least significant difference test. A *p*-value of less than 0.05 was considered to be significant.

RESULTS

Plasma Levels of Nicotine and Cotinine

Determination of plasma levels of nicotine and its major metabolite cotinine showed consistency from animal to animal using the osmotic minipumps. Both 1- and 14-day administration of nicotine via the osmotic minipumps at a dose of 1.5 mg/kg/day maintained steady plasma nicotine and cotinine levels in these animals and their levels were significantly different from the saline-treated controls (Table 1).

Effect of Nicotine Pretreatment on Locomotor Activity

Systemic administration of apomorphine and (+)-amphetamine elicited hyperactivity in 14-day saline-treated animals. It is noteworthy in 14-day nicotine-treated rats that the behavioral responses to apomorphine and (+)-amphetamine were potentiated (Figs. 1 and 2).

Nicotine Treatment on Striatal [^{3}H]Spiperone Binding Sites

[^{3}H]Spiperone was used in this study to quantitate the D_2 receptor binding sites in the rat striatum. A dose-dependent [^{3}H]spiperone (0.1–5 nM) binding curve was determined in each of the control and nicotine-pretreated animals, and their respective K_D and B_{max} were compared. The K_D value for [^{3}H]spiperone binding was not affected throughout the time course of nicotine pretreatment (Table 2). We found an increase in the number of [^{3}H]spiperone binding sites in animals that were pretreated with nicotine for 14 days.

Effect of Nicotine Treatment on (+)-Amphetamine-Stimulated Formation and Release of [^{3}H]DA From [^{3}H]Tyrosine

We further examined the effect of short- and long-term

TABLE 2

EFFECT OF NICOTINE TREATMENT ON STRIATAL D_2 RECEPTOR BINDING SITES

Days	Treatment	[^{3}H]Spiperone Binding K_D (nM)	[^{3}H]Spiperone Binding B_{max} (fmol/mg)
1	Saline	0.15 ± 0.01	201.8 ± 11.6
	Nicotine	0.16 ± 0.02	195.5 ± 33.3
14	Saline	0.14 ± 0.01	210.0 ± 11.2
	Nicotine	0.12 ± 0.01	276.0 ± 10.2*

Animals were implanted subcutaneously with osmotic minipumps containing saline or nicotine (1.5 mg/kg/day) for 1 or 14 days. Animals were killed at the end of each period and striata were used for [^{3}H]spiperone binding assay. Values are presented as mean ± S.E.M. of 5–6 independent experiments.

*Significantly different from saline-treated controls ($p<0.05$, Student's t-test).

TABLE 3

EFFECT OF NICOTINE TREATMENT ON (+)-AMPHETAMINE-STIMULATED FORMATION AND RELEASE OF [^{3}H]DA IN RAT STRIATAL SLICES

Days	Pretreatment	Drug Added to Medium	[^{3}H]DA Formed (nmol/g/20 min)	[^{3}H]DA Released (%)
1	saline	none	2.5 ± 0.2	18.8 ± 1.0
1	nicotine	none	3.2 ± 0.4	24.4 ± 3.0
1	saline	amph.	6.3 ± 0.4	60.0 ± 2.0
1	nicotine	amph.	4.4 ± 0.5*	53.2 ± 2.2
14	saline	none	2.3 ± 0.4	16.7 ± 2.0
14	nicotine	none	2.6 ± 0.3	23.0 ± 2.8
14	saline	amph.	6.0 ± 0.3	61.2 ± 3.0
14	nicotine	amph.	5.2 ± 0.3	64.0 ± 3.6

Striatal slices (25 mg) from saline-treated or nicotine-treated (1.5 mg/kg/day) animals were incubated in normal medium with or without (+)-amphetamine (10^{-6} M). [^{3}H]Tyrosine was added and the reaction was continued for 20 min. [^{3}H]DA formation and release were determined (see the Method section for details). Data are presented as mean ± S.E.M. of 5–7 determinations.

*Significantly different from saline-pretreated (+)-amphetamine group ($p<0.05$, Student's t-test).

TABLE 4

EFFECT OF NICOTINE TREATMENT ON ENDOGENOUS STRIATAL DOPAMINE LEVELS

Days	Treatment	DA Concentration (μg/g tissue)
1	Saline	15.7 ± 0.6
	Nicotine	16.8 ± 0.8
14	Saline	14.6 ± 0.7
	Nicotine	14.3 ± 1.1

Animals were implanted subcutaneously with osmotic minipumps containing either saline or nicotine (1.5 mg/kg/day) for 1 or 14 days. Animals were killed at the end of each period and striata were used for the measurement of dopamine concentrations. Results are expressed as mean ± S.E.M. of 6 animals.

All values are not significantly different ($p>0.05$ Student's t-test).

nicotine administration on the ability of (+)-amphetamine to stimulate formation and release of [^{3}H]DA from [^{3}H]tyrosine in rat striatal slices. Since the maximal stimulation of DA formation and release occurred at 10^{-6} M concentration of (+)-amphetamine (24), this concentration was chosen in the present study. Addition of (+)-amphetamine to tissue slices significantly stimulated [^{3}H]DA formation and release. The results in Table 3 show that the ability of (+)-amphetamine to stimulate formation of [^{3}H]DA was attenuated in striatal slices from rats that were pretreated with nicotine for 1 day, although the ability of (+)-amphetamine to stimulate the release of [^{3}H]DA was not affected.

Nicotine Treatment on Striatal DA Levels

We examined the effect of nicotine treatment on striatal DA concentrations. The DA levels in 1- or 14-day nicotine-treated rats were not significantly different from saline-treated animals (Table 4).

Effect of Nicotine Treatment on Striatal DA Turnover

Rats which received nicotine for 1 day had shown no change in the rate of striatal DA turnover (Fig. 3). However, rats which received nicotine for 14 days showed a significant decrease in the rate of striatal DA turnover (Fig. 4). Thus, in these chronic nicotine-treated rats 1 and 2 hours after alpha methyl-p-tyrosine administration, striatal DA was reduced by 27% and 40% respectively, whereas in saline-treated controls, the reduction in DA was 40% and 56%.

DISCUSSION

In this study, nicotine was administered to rats at a dose of 1.5 mg/kg/day. This dose of nicotine produced plasma nicotine levels in rats similar to plasma nicotine levels found in an individual who smokes one pack of cigarettes a day (4, 14, 22, 23). Thus, the present study is designed to provide information more closely to nicotine intake as in the case of cigarette smoking in humans.

Our early studies showed that short-term (1-day) administration of nicotine antagonized the stimulatory effect of (+)-amphetamine on locomotor activity, whereas the direct action of apomorphine on locomotor activity was not affected (8). In the present study, we extended our investigation by examining the possible mechanisms for this behavioral difference. We had measured the number of striatal DAergic receptor binding sites as well as DA levels one day after continuous administration of nicotine. None of these parameters was affected by this short-term administration of nicotine. Nevertheless, using striatal tissue slices from one-day nicotine-treated rats, we found that the formation of [^{3}H]DA was significantly reduced, while the release of [^{3}H]DA from striatal slices was not affected. The behavioral effects of (+)-amphetamine are known to be mediated by releasing a pool of newly synthesized DA from nerve termi-

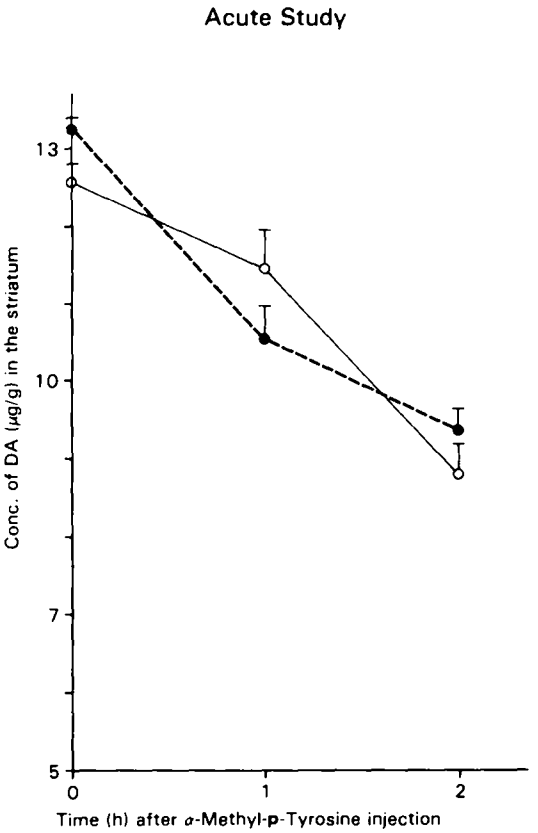

FIG. 3. Rate of DA depletion ($\mu g/g \pm$S.E.M.) in the striata of control (○) and 1-day nicotine-treated (●) rats. At the end of the pretreatment period, each animal was injected with alpha methyl-p-tyrosine methyl ester (300 mg/kg, IP). The striata were dissected and their DA concentrations were determined by high performance liquid chromatography, N=4–5 for each data point. The results between the saline and nicotine-treated groups are not statistically different ($p>0.05$, Student's t-test).

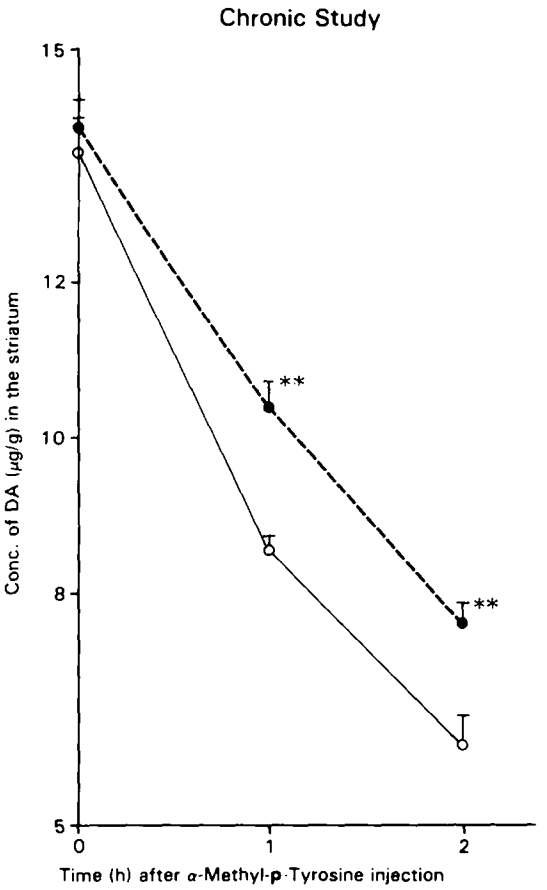

FIG. 4. Rate of DA depletion ($\mu g/g \pm$S.E.M.) in the striata of control (○) and 14-day nicotine-treated (●) rats. At the end of the pretreatment period, each animal was injected with alpha methyl-p-tyrosine methyl ester (300 mg/kg, IP). The striata were dissected and their DA concentrations were determined by high performance liquid chromatography, N=4–5 for each data point. *Significantly different from saline-treated group ($p<0.05$, Student's t-test).

nals in the striatum (5,9). If the amount of [^{3}H]DA released into the medium in the slice preparation represented the amount of DA released from striatal nerve terminals in vivo, we may conclude that the attenuation of (+)-amphetamine-induced hyperactivity in 1-day nicotine-treated rats is associated with an inhibition of DA synthesis in the striatum of these animals.

Other studies have shown that repeated systemic injections of nicotine for 7–10 days resulted in an up-regulation of nicotinic receptors in the striatum (15, 20, 21). Delivering nicotine to rats via osmotic minipumps, we were able to maintain a steady plasma level of nicotine throughout the treatment period. Using this method of nicotine administration, we observed an increase in L-[^{3}H]nicotine binding sites 5 days after the initiation of nicotine treatment (data not shown). However, receptor adaptation may have occurred so that after 14 days, the number of L-[^{3}H]nicotine binding sites had returned to control level (data not shown).

Interestingly, both the apomorphine and (+)-amphetamine-stimulated locomotor hyperactivity were potentiated in rats treated with nicotine for 14 days. Concurrently, we examined the ability of the striatal slices from these nicotine-treated animals to synthesize and release [^{3}H]DA from [^{3}H]tyrosine. Although this parameter was not significantly altered, we found an increase in the number of [^{3}H]spiperone binding sites in the striatum of the nicotine-treated animals. Consequently, the endogenous DA released by (+)-amphetamine or apomorphine, a direct-acting DA agonist, could interact with the increased number of postsynaptic DAergic receptors to enhance the locomotor activity.

Several studies have reported that acute administration of nicotine increases the rate of DA turnover in the striatum (1, 2, 11). In these studies, nicotine was generally administered to animals by bolus injections. Delivering nicotine to rats via the osmotic minipumps, we could not detect any abrupt change in the rate of DA turnover after 1 day. However, nicotine did have a chronic effect on the rate of DA turnover in the striatum. We observed a decreased DA turnover in the 14-day nicotine-treated rats.

The possible mechanism which may account for an increase in the number of striatal DA receptors in the 14-day nicotine-treated rats remains unclear. It is possible that a reduction in DA utilization in these animals could reduce the firing of the ascending DAergic pathway. The decrease in DAergic neuronal activity could lead to the development of supersensitivity of the postsynaptic DAergic receptors.

In summary, this study demonstrated that in one-day nicotine-treated animals, the (+)-amphetamine-stimulated synthesis of [^{3}H]DA in the striatum was reduced. This neurochemical change is probably responsible for the attenuation of (+)-amphetamine-induced hyperactivity in these animals. Chronic administration of nicotine via osmotic minipumps to rats decreased the rate of DA turnover and led to the development of postsynaptic DA receptor supersensitivity in the striatum. The increase in postsynaptic DA receptors may explain the potentiated locomotor responses induced by both apomorphine and (+)-amphetamine in these nicotine-treated animals.

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