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Nicotine Potentiation of Haloperidol-Induced Catalepsy: Striatal Mechanisms

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SANBERG, P. R., D. F. EMERICH, M. M. EL-ETRI, M. T. SHIPLEY, M. D. ZANOL, D. W. CAHILL AND A. B. NORMAN. *Nicotine potentiation of haloperidol-induced catalepsy: Striatal mechanisms.* PHARMACOL BIOCHEM BEHAV 46(2) 303–307, 1993.—Nicotine potentiated the catalepsy produced by haloperidol. The excitotoxin quinolinic acid (QA) selectively destroys striatal neurons when injected directly into the striatum. Bilateral QA lesions of the rat striatum (150 nmol) significantly reduced the catalepsy produced by haloperidol as well as the ability of nicotine to potentiate haloperidol-induced catalepsy. A second experiment examined whether the ability of nicotine to potentiate haloperidol-induced catalepsy was associated with a potentiation of dopamine turnover following haloperidol. Nicotine alone produced a mild increase in dopamine turnover relative to saline treated controls while haloperidol produced a marked increase in dopamine turnover relative to saline- and nicotine-treated controls. However, the combined administration of haloperidol and nicotine did not further elevate dopamine turnover over that observed following haloperidol alone. The results indicated that 1) nicotine could not potentiate haloperidol-induced catalepsy without an intact striatum and 2) the behavioral effect of nicotine and haloperidol cotreatment was not due to any change in dopamine turnover.

Nicotine Haloperidol Catalepsy Quinolinic acid Striatum Dopamine HPLC Tourette's syndrome

PREVIOUS reports suggested that systemic and intracaudate injections of nicotine potentiated reserpine-induced catalepsy in the rat (15, 16). We reported that nicotine produced more than a fivefold increase in haloperidol-induced catalepsy in rats (7,8,12,22) while producing no catalepsy when given alone. The potentiation of haloperidol-induced catalepsy by nicotine suggested that nicotine might increase the efficacy of neuroleptics in hyperkinetic motor disorders.

Tourette syndrome (TS) is a complex disorder characterized by motor tics and involuntary verbalizations (3,26). Although the underlying pathology of TS is unclear, it has been suggested that the symptomatology of TS is a result of altered extrapyramidal dopamine neurotransmission (24,27). The contention that excessive dopamine neurotransmission underlies the behavioral consequences of TS is supported by the improvement of motor tics following haloperidol and the occasional precipitation of TS following administration of dopaminergic stimulants (25). Our results indicated that chewing nicotine gum, when combined with ongoing haloperidol treatment, produced a rapid and pronounced relief from motor and verbal tics and attentional difficulties in the patients (13,14,21,22). These results suggested that nicotine might be a useful adjunct treatment for augmenting the therapeutic effects of neuroleptics in patients with movement disorders, such as TS.

The mechanism by which nicotine markedly potentiated the effects of haloperidol is unclear. Neuroleptic-induced catalepsy is believed to be mediated by the nigrostriatal dopamine system (4,18). Pharmacological studies have indicated positive correlations between striatal dopamine activity and the extent of haloperidol-induced catalepsy (28). On the other hand, neuroleptics with little effect on striatal dopamine produce little,

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if any, catalepsy (9,10). In addition, alterations of this system following neurotoxic damage have been shown to reduce the cataleptic response following neuroleptic treatment. It was demonstrated that kainic acid (KA) lesions of the intrinsic neurons within the striatum significantly reduced haloperidol-induced catalepsy (18,23). Similarly, Calderon et al. (4) reported that intrastriatal injections of the excitotoxin quinolinic acid (QA) attenuated neuroleptic-induced catalepsy. The following experiments examined 1) the effects of QA-induced striatal lesions on nicotine potentiation of haloperidol-induced catalepsy and 2) whether nicotine's potentiation of haloperidol-induced catalepsy is mediated via an interaction with striatal dopamine turnover. Because nicotine induces dopamine release in the nucleus accumbens and striatum (1,5), it is conceivable that the nicotine potentiation of neuroleptic catalepsy would be manifested as an alteration in striatal dopamine activity.

METHOD

Subjects

Eighteen male Sprague-Dawley rats obtained from Zivic-Miller breeders (PA) and weighing 300–350 g were housed in pairs and provided with food and water ad lib. Throughout the experiment the animals were housed in colony room maintained on a 12 h light/dark cycle with lights on at 07:00 h.

Surgery

Under sodium pentobarbital anesthesia (45 mg/kg, IP), animals were placed in a stereotaxic instrument (Kopf) and injected bilaterally with 150 nmol of QA (n = 8) or the phosphate-buffered saline vehicle (n = 10) into the striatum at the following coordinates: AP = +1.3 mm, ML = ± 2.6 mm and DV = 5.2 mm ventral from the surface of the brain. QA (Sigma Chemical Co., St. Louis, MO) was dissolved in 2 N sodium hydroxide and diluted with phosphate buffer at pH 7.2 to a final pH of 7.4 and a concentration of 150 nmol/μl. QA was infused into each striatum using a 28-ga Hamilton syringe over 5 min in a volume of 1 μl. The injection cannula was left in place for an additional 2 min to allow for diffusion of the perfusate.

Immediately following surgery, animals were injected IP with 3 ml of lactated Ringer's solution. Postoperatively, animals were housed with food mash and water available ad lib. Rats were weighed each day for 30 days postlesion. Rats that lost body weight for 2 consecutive days or exhibited and initial postoperative weight loss of 10% or more were intragastrically tube-fed 10 ml/day of a high caloric supplement (Similac) until the rat began to gain weight and eat and drink on its own.

Behavioral Testing and Experimental Design

Prior to testing, animals received an IP injection of either haloperidol or 0.9% saline. One hour later, these same animals received a second IP injection of either nicotine (free-base) or saline. This procedure resulted in the formation of six experimental groups; saline plus saline, saline plus nicotine (0.1 mg/kg), haloperidol (0.35 or 0.6 mg/kg) plus saline, or haloperidol (0.35 or 0.6 mg/kg) plus nicotine (0.1 mg/kg). All animals received each possible drug combination according to a cross-over design. Drugs or vehicle were administered with an interval of 2 days between each test day.

Two hours following injection, hypokinesia (catalepsy) was measured using the bar test as previously described (19). Briefly, the rear feet of the animals were placed on a platform and their front feet were placed on a horizontal bar (0.6 cm in diameter) suspended 9.0 cm above the platform. The degree of catalepsy produced in the animals was measured by how long it took for each animal to remove itself from the bar. A maximum of 900 s was allowed. Two hours was chosen because this is a maximal time for the nicotine potentiation of haloperidol catalepsy (22).

Histology

At the conclusion of behavioral testing animals were deeply anesthetized with pentobarbitol and transcardially perfused with isotonic saline followed by 4% paraformaldehyde. The

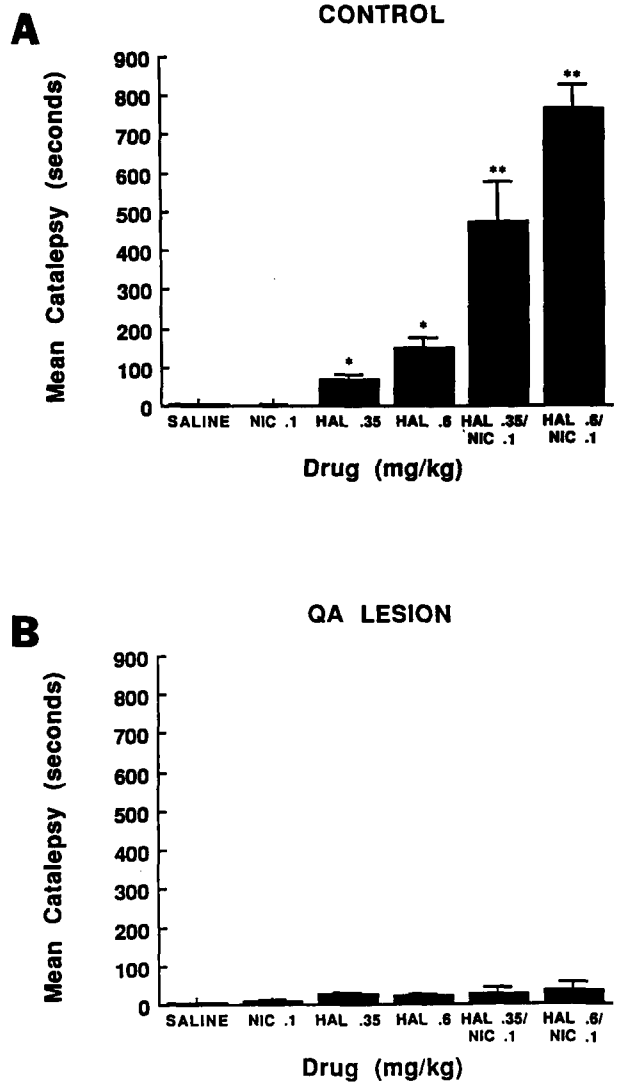

FIG. 1. Effects of bilateral quinolinic acid (QA) (150 nmol) lesions of the striatum on nicotine potentiation of haloperidol-induced catalepsy. This figure presents the mean ± SEM catalepsy (bar times) produced by haloperidol alone or in combination with nicotine 2 h following injection of nicotine in controls (A) and QA-lesioned (B) rats. *$p < 0.05$ vs. saline treated animals; **$p < 0.005$ vs. animals treated with same dose of haloperidol and saline.

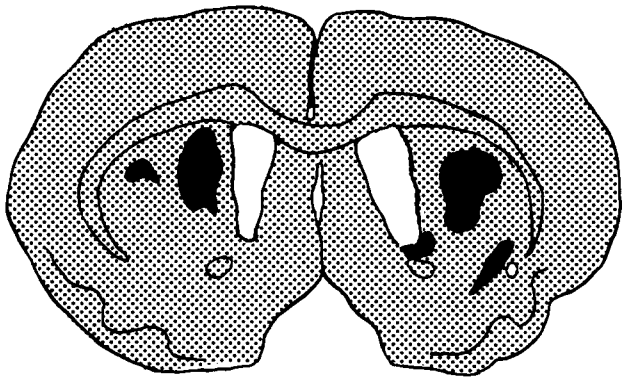

FIG. 2. Illustration of coronal section of a rat brain following bilateral QA (150 nmol) lesions of the striatum. Rats were perfused following conclusion of the behavioral testing at approximately 4 weeks postlesion. Dark areas correspond to areas of necrosis and reactive gliosis. Note the enlargement of the lateral ventricles and the shrinkage of the striatum typical of excitotoxin lesions.

brains were extracted and postfixed in 4% paraformaldehyde and 20% sucrose prior to sectioning. Coronal sections (30 μm thick) were cut on a freezing microtome and stained for cresyl violet.

Neurochemistry

For neurochemical analysis, a separate group of animals was treated with haloperidol (0.3 mg/kg) and/or nicotine (0.1 mg/kg) as described above. Two hours postinjection, the animals were sacrificed, the striatum dissected on ice and stored at −70°C until HPLC analysis as described below.

HPLC apparatus. HPLC determinations were achieved using a computerized Bioanalytical Systems (West Lafayette, IN) Model 200 Liquid Chromatograph. The reserved-phase (C_{18}) ion-pair separation was performed on a 100 × 3.2 mm Biophase ODS 3 μm column (Bioanalytical Systems). Electrochemical detections used a Bioanalytical Systems Model LC-4B electrochemical detector and a glassy carbon working electrode which was kept at a constant potential of 0.67 V vs. Ag/AgCl reference electrode. The sensitivity of the detector was kept at 10.0 nA full scale. The column and the detector were kept in a constant temperature environment of 40°C and 41°C, respectively.

Materials. Monochloracetic acid, octyl sodium sulfate, 3-hydroxytyramine hydrochloride (DA), homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), and the internal standard 3,4-dihydroxybenzylamine hydrobromide (DHBA) were obtained from Sigma Chemical Co. L-cysteine, Na_2EDTA, perchloric acid and acetonitrile (HPLC grade) were obtained from Fisher Scientific (Pittsburgh, PA).

For determination of biogenic amines in striatum, a low ionic-strength buffer (pH = 2.75) was used for the separation of the biogenic amines, plus the internal standard (DHBA) in an approximately 25-min run. The mobile phase consisted of 0.06 M monochloracetic acid, 1.2 mM octyl sodium sulfate and 0.1 mM Na_2EDTA in the aqueous phase and 4.2% acetonitrile in the organic phase. The mobile phase was filtered using a 0.22 μm filter, degassed with helium and kept at 35μC. The flow rate was kept at 1 ml/min. Working standard solutions containing DOPAC, HVA (5.0 ng/50 μl), and DA (12.5 ng/50 μl) were made up in 0.1 M perchloric acid containing 0.1% cysteine.

Extractions of DA and its metabolites were carried out as follows. The striata of each rat were individually homogenized in 750 μl of 0.1 M perchloric acid containing 0.1% cysteine and 15 ng of the internal standard (DHBA). Homogenization was performed at 0°C for 1 min prior to centrifugation at 1360 × g for 5 min at 4°C. For HPLC injection, 100 μl of the supernatant were diluted with 100 μl of the homogenization solvent and 10 μl of the final solution were injected into the HPLC. For peak height measurements, the same volume of 10 μl of the standards containing a constant amount (0.2 ng) of the internal standard DHBA were injected. Standards were injected between the runs to account for any loss in sensitivity of the working electrode and quantitation was done by comparing peak heights of unknowns to standards.

Statistical Analysis

Overall treatment effects were assessed with a two-way analysis of variance (ANOVA). The degree of catalepsy was analyzed separately for the control and QA-lesioned animals. Likewise, DA and metabolites were individually analyzed. Appropriate pairwise comparisons were performed with a Fisher's Least Significant Difference (LSD) test. Acceptable statistical significance was established as $p < 0.05$.

TABLE 1

EFFECTS OF HALOPERIDOL AND NICOTINE ON LEVELS OF STRIATAL DOPAMINE, DOPAC, AND HVA. DATA ARE EXPRESSED AS ng TRANSMITTER/g TISSUE ± SEM

	Control	Nicotine	Haloperidol	Haloperidol Nicotine
Dopamine	7,238 ± 288	7,150 ± 447	6,469 ± 532	6,717 ± 36
DOPAC	1,025 ± 69	1,406 ± 91*	3,707 ± 308†	3,835 ± 354†
HVA	894 ± 51	1,199 ± 77*	3,162 ± 284†	3,256 ± 249†
DOPAC/DA	0.14 ± 0.01	0.22 ± 0.01*	0.57 ± 0.03†	0.58 ± 0.04†
HVA/DA	0.12 ± 0.01	0.17 ± 0.01*	0.49 ± 0.03†	0.48 ± 0.02†

Animals received IP injections of haloperidol (0.3 mg/kg) followed by nicotine (0.1 mg/kg). One hundred and twenty minutes later, animals were sacrificed and their striata assayed for dopamine and metabolites using HPLC with electrochemical detection.

*Significantly different from Control, $p < 0.05$.

†Significantly different from Control and Nicotine Groups, $p < 0.05$.

RESULTS

Catalepsy

Figure 1 demonstrates that in control animals nicotine potentiated the catalepsy produced by haloperidol administration. A two-way ANOVA revealed significant effects of haloperidol [$F(5, 54) = 47.2, p < 0.0001$] and nicotine [$F(5, 54) = 6.72, p < 0.05$] as well as a significant interaction between haloperidol and nicotine [$F(25, 24) = 7.38, p < 0.05$]. Post-hoc analysis revealed that both doses of haloperidol (0.35 and 0.6 mg/kg) produced significant catalepsy relative to saline injected controls. This analysis further revealed that nicotine potentiated the cataleptic effects of haloperidol with the potentiation greatest following the 0.6 mg/kg dose of haloperidol. In contrast, animals receiving QA did not exhibit any catalepsy following either dose of haloperidol (F's < 1.0, $p > 0.05$). Likewise, nicotine did not produce any significant catalepsy when combined with haloperidol. Nicotine alone had no effect on catalepsy in either the control or QA-lesioned animals. Histological analysis revealed that the quinolinic acid injections produced lesions of striatal neuronal perikarya. This has been described in detail elsewhere (20). Figure 2 depicts a pictoral illustration of the typical extent of the lesion.

HPLC

While nicotine potentiated haloperidol-induced catalepsy, HPLC analysis demonstrated that the behavioral effects produced by nicotine co-treatment were not associated with a potentiation of haloperidol-induced dopamine turnover. Statistical analysis using two-way ANOVAs did not reveal any significant effects of haloperidol [$F(3, 29) = 1.1, p > 0.05$] or nicotine [$F(3, 29) = 1.8, p > 0.05$] on striatal levels of DA. This analysis did, however, reveal significant effects of haloperidol and nicotine on striatal levels of DOPAC [$F(3, 29) = 38.9, p < 0.05$]; [$F(3, 29) = 15.4, p < 0.05$], HVA [$F(3, 29) = 32.6, p < 0.05$]; [$F(3, 29) = 9.4, p < 0.05$], as well as the ratios of DOPAC/DA [$F(3, 29) = 104.5, p < 0.05$]; [$F(3, 29) = 36.7, p < 0.05$], and HVA/DA [$F(3, 29) = 102.3, p < 0.05$]; [$F(3, 29) = 30.8, p < 0.05$]. There were no significant interactions between haloperidol and nicotine for any of the above measures (F's > 0.05). As shown in Table 1, nicotine alone produced a moderate increase in DOPAC (37%) and HVA (34%) levels as well as the ratios of DOPAC/DA (57%) and HVA/DA (42%) when compared to saline-injected controls. Haloperidol alone produced a marked increase in dopamine turnover relative to saline and nicotine treated controls. This analysis revealed that DOPAC and HVA levels were increased 262% and 253% respectively, while the ratios of DOPAC/DA and HVA/DA were increased 307% and 308%. The combination of haloperidol and nicotine did not further increase haloperidol-induced DA turnover.

DISCUSSION

Quinolinic acid-induced striatal damage abolished the ability of haloperidol to elicit catalepsy as well as the ability of nicotine to potentiate haloperidol-induced catalepsy. The findings that QA abolished haloperidol-mediated catalepsy is consistent with previous reports that excitotoxic damage to the striatum attenuates haloperidol-induced catalepsy (4,18). Even though haloperidol-induced catalepsy itself is reduced by striatal lesions, one might expect that if nicotine's potentiation effect was extrastriatal, that it may have been able to produce potentiation in this experiment. However, the fact that nicotine could not potentiate cataleptic behavior without an intact striatum suggests a role for the striatum as the site of interaction for these two drugs on cataleptic behavior.

HPLC analysis indicated that nicotine alone produced a mild increase in dopamine turnover in the striatum while haloperidol markedly increased dopamine turnover. However, while the combined administration of haloperidol and nicotine drastically increased catalepsy, there was no parallel potentiation of haloperidol-induced dopamine turnover. The inability of nicotine to further increase dopamine turnover following haloperidol may represent a ceiling effect. That is, the increases in turnover following haloperidol alone may be maximal and cannot be further increased. Further studies with lower doses of haloperidol are warranted to test this hypothesis. Another possible explanation for further testing is that the acid metabolites might be working under first order kinetics. That is, the more metabolites being produced in the striatum, the more efficient the pumping out of metabolites from the brain. The slightly more metabolite in the combined group vs. the haloperidol alone group, may mean that the efficiency of the pumping mechanisms might be a factor. Future studies may want to block these pumps pharmacologically (i.e., probenicid) and measure changes in the metabolite concentrations.

More likely, the behavioral effects of nicotine in combination with haloperidol may be mediated via transmitter systems other than the striatal dopaminergic system. Several lines of evidence indicate that pharmacological manipulations of striatal GABAergic and cholinergic systems modulate the appearance of cataleptic behavior (19). For example, GABA agonists have been demonstrated to produce catalepsy as well as potentiate haloperidol-induced catalepsy (2,17). Likewise, catalepsy can be induced by cholinergic agonists with the extent of catalepsy subject to modification by the subsequent administration of dopaminergic antagonists. Moreover, haloperidol-induced catalepsy is antagonized by cholinergic antagonists (6,11). These results underscore the interplay between striatal dopaminergic, GABAergic, and cholinergic systems in mediating the functional output of the striatum. Because the output of the striatum depends on an interdependent series of synaptic connections utilizing dopamine, GABA and acetylcholine, it is possible that the effects of nicotine on neuroleptic-induced catalepsy may be related to alterations in one or more of these transmitter systems.

In conclusion, these data demonstrate that the ability of nicotine to potentiate haloperidol-induced catalepsy is dependent on an intact striatum. In addition, the potentiation of catalepsy following nicotine and haloperidol cotreatment is not associated with a parallel potentiation of haloperidol-induced dopamine turnover.

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