Pharmacology Biochemistry & Behavior, Vol. 38, pp. 875–880. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Nicotine Potentiates Haloperidol-Induced Catalepsy and Locomotor Hypoactivity

DWAINE F. EMERICH,# MARIE D. ZANOL,* ANDREW B. NORMAN,*†‡§¶
BRIAN J. McCONVILLE* AND PAUL R. SANBERG*†‡§¶#[1]

*Departments of *Psychiatry, †Anatomy, ‡Neurosurgery, §Psychology, and ¶Physiology*
University of Cincinnati, Cincinnati, OH 45267-0559
and #Cellular Transplants, Inc., Four Richmond Square, Providence, RI 02906

Received 20 November 1990

EMERICH, D. F., M. D. ZANOL, A. B. NORMAN, B. J. McCONVILLE AND P. R. SANBERG. *Nicotine potentiates haloperidol-induced catalepsy and locomotor hypoactivity*. PHARMACOL BIOCHEM BEHAV **38**(4) 875–880, 1991.—Nicotine was found to potentiate the catalepsy and reduced locomotion following the administration of haloperidol. The ability of various doses of nicotine (0.1, 0.2, or 0.3 mg/kg) to potentiate the catalepsy produced by haloperidol (0.1, 0.2, or 0.4 mg/kg) was investigated. Nicotine potentiated the cataleptic effects of both the 0.2 and 0.4 mg/kg doses of haloperidol, but had no effect following the lowest (0.1 mg/kg) dose of haloperidol. The nicotine potentiation of catalepsy produced by the highest dose of haloperidol was independent of the dose of nicotine used. Nicotine alone did not produce catalepsy. A second experiment evaluated the ability of nicotine to potentiate the decreases in spontaneous locomotor activity produced by haloperidol. Animals received nicotine (0.1 mg/kg) alone or in conjunction with haloperidol (0.1 or 0.4 mg/kg) and were tested in Digiscan Animal Monitors. Haloperidol produced a dose-related decrease in locomotion. Nicotine significantly potentiated the hypoactivity produced by both doses of haloperidol. These results indicated that: 1) nicotine produces a significant potentiation of both the catalepsy and locomotor decreases following haloperidol and 2) the Digiscan Animal Activity Monitors may provide a more sensitive assessment of the interaction between nicotine and haloperidol than the catalepsy bat test. These data suggest that adjunct treatment with nicotine may prove useful for treating neuroleptic responsive disorders such as Tourette Syndrome, schizophrenia and Huntington's disease.

Nicotine Haloperidol Catalepsy Locomotor activity

NEUROLEPTICS comprise a class of drugs which are commonly used for the treatment of a variety of psychiatric illnesses. Haloperidol has been used with varying degrees of success in treating the behavioral sequelae of schizophrenia, psychosis and mania. Tourette Syndrome (TS) is a complex disorder characterized by motor tics and involuntary verbalizations (4,24). Although the underlying pathology of TS is not well understood, current research has focused on the role of altered extrapyramidal dopamine neurotransmission in the production of the symptomatology of TS (25). The clinical improvement on motor tics following haloperidol and the occasional precipitation of TS following administration of dopaminergic stimulants has suggested that excessive dopamine neurotransmission may underlie the behavioral consequences of TS.

Although treatments are limited, TS is most commonly treated by neuroleptic medication, particularly haloperidol (23). While effective in approximately 70% of all TS cases, the utility of haloperidol treatment is restricted by the occurrence of deleterious side effects including decreased concentration (23). In addition, there is considerable long-term risk of tardive dyskinesia (9). In fact, Erenberg (8) reported that the majority of TS patients discontinue neuroleptic medication because of dissatisfaction with the side effects. A pharmacotherapeutic strategy which could potentiate the therapeutic action of haloperidol or other neuroleptics, and possibly reduce the side effects, would, therefore, be useful for individuals with TS or other psychiatric illnesses typically treated by neuroleptics.

Previous reports suggested that both systemic and intracaudate injections of nicotine potentiated reserpine-induced catalepsy in the rat (15). We recently reported that nicotine produced an almost 5-fold increase in haloperidol-induced catalepsy in rats (13,22). In contrast, nicotine alone had no effect on catalepsy. Given these results, we evaluated the possibility that nicotine might increase the efficacy of neuroleptic treatment in hyperkinetic disorders such as TS (21,22). 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. 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 present set of studies evaluated the effects of a series of doses of nicotine on catalepsy and locomotor activity following various doses of haloperidol. These experiments should help to

[1]Requests for reprints should be addressed to Dr. Paul R. Sanberg, Cellular Transplants, Inc., Four Richmond Square, Providence, RI 02906.

determine if a moderate to high dose of nicotine, in combination with a low dose of neuroleptic, can produce a behavioral effect equivalent to that produced by a high dose of neuroleptic alone. If so, then the use of nicotine as an adjunct treatment may allow the reduction of the dose of neuroleptic required clinically and reduce or eliminate the occurrence of both the short- and long-term effects produced by high dose neuroleptic treatment.

EXPERIMENT ONE

This study evaluated the effects of various doses of nicotine on the catalepsy elicited by haloperidol. If nicotine, in conjunction with a low to moderate dose of haloperidol, does indeed produce a behavioral effect (i.e., catalepsy times) which is similar in magnitude to that produced by a high dose of neuroleptic alone, then nicotine cotreatment may obviate the negative side effects associated with high dose neuroleptic treatment.

METHOD

Subjects and Experimental Design

Twenty-five male Sprague-Dawley rats obtained from Zivic-Miller breeders (PA) and weighing 25–350 grams were housed in pairs and provided with food and water ad lib. Throughout the experiment the animals were on a reverse 12-hour light/dark cycle with lights on at 1100 hours.

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 or saline. This procedure resulted in the formation of 4 experimental groups: saline plus saline, saline plus nicotine, haloperidol plus saline, or haloperidol plus nicotine. The doses of haloperidol were 0.1, 0.2, and 0.4 mg/kg and the doses of nicotine were 0.1, 0.2 and 0.3 mg/kg. All animals received each possible drug combination according to a cross over design. Drugs or vehicle were administered with an interval of 3 days between each test day.

Catalepsy

Hypokinesia (catalepsy) was measured using the bar test as previously described (20). 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 seconds was allowed. Bar tests were conducted 4 hours after administration of drug and/or control vehicle.

Statistical Analysis

Overall treatment effects were assessed with a two-way analysis of variance (ANOVA). Appropriate pair-wise comparisons were performed with a Fisher's Least Significant Difference (LSD) test. Acceptable statistical significance was established as $p<0.05$.

RESULTS

Figure 1 demonstrates that haloperidol produced a dose-related increase in catalepsy. While the lowest dose haloperidol (0.1 mg/kg) did not elicit a significant catalepsy the 0.2 and 0.4 mg/kg doses produced a marked catalepsy relative to saline-injected controls. A two-way repeated ANOVA revealed significant effects of haloperidol, $F(3,101)=72.0$, $p<0.0001$, and nicotine

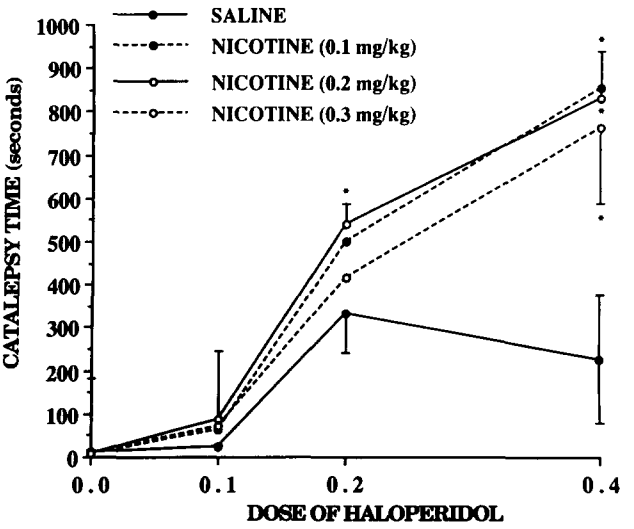

FIG. 1. The effects of nicotine (0.1, 0.2, or 0.3 mg/kg) on haloperidol-induced (0.1, 0.2, or 0.4 mg/kg) catalepsy. This figure presents the mean ± SEM catalepsy (bar times) produced by haloperidol alone or in combination with nicotine 4 hours following injection of nicotine. Figures in parentheses indicate dose of drug (mg/kg). *$p<0.05$ vs. haloperidol plus saline-treated animals.

treatment, $F(3,101)=4.28$, $p<0.05$, as well as a significant interaction between haloperidol and nicotine, $F(9,101)=3.0$, $p<0.05$. Post hoc analysis further revealed that nicotine potentiated the haloperidol-induced catalepsy. None of the doses of nicotine tested potentiated the effects of the lowest dose of haloperidol (0.1 mg/kg). The 0.2 mg/kg, but not the 0.1 or 0.3 mg/kg doses of nicotine, produced a significant potentiation in the catalepsy produced by the 0.2 dose of haloperidol. All doses of nicotine tested produced a significant and equivalent potentiation of the catalepsy produced by 0.4 mg/kg of haloperidol. Moreover, the extent of nicotine's potentiation was dependent on the dose of haloperidol used; those animals receiving the 0.4 mg/kg dose of haloperidol plus nicotine exhibited significantly greater potentiation of catalepsy than did the group receiving 0.2 mg/kg of haloperidol and the same dose of nicotine. Nicotine alone did not elicit any significant cataleptic effect at any of the doses used.

EXPERIMENT TWO

The results of Experiment One indicated that nicotine produced a marked and stable potentiation of haloperidol-induced catalepsy. However, this potentiation was not observed at the lowest dose of haloperidol used. Since low doses of haloperidol do not reliably elicit a pronounced catalepsy, the bar test may underestimate the interaction between nicotine and haloperidol (20). Lower doses of haloperidol may more closely approximate the doses of haloperidol used clinically. Accordingly, a more sensitive measure might be appropriate for evaluating the effects of a low dose of haloperidol in conjunction with nicotine. The following studies used the Digiscan Animal Activity Monitor for assessing locomotion. This instrument allows for the simultaneous collection of multiple indices of movement and permits a more precise analysis of motoric function than is possible with other methods (19). We have previously shown that low doses of haloperidol which do not produce a cataleptic effect in the bar test, significantly decreased locomotion as evaluated by the Digiscan system (4). The following studies evaluated the ability of nicotine

to potentiate the locomotor effects of haloperidol.

Subjects and Experimental Design

Sixty male Sprague-Dawley rats (250–350 grams) housed under identical conditions as those in Experiment One were used in the following study.

Animals were randomly assigned to one of 6 treatment groups: High dose haloperidol (0.4 mg/kg) plus nicotine (0.1 mg/kg), low dose haloperidol (0.1 mg/kg) plus nicotine (0.1 mg/kg), nicotine alone, high dose haloperidol alone, low dose haloperidol alone or vehicle control.

Spontaneous Locomotor Activity

Each animal was placed individually into one of eight open-field boxes ($40 \times 40 \times 35$ cm) in an automated Digiscan-16 Animal Activity Monitor System (Omnitech Electronics, Columbus, OH) for a 1-hour habituation period immediately prior to the 6-hour nocturnal testing period (1500–2100). Each box permitted free access to water and contained 35 grams of food pellets and approximately 50 grams of chip bedding. Data for the following 14 variables of locomotor activity detected by the digiscan Activity Monitors were collected by an IBM PB/XT compatible computer system: 1) horizontal activity (HA), the total number of interruptions of the horizontal sensors; 2) total distance (TD), the distance travelled by the animal in inches; 3) movement time (MT), the time in seconds that the animal spent in motion; 4) number of movements (NM), this parameter increased by one each time a movement was registered by the breaking of a beam separated by at least 1 second from the last interruption; 5) rest time (RT), the difference between total time and movement time; 6) average speed (SP), the average speed of the animals movement in cm/second; 7) average distance (AD), the average distance the animal moved in inches during a movement bout; 8) vertical activity (VA), the total number of beam interruptions in the vertical sensor; 9) vertical time (VT), this parameter increased while an animal was breaking the beam of a vertical sensor; 10) number of vertical movements (VM), this increased with vertical sensor beam interruptions that were separated by at least 1 second; 11) number of stereotypic movements (NS), this parameter increased when the same beams were broken repeatedly with 1 second in between; 12) stereotypy time (ST), the accumulated time spent in stereotypy; 13) clockwise rotations (CL), reported in number; 14) anticlockwise revolutions (AC), reported in number. The vertical beam level was set at 16.5 cm and the monitor interval was set at 1 hour.

Statistical Analysis

Data for each of the 14 locomotor variables was collapsed over the 6-hour test period and expressed as a percentage of control values. Treatment effects were assessed using a two-way factorial ANOVA. A two-way ANOVA, rather than a multiple factorial ANOVA, was used in order to evaluate each locomotor variable on an individual basis and obtain a detailed profile of activity or an "activity print" following haloperidol and/or nicotine (4, 18, 19). Appropriate pair-wise comparisons were performed using the Bonferroni multiple comparison method in order to control for experiment-wise error rate. Acceptable statistical significance was $p<0.05$.

RESULTS

Figure 2 demonstrates the topography of the animal's locomotion following haloperidol and/or nicotine as a percentage of control (i.e., saline/saline-treated animals). Haloperidol produced a dose-related decrease in locomotion. While the lowest dose of haloperidol (0.1 mg/kg) decreased only total distance and the number of stereotypic movements, 0.4 mg/kg of haloperidol significantly decreased all variables with the exception of rest time and average speed. Statistical analysis using two-way ANOVA's revealed significant effects of haloperidol as well as significant interactions between haloperidol and nicotine on the following locomotor variables: HA, $F(5,54)=13.27$, $p<0.01$; $F(25,54)=24.54$, $p<0.01$, TD, $F(5,54)=13.76$, $p<0.01$; $F(25,54)=31.23$, $p<0.01$, MT, $F(5,54)=5.44$, $p<0.05$; $F(25,54)=17.97$, $p<0.01$, NM, $F(5,54)=15.83$, $p<0.01$; $F(25,54)=12.53$, $p<0.05$, AD, $F(5,54)=4.09$, $p<0.05$; $F(25,54)=9.34$, $p<0.05$, VA, $F(5,54)=25.12$, $p<0.01$; $F(25,54)=35.79$, $p<0.01$, VT, $F(5,54)=23.32$, $p<0.01$; $F(25,54)=28.75$, $p<0.01$, VM, $F(5,54)=15.47$, $p<0.01$; $F(25,54)=30.10$, $p<0.01$, ST, $F(5,54)=10.69$, $p<0.01$; $F(25,54)=34.51$, $p<0.01$, NS, $F(5,54)=13.00$, $p<0.01$; $F(25,54)=35.43$, $p<0.01$, CL, $F(5,54)=6.00$, $p<0.05$; $F(25,54)=21.58$, $p<0.01$, and AC, $F(5,54)=4.11$, $p<0.05$; $F(25,54)=18.95$, $p<0.01$. No significant effects were found for nicotine alone on any of the locomotor indices (p's>0.5).

Post hoc analyses demonstrated that nicotine significantly potentiated the hypoactivity produced by haloperidol. Following 0.1 mg/kg of haloperidol, nicotine potentiated the haloperidol-induced decreases in TD, NM, AD, VA, VT, VM, ST, and CL. Following 0.4 mg/kg of haloperidol, nicotine significantly potentiated the decreases in HA, MN, and VM. Therefore, these data indicate that nicotine is able to potentiate the locomotor effects of a dose of haloperidol (shown in the previous experiment) to be subcataleptic. These analysis also revealed that nicotine in conjunction with a low dose of haloperidol (0.1 mg/kg) produced decreases in locomotion equivalent to those produced by a high (0.4 mg/kg) dose of haloperidol alone. The dose of nicotine used in these studies did not produce any significant locomotor alterations when given alone. The dose-effect function for nicotine on locomotor activity has been previously reported (11).

DISCUSSION

Nicotine significantly potentiated the catalepsy and locomotor hypoactivity produced by haloperidol. While the observation that nicotine cotreatment significantly increased catalepsy times is consistent with our previous reports (21,22), these data further indicated that nicotine is without effect following doses of haloperidol which are themselves subcataleptic. However, using the Digiscan Animal Activity Monitor, nicotine was observed to markedly potentiate the hypoactivity produced by the same subcataleptic dose of haloperidol. It appeared then, that the bar test for catalepsy may actually underestimate the behavioral interaction between nicotine and haloperidol. Using the activity monitors, it was apparent that nicotine, in conjunction with a low dose of haloperidol, produced a behavioral effect which closely resembled that obtained using a high dose of haloperidol alone. It should be pointed out, however, that the two present experiments do not provide direct statistical comparisons of the sensitivity of the catalepsy and locomotor testing situations. Regardless, given that the use of neuroleptics is often precluded by the occurrence of both short- and long-term deleterious side effects, nicotine cotreatment may prove useful ameliorating these negative side effects.

Although it has been suggested that nicotine has little or no therapeutic value (1), recent reports indicated that nicotine may ameliorate panic attacks (3), reduce pain anxiety (17), reduce apnea (10), improve Alzheimer's disease (16) and relieve hemidystonia (12). While these studies have examined the effects of nicotine alone, comparatively few studies have examined the in-

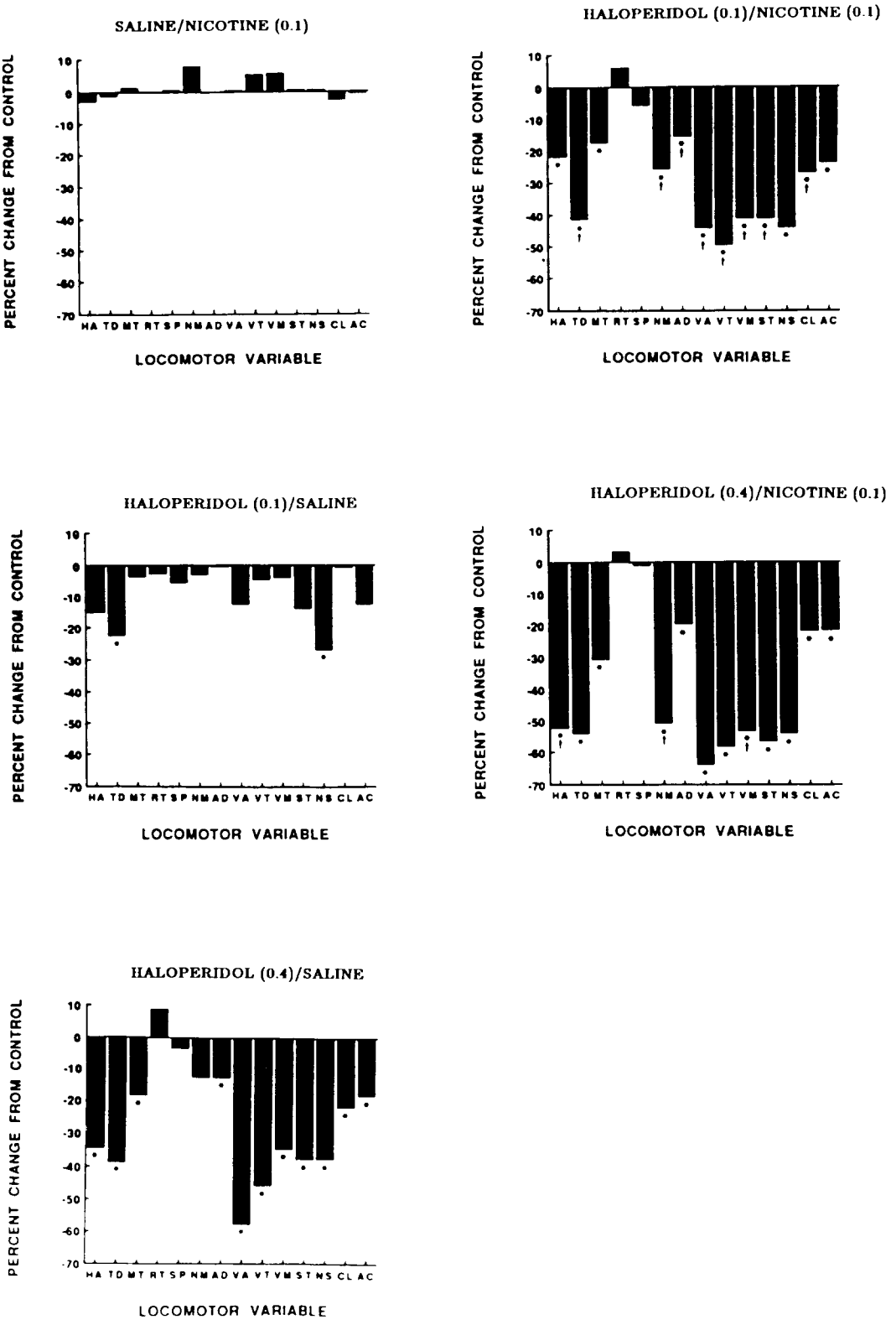

FIG. 2. The effects of nicotine (0.1 mg/kg) on the decreases in locomotion produced by haloperidol (0.1 or 0.4 mg/kg) as assessed using Digiscan 16 Animal Activity Monitors. Data are presented as mean percentages of control values (saline/saline-treated animals) for the 6-hour period. HA, horizontal activity; TD, total distance; MT, movement time; NM, number of movements; RT, rest time; AS, average speed; AD, average distance; VA, vertical activity; VT, vertical time; NV, number of vertical movements; NS, number of stereotypic movements; ST, stereotypy time; CL clockwise rotations; AC, anticlockwise revolutions. *$p<0.05$ vs.controls; †$p<0.05$ vs. animals treated with same dose of haloperidol plus saline.

teraction of nicotine with other psychotherapeutic drugs. Given the powerful potentiation of neuroleptic catalepsy in animals by nicotine, we examined the ability of nicotine to increase the efficacy of neuroleptic treatment in hyperkinetic motor disorders, such as TS. We reported that chewing nicotine gum, when combined with continuing haloperidol treatment, produced a rapid and pronounced relief from tics and attentional problems in TS patients (21,22). After 15–20 minutes, the severity and intensity of motor and verbal tics were decreased and an increase in concentration and attention was noted by both the patients and their parents in 80% of the cases. Moreover, in a pilot placebo trial, two patients who were administered regular nonnicotine gum showed no change in TS symptoms. In our open trials completed so far, the results showed a highly significant decrease in the frequency and severity of tics, both during the gum chewing period and for a subsequent one-hour period. Together, the animal and human studies suggested that nicotine is only of value when combined with a neuroleptic. Interesting, previous reports have suggested that nicotine alone may reduce the severity of the symptoms of TS (6). We are currently conducting a series of clinical studies to more carefully evaluate the possibility that nicotine alone is of some benefit in the treatment of the behavioral consequences of TS.

The mechanism by which nicotine can markedly potentiate the effects of haloperidol is unclear. Because nicotine induces dopamine release in the nucleus accumbens and striatum (2,5) we investigated the effects of nicotine on striatal HVA and DOPAC concentrations 120 minutes postinjection. Haloperidol produced a marked increase in dopamine turnover which has previously been shown to be the result of compensatory neuronal activity of dopamine neurons following blockade of postsynaptic dopamine receptors. However, the combination of nicotine and haloperidol did not produce any significantly greater effect on dopamine turnover even though these animals showed a synergistic potentiation in the cataleptic response (7). Thus it was unlikely that the behavioral effects of nicotine and haloperidol cotreatment were due to any change at the level of dopamine release. We are currently in the process of investigating neurochemical alterations and receptor changes at the intrinsic cholinergic synapse and the efferent GABAergic output from the striatum. Nicotine is a potent agonist of nicotinic cholinergic receptors. The blockade of striatal dopamine receptors by haloperidol increases striatal cholinergic activity. It is possible that the combined increase cholinergic activity by dopamine inhibition and nicotine activation may stimulate the efferent inhibitory influence of the striatum (presumably GABAergic) on motor activity.

In conclusion, these data indicated that nicotine, in conjunction with haloperidol, markedly potentiates the haloperidol-induced catalepsy and locomotor decreases. These data also indicated that the Digiscan Animal Activity Monitors provide a more sensitive assessment of the interaction between nicotine and haloperidol than the bar test. Nicotine may prove useful for the treatment of neuroleptic responsive disorders such as TS, schizophrenia and Huntington's disease.

REFERENCES

1. AMA Council on Scientific Affairs. Health effects of smokeless tobacco. Conn. Med. 51:53–60; 1987.
2. Anderson, K.; Fuxe, K.; Agnati, L. F. Effects of single injections of nicotine on the ascending dopamine pathways in the rat: evidence for increases in dopamine turnover in the mesostriatal and mesolimbic dopamine neurons. Acta Physiol. Scand. 112:345–347; 1981.
3. Brunn, R. D. Gilles de la Tourette Syndrome: An overview of clinical experience. J Am. Acad. Child Psychiatry 23:126–133; 1984.
4. Bunsey, M. D.; Sanberg, P. R. The topography of the locomotor effects of haloperidol and domperidone. Behav. Brain Res. 19:147–152; 1986.
5. Clarke, P. B. S.; Fu, D. S.; Jakubovic, A.; Fibiger, H. C. Evidence that mesolimbic dopamine activation underlies the locomotor stimulant action of nicotine in rats. J. Pharmacol. Exp. Ther. 246:701–708; 1988.
6. DeVor, E. J.; Isenberg, K. E. Nicotine and Tourette's syndrome. Lancet 2:1046; 1986.
7. Emerich, D. F.; Sanberg, P. R.; Manderscheid, P. Z.; McConville, B. J.; Rich, J. M.; El-Etri, M. M.; Shipley, M. T.; Norman, A. B. Differential effect of nicotine on D1 vs D2 antagonist-induced catalepsy. Soc. Neurosci. Abstr. 16:247; 1990.
8. Erenberg, E.; Cruse, R. P.; Rothner, A. D. The natural history of Tourette syndrome: a follow-up study. Ann. Neurol. 22:383–385; 1987.
9. Golden, G. S. Tardive dyskinesia in Tourette syndrome. Pediatr. Neurol. 1:192–194; 1985.
10. Gothe, B.; Strohl, K. P.; Levin, S.; Cherniack, N. S. Nicotine: A different approach to treatment of obstructive sleep apnea. Chest 87: 279–283; 1985.
11. Jerome, A.; Sanberg, P. R. The effects of nicotine on locomotor behavior in nontolerant rats: a multivariate analysis. Psychopharmacology (Berlin) 93:397–400; 1987.
12. Lees, A. J. Hemidystonia relieved by nicotine. Lancet 1:871; 1984.
13. Manderscheid, P. Z.; Sanberg, P. R.; Norman, A. B.; Fogelson, H. M.; McConville, B. J.; Moss, D. E. Nicotine markedly potentiates neuroleptic-induced catalepsy. Soc. Neurosci. Abstr. 14:1257; 1988.
14. Montgomery, S. P.; Moss, D. E.; Manderscheid, P. Z. Tetrahydrocannabinol and levonantradol effects on extrapyramidal motor behaviors: neuroanatomical location and hypothesis of mechanism. In: Harvey, D. J.; Paton, W. D. M., eds. Marijuana 84. Oxford: IRL Press; 1985:295–302.
15. Moss, D. E.; Manderscheid, P. Z.; Kobayashi, H.; Montgomery, S. P. Evidence for the nicotine cholinergic hypothesis of cannabinoid action within the central nervous system: extrapyramidal behaviors. In: Chesher, G.; Consroe, P.; Musty, R., eds. Marijuana: An international research report, Monograph Series No. 7. Canberra, Australia: Australian Government Publishing Service; 1988:359–364.
16. Newhouse, P. A.; Sunderland, T.; Thompson, K.; Tariot, P. N.; Weingartner, J.; Mueller, E. R.; Cohen, R. M.; Murphy, D. L. Intravenous nicotine in a patient with Alzheimer's disease. Am. J. Psychiatry 143:1494–1495; 1986.
17. Pomerleau, D. F. Nicotine as a psychoactive drug: anxiety and pain reduction. Psychopharmacol. Bull. 22:865; 1986.
18. Sanberg, P. R.; Hagenmeyer, S. H.; Henault, M. A. Automated measurement of multivariate locomotor behavior in rodents. Neurobehav. Toxicol. Teratol. 7:87–94; 1985.
19. Sanberg, P. R.; Henault, M. A.; Hagenmeyer-Houser, S. H.; Russell, K. H. The topography of amphetamine and scopolamine-induced hyperactivity: toward an activity print. Behav. Neurosci. 101:131–135; 1987.
20. Sanberg, P. R.; Bunsey, M. D.; Giordano, M.; Norman, A. B. The catalepsy test: its ups and downs. Behav. Neurosci. 102:748–759; 1988.
21. Sanberg, P. R.; Fogelson, H. M.; Manderscheid, P. Z.; Parker, K. W.; Norman, A. B.; McConville, B. J. Nicotine gum and haloperidol in Tourette syndrome. Lancet 1:592; 1988.
22. Sanberg, P. R.; McConville, B. J.; Fogelson, H. M.; Manderscheid, P. Z.; Parker, K. W.; Blythe, M. M.; Klyklyo, W. M.; Norman, A. B. Nicotine potentiates the effects of haloperidol in animals and in patients with Tourette's syndrome. Biomed. Pharmacother. 43:19–23; 1989.
23. Shapiro, A. K.; Shapiro, E. Treatment of tic disorders with haloperi-

dol. In: Cohen, D. J.; Brunn, R. D.; Lackman, J. F., eds. Tourette syndrome and tic disorders: clinical understanding and treatment. New York: John Wiley and Sons; 1988.
24. Singer, H. S. Tics and Tourette syndrome. Johns Hopkins Med. J. 151:30–35; 1982.
25. Singer, H. S.; Butler, I. J.; Tune, L. E.; Seigert, W. E.; Coyle, J. T. Dopaminergic dysfunction in Tourette syndrome. Ann. Neurol. 12:361–366; 1982.