Pharmacology, Biochemistry and Behavior 94 (2010) 410–415

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Acute nicotine and phencyclidine increase locomotor activity of the guinea pig with attenuated potencies relative to their effects on rat or mouse

Mark A. Simmons [a,b,*], Jennifer L. Werkheiser [a], Thomas J. Hudzik [a]

[a] Department of Neuroscience Biology, AstraZeneca Pharmaceuticals, Wilmington, Delaware, USA
[b] Department of Integrative Medical Sciences, Northeastern Ohio Universities College of Medicine, Rootstown, Ohio, USA

ARTICLE INFO

Article history:
Received 22 May 2009
Received in revised form 2 October 2009
Accepted 9 October 2009
Available online 17 October 2009

Keywords:
Nicotine
Phencyclidine
MK-801
Dizocilpine
Locomotor activity
Guinea pig

ABSTRACT

Behavioral assays of the responses to psychomotor stimulants can be used to model certain aspects of CNS pathologies such as psychosis and addiction. However, species-dependent differences in the effects of neuromodulators in these assays can confound the interpretation of the results. The goal of this study was to determine the utility of the guinea pig as a model for assessing the behavioral actions of nicotinic receptor agonists and NMDA receptor antagonists. In the present study, the locomotor activity of adult male guinea pigs was measured, prior to and following an acute injection of nicotine, MK-801 or phencyclidine. Each animal received a single dose of the drug.

Nicotine produced a dose-dependent increase in activity with an ED_{50} of 1.5 mg/kg. Phencyclidine also increased activity, with an ED_{50} of 3.4 mg/kg. Nicotine produced increases in locomotion in all individual subjects tested, whereas at the maximally-effective dose of phencyclidine, only a fraction of the animals had locomotor activation. There was no change in activity in response to a single dose of MK-801 (0.5 mg/kg). Haloperidol had a significant inhibitory effect on locomotor activity independent of the stimulant administered. Thus, both phencyclidine and nicotine are psychomotor stimulants when given to guinea pigs, although the intensity of the response and the potencies of these drugs are lower than in mice or rats under otherwise similar conditions.

The behavioral effects of nicotine and phencyclidine have been well documented in rat and mouse. In rats, the response to nicotine, as well as to other psychomotor stimulants, is biphasic, depending upon a number of factors. Among the most important are the dose administered and the baseline level of activity. Age, gender and strain also play a role (Clarke and Kumar, 1983a,b; Nordberg and Bergh, 1985; Freeman et al., 1987; Ksir et al., 1987; Itzhak and Martin 1999; Domino, 2001). Similar factors determine the effects of the NMDA antagonists, phencyclidine and ketamine. These, too, result in biphasic effects on locomotor activity, with an increase in activity at intermediate doses and ataxia progressing to dissociative anesthesia at higher doses (Sturgeon et al., 1979; Contreras et al., 1988; Hargreaves and Cain, 1995). Phencyclidine appears to have stronger locomotor stimulant effects than ketamine, due to its greater potency at the NMDA receptor (Wong et al., 1988; Koek et al., 1990) and concurrent inhibition of synaptic monoaminergic transporters (Kari et al., 1978; Snell et al., 1988; Hiramatsu et al., 1989).

Besides the above-mentioned factors, there are also species-specific differences in the behavioral and biochemical responses to some psychoactive agents. Potential sources of this species-specific variability include differences in pharmacokinetics, receptor composition and receptor distribution among different species. For example, guinea pigs may provide a better model for behavioral studies of ligands interacting with 5-HT_{1B} and NK_3 receptors than rats or mice (Regoli et al., 1994; Wu et al., 1994; Chung et al., 1995; Zgombick et al., 1997; Pauwels et al., 1998; Sarau et al., 1997, 2000; Emonds-Alt et al., 2002).

Both the 5-HT_{1B} and NK_3 receptors alter the effects of psychomotor stimulants (Przegalinski et al., 2001; Fletcher et al., 2002; Silva et al., 2008). Given that behavioral assays of the responses to psychomotor stimulants are used as models of human disorders such as psychosis or addiction, species-dependent differences in the effects of neuromodulators can confound the interpretation of the results. This can be a particular concern when attempting to correlate the pharmacology of these modulators to the effects of these agents in primate models.

The goal of this study was to determine the utility of the guinea pig as a model for assessing the behavioral actions of drugs representing two different classes of agents that have been shown to have locomotor stimulant activity in other species: a nicotinic receptor agonist and a NMDA receptor antagonist.

1. Methods

1.1. Subjects

96 male Dunkin Hartley guinea pigs (Harlan), weighing 300–400 g, were used. Subjects were housed 4 per cage, and were

* Corresponding author. Department of Integrative Medical Sciences, Northeastern Ohio Universities College of Medicine, 4209 State Route 44, P.O. Box 95, Rootstown, OH 44272-0095, USA. Tel.: +1 330 325 6525; fax: +1 330 325 5912.
E-mail address: simmons@neoucom.edu (M.A. Simmons).

0091-3057/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2009.10.002

acclimated to the facility for at least a week, and given access to food and water ad libitum except during experimental testing.

1.2. Apparatus

Animals were placed into plexiglass Med Associates locomotor activity boxes (43 × 43 × 30 cm). The boxes are within ventilated, sound-attenuating external chambers. Locomotor activity was measured by infrared photobeam breaks and distance traveled calculated.

1.3. Procedure

Animals were weighed and placed in the locomotor activity boxes for a 30 min habituation period. After the habituation period, the animals were removed one at a time, injected subcutaneously with nicotine, phencyclidine, MK-801 or saline, and immediately returned to the boxes for an additional 60 min. Acquisition of data was paused briefly during the injections. Data were continuously acquired before and after injections, cumulated and written each minute. Haloperidol injections were given just prior to placing the animals in the boxes for the 30 min habituation period, i.e. 30 min prior to nicotine or phencyclidine.

1.4. Drugs

Nicotine bitartrate, MK-801 maleate and phencyclidine HCl (Sigma Chemical) were dissolved in phosphate buffered saline. The pH of nicotine solutions was adjusted to 7.4. Haloperidol (Sigma Chemical) was dissolved in distilled water, to which was added a few drops of lactic acid to promote dissolution. All doses are expressed as the free base of drug.

1.5. Data analysis and statistics

Locomotor activity is expressed as distance traveled (DT) in cm as calculated by the Med Associates software. Data are expressed as mean ± s.e.m. The statistical significance of the changes in DT as a function of time and dose were analyzed by a two-way repeated measure ANOVA using the SigmaStat program. Post hoc multiple comparisons were made using the Student-Newman-Keuls method with significance level set to $p < 0.05$. ED_{50}s were calculated by fitting the dose–response data to the sigmoidal equation: $E = (E_{max} * [drug]) / (ED_{50} + [drug])$.

2. Results

2.1. Baseline

Following first placement in the chambers, animals exhibited exploratory activity (Fig. 1A). This initial activity decreased to almost zero by 25 min, reflecting habituation. A two-way repeated measures ANOVA showed that there was no difference between the different treatment groups during this initial period [$F(5,35) = 1.3$, $p = 0.29$] but there was a significant effect of time [$F(5,175) = 152.1$, $p < 0.001$]. Upon being returned to the chambers following handling and vehicle injection, there was a brief increase in activity observed for an additional 5 min, after which vehicle-injected animals exhibited very little activity (Fig. 1B, x).

2.2. Nicotine

Following injection of 1 mg/kg or higher doses of nicotine there was an immediate increase in activity that subsided over the following 30 min (Fig. 1B). A two-way repeated measures ANOVA showed significant treatment [$F(5,35) = 5.5$, $p < 0.001$] and time [$F(11,385) = 13.1$, $p < 0.001$] effects as well as a significant treatment × time interaction [$F(55,385) = 2.6$, $p < 0.001$]. The post hoc test revealed that the activity of the animals that received 1, 3 or 6 mg/kg nicotine was significantly greater than the other groups at 10 and 15 min after injection (*). At 20 min, the activity of the animals that received 3 and 6 mg/kg was greater than that of the other groups (‡) and at 25 min the 6 mg/kg group showed greater activity (#).

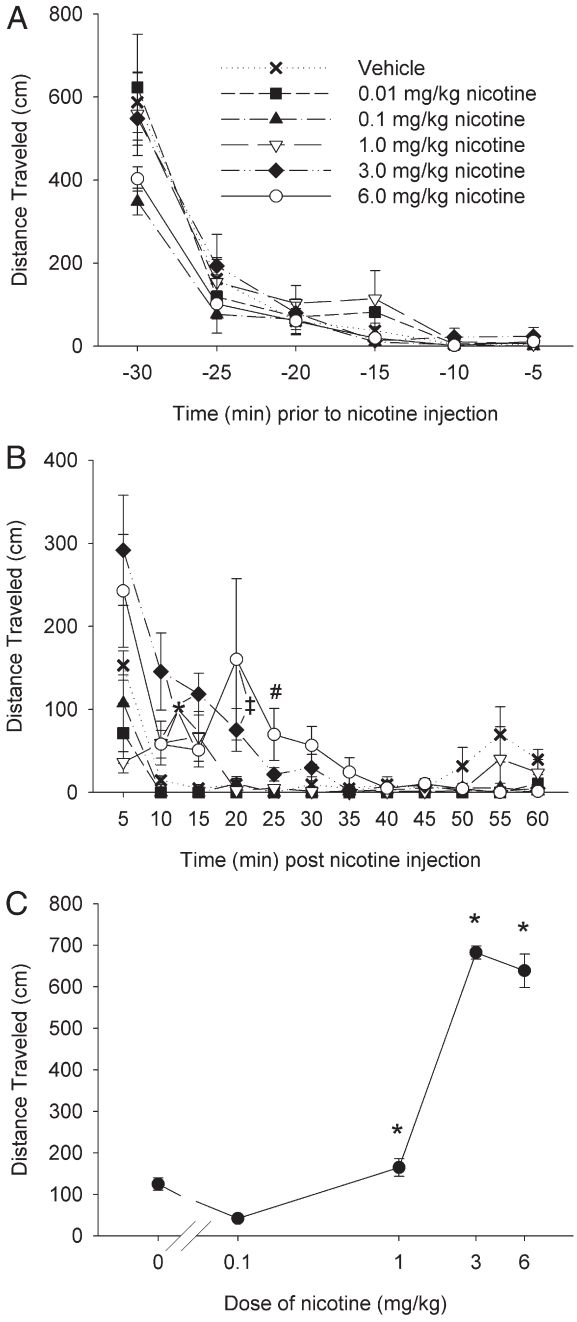

Fig. 1. Time and dose-dependence of the effects of nicotine on locomotor activity of the guinea pig. A. Habituation to the locomotor chambers. Naïve animals were placed in the chamber for 30 min prior to nicotine injection. The plots show the activity as a function of time and subsequent nicotine dose. Two-way analysis of variance showed a significant effect of time but no effect of subsequent dose. B. The effects of various doses of nicotine on locomotor activity. After the habituation period shown in A, animals were injected with various doses of nicotine. Nicotine produced significant dose-dependent increases in locomotor activity. *, ‡ and # indicate points at which the activity of the animals in the indicated groups was significantly greater than the other groups ($p < 0.05$). C. Dose–response curve for nicotine-induced locomotor activity. The total distance traveled for the 30 min following nicotine injection was calculated and is plotted as a function of nicotine dose. There was a significant increase in activity with nicotine at 1 mg/kg or above that peaked at 3–6 mg/kg. *indicates points at which the activity of the animals at the indicated doses was significantly greater than the vehicle group ($p < 0.05$).

The dose–response curve for nicotine is shown in Fig. 1C. Nonlinear regression of this data gave an ED_{50} of 1.5 mg/kg. The number of animals that responded to each dose of nicotine is shown in Table 1. All but one of the animals injected with nicotine at a dose of 1 mg/kg or higher showed an increase in locomotor activity in response to the drug (Table 1).

2.3. Phencyclidine

The animals that received phencyclidine exhibited the same pattern of baseline activity prior to injection (Fig. 2A). A two-way repeated measures ANOVA showed that there was no difference between the different treatment groups during this initial period [$F(4,32)=10.6$, $p=0.67$], but there was a significant effect of time [$F(5,158)=144.4$, $p<0.001$]. The response to phencyclidine differed from the response to nicotine in terms of the number of animals that responded to the drug with an increase in locomotor activity. While 96% of the animals responded to nicotine, only half of the animals responded to phencyclidine (Table 1). This variability in number animals responding accounts for the large error in the mean values seen at doses of 6 and 10 mg/kg phencyclidine. The two-way ANOVA showed significant drug [$F(11,274)=2.7$, $p=0.002$] and time [$F(11,274)=2.7$, $p<0.001$] effects as well as a significant treatment x time interaction [$F(44,274)=2.0$, $p=0.014$].

The activity following injection of 1 mg/kg phencyclidine (Fig. 2B, ■) was similar to that following vehicle injection (Fig. 2B, ×). Following injection of 3 mg/kg phencyclidine there was an increase in the average DT for the group at 5 min following the injection due to a huge increase in activity of one animal. Otherwise, responses to this dose were not different from vehicle-injected animals (Fig. 2B, ▲). Following injection of 6 mg/kg phencyclidine an increase in activity appeared at 20–50 min after the injection (Fig. 2B, ▽). A post hoc test revealed that the activity of the group that received 6 mg/kg phencyclidine had significantly elevated activity at 20–45 min after injection (#). After injection of 10 mg/kg phencyclidine there was an immediate increase in activity as well as an increase that appeared even later, 50–60 min after injection (Fig. 2B, ♦). For the group receiving 10 mg/kg, the activity was significantly greater than the other groups at 60 min (‡).

The dose–response curve for phencyclidine is shown in Fig. 2C. Nonlinear regression of this data gave an ED_{50} of 3.4 mg/kg.

2.4. MK-801

A single dose of MK-801 (0.5 mg/kg) was tested. This dose has been shown to increase locomotor activity of rats (Hiramatsu et al., 1989) and mice (Tricklebank et al., 1989). This dose of MK801 had no effect on guinea pig locomotor activity (Fig. 3).

Table 1
Number of animals responding in each treatment group.

Pre-treatment $t=-30$ min	Drug treatment $t=0$ min	Dose	Number tested	Number responding	Percent responding
	Saline	0.25 ml/kg	8	1	13
	Nicotine	0.01 mg/kg	4	0	0
	Nicotine	0.1 mg/kg	6	1	17
	Nicotine	1 mg/kg	8	4	50
	Nicotine	3 mg/kg	8	8	100
	Nicotine	6 mg/kg	8	7	88
	PCP	1 mg/kg	6	3	50
	PCP	3 mg/kg	8	3	38
	PCP	6 mg/kg	8	5	63
	PCP	10 mg/kg	8	4	50
	MK-801	0.5 mg/kg	8	1	13
Vehicle	Nicotine	3 mg/kg	8	7	88
Haloperidol	Nicotine	3 mg/kg	9	8	89
Vehicle	PCP	6 mg/kg	8	2	25
Haloperidol	PCP	6 mg/kg	8	1	13

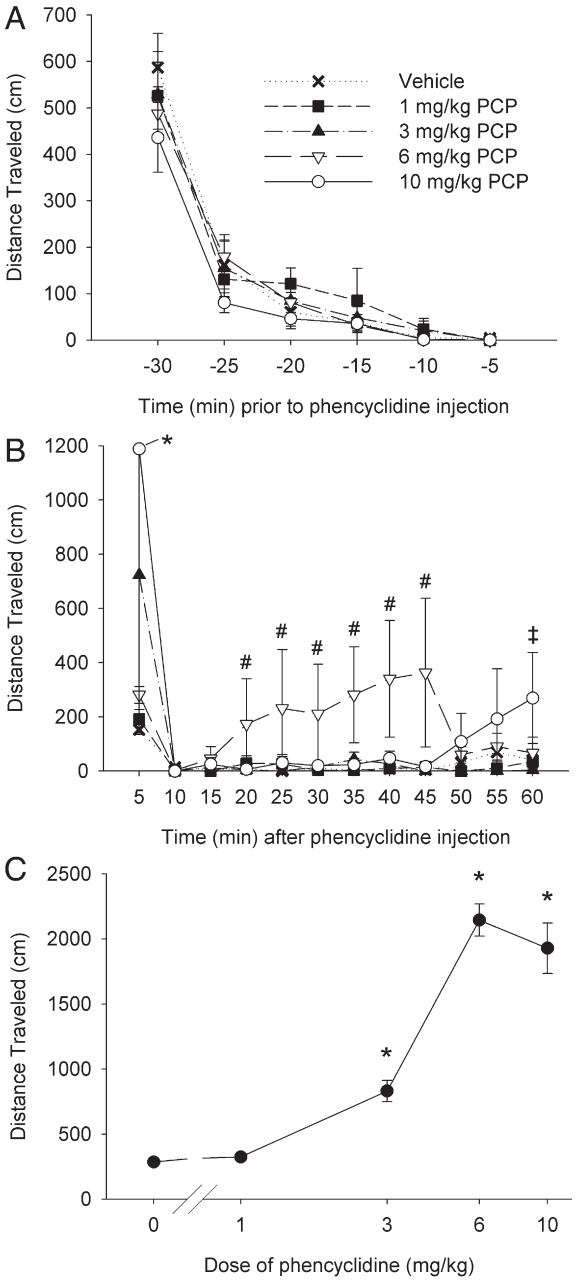

Fig. 2. Time and dose-dependence of the effects of phencyclidine on locomotor activity of the guinea pig. A. Habituation to the locomotor chambers. Naïve animals were placed in the chamber for 30 min prior to phencyclidine injection. The plots show the activity as a function of time and subsequent phencyclidine dose. Two-way analysis of variance showed a significant effect of time but no effect of subsequent dose. B. The effects of various doses of phencyclidine on locomotor activity. After the habituation period shown in A, animals were injected with various doses of phencyclidine. Phencyclidine produced significant dose-dependent increases in locomotor activity. *, ‡ and # indicate points at which the activity of the animals in the indicated groups was significantly greater than the other groups ($p<0.05$). C. Dose–response curve for phencyclidine-induced locomotor activity. The total distance traveled for the 30 min following phencyclidine injection was calculated and is plotted as a function of phencyclidine dose. There was a significant increase in activity with phencyclidine at 1 mg/kg or above that peaked at 6–10 mg/kg. *indicates points at which the activity of the animals at the indicated doses was significantly greater than the vehicle group ($p<0.05$).

2.5. Haloperidol

Both nicotine and phencyclidine increase DA release in the striatal areas implicated in locomotory responses and in the DA mesolimbic and

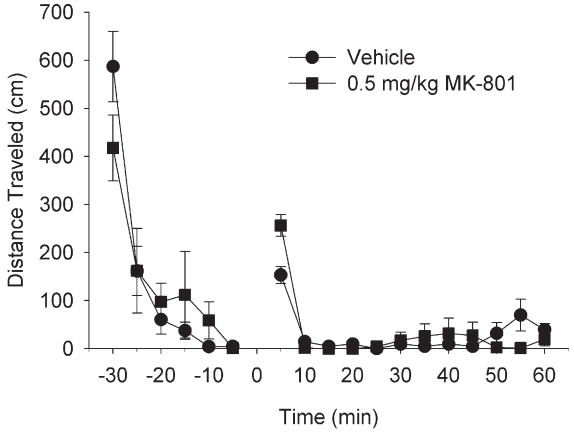

Fig. 3. Time-dependence of a single dose of MK-801 on locomotor activity of the guinea pig. Naïve animals were placed in the chamber for 30 min prior to phencyclidine injection. At time 0, animals were injected with 0.5 mg/kg MK-801, which produced no statistically significant change in locomotor activity.

mesocortical pathways related to drug reinforcement and addictive behaviors (Ary and Komiskey, 1980; Vickroy and Johnson, 1980, 1982; DiChiara and Imperato, 1988). To test if the acute effects of these psychomotor stimulants are mediated through the D_2 system, haloperidol, an antagonist at D_2 receptors, was injected prior to nicotine or phencyclidine. The effects of administering 1 mg/kg haloperidol, a dose that has been shown to be an effective dose in guinea pigs (Klawans et al., 1977; Carlson and Almasi, 1978; Brent, 1991, 1995), 30 min prior to either 3 mg/kg nicotine or 6 mg/kg phencyclidine were tested. Haloperidol alone had a significant inhibitory effect on the initial exploratory activity (Fig. 4A). The ANOVA revealed significant group and time effects before nicotine [group: $F(2,22)=5.0$, $p=0.02$; time: $F(2,22)=36.0$, $p<0.001$] or phencyclidine injection [group: $F(2,21)=4.5$, $p=0.02$; time: $F(1,21)=53.0$, $p<0.001$]. The post hoc test showed that following haloperidol injection the DT was significantly decreased compared to the vehicle-treated animals for the time period of −30 min to −15 min prior to either nicotine or phencyclidine (*). There was no difference between the groups for the −15 to 0 min time block.

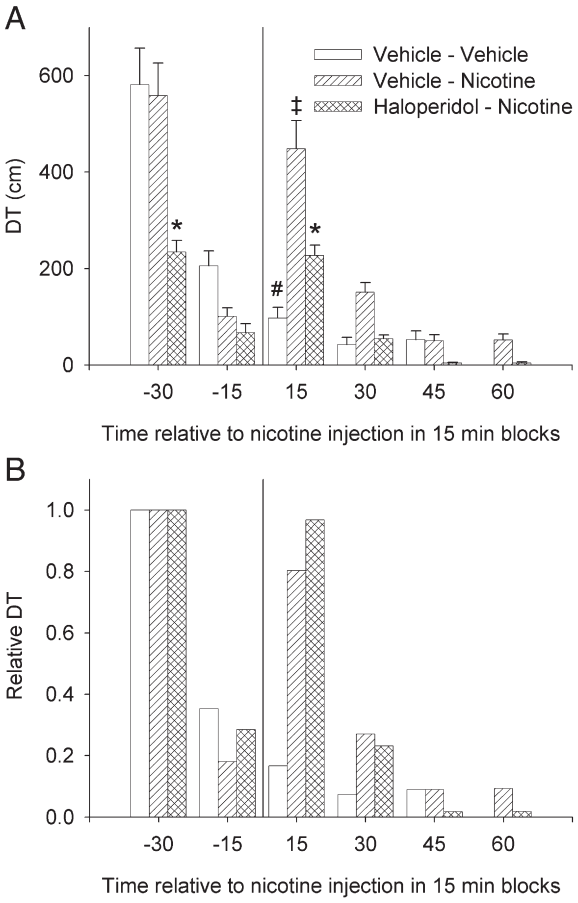

Fig. 4. Effects of haloperidol on nicotine-induced locomotor activity. Data have been cumulated into 15 min blocks for 30 min prior to and 60 min following nicotine injection. Animals received an injection of either vehicle or haloperidol (1 mg/kg) just prior to being placed in the chamber at time = −30 min. At time = 0, the animals received either 3 mg/kg nicotine or an equivalent volume of the vehicle. A. Haloperidol significantly decreased the exploratory activity normally observed during the animals' first 15 min in the chamber. The distance traveled in response to nicotine was reduced in the haloperidol-injected animals. *, ‡ and # indicate points at which the activity of the animals in the indicated groups was significantly different from that of the other groups ($p<0.05$). B. Since the activity during the −30 to −15 min period was decreased by haloperidol, the data have been normalized to the initial activity exhibited by each animal. For normalization, the DT during the time period from −30 to −15 min was set to 100% for each animal. DT during subsequent time periods is expressed as a percentage of that initial value. This permits a comparison of the relative ability of nicotine to alter activity relative to the baseline −30 to −15 min behavior. When the activities were normalized to the distance traveled during the first 15 min, however, haloperidol had no significant effect on the response to nicotine.

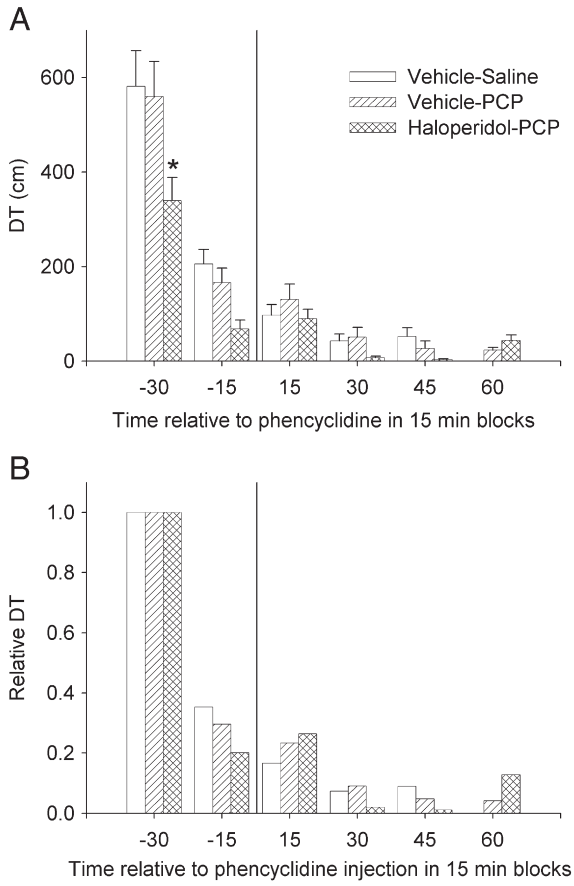

Fig. 5. Effects of haloperidol on phencyclidine-induced locomotor activity. Data have been cumulated into 15 min blocks for 30 min prior to and 60 min following phencyclidine injection. Animals received an injection of either vehicle or haloperidol (1 mg/kg) just prior to being placed in the chamber at time = −30 min. At time = 0, the animals received either 6 mg/kg phencyclidine or an equivalent volume of the vehicle. A. Haloperidol significantly decreased the exploratory activity normally observed during the animals' first 15 min in the chamber. The distance traveled in response to phencyclidine was reduced in the haloperidol-injected animals. *Indicates the activity of the indicated group was significantly less than the other groups ($p<0.05$). B. Since the activity during the −30 to −15 min period was decreased by haloperidol, the data have been normalized to the initial activity exhibited by each animal. For normalization, the DT during the time period from −30 to −15 min was set to 100% for each animal. DT during subsequent time periods is expressed as a percentage of that initial value. This permits a comparison of the relative ability of phencyclidine to alter activity relative to the baseline −30 to −15 min behavior. When the activities were normalized to the distance traveled during the first 15 min, however, haloperidol had no significant effect on the response to phencyclidine.

There were significant group and time effects post nicotine (3 mg/kg) injection following haloperidol [group: $F(2,22)=5.1$, $p=0.02$; time: $F(3,66)=29.0$, $p<0.001$; group×time: $F(6,66)=4.8$, $p<0.001$]. All three groups were significantly different from one another for the first 15 min following nicotine injection (*,#,‡). The differences between the groups at later times, when the overall level of activity is decreasing, were not different.

There were no significant differences between the groups post phencyclidine (3 mg/kg) injection in the presence of haloperidol [group: $F(2,21)=0.4$, $p=0.676$ (Fig. 5A) due to the fact that only 2 of 8 animals in the vehicle-phencyclidine group responded to the drug. Including only those responders in the analysis revealed significant group and time effects [group: $F(2,15)=12.5$, $p=<0.001$; time: $F(3,45)=3.8$, $p=0.02$], with the post hoc test showing a significant increase in DT for the vehicle-phencyclidine group but no difference between the vehicle–vehicle and haloperidol–phencyclidine groups.

Since haloperidol alone decreased locomotor activity, the data were normalized relative to the activity prior to nicotine or phencyclidine injection, as described in the figure legends. Graphs of the relative changes in activity as compared to this initial level of activity are shown in Figs. 4B and 5B. When normalized in this manner, the data show no difference in the responses to nicotine in the presence and absence of haloperidol.

3. Discussion

The major conclusion of these studies is that phencyclidine and nicotine each produce increases in the locomotor activity of guinea pigs, although both the magnitude and the duration of the response to these drugs is lower than the responses observed utilizing mice or rats under otherwise similar conditions. Additionally, the potencies of these agents to produce behavioral effects are lower in the guinea pig than in other species.

Clarke and Kumar (1983a,b) observed depression of locomotor activity and ataxia 20-min following administration of nicotine (0.1–0.5 mg/kg) in rats. After this time, nicotine resulted in an increased locomotor activity up to a certain dose (0.4–0.8 mg/kg). Higher doses of nicotine produced only a monotonic decrease in activity (Clarke and Kumar, 1983a,b; Ksir et al., 1987), although some studies report only decreases in activity with acute nicotine across a wide dose range (Domino, 2001). In addition, a biphasic dose–response relationship following nicotine has been noted in mice (Itzhak and Martin, 1999; Nordberg and Bergh, 1985).

Stolerman et al. (1995) suggested that the differential effects of nicotine in rats may be associated with the use of experimentally-naïve rats in studies which have observed locomotor depression versus the use of rats that have been previously exposed or habituated to the chambers in studies which saw an increase in locomotor activity. This suggests that the effect of nicotine may be dependent on the baseline activity level prior to its administration. In our study, the level of habituation of guinea pigs that occurs during the first 30 min following placement in the chamber is comparable to that of rats. As a result, we observed a significant enhancement in locomotor activity following nicotine (1–6 mg/kg) administration in guinea pig.

Our data for effective doses of phencyclidine in the guinea pig are similar to previous studies. Johnson et al. (1978) showed enhanced motor activity of guinea pigs given 2.5, 5.0 or 7.5 mg/kg phencyclidine. In their study, all of the animals responded with an increase in activity to the lower doses but only a fraction responded to the highest dose. Their study differed in several respects from the protocol used here. Major differences are that the animals were habituated for up to 3 weeks prior to drug administration and that each animal received all 3 doses of the drug given three or four days apart. Such extensive habituation could serve to maximize the ability of the procedure to assess the locomotor stimulant effects of drugs, but because the baseline would be low, might diminish its ability to assess locomotor suppressant effects of drugs (i.e., floor effect). In this regard, the present procedure, with more limited habituation, and only a single administration of drug, might be more sensitive to both types of drug action.

A number of other studies have shown phencyclidine-induced increases in locomotor in rats (Murray and Horita, 1979; Castellani and Adams, 1981; Kitaichi et al., 1994; Ogren and Goldstein, 1994) and mice (Stavchansky et al., 1985; Gleason and Shannon, 1997) at dose ranges similar to those that produces increases in activity of guinea pigs, although the doses required are slightly higher for the guinea pig, and the absolute amount of stimulation was lower in the guinea pig. A third difference is that at the maximally-effective dose (6 mg/kg) only 50% of the guinea pigs tested showed enhancement in locomotor activity following phencyclidine administration.

Both nicotine and phencyclidine increase DA release in the striatal areas implicated in locomotor responses and in the DA mesolimbic and mesocortical pathways related to drug reinforcement and addictive behaviors (DiChiara and Imperato, 1988; Koob and Bloom, 1988; Vickroy and Johnson, 1980, 1982). In this regard, it was worthwhile to test the effects of the D2-selective antagonist, haloperidol in order to assess whether the stimulant effects could be blocked. However, haloperidol at the dose tested, reduced the baseline level of activity prior to administration of the stimulant drugs, thereby confounding the assessment of antagonism. Previous studies in rats and mice have shown that baseline activity decreases following antagonist doses of haloperidol (Kuo et al., 1999; Emerich et al., 1991). When the data were normalized to account for this decrease in baseline activity, nicotine resulted in the same percentage increase over baseline in the presence or absence of haloperidol. Thus, it cannot be concluded that haloperidol had a specific effect on nicotine-induced locomotor activation. Testing of lower doses of haloperidol in combination should be considered in future studies.

In summary, the effects of nicotine and phencyclidine in guinea pigs are qualitatively similar to those in rats or mice, but the magnitude of effect appears to be significantly lower in guinea pigs. The low level of baseline activity in guinea pigs did not allow for sufficient dynamic range under the current conditions within which to reliably assess the locomotor suppressant effects of drugs. It will be interesting to further explore to what extent this quantitative difference holds for other pharmacological classes of drugs.

Acknowledgement

Work in Dr. Simmons' lab was supported by the Ohio Valley Affiliate of the American Heart Association.

References

Ary TE, Komiskey HL. Phencyclidine: effect on the accumulation of 3H-dopamine in synaptic vesicles. Life Sci 1980;26:575–8.
Brent PJ. Similar behavioural effects of sigma agonists and PCP-like non-competitive NMDA antagonists in guinea-pigs. Psychopharmacology (Berl) 1991;105:421–7.
Brent PJ. Haloperidol and reduced haloperidol-induced exacerbation of the dystonia produced by the kappa opioid U50, 488H in guinea-pigs is associated with inhibition of sigma binding sites: behavioural and autoradiographical studies. Brain Res 1995;684:115–26.
Carlson KR, Almasi J. Behavioral supersensitivity to apomorphine following chronic narcotic treatment in the guinea pig. Psychopharmacology (Berl) 1978;57:273–7.
Castellani S, Adams PM. Acute and chronic phencyclidine effects on locomotor activity, stereotypy and ataxia in rats. Eur J Pharmacol 1981;73:143–54.
Chung FZ, Wu LH, Tian Y, Vartanian MA, Lee H, Bikker J, et al. Two classes of structurally different antagonists display similar species preference for the human tachykinin neurokinin3 receptor. Mol Pharmacol 1995;48:711–6.
Clarke PB, Kumar R. Characterization of the locomotor stimulant action of nicotine in tolerant rats. Br J Pharmacol 1983a;80:587–94.
Clarke PB, Kumar R. The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. Br J Pharmacol 1983b;78:329–37.
Contreras PC, Contreras ML, O'Donohue TL, Lair CC. Biochemical and behavioral effects of sigma and PCP ligands. Synapse 1988;2:240–3.

DiChiara CG, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 1988;85:5274–8.
Domino EF. Nicotine induced behavioral locomotor sensitization. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:59–71.
Emerich DF, Zanol MD, Norman AB, McConville BJ, Sanberg PR. Nicotine potentiates haloperidol-induced catalepsy and locomotor hypoactivity. Pharmacol Biochem Behav 1991;38:875–80.
Emonds-Alt X, Proietto V, Steinberg R, Advenier C, Daoui S, Naline E, et al. Biochemical and pharmacological activities of SSR 146977, a new potent nonpeptide tachykinin NK3 receptor antagonist. Can J Physiol Pharmacol 2002;80:482–8.
Fletcher PJ, Azampanah A, Korth KM. Activation of 5-HT(1B) receptors in the nucleus accumbens reduces self-administration of amphetamine on a progressive ratio schedule. Pharmacol Biochem Behav 2002;71:717–25.
Freeman GB, Sherman KA, Gibson GE. Locomotor activity as a predictor of times and dosages for studies of nicotine's neurochemical actions. Pharmacol Biochem Behav 1987;26:305–12.
Gleason SD, Shannon HE. Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine and serotonin receptor subtype selective antagonists in mice. Psychopharmacology (Berl) 1997;129:79–84.
Hargreaves EL, Cain DP. MK801-induced hyperactivity: duration of effects in rats. Pharmacol Biochem Behav 1995;51:13–9.
Hiramatsu M, Cho AK, Nabeshima T. Comparison of the behavioral and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. Eur J Pharmacol 1989;166:359–66.
Itzhak Y, Martin JL. Effects of cocaine, nicotine, dizocipline and alcohol on mice locomotor activity: cocaine-alcohol cross-sensitization involves upregulation of striatal dopamine transporter binding sites. Brain Res 1999;818:204–11.
Johnson SM, Westfall DP, Howard SA, Fleming WW. Sensitivities of the isolated ileal longitudinal smooth muscle–myenteric nerve–vas deferens of the guinea pig after chronic morphine pellet implantation. J Pharmacol Exp Ther 1978;203:54–66.
Kari HP, Davidson PP, Kohl HH, Kochhar MM. Effects of ketamine on brain monoamine levels in rats. Res Commun Chem Pathol Pharmacol 1978;20:475–88.
Kitaichi K, Yamada K, Hasegawa T, Furukawa H, Nabeshima T. Effects of risperidone on phencyclidine-induced behaviors: comparison with haloperidol and ritanserin. Jpn J Pharmacol 1994;66:181–9.
Klawans HL, D'amico DJ, Nausieda PA, Weiner WJ. The specificity of neuroleptic- and methysergide-induced behavioral hypersensitivity. Psychopharmacology (Berl) 1977;55:49–52.
Koek W, Woods JH, Colpaert FC. *N*-methyl-D-aspartate antagonism and phencyclidine-like activity: a drug discrimination analysis. J Pharmacol Exp Ther 1990;253:1017–25.
Koob GF, Bloom FE. Cellular and molecular mechanisms of drug dependence. Science 1988;242:715–23.
Ksir C, Hakan RL, Kellar KJ. Chronic nicotine and locomotor activity: influences of exposure dose and test dose. Psychopharmacology (Berl) 1987;92:25–9.
Kuo DY, Lin TB, Huang CC, Duh SL, Liao JM, Cheng JT. Nicotine-induced hyperlocomotion is not modified by the estrous cycle, ovariectomy and estradiol replacement at physiological level. Chin J Physiol 1999;42:83–8.
Murray TF, Horita A. Phencyclidine-induced stereotyped behavior in rats: dose response effects and antagonism by neuroleptics. Life Sci 1979;24:2217–25.
Nordberg A, Bergh C. Effect of nicotine on passive avoidance behaviour and motoric activity in mice. Acta Pharmacol Toxicol (Copenh) 1985;56:337–41.
Ogren SO, Goldstein M. Phencyclidine- and dizocilpine-induced hyperlocomotion are differentially mediated. Neuropsychopharmacology 1994;11:167–77.
Pauwels PJ, Wurch T, Palmier C, Colpaert FC. Pharmacological analysis of G-protein activation mediated by guinea-pig recombinant 5-HT1B receptors in C6-glial cells: similarities with the human 5-HT1B receptor. Br J Pharmacol 1998;123:51–62.
Przegalinski E, Siwanowicz J, Nowak E, Papla I, Filip M. Role of 5-HT(1B)receptors in the sensitization to amphetamine in mice. Eur J Pharmacol 2001;422:91–9.
Regoli D, Boudon A, Fauchere JL. Receptors and antagonists for substance P and related peptides. Pharmacol Rev 1994;46:551–98.
Sarau HM, Griswold DE, Potts W, Foley JJ, Schmidt DB, Webb EF, et al. Nonpeptide tachykinin receptor antagonists: I. Pharmacological and pharmacokinetic characterization of SB 223412, a novel, potent and selective neurokinin-3 receptor antagonist. J Pharmacol Exp Ther 1997;281:1303–11.
Sarau HM, Griswold DE, Bush B, Potts W, Sandhu P, Lundberg D, et al. Nonpeptide tachykinin receptor antagonists. II. Pharmacological and pharmacokinetic profile of SB-222200, a central nervous system penetrant, potent and selective NK-3 receptor antagonist. J Pharmacol Exp Ther 2000;295:373–81.
Silva MA, Jocham G, Barros M, Tomaz C, Müller CP. Neurokinin3 receptor modulation of the behavioral and neurochemical effects of cocaine in rats and monkeys. Rev Neurosci 2008;19:101–11.
Snell LD, Yi SJ, Johnson KM. Comparison of the effects of MK-801 and phencyclidine on catecholamine uptake and NMDA-induced norepinephrine release. Eur J Pharmacol 1988;145:223–6.
Stavchansky S, Riffee W, Geary R. Comparison between locomotor activity changes produced by phencyclidine and D-amphetamine in CD-1 male mice. Res Commun Chem Pathol Pharmacol 1985;48:189–202.
Stolerman IP, Garcha HS, Mirza NR. Dissociations between the locomotor stimulant and depressant effects of nicotinic agonists in rats. Psychopharmacology (Berl) 1995;117:430–7.
Sturgeon RD, Fessler RG, Meltzer HY. Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. Eur J Pharmacol 1979;59:169–79.
Tricklebank MD, Singh L, Oles RJ, Preston C, Iversen SD. The behavioural effects of MK-801: a comparison with antagonists acting non-competitively and competitively at the NMDA receptor. Eur J Pharmacol 1989;167:127–35.
Vickroy TW, Johnson KM. In vivo administration of phencyclidine inhibits 3H-dopamine accumulation by rat brain striatal slices. Subst Alcohol Actions/Misuse 1980;1:351–4.
Vickroy TW, Johnson KM. Similar dopamine-releasing effects of phencyclidine and nonamphetamine stimulants in striatal slices. J Pharmacol Exp Ther 1982;223:669–74.
Wong EH, Knight AR, Woodruff GN. 3H]MK-801 labels a site on the *N*-methyl-D-aspartate receptor channel complex in rat brain membranes. J Neurochem 1988;50:274–81.
Wu LH, Vartanian MA, Oxender DL, Chung FZ. Identification of methionine134 and alanine146 in the second transmembrane segment of the human tachykinin NK3 receptor as reduces involved in species-selective binding to SR 48968. Biochem Biophys Res Commun 1994;198:961–6.
Zgombick JM, Bard JA, Kucharewicz SA, Urquhart DA, Weinshank RL, Branchek TA. Molecular cloning and pharmacological characterization of guinea pig 5-HT1B and 5-HT1D receptors. Neuropharmacology 1997;36:513–24.