Pharmacology Biochemistry & Behavior, Vol. 25, pp. 1175–1180, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Sensitization to Amphetamine and Tolerance to Cocaine and Phencyclidine Stimulation in Mice

LARRY KOKKINIDIS

Department of Psychology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, S7N 0W0

Recieved 25 November 1985

KOKKINIDIS, L. *Sensitization to amphetamine and tolerance to cocaine and phencyclidine stimulation in mice.* PHARMACOL BIOCHEM BEHAV **25**(6) 1175–1180, 1986.—Amphetamine (1.0–7.0 mg/kg), cocaine (5.0–40.0 mg/kg) and phencyclidine (1.0–7.0 mg/kg) increased acoustic startle responding in mice. These drugs, however, had varying effects on habituation of the startle response after repeated exposure to the auditory stimulus. The primary effect of phencyclidine was to disrupt the habituation process, whereas increased startle responding after cocaine developed without modification of the habituation curve. Amphetamine facilitated acoustic startle at all doses, and after administration of 3.0 mg/kg a significant response sensitization as a function of repeated stimulus presentation was evident. Consistent with previous reports the excitatory effects of cocaine and amphetamine on acoustic startle were blocked by pretreatment with haloperidol. Haloperidol, which decreased startle responding, attenuated the facilitating effects of PCP on acoustic startle as well. Chronic exposure to amphetamine, cocaine and phencyclidine had differential effects on startle responding. The facilitating effects of amphetamine on startle were further enhanced after long-term exposure to the drug and the sensitizing effect of repeated amphetamine exposure was observed only when animals were tested with amphetamine. In contrast, tolerance developed after chronic exposure to both cocaine and phencyclidine, and the response attenuation was evident when animals were tested for acoustic startle after cocaine, amphetamine and phencyclidine.

Cocaine Phencyclidine Amphetamine Acoustic startle Tolerance Cross tolerance Sensitization

CONSIDERABLE research on the behavioral consequences of phencyclidine (PCP), cocaine and amphetamine has been conducted recently, and apart from the inherent heuristic value of this research, a great deal of attention has been devoted to assessing the behavioral profiles of these drugs as a direct result of their potential for abuse. Although PCP, cocaine and amphetamine have a complex spectrum of behavioral effects, some clear similarities are evident. All three drugs, for example, have been described as "psychotomimetic" since in humans PCP, cocaine and amphetamine are known to induce behavioral syndromes resembling schizophrenic-like psychosis [9, 14, 15]. Commonalities are evident with respect to the behavioral effects of these drugs in animals, as well. After low doses of PCP, cocaine and amphetamine, marked increases in locomotor activity are evident and in high doses these drugs induce a variety of stereotyped motor movements [1, 10, 17].

In addition to the motor consequences of PCP, amphetamine and cocaine, these drugs have effects on behavioral reactivity to sensory stimulation. Specifically, the startle reflex has been used successfully as a sensitive measure of sensory-motor reactivity (for review see [3]), and it is well documented that d-amphetamine administration enhances the startle reflex to an acoustic stimulus [4,11]. More recently, it was demonstrated that cocaine also facilitated acoustic startle [2], and PCP increased the startle response to tactile stimulation [6]. Although PCP, cocaine and amphetamine enhance startle it appears they do so by affecting different components of the response curve. Whereas cocaine increased the amplitude of the startle reflex [2], PCP attenuated habituation of startle responding to repeated stimulus presentation [6]. In contrast, amphetamine increased the amplitude of acoustic startle and the strength of the response did not wane as a function of repeated exposure to the stimulus, rather acoustic startle increased with repeated presentation of the stimulus [4,11].

In the present investigation the effects of several doses of amphetamine, PCP and cocaine on acoustic startle were assessed in order to compare within the same study drug-induced changes in startle and habituation of the startle response after repeated exposure to an acoustic stimulus. In addition, since there is good evidence to suggest that dopamine is important in modulating increased acoustic startle after amphetamine and cocaine treatment [2,8], the effects of pretreatment with haloperidol on amphetamine, cocaine and PCP-induced startle arousal were investigated. Finally, the detrimental behavioral effects of these drugs in humans generally develop after long-term abuse, thus the effects of chronic exposure to amphetamine, PCP and cocaine on acoustic startle were evaluated.

METHOD

Subjects

Five hundred and ten Swiss mice procured from the Animal Resources Centre, University of Saskatchewan

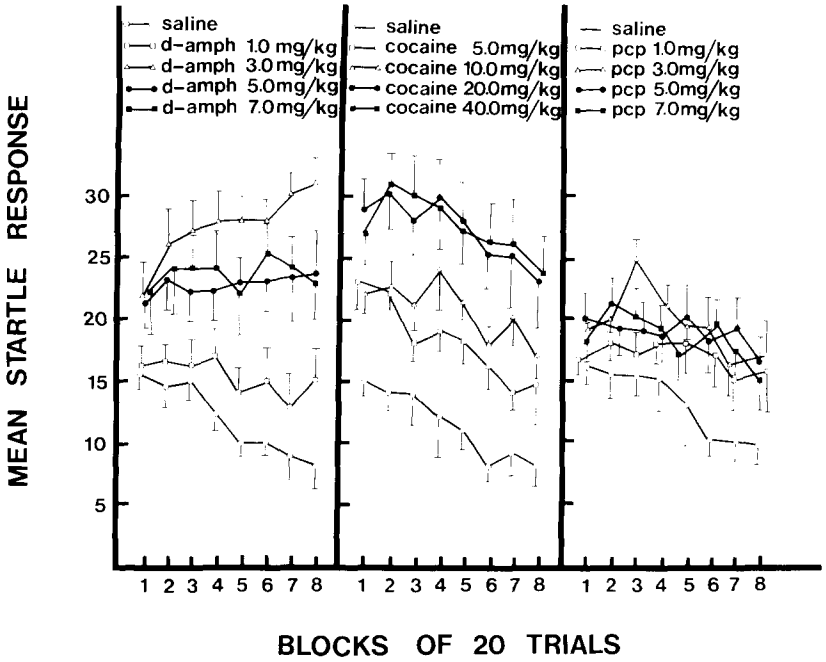

FIG. 1. Mean startle response (±S.E.M.) over 8 blocks of 20 tone presentations after injection of either saline or 1.0, 3.0, 5.0 or 7.0 mg/kg of d-amphetamine (left); saline or 5.0, 10.0, 20.0 or 40.0 mg/kg of cocaine (centre), and saline or 1.0, 3.0, 5.0 or 7.0 mg/kg of phencyclidine (right).

served as subjects. Mice were housed individually in standard polypropylene cages and allowed free access to food and water. Animals were 60–70 days of age and weighed 30–35 g at the time of testing. Subjects were housed in a 12 hr light/dark cycle and behavioral testing was carried out during the light portion of the cycle.

Apparatus

Startle behavior was recorded in two acoustically insulated styrofoam (2.0 cm thick) circular chambers 28.0 cm in diameter and 21.0 cm high. The styrofoam floor of each chamber was situated on an 8-W speaker (28.0 cm in diameter). Voltages produced by movements on the floor were fed to a Commodore PET Series 2001 computer. The analogue signal from the speaker was amplified and digitized by an 8-bit A/D converter. The digitized output could vary from 1–5000 units depending on the sampling interval and was printed out on a Data Terminal Mart printer. Only responses made during the tone presentation were measured and it was demonstrated previously that this measure was a sensitive index of acoustic startle and was not related to general levels of motor activity [12]. The 2700 Hz tone (700 msec in duration, 5 msec rise-fall time) was generated by a Piezo Crystal Audio Transistor (Projects Unlimited, Dayton, OH) situated in the centre of the styrofoam roof of each chamber. The intensity of the tone in the chambers was 97 dB and background noise in the chambers was 44 dB. Sound intensity measurements were made with a Bruel Kjaer sound level meter (model 2203; A-scale).

Procedure

Experiment 1—dose response curves. One hundred and fifty mice served as subjects in this experiment. Essentially this experiment consisted of 3 sub-experiements. In Experiment 1a, 50 mice were randomly assigned to one of five groups (N=10 per group) and received an intraperitoneal (IP) injection of either saline, 1.0, 3.0, 5.0, or 7.0 mg/kg of d-amphetamine sulfate. Immediately after this injection, mice were placed into the startle chambers and allowed a 10 min adaptation period. Following the adaptation period mice were exposed to 160 tone presentations with a 10 sec inter-tone interval.

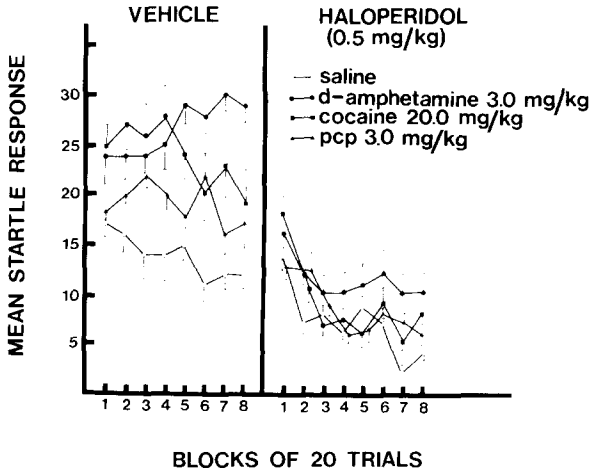

FIG. 2. Mean startle response (±S.E.M.) over 8 blocks of 20 tone presentations after pretreatment with either vehicle or haloperidol (0.5 mg/kg) and treatment with saline, 3.0 mg/kg of d-amphetamine, 20.0 mg/kg of cocaine and 3.0 mg/kg of phencyclidine.

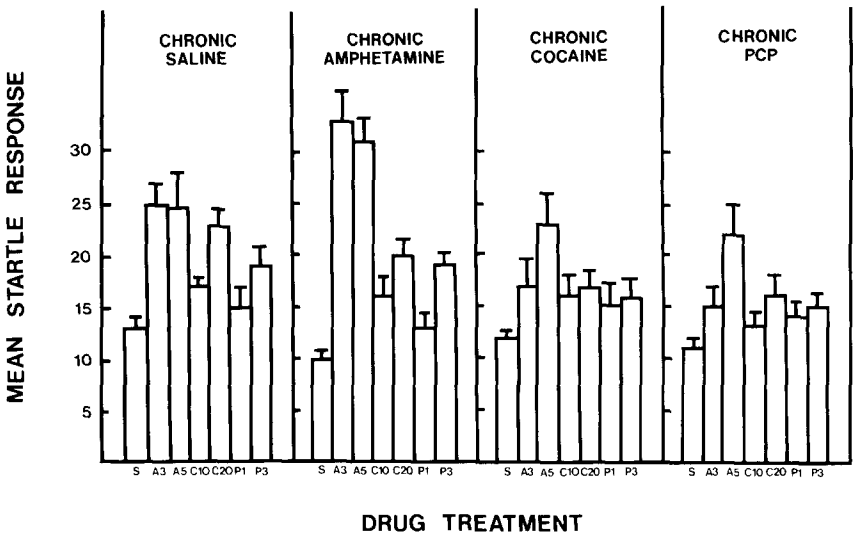

FIG. 3. Mean startle response (±S.E.M.) as a function of chronic exposure to saline, amphetamine, cocaine and phencyclidine and test day drug treatment [saline (S), 3.0 or 5.0 mg/kg of d-amphetamine (A3, A5); 10 or 20 mg/kg of cocaine (C10, C20); and 1.0 or 3.0 mg/kg of phencyclidine (P1, P3)].

In Experiment 1b, 50 naive mice were randomly placed into 5 groups and injected IP with either saline, 5.0, 10.0, 20.0 or 40.0 mg/kg of cocaine hydrochloride, and in Experiment 1c naive mice received an IP injection of either saline, 1.0, 3.0, 5.0 or 7.0 mg/kg of phencyclidine hydrochloride. Mice were immediately placed into the startle chambers after drug injection, allowed a 10 min adaptation period and then presented with 160 tone presentations with a 10 sec intertone interval.

Experiment 2—effects of haloperidol. Eighty naive mice were pretreated with 0.5 mg/kg of haloperidol dissolved in a minimal amount of glacial acetic acid or vehicle (acidified saline solution). One hour after injection mice received a second IP injection of either saline, amphetamine (3.0 mg/kg), cocaine (20.0 mg/kg) or PCP (3.0 mg/kg). Immediately after the second injection animals were placed into the startle chambers, allowed a 10 min adaptation period followed by 160 presentations of the tone.

Experiment 3—chronic effects of amphetamine, cocaine and PCP. Two hundred and eighty mice served as subjects in Experiment 3. Mice were randomly divided into 4 groups (N=70 per group) and were treated twice daily (10:00 a.m. and 4:00 p.m.) with IP injections of either saline, 5.0 mg/kg of d-amphetamine, 20.0 mg/kg of cocaine or 5.0 mg/kg of phencyclidine for 20 consecutive days. Twenty-four hr following the final injection mice in each group were further subdivided into 7 groups (N=10 per group) and were injected with an IP injection of saline, 3.0 or 5.0 mg/kg of d-amphetamine, 10.0 or 20.0 mg/kg of cocaine, and 1.0 or 3.0 mg/kg of phencyclidine. Immediately following drug treatment mice were placed into the startle chambers and allowed a 10 min adaptation period after which they were exposed to 160 tone presentations with a 10 sec intertone interval.

RESULTS

Figure 1 shows the mean startle response during the stimulus presentation over blocks of 20 trials after injection of saline or 1.0, 3.0, 5.0 and 7.0 mg/kg of d-amphetamine (left panel); saline, 5.0, 10.0, 20.0 and 40.0 mg/kg of cocaine (middle panel); and saline, 1.0, 3.0, 5.0 and 7.0 mg/kg of PCP (right panel). Startle scores were transformed $\sqrt{X}$ in order to reduce the heterogeneity of variance and an independent two factor analysis of variance with repeated measures on tone presentation for each drug treatment was carried out. Analysis of variance of the startle scores after amphetamine treatment yielded significant main effects for Drug Treatment, $F(4,45)=10.78$, $p<0.01$, Tone Presentation, $F(7,315)=2.12$, $p<0.05$, and a significant Drug Treatment × Tone Presentation interaction, $F(28,315)=4.14$, $p<0.01$. Newman-Keuls multiple comparisons ($\alpha=0.05$) revealed that 1.0 mg/kg of d-amphetamine significantly increased acoustic startle relative to saline controls towards the last half of the startle test (blocks 4–8). The higher doses of amphetamine (3.0, 5.0 and 7.0 mg/kg) increased startle responding during the entire test session. Moreover, as is evident in Fig. 1 (left panel) saline treated animals showed a significant response decrement of startle responding as a function of repeated stimulus presentations. In contrast, mice tested with 1.0, 3.0, 5.0 and 7.0 mg/kg of amphetamine did not demonstrate significant habituation, and after 3.0 mg/kg of the drug a significant response sensitization after repeated exposure to the tone was evident.

Figure 1 (center panel) shows that cocaine increased startle responding. Analysis of variance of these data revealed a significant main effect for Cocaine Treatment, $F(4,45)=10.92$, $p<0.01$, and Tone Presentation, $F(7,315)=10.64$, $p<0.01$. Startle activity was increased after all doses of the drug and responding was enhanced during the entire test session. Like saline treated mice, significant habituation of acoustic startle after repeated exposure to the tone was evident in mice administered cocaine.

Analysis of variance of the startle scores after PCP treatment yielded significant main effects for Drug Treatment, $F(4,45)=7.09$, $p<0.01$, and Tone Presentation, $F(7,315)=3.04$, $p<0.01$. As is shown in Fig. 1 (right panel), all doses of PCP increased acoustic startle and the facilitating effects of the drug were observed primarily towards the end

of the test session (blocks 5–8), with the exception of the 3.0 mg/kg dose which enhanced startle on trial blocks 3–8. Whereas significant habituation was observed in saline treated mice, a similar response decrement as a function of repeated tone presentations was not significant in PCP treated animals.

Figure 2 depicts the effects of pretreatment with haloperidol on the enhanced acoustic startle after amphetamine, cocaine and PCP administration. A three factor analysis of variance with repeated measures on Tone Presentation revealed a significant Drug Preatreatment × Drug Treatment × Tone Presentation interaction, $F(21,504)=2.75$, $p<0.01$. Consistent with the results of Experiment 1, PCP, cocaine and amphetamine enhanced acoustic startle. Once again, whereas startle decreased as a function of repeated tone presentations in the case of cocaine, the effects of amphetamine were observed to increase over the test session and PCP had fairly consistent effects on startle over time. As is evident in Fig. 2, pretreatment with haloperidol attenuated the effects of amphetamine, cocaine and PCP on startle and facilitated the decrement in responding after repeated presentation of the stimulus in control animals. In amphetamine treated animals startle responding was comparable to controls during the first 20 tone presentations. The sensitization typically observed after amphetamine was observed not to develop, rather a response decrement as a function of tone presentation was evident. Startle responding however was still significantly higher after amphetamine treatment towards the end of the test session. Acoustic startle in PCP and cocaine treated mice was similar to that of controls throughout the test session.

A two factor analysis of variance of the startle scores in Experiment 3 revealed significant main effects for Chronic Drug Treatment, $F(3,252)=3.42$, $p<0.05$, Acute Drug Treatment, $F(6,252)=17.09$, $p<0.01$, and a significant Chronic × Acute Drug Treatment interaction, $F(18,252)=3.75$, $p<0.01$. Subsequent multiple comparisons showed that amphetamine (3.0 and 5.0 mg/kg), cocaine (20.0 mg/kg), and PCP (3.0 mg/kg) significantly increased acoustic startle in mice chronically treated with saline (see Fig. 3). Long-term exposure to amphetamine did not modify startle responding in saline pretreated mice, but significantly facilitated startle activity after 3.0 mg/kg of amphetamine. A similar sensitization was observed on acoustic startle in animals chronically exposed to amphetamine and tested after 5.0 mg/kg of the drug, however this effect was only marginally significant ($p<0.1$). As can be seen in Fig. 3, exposure to chronic amphetamine treatment only sensitized the startle response to amphetamine and had no effect on startle responding after administration of cocaine and PCP. Unlike the effects of long-term amphetamine treatment, mice chronically treated with either cocaine or PCP did not develop a sensitized startle response to any of the acute drug treatments. Rather, long-term exposure to cocaine and PCP, which did not modify startle after saline injection, had a general depressing influence on acoustic startle responding after administration of amphetamine, cocaine and PCP. In fact, as can be seen in Fig. 3, only the 5.0 mg/kg dose of amphetamine significantly increased acoustic startle in mice chronically exposed to cocaine and PCP.

DISCUSSION

Consistent with previous reports cocaine and amphetamine increased startle responding to an acoustic stimulus [2, 4, 11]. Although in both cases all doses of the drug enhanced acoustic startle, 3.0 mg/kg of amphetamine was optimal in this respect, whereas 20.0 and 40.0 mg/kg of cocaine were maximal in increasing acoustic startle. Davis [2] recently reported that in rats cocaine increased acoustic startle monotonically from 2.5–10 mg/kg and that higher doses (20 mg/kg) were without effect on acoustic startle. This discrepancy in dose response curves in all likelihood can be attributed to species differences. Such variations in optimal dose effects between species is not uncommon. For example, whereas 1.0–3.0 mg/kg of d-amphetamine increased motor activity in rats, 3.0–10.0 mg/kg of the drug is necessary for locomotor excitation in the mouse (for review see [10]).

Although both amphetamine and cocaine facilitated startle responding, different effects of these drugs emerged when acoustic startle as a function of repeated tone presentations was considered. Whereas amphetamine increased startle responding, a response decrement after repeated tone presentations was not observed. In fact, acoustic startle after the optimal dose of the drug showed sensitization to repeated stimulus presentation (see also [4,11]). Cocaine also facilitated startle responding, however, in contrast to the effects of amphetamine significant habituation of acoustic startle was observed over trials at all dose levels and there was no evidence of a sensitization effect.

Like amphetamine and cocaine, PCP increased acoustic startle. All doses of the drug were effective in this respect, with the 3.0 mg/kg dose having the maximal effect. These findings are consistent with a recent report [6] which assessed the effects of PCP on tactile startle. It was demonstrated in Experiment 1 that after PCP treatment a significant decrement in responding was not evident after repeated exposure to the stimulus. Geyer *et al.* [6] made similar observations after assessing the effects of lower doses of PCP on tactile startle, and concluded that the primary effect of PCP on startle responding was an impairment of the habituation process. The results of this study provide further support for this conclusion.

It is unlikely that the different response profiles of amphetamine, cocaine and PCP are the results of variations in the time course of drug action. It is the case, at least with respect to amphetamine, that the development of a response sensitization as a function of repeated exposure to the tone is dependent on the interval between drug injection and behavioral testing. For example, sensitization is optimal when testing for startle commenced immediately after amphetamine injection [4,11]. When testing was initiated 15 minutes after drug injection, acoustic startle was still facilitated but sensitization as a function of repeated stimulus presentation did not develop [11]. In this study startle was evaluated 10 minutes after injection of amphetamine, cocaine and PCP, thus it is possible that the response profiles of these drugs may have been different had startle been evaluated immediately after drug injection. It was found however, that cocaine did not induce a response sensitization when animals were tested immediately after drug administration [4], and a sensitization effect was not evident with respect to tactile startle when testing was initiated 5 minutes after PCP administration [6], suggesting that possible variations in the time course of drug action were in all likelihood not responsible for the different response profiles of amphetamine, cocaine and PCP.

Consistent with previous reports demonstrating the attenuation of the excitatory effects of amphetamine and cocaine by dopamine receptor blockers [2,8], it was observed that increased startle after administration of cocaine and amphetamine was attenuated by pretreatment with the

dopamine receptor antagonist haloperidol. In addition, increased acoustic startle after PCP administration was also completely antagonized following haloperidol pretreatment. These data, however, must be interpreted with a degree of caution. Specifically, the observation that haloperidol depressed acoustic startle in mice tested after saline injection, raises the possibility that the attenuating effects of haloperidol on stimulant-induced facilitation of acoustic startle may have been non-specific and involved a general depressing effect of the drug on behavior. Similar findings involving neuroleptics have been reported in other studies investigating the role of dopamine on the facilitating effects of amphetamine and cocaine on startle responding [2,8]. Further work employing lower doses of dopamine receptor antagonists is necessary before conclusions involving the specific actions of these drugs on stimulant-induced excitation of acoustic startle can be made.

One of the most striking findings of this study was that although amphetamine, cocaine and PCP enhanced acoustic startle, the long-term administration of these drugs did not produce congruent effects on startle responding. After chronic amphetamine treatment, acoustic startle responding after amphetamine administration was substantially increased over that ordinarily observed in naive animals (see also [13]). A similar sensitization effect did not develop in animals chronically treated with amphetamine and tested after cocaine and PCP. Unexpectedly, chronic cocaine administration did not result in a sensitization of acoustic startle after testing with cocaine. To the contrary, long-term cocaine administration had a general depressing effect not only on acoustic startle after injection of cocaine but after amphetamine and PCP treatment, as well. This finding was surprising since it is well documented that like amphetamine many of the behavioral effects of cocaine (e.g., locomotor activity, stereotypy) are sensitized after long-term exposure to the drug [15].

In contrast to amphetamine, and consistent with the effects of chronic cocaine treatment, animals with prior exposure to PCP did not develop sensitized acoustic startle responsing after PCP injection. Rather, an attenuation of the enhancing effects of PCP on acoustic startle was evident indicating the development of tolerance. This is consistent with reports showing significant tolerance to PCP-induced stereotypy and ataxia [19]. Like cocaine, the tolerance development after PCP was generalized to the effects of the other drugs (i.e., cross tolerance). That is, after chronic PCP treatment the optimal dose of amphetamine and cocaine did not enhance acoustic startle, and increased startle was only observed after the high dose of amphetamine.

It appears then that the effects of amphetamine, cocaine and PCP on acoustic startle can be distinguished not only by their habituation and dose response curves (Experiment 1), but by their long-term consequences as well. In the case of amphetamine, prior repeated exposure to the drug sensitized startle responding after amphetamine treatment and the sensitization did not generalize to either cocaine or PCP. After chronic administration of cocaine and PCP an attenuation of the excitatory effects on acoustic startle after amphetamine, cocaine and PCP was observed. This is probably indicative of tolerance development as opposed to a general depressing effect on acoustic startle or possible toxic effects resulting from prolonged exposure to cocaine and PCP, since chronic exposure to these drugs did not affect acoustic startle in animals tested after saline.

Amphetamine, cocaine and PCP have several similar neurochemical effects [1, 3, 9, 15, 17], however there are pharmacological and neurochemical distinctions between these drugs that may be involved in the development of tolerance and sensitization. Unlike amphetamine, both PCP and cocaine are anesthetics. It is likely however, that this property of cocaine and PCP is not involved in tolerance development since both drugs facilitated startle when administered acutely, and long-term exposure to cocaine and PCP did not depress acoustic startle in saline treated animals. Alternatively, cocaine and PCP are considered to be non-amphetamine like stimulants. That is, the behavioral effects of cocaine and PCP are blocked by reserpine pretreatment [2,5], whereas reserpine enhanced the behavioral consequences of amphetamine [2,18]. Recent data also suggest that PCP may exert some of its behavioral effects by interacting with opiate receptor systems [7]. Further studies directed towards monoaminergic and possibly opiate systems may provide some insight into the neuronal mechanisms underlying the differential effects of these drugs on responses to sensory stimulation.

ACKNOWLEDGEMENTS

This research was supported by grant A7042 from the Natural Sciences and Engineering Council of Canada. Appreciation is extended to Smith, Kline and French for their gift of d-amphetamine.

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