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Effects of Calcium Antagonists on Phencyclidine Behaviors

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BOLGER, G. T., M. F. RAFFERTY, J. N. CRAWLEY, S. M. PAUL AND P. SKOLNICK. *Effects of calcium antagonists in phencyclidine behaviors.* PHARMACOL BIOCHEM BEHAV **25**(1) 45–49, 1986.—The calcium antagonists nifedipine and verapamil were evaluated for their potential behavioral interactions with phencyclidine induced changes in mouse rotarod performance and motor activity. Nifedipine (2 and 10 mg/kg) and verapamil (2 mg/kg) significantly potentiated impairment of rotarod performance produced by phencyclidine. These doses of nifedipine and verapamil did not by themselves affect rotarod performance. This action does not appear to be dependent on the hypotensive properties of these drugs, since hypotensive doses of prazosin did not alter the effect of phencyclidine on rotarod performance. Nifedipine, 4.0 mg/kg, antagonized increases in ambulatory motor activity, and potentiated decreases in vertical motor activity (rearing) induced by phencyclidine. The effects of calcium antagonists to alter the behavioral actions of phencyclidine in mice may occur through an interaction with the dihydropyridine calcium antagonist binding site present in the central nervous system.

Calcium antagonist Dihydropyridine Nifedipine Verapamil Phencyclidine

HIGH affinity, distinct binding sites for both dihydropyridine (DHP) (e.g., [^{3}H]nitrendipine) and diphenylalkylamine (e.g., [^{3}H]verapamil) calcium antagonists have been found in smooth and cardiac muscles, and the central nervous system (CNS) [3, 4, 9, 13, 14, 17, 27, 32, 36]. While it is well documented that the therapeutic capacity of calcium antagonists arises from an inhibition of voltage sensitive calcium currents in cardiac and a variety of smooth muscles [16, 20, 37], a clear functional role has yet to be determined for these sites within the CNS [9, 11, 15, 26, 40]. Nonetheless, recent evidence indicating that DHP binding sites are localized to synaptic junctions [10,33] and mediate alterations in behavior, neuronal calcium currents and neurotransmitter release [5, 20, 24, 26, 28, 29, 35, 43, 44], suggest specific roles for DHP binding sites in the CNS. Recently, it was observed that phencyclidine (PCP) increased the affinity of the neuronal DHP binding site at a locus independent from the high affinity binding site for PCP in brain [6]. While the behavioral actions of PCP [8, 25, 34, 41] and related compounds are best correlated with binding of these drugs to the high affinity [^{3}H]PCP binding site in brain [45,47] and with inhibition of potassium efflux from presynaptic voltage dependent potassium channels [1, 2, 42], not all the pharmacologic actions of PCP can be interpreted by an interaction with these sites [2,34]. Previous studies have indicated that DHP calcium antagonists could alter the behavioral effects of PCP in the rat [39] and mouse [18].

These observations prompted us to further investigate the behavioral effects of PCP in mice. We now report that the DHP calcium antagonist nifedipine and the non-DHP calcium antagonist verapamil can selectively alter certain behavioral responses to PCP in mice. It is suggested that the behavioral interactions of PCP and nifedipine are mediated through an interaction with the high affinity brain DHP binding site.

METHOD

Animals

Male, NIH mice (Veterinary Resources Branch, National Institutes of Health, Bethesda, MD; 18–22 g) were used in all studies. The animals were housed 30 per cage in a 12:12 hour light/dark cycle with free access to food and water.

Rotarod Performance

Prior to drug treatment, mice were placed on a rotarod apparatus (Rotamex, Columbus Instruments; speed 6 rpm). Only those mice which remained on the rotating rod for a 2 min period prior to drug administration were used.

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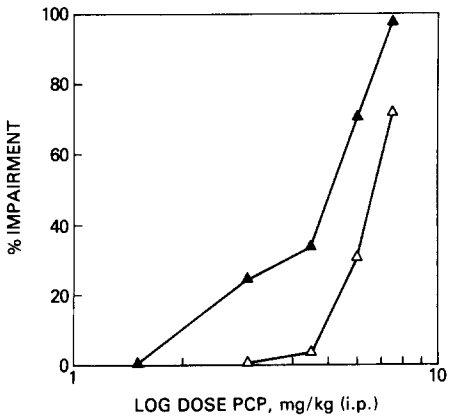

FIG. 1. PCP impairment of rotarod performance in mice: Effect of nifedipine. Impairment of rotarod performance by PCP was measured in the absence (▲) of nifedipine 2.5 mg/kg (see the Method section for details of dosing). The ED_{50} of PCP for impairment of rotarod performance was 4.8 mg/kg and 6.7 mg/kg respectively in the presence and absence of nifedipine. Each point represents the mean % impairment (see the Method section) of 3–4 experiments.

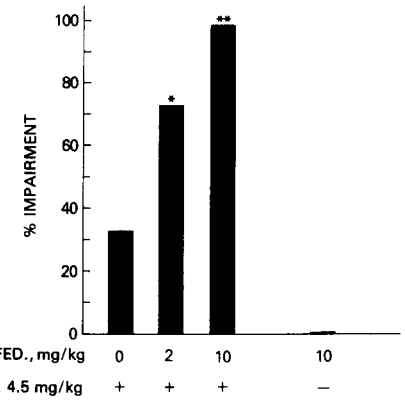

FIG. 2. Enhancement of PCP impairment of rotarod performance by nifedipine: Dose dependence. The effects of 2 and 10 mg/kg nifedipine were evaluated on PCP (4.5 mg/kg) impairment of rotarod performance. Nifedipine (10 mg/kg) alone was without effect on mouse rotarod performance. Values represent the mean percent sign impairment of 3–4 experiments. *Significantly different from PCP alone, $p<0.05$, χ^2 test. **Significantly different from 2 mg/kg nifedipine, $p<0.05$, χ^2 test.

Nifedipine, verapamil, prazosin, or saline were administered (IP) to groups of 5 mice each, followed 10 min later by PCP or an equal volume of saline solution injected on the opposite side of the abdomen (injection volumes were 0.1–0.2 ml). Ten min after the second injection, mice were placed on a rotarod and monitored for a maximum of 5 min.

Impairment of rotarod performance was scored as follows. Animals were scored as impaired if they fell from the rotating rod twice in the allotted 5 min period. Instances where an animal dropped once were given a score of 50%. This method of scoring was intended to account for normal exploratory behavior which might cause the animals to lose balance during the 5 min period. Animals which were repeatedly unable to grasp the rotarod were scored as incapacitated. At least three different groups of 5 mice were used for each drug treatment. Drugs were administered at different times of the day in an attempt to minimize possible diurnal influences on drug-induced behavior.

Motor Activity Studies

A Digiscan motor activity box (Omnitech Electronics, Columbus, OH) was used to assess motor activity. Dosing schedules were as described for the rotarod experiments. Mice were placed in the activity field following the second injection and activity counts (crossing a grid of infrared photocell detection beams) were taken for a 10 min period, beginning 20 min after the second injection. Counts for horizontal (all beams crossed), vertical (beams crossed by upright postures), and ambulatory (crossing of two perpendicular beams) movements were accumulated.

Drugs

Nifedipine and prazosin (as the hydrochloride salt) were obtained from Pfizer Inc. (Groton, CT). Verapamil hydrochloride was obtained from A. G. Knoll, West Germany. Phencyclidine hydrochloride (PCP) was obtained from the National Institute for Drug Abuse. All drugs were prepared for use daily. PCP, prazosin and verapamil were dissolved in a physiologic saline solution. Solutions of nifedipine were prepared by first dissolving in one volume of diluted Emulphor and subsequently nine volumes of distilled water. Diluted Emulphor is 50% Emulphor (EL 620, GAF Corporation, New York, NY), 50% ethanol (W/W).

RESULTS

PCP produced a dose dependent impairment of mouse rotarod performance (Fig. 1) with an ED_{50} of 6.7 mg/kg. Nifedipine pretreatment (2.5 mg/kg), significantly enhanced impairment of rotarod performance by PCP in a dose dependent fashion (ED_{50} 4.8 mg/kg) (Figs. 1, 2 and 3A) and increased the number of mice incapacitated by PCP (Fig. 3B). Doses that significantly increased both the deficit in rotarod performance and incapacitating actions of PCP did not produce appreciable effects on mouse behavior or rotarod performance when administered alone (Fig. 1) [5].

The ability of other drugs to alter impairment of mouse rotarod performance by PCP (4.5 mg/kg) is presented in Fig. 3. Verapamil (2 mg/kg) significantly enhanced the impairment of mouse rotarod performance by PCP (Fig. 3A). Prazosin (1 and 2 mg/kg) did not enhance the impairment of mouse rotarod performance by PCP (4.5 and 6 mg/kg) (Fig. 3A). However, prazosin (1 mg/kg), significantly antagonized the effects of a lower dose of PCP (3 mg/kg) on rotorod performance. Prazosin and verapamil by themselves did not produce any impairment of mouse rotarod performance at the doses utilized. However, a marked ptosis was observed in mice treated with prazosin.

Nifedipine (2.5 mg/kg) also enhanced the effect of PCP to incapacitate mice on the rotarod (Fig. 3B). A statistically significant increase in the number of mice incapacitated was observed at 4.5 mg/kg PCP, and a smaller statistically insignificant increase was observed at 6 mg/kg PCP.

The influence of nifedipine on PCP induced increases in spontaneous motor activity are presented in Table 1. PCP (4.5 mg/kg) significantly increased ambulatory motor activity and decreased vertical motor activity. Nifedipine (1.0 mg/kg) pretreatment completely antagonized the increase in ambulatory motor activity produced by PCP. Vertical motor activ-

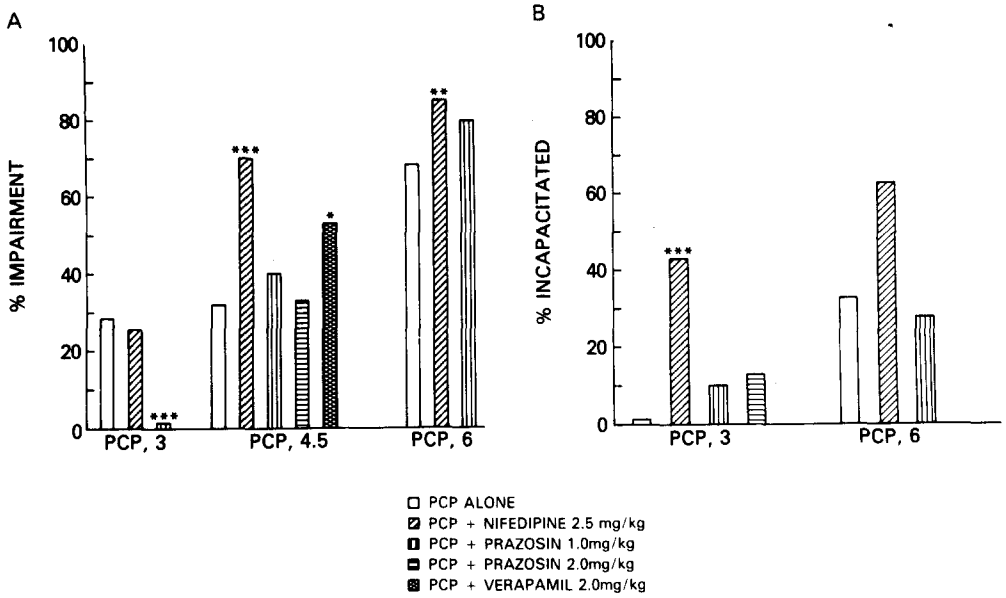

FIG. 3. The effect of calcium antagonists and prazosin on PCP impairment of rotarod performance. The effects of nifedipine, verapamil and prazosin on (A) the % impairment (see the Method section) of rotarod performance and (B) the % incapacitation on the rotarod (see the Method section) by different doses of PCP (mg/kg) were evaluated. Values are the mean of 3–4 experiments. Significantly different when compared to PCP alone $*p<0.05$, $**p<0.025$, $***p<0.005$, χ^2 test.

TABLE 1

THE EFFECT OF NIFEDIPINE ON PCP MEDIATED CHANGES IN MOUSE MOTOR ACTIVITY

Drug Treatment[a]	Motor Activity Score		
	Horizontal	Vertical	Ambulatory
Vehicle	2460 ± 277	98 ± 17	910 ± 145
PCP 4.5 mg/kg	2757 ± 139	28 ± 14*	1632 ± 353*
Nifedipine 4.0 mg/kg	2802 ± 211	37 ± 8*	1050 ± 135
Nifedipine 4.0 mg/kg + PCP 4.5 mg/kg	2973 ± 836	0.2 ± 0.4*	1018 ± 279

Values represent the mean ± S.E.M. motor activity score of from 5–9 mice.

[a]See the Method section for a detailed description of drug dosing.

*Significantly different $p<0.05$ (two tailed) t-test, from vehicle.

ity, already reduced by PCP, was completely abolished by pretreatment with nifedipine, which by itself also produced a significant reduction in vertical motor activity. None of the drug treatments significantly altered horizontal motor activity.

DISCUSSION

The presence of DHP binding sites in the CNS has prompted several recent studies to determine the physiologic and pharmacologic function of these sites [5, 10, 20, 24, 28, 29, 35, 39, 44]. However, in contrast to the actions of DHP calcium antagonists in smooth and cardiac muscles [16,21], these compounds are either ineffective or far less potent at inhibiting calcium dependent events in neuronal tissue [11, 21, 26, 40]. Nonetheless, the biochemical similarities between the brain dihydropyridine binding site and that in smooth and cardiac muscle [4, 21–23, 32], coupled with the finding that DHP calcium antagonists can inhibit a portion of the rapid phase of synaptosomal calcium uptake [44] is consistent with a functional role for these drugs in modulating neuronal calcium currents. This neuronal action might provide a biochemical basis for the behavioral actions and modulation of neurotransmitter release mediated by DHPs [5,29].

The recent observation that PCP and related compounds [6] increased the apparent affinity of the DHP binding sites (an effect not mediated via the high affinity [^{3}H]PCP binding site in brain) prompted a further investigation of the effects of calcium antagonists on the behavioral effects of PCP. Nifedipine enhanced the impairment of rotarod performance by PCP in mice, at doses that had no effect on rotarod performance on their own. The interaction of DHP calcium antagonist with PCP induced behaviors is supported by previous findings. Nisoldipine, a DHP calcium antagonist, blocked PCP induced stereotypy in rats [39], although the dose of nisoldipine used in this study produced behavioral effects of its own [19,39]. DHP calcium antagonists have also been shown to inhibit PCP mediated increases in the motor activity of mice [18]. Nifedipine, but not verapamil, increased the number of mice incapacitated by low doses of PCP, perhaps a consequence of the specific interaction between PCP and the DHP binding site in neuronal tissue [6]. The enhancement of PCP impairment of rotorod performance by verapamil at the dose used (2 mg/kg) was less than nifedipine (2.5 mg/kg), an indication that verapamil was less efficacious. The lower efficacy and inability of verapamil to increase the number of mice incapacitated by PCP may be a consequence of pharmacokinetic factors (cationic properties

of verapamil reducing its entry into the CNS), an interaction between verapamil and its specific binding site in brain [36] or an allosteric regulation of the DHP binding site by verapamil [4,26].

Since nifedipine and verapamil are both hypotensive drugs [19,31] (doses of 1 mg nifedipine and 7.5–12.5 mg verapamil intravenously in humans producing a 20 and 33 percent decrease in total peripheral resistance respectively [19]), prazosin, an α-adrenergic antagonist which is a potent hypotensive [12,46], was also evaluated for its effect on PCP induced behavior in mice. The inability of prazosin to later PCP impairment of rotarod performance in mice suggests that the hypotensive actions of verapamil and nifedipine would not significantly contribute to their behavioral interactions with PCP. Rather, the effect of low doses of prazosin to inhibit the ataxic effects of PCP is in agreement with a previous report indicating that hypotensive adenosine analogs, could antagonize the discriminative cue of PCP [7]. More recent studies indicate that this effect is due to the hypotensive actions of adenosine agonists reducing the transport of PCP to the CNS (R. B. Browne, personal communication). These results coupled with the facility with which DHP calcium antagonists cross the blood-brain barrier [10,38], implies a CNS, rather than peripheral site of action for the DHPs in increasing PCP induced ataxia in mice. Additional evidence of a behavioral interaction between nifedipine and PCP was demonstrated through inhibition of the PCP induced increases in ambulatory motor activity by nifedipine. This observation is consistent with the antagonism of PCP-induced behavioral stimulation in mice by DHP calcium antagonists [18]. Furthermore, nifedipine substantially potentiated the decrease in mouse vertical motor activity produced by PCP, which may likely be a consequence of the hypotensive effect of this drug to reduce vertical motor activity.

Our findings indicate that calcium antagonists can alter behavioral responses to PCP. Coupled with the recent observation that the DHP calcium agonist BAY K 8644 produced marked ataxia and motor incapacitation in mice through interaction with the CNS DHP binding site [5], it is possible that an interaction between PCP and the DHP binding site in the CNS might account for some of the behavioral effects of PCP. The DHP binding site as an additional site of interaction for PCP to those already characterized within the CNS [1, 2, 45, 47] might provide a neuropharmacologic explanation for the observation that, while electrolytic lesioning of the striatum and nucleus accumbens in rats lead to a decrease in [^{3}H]PCP binding and an inhibition of PCP induced stereotyped behaviors, there was no decrease in PCP induced hyperactivity [34].

The psychopharmacologic actions of calcium antagonists, in particular the DHP's, remains unclear. However, the interaction of calcium antagonist with PCP at the behavioral and the molecular level suggests that a potentially important relationship exists between the DHP calcium antagonist binding site and PCP. The very recent finding that verapamil could reduce PCP induced aggressive behavior in man [30] in a manner independent from its cardiovascular actions, supports this contention.

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