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Short Communication

Phencyclidine-like catalepsy induced by the excitatory amino acid antagonist DL-2-amino-5-phosphonovalerate

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This study presents experimental evidence for the mediation of a behavioral effect of phencyclidine-like drugs by inhibition of neurotransmission at excitatory synapses utilizing N-methyl-aspartate (NMA) receptors by showing that DL-2-amino-5-phosphonovalerate, a selective NMA antagonist, produces phencyclidine-like catalepsy in pigeons. This finding suggests the possibility that other behavioral actions of phencyclidine-like substances may be mediated in a similar fashion.

Phencyclidine (PCP), a major drug of abuse, has anesthetic actions and produces effects that resemble schizophrenia. The mechanism of action of PCP-like drugs has not been established, although specific binding sites in brain have been identified that appear to be pharmacologically relevant[4,7,9]. PCP-like drugs selectively antagonize excitation of spinal neurons by N-methyl-aspartate (NMA)[1,2]. Therefore, the behavioral effects of PCP-like drugs might result from reduced neurotransmission at excitatory synapses utilizing NMA receptors in higher centers of the central nervous system. Until now, this proposed explanation of the behavioral effects of PCP-like drugs is based exclusively on electrophysiological findings. In the present study, we have made an initial attempt to evaluate experimentally the possible involvement of NMA receptors in the mediation of behavioral actions of PCP-like drugs.

If PCP-like drugs produce behavioral effects primarily through antagonism at excitatory synapses utilizing NMA receptors, drugs that are known to antagonize electrophysiological effects of NMA should produce PCP-like behavioral effects. DL-2-Amino-5-phosphonovalerate (AP5) is a potent and highly selective NMA antagonist[8]. A procedure for the measurement of catalepsy in pigeons, suitable for studying PCP-like activity of compounds, has been described[5]. PCP-induced catalepsy was shown to be pharmacologically specific and stereoselective, as evidenced by the observation that pentobarbital fails to induce catalepsy and that catalepsy is induced by the (+)-isomers but not by the (−)-isomers of PCP-like drugs. The catalepsy test was used to investigate possible PCP-like effects of the NMA-antagonist, AP5.

The subjects were 10 experimentally naive White Carneaux pigeons (weighing between 450–550 g), which were housed individually, with

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food and water freely available. A chronic, indwelling guide cannula was implanted under anesthesia with the tip directly into the lateral ventricle[3]. Cannula patency was assessed by a radiographic method[3]. Five pigeons were tested after intracerebroventricular (i.c.v.) injections (10 μl/pigeon) of PCP (free base, dissolved in sterile water; pH 6–8; Warner-Lambert/Parke-Davis, Ann Arbor). The other 5 pigeons were tested with AP5 (dissolved in 1 N NaOH, to which sterile water was added; pH 6–8; Tocris Chemicals, Buckhurst Hill, England). Presence or absence of catalepsy (defined as loss of righting, without head-drop and without eye closure) was assessed at successive time-intervals after each injection. Tests of different doses were separated by 48 h.

Catalepsy was induced dose- and time-dependently by i.c.v. administration of PCP (Fig. 1, upper panels). AP5 produced catalepsy that had each of the signs of PCP-induced catalepsy noted above, and these effects were also dose- and time-dependent (Fig. 1, upper lefthand panel, lower panel). AP5 was more potent and had a longer duration of action than PCP. The mean threshold dose (average of the lowest dose which produced catalepsy at 15 min postinjection in each pigeon) of PCP was 2.7 ± 0.4 (S.E.M.) μmol/pigeon (ca. 1.3 mg/kg). The mean threshold dose of PCP, when administered i.m., has been shown to be 1.5 ± 0.3 mg/kg[5], suggesting that PCP is equipotent when given i.c.v. or i.m. The mean threshold dose of AP5 was 0.5 ± 0.2 μmol, about 5 times smaller than the mean threshold dose of PCP (Student's $t = 4.17$, df = 8, $P < 0.01$). The mean duration of catalepsy (average of duration of catalepsy in each pigeon) was 33 ± 7 min after 4.1 μmol of PCP and was about 5 times longer (i.e. 183 ± 83 min) after 1 μmol of AP5 ($t = 1.97$, df = 8, $P < 0.10$).

That AP5 had the capacity to produce catalepsy of a form comparable to PCP was striking. This finding shows that a drug previously identified as an NMA antagonist appears to have PCP-like behavioral effects and adds behavioral evidence to the electrophysiological observations of a coincidence of PCP-agonist and NMA-antagonist effects of a variety of drugs. Structure-

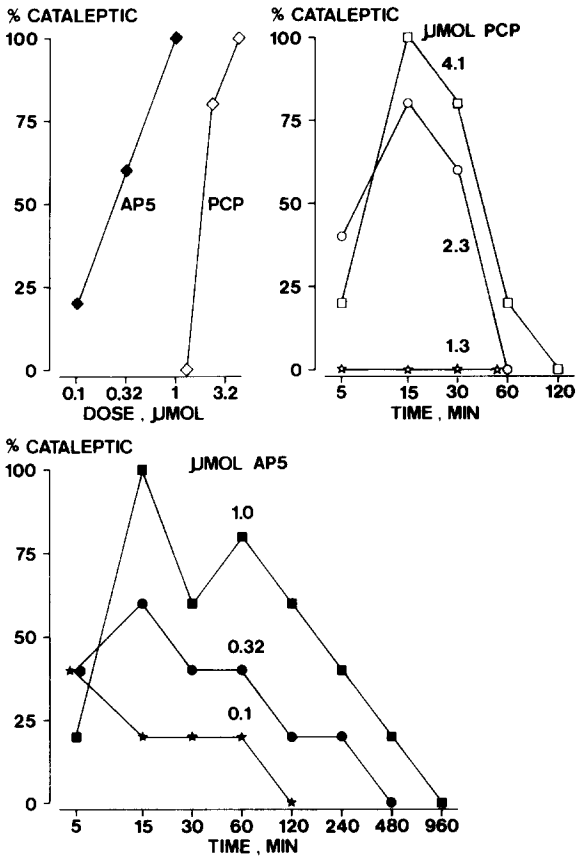

Fig. 1. Upper lefthand panel: dose–effect curves of AP5- and PCP-induced catalepsy (loss of righting without head-drop and without eye closure) in pigeons (n = 5 per drug) assessed 15 min after i.c.v. administration. Ordinate: percentage of subjects showing catalepsy. Abscissa: dose administered. Upper righthand panel and lower panel: time-effect curves of PCP- and AP5-induced catalepsy at different dose levels. Ordinates: percentage of subjects showing catalepsy. Abscissae: time after injection.

activity studies are necessary to study whether this PCP-like behavioral action of AP5 is dependent upon the NMA-antagonist properties of AP5. However, the present result makes viable the hypothesis stated above that catalepsy and, perhaps, other behavioral effects of PCP-like substances, may be mediated by inhibition of neurotransmission at excitatory synapses utilizing NMA receptors. There is a strong association between PCP-induced catalepsy in pigeons, PCP-like discriminative stimulus effects in pigeons[6], and PCP-like anesthesia. Therefore, NMA antagonists might have PCP-like anesthetic actions.

Conversely, NMA agonists might antagonize behavioral effects of PCP.

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1 Anis, N.A., Berry, S.C., Burton, N.R. and Lodge, D., The dissociative anaesthetics, ketamine and phencyclidine selectively reduce excitation of central mammalian neurones by N-methyl-aspartate, *Br. J. Pharmacol.*, 79 (1983) 565–575.

2 Berry, S.C. and Lodge, D., Benz(f)isoquinolines as excitatory amino acid antagonists: an indication of their mechanism of action, *Biochem. Pharmacol.*, 33 (1984) 3829–3832.

3 France C.P., Adams, J.U. and Woods, J.H., Intracerebroventricular drug administration in pigeons, *Pharmacol. Biochem. Behav.*, 23 (1985) 731–736..

4 Hampton, R.Y., Medzihradsky, F., Woods, J.H. and Dahlstrom, P.J., Stereospecific binding of phencyclidine in brain membranes, *Life Sci.*, 30 (1982) 2147–2154.

5 Koek, W., Woods, J.H., Rice, K.C., Jacobson, A.E., Huguenin, P.N. and Burke, T.R., Jr., Phencyclidine-induced catalepsy in pigeons: specificity and stereoselectivity, *Eur. J. Pharmacol.*, 106 (1984) 635–638.

6 Leander, J.D., Wood, C.R., Zimmerman, D.M. and Dykstra, L.A., Phencyclidine-type catalepsy in the pigeon: an update on Chen, *Drug Dev. Res.*, in press.

7 Vincent, J.P., Kartalovsky, B., Geneste, P., Kamenka, J.M. and Lazdunski, M., Interaction of phencyclidine ('angel dust') with a specific receptor in rat brain membranes, *Proc. Natl. Acad. Sci. U.S.A.*, 76 (1979) 4678–4682.

8 Watkins, J.C. and Evans, R.H., Excitatory amino acid transmitters, *Ann. Rev. Pharmacol. Toxicol.*, 21 (1981) 165–204.

9 Zukin, S.R. and Zukin, R.S., Specific [^{3}H]phencyclidine binding in rat central nervous system, *Proc. Natl. Acad. Sci. U.S.A.*, 76 (1979) 5372–5376.