

EFFECT OF PIRACETAM, A CYCLIC GABA ANALOGUE, ON HALOPERIDOL-INDUCED CATALEPSY IN THE RAT

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Summary: Piracetam, 2-oxo-1-pyrrolidine acetamide (Nootropil), is a cyclic GABA analogue. As GABA-mimetic compounds have been reported to potentiate haloperidol-induced catalepsy it was decided to study the effect of piracetam on haloperidol-induced catalepsy in rats. Piracetam, in high doses, was found to induce catalepsy while sub-cataleptic doses of piracetam were found to potentiate haloperidol-induced catalepsy. Piracetam, however, failed to antagonise apomorphine stereotypy in rats thereby ruling out the possibility of its possessing dopamine receptor blocking activity.

The possible mechanism involved in the induction of catalepsy by piracetam and in the potentiation of haloperidol-induced catalepsy by sub-cataleptic doses of piracetam is discussed on the basis of its chemical relationship to GABA.

Key words: piracetam haloperidol apomorphine catalepsy stereotypy

INTRODUCTION

The cataleptogenic effect of neuroleptics has been attributed to blockade of striatal dopamine receptors (3, 11). Recently many workers have proposed that GABA-ergic neurons originating in the striatum and terminating in the substantia nigra exert an inhibitory influence upon nigro-striatal dopaminergic neurons (2). Further, Worms *et al.* (15) have recently reported that GABA-mimetic agents potentiated haloperidol induced catalepsy while GABA antagonists (bicuculline, allylglycine), in subconvulsant doses, significantly decreased the cataleptic effect of haloperidol thereby suggesting an involvement of GABA in neuroleptic-induced catalepsy. In the present study we have therefore investigated the effect of piracetam, 2-oxo-1-pyrrolidine acetamide, a cyclic γ -aminobutyric acid (GABA) analogue (10), on the cataleptogenic effect of haloperidol.

MATERIALS AND METHODS

Male albino rats, 120 to 220 g, with free access to a standard diet and tap water used. Each animal was used only once. All observations were made between 10.00 and 16.00 hr at 27 to 30°C in a noiseless, diffusely illuminated room.

Catalepsy was scored according to Costall and Naylor (6). The animals were individually placed in perspex cages 30 min before drug treatment to allow adaptation to the new environment. The animals were tested for the presence of catalepsy by placing both front paws on a 8 cm high horizontal bar. The scores were given as follows: animals maintaining the cataleptic posture from 0 to 10 sec = 0; 10 to 30 sec = 1; 30 sec to 1 min = 2; 1 to 2 min = 3; 2 min to ∞ = 4. The animals were tested for catalepsy 0.5, 1.0, 2.0, 3.0 and 4.0 hr after haloperidol treatment. The effect of piracetam pretreatment on apomorphine-induced stereotyped behaviour (SB) was studied by the method of Costall and Naylor (5). For observation the animals were placed in individual cages made of wire netting, measuring 30 cm x 20 cm and 20 cm high. They were placed in the observation cages 30 min before drug treatment to allow adaptation to the environment. The intensity of SB was assessed at 5 min intervals for 30 min according to the following scoring system: 0: no change; 1: discontinuous sniffing, constant exploratory activity; 2: continuous sniffing, periodic exploratory activity; 3: continuous sniffing, discontinuous biting, gnawing or licking and very brief periods of locomotor activity and 4: continuous biting, gnawing or licking but no exploratory activity.

The drugs used were piracetam ('Nootropil, Unichem), haloperidol ('Serenace injection, Searle) and apomorphine hydrochloride (Burroughs Wellcome). Piracetam (PIR) was dissolved in distilled water, apomorphine (APO) was dissolved in distilled water containing 0.2 mg/ml ascorbic acid; haloperidol injection solution was diluted to required strength with distilled water. Piracetam was injected in a volume of 10 ml/kg body weight, and haloperidol and apomorphine were injected in a volume of 2 ml/kg body weight. All drugs were administered intraperitoneally. For each dose, 10 animals were used. Haloperidol was injected 30 min and apomorphine 60 min after piracetam treatment. Control groups received requisite volume of vehicle intraperitoneally.

The statistical significance of differences between means was calculated by the Student's unpaired t-test.

RESULTS

Piracetam (50, 100 and 150 mg/kg) did not produce any detectable changes in the gross behaviour of the animals nor did it induce catalepsy. However, higher doses (250, 500 and 1000 mg/kg), which are far below the reported LD₅₀ (>8 g/kg, iv) (7), induced a state of sedation and dose-dependent degree of catalepsy, without loss of righting reflex or apparent change in muscle tone. The cataleptic effect was present at 30 min and reached maximum at 1 hr (Fig. 1).

Pretreatment with 50 mg/kg of piracetam did not significantly affect the cataleptic effect of haloperidol (1 mg/kg) while pretreatment with 100 mg/kg of piracetam was

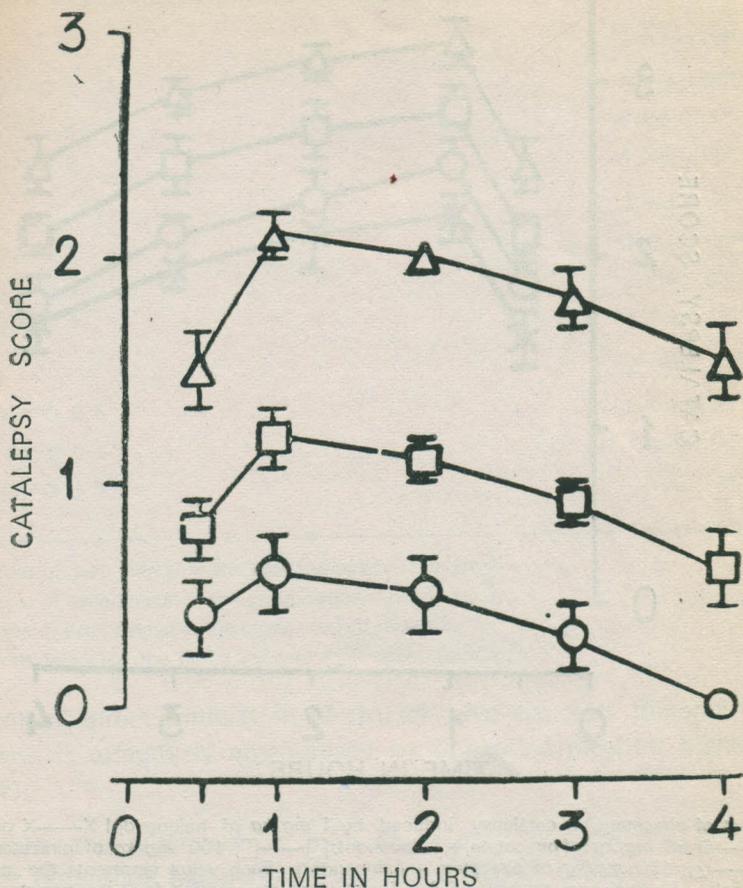


Fig. 1 : Dose-dependency of the cataleptic effect induced by 250 (O—O), 500 (□—□) and 1000 (△—△) mg/kg piracetam in the rat. Each value represents the mean score of 10 animals. Vertical bars represents S.E. Times given are counted from the injection of piracetam.

found to significantly ($P < 0.05$) potentiate it at all the testing time intervals. Similarly, pretreatment with 150 mg/kg of piracetam was found to significantly ($P < 0.01$) potentiate the cataleptic effect of haloperidol (1 mg/kg) at all the testing time intervals (Fig. 2).

Pretreatment with piracetam (125, 250 and 500 mg/kg) failed to antagonise apomorphine-induced SB (Table I).

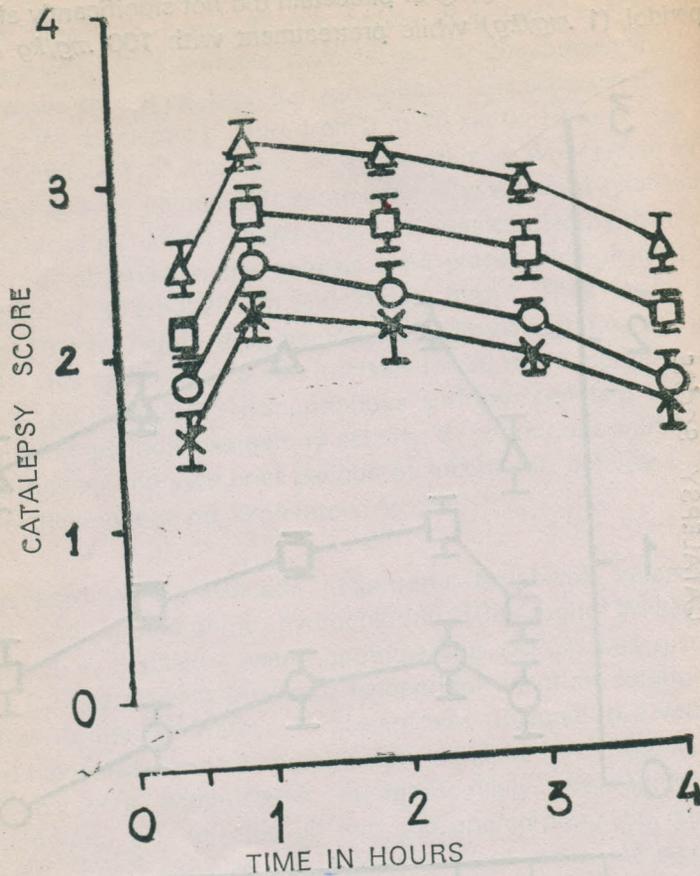


Fig. 2 : Effect of piracetam on catalepsy induced by 1 mg/kg of haloperidol X—X only haloperidol; O—O 50 mg/kg of piracetam + haloperidol; □—□ 100 mg/kg of piracetam + haloperidol; Δ—Δ 150 mg/kg of piracetam + haloperidol). Each value represents the mean score of 10 animals. Vertical bars represent S.E. Times given are counted from the injection of haloperidol.

DISCUSSION

Catalepsy has been attributed to a functional lack of dopamine at striatal dopaminergic receptors (14). Neuroleptics such as haloperidol achieve this effect by blocking post-synaptic striatal dopamine receptors (3). In our study, high doses of piracetam (2 to 1000 mg/kg) were found to induce catalepsy, suggesting thereby that piracetam, like haloperidol, may be possessing post-synaptic striatal dopamine receptor blocking activity. This possibility is however, ruled out by our observation that piracetam failed to antagonize apomorphine-induced stereotyped behaviour. Apomorphine stereotypy is believed

TABLE I : Effect of piracetam pretreatment on apomorphine induced stereotyped behaviour in rats.

Study	Treatment dose mg/kg	Intensity score	
		Mean	± S.E.M.
I	1. APO 2	4.0	±0.00*
	2. PIR 125+APO 2	4.0	±0.00*
	3. PIR 250+APO 2	4.0	±0.00*
	4. PIR 500+APO 2	4.0	±0.00*
II	1. APO 1	3.0	±0.00**
	2. PIR 125+APO 1	3.0	±0.00**
	3. PIR 250+APO 1	3.0	±0.00**
	4. PIR 500+APO 1	3.0	±0.00**
III	1. APO 0.5	2.0	±0.00***
	2. PIR 125+APO 0.5	2.0	±0.00***
	3. PIR 250+APO 0.5	2.0	±0.00***
	4. PIR 500+APO 0.5	2.0	±0.00***

*The score of each animal in the group worked out to be 4.

**The score of each animal in the group worked out to be 3.

***The score of each animal in the group worked out to be 2.

Numerals following the drugs indicate their doses (mg/kg).

occur as a result of direct stimulation of striatal post-synaptic dopamine receptors by apomorphine and is effectively antagonised by dopamine receptor blocking drugs like haloperidol (11).

Our results, that piracetam in high doses induces catalepsy, while lower sub-cataleptic doses potentiate haloperidol-induced catalepsy, can be explained on the basis of chemical relationship of piracetam to GABA. GABA is reported to produce a functional lack of dopamine at striatal dopamine receptors by exerting an inhibitory influence upon the nigro-striatal dopaminergic neurons (12) and piracetam being a cyclic GABA analogue (10), may have also exerted an inhibitory influence on the nigro-striatal dopaminergic neurons and produced a functional lack of dopamine at striatal dopamine receptors with resultant induction of catalepsy. Further, the potentiation of haloperidol-induced catalepsy by sub-cataleptic doses of piracetam may be explained on the basis that piracetam, by exerting an inhibitory effect on the nigro-striatal dopaminergic neurons, may be reducing the compensatory 'feed back' increase of dopaminergic activity which normally follows the blockade of dopamine receptors by neuroleptics (1). Such an explanation was put

forth by Keller *et al.* (9) to explain the potentiation of haloperidol induced catalepsy by aminooxyacetic acid, which elevates brain GABA levels by inhibiting the enzyme GABA-transaminase (4), and benzodiazepines which facilitate GABA-ergic transmission (8).

In conclusion we would like to state, on the basis of our results, that as piracetam a cyclic GABA analogue, is capable of modulating the functioning of central dopaminergic systems, it may be used as an adjuvant to neuroleptics in the treatment of schizophrenia. Such a therapeutic application for GABA analogues has already been put forth by Van Kammen(13).

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REFERENCES

- Anden, N.E., S.G. Butcher, H. Corrodi, K. Fuxe and U. Ungerstedt. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.*, **11** : 303-314, 1970.
- Bartholini, G. and H. Stadler. Cholinergic and GABA-ergic influences on the dopamine turnover in extrapyramidal system. In "Chemical Tools in Catecholamine Research, Vol. II. Regulation of Catecholamine Turnover" by Almgren, O., A. Carlsson and J. Engél, Amsterdam, North Holland Publishing Co., p. 235, 1975.
- Carlsson, A. and M. Lindqvist. Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmac. Toxicol.*, **20** : 140-144, 1963.
- Collins, G.G.S. Effect of aminooxyacetic acid, thiosemicarbazide and haloperidol on the metabolism and half-lives of glutamate and GABA in rat brain. *Biochem. Pharmac.*, **22** : 101-111, 1973.
- Costall, B. and R.J. Naylor. On the mode of action of apomorphine. *Eur. J. Pharmac.*, **21** : 350-361, 1974.
- Costall, B. and R.J. Naylor. Mesolimbic involvement with behavioural effects indicating antipsychotic activity. *Eur. J. Pharmac.*, **27** : 46-58, 1974.
- Giurgea, C.E., F.E. Moeyersoons and A.C. Evraerd. A GABA-related hypothesis on the mechanism of action of the antinotion-sickness drugs. *Arch. Int. Pharmacodyn.*, **166** : 238-251, 1967.
- Haefely, W., A. Kulcsar, H. Mohler, L. Pieri, P. Polc and R. Schaffner. Possible involvement of GABA in the central actions of benzodiazepines. In "Mechanism of Action of Benzodiazepines" by Costa, E. and P. Greengard, New York, Raven Press, p. 131, 1975.
- Keller, H.H., R. Schaffner and W. Haefely. Interactions of benzodiazepines with neuroleptics at central dopamine neurones. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **294** : 1-7, 1976.
- Meldrum, B.S. Gamma-Aminobutyric acid and the search for new anticonvulsant drugs. *Lancet*, **2** : 304-308, 1978.
- Randrup, A. and I. Munkvad. Behavioural stereotypies induced by pharmacological agents. *Pharmacopsychiat. Neuropsychopharmacol.*, **1** : 18-26, 1968.
- Roberts, E. A model of the vertebrate nervous system based on distribution : a key role of the GABA system. In "Neurohumoral Coding of Brain Function" by Myers, R.D. New York, Plenum, p. 419, 1974.
- Van Kammen, D.P. γ -Aminobutyric acid (GABA) and the dopamine hypothesis of schizophrenia. *Am. J. Psychiatry*, **134** : 138-143, 1977.
- Van Rossum, J.M. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch. Int. Pharmacodyn.*, **160** : 492-494, 1966.
- Worms, P., M.T. Willigens and K.G. Lloyd. GABA involvement in neuroleptic-induced catalepsy. *J. Pharmac.*, **30** : 716-718, 1978.