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THE EFFECT OF BACLOFEN ON α-FLUPENTHIXOL-INDUCED CATALEPSY IN THE RAT

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1 α-Flupenthixol (α-FPT; 0.2 mg/kg i.p.) when administered to rats produced catalepsy.
2 Baclofen (10 mg/kg i.p.) given 30 min after α-FPT had a biphasic effect on the catalepsy. Initially there was a potentiation of the effect, followed by a significant attenuation of the degree of catalepsy.
3 Possible mechanisms of action are discussed.

Introduction

α-Flupenthixol (α-FPT) is a neuroleptic of the thioxanthene group which has been reported to be a potent low dose neuroleptic in man with little sedative action (Moller Nielsen, Pedersen, Nymark, Franck, Boeck, Fjalland & Christensen 1973). The cataleptogenic effect of neuroleptics has been attributed to blockade of striatal dopamine receptors (Carlsson & Lindquist 1963; Van Rossum 1966). More recently many workers have proposed that γ-aminobutyric acid (GABA)-ergic neurones originating in the striatum and terminating in the substantia nigra exert an inhibitory influence upon nigro-striatal dopaminergic neurones (Kim, Bak, Hassler & Okada 1971; Bartholini & Stadler, 1975). Baclofen (β-*p*-chlorophenyl-GABA) is used clinically in the treatment of spasm of voluntary muscles. Its mode of action has been attributed to the facilitation of GABA-mediated transmission in the central nervous system. Baclofen would therefore be expected to inhibit the activity of nigro-striatal dopaminergic neurones and in the process potentiate the cataleptogenic effect of α-FPT.

Gianutsos & Moore (1977) reported that baclofen produced a dose-dependent increase in the concentration of brain dopamine in mice without affecting noradrenaline levels. They suggested that this effect was achieved by a reduction in impulse flow in dopaminergic neurones in a similar way to that produced by γ-butyrolactone (GBL), (Roth, Walters, Murrin & Morgenroth, 1975). This study examines the effect of baclofen on the cataleptogenic effect of α-FPT.

Methods

Female Wistar rats weighing 130–150 g were injected (i.p.) with α-FPT 0.2 mg/kg followed 30 min later by baclofen 10 mg/kg intraperitoneally. Control animals received distilled water in place of baclofen. A further control group received distilled water followed 30 min later by baclofen (10 mg/kg i.p.).

Catalepsy was evaluated every 30 min for 2 h following the administration of α-FPT and thereafter every 60 min by placing the fore paws of the animal over an 8 cm high horizontal bar and measuring the time for which the animal maintained this posture. Scoring was modified from that used by Costall & Naylor (1974). Animals maintaining the cataleptic posture from 0 to 10 s scored 0; 10 s to 1 min = 1; 1 to 2 min = 2; 2 to 3 min = 3; 3 to 4 min = 4; 4 min to α = 5. Results were analysed by the Mann-Whitney U-Test for non-parametric data.

α-FPT was dissolved in distilled water to a concentration of 0.2 mg/ml. Baclofen was prepared by dissolving 10 mg in 1 ml of 0.4 N HCl and adding 2 ml of 0.4 N $NaHCO_3$. Final pH after mixing was 6.8. Volumes for α-FPT injection were 1 ml/kg and for baclofen 3 ml/kg. All injections were made intraperitoneally.

Results

The administration of α-FPT (0.2 mg/kg) produced a time-related increase in catalepsy, maximum scores being attained at 5 to 6 h following its administration. The administration of baclofen (10 mg/kg) 30 min after α-FPT potentiated the catalepsy for the first 90 min, the potentiation being statistically significant ($P < 0.01$) at 60 min (see Figure 1). At all times after 90 min the degree of catalepsy was significantly

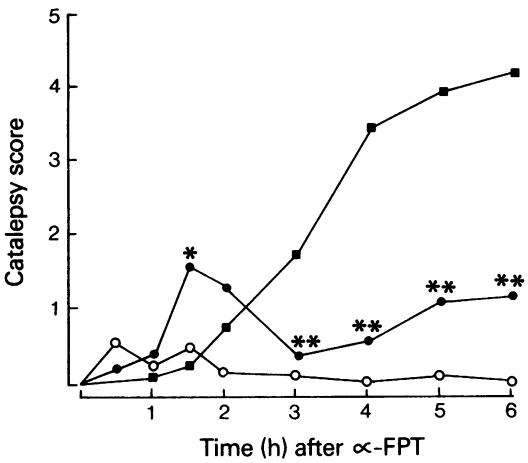

Figure 1 The effect of baclofen on α-flupenthixol (α-FPT)-induced catalepsy. (●) α-FPT (0.2 mg/kg i.p.) + baclofen (10 mg/kg i.p. 30 min later) $n = 12$; (■) α-FPT + distilled water (1 ml/kg, 30 min later), $n = 8$; (○) distilled water (1 ml/kg i.p.) + baclofen (10 mg/kg i.p., 30 min later), $n = 10$. Results were analysed by the Mann-Witney U-test: $^{*}P < 0.01$, $^{**}P < 0.001$.

attenuated by baclofen ($P < 0.001$ at all times). Baclofen (10 mg/kg) 30 min after distilled water had no significant effect (Figure 1).

Discussion

Catalepsy has been attributed to a functional lack of dopamine at striatal dopaminergic receptors (Van Rossum 1966). Neuroleptics such as α-FPT achieve this effect by blocking post-synaptic dopamine receptors. It is also possible that α-FPT blocks presynaptic or autoreceptors that regulate the synthesis of dopamine by a 'feedback' mechanism. The overall effect is an increased turnover of dopamine and an inhibition of dopamine receptor stimulation. Baclofen has been reported to antagonize the increase in turnover of dopamine produced by neuroleptics, presumably by depressing the firing rate of dopaminergic neurones and thus rendering them unresponsive to neuronal 'feedback' mechanisms (Fuxe, Hokfelt, Ljungdahl, Agnati, Johansson & Perez de la Mora 1975). It has been proposed that baclofen increases the concentration of brain dopamine in a dose-dependent manner similar to that proposed for GBL (Gianutsos & Moore 1977), whereby the reduction in impulse flow in dopaminergic neurones results in an increased activation of tyrosine hydroxylase (Roth *et al.*, 1975).

Since a GABA-ergic system has been proposed, that exerts an inhibitory effect on the nigro-striatal dopaminergic system (Kim *et al.*, 1971), a potentiation of GABA-ergic transmission by either structural analogues or by elevation of endogenous brain GABA levels would be expected to increase the cataleptogenic effect of neuroleptics. Keller, Schaffner & Haefely (1976) proposed a similar mechanism and reported that amino-oxyacetic acid which elevates brain GABA levels by inhibiting the enzyme GABA-transaminase (Collins, 1973) and benzodiazepines which have been reported to facilitate GABA-ergic transmission (Haefely, Kulcsar, Mohler, Pieri, Polc & Schaffner 1975), potentiated the cataleptogenic effect of haloperidol.

The results described in this paper agree with the above findings in that there is a potentiation of catalepsy up to 90 minutes. However, we found that after 90 min the cataleptogenic effect of α-FPT was attenuated and remained significantly so when compared to control animals for up to 6 hours. It would appear that the facilitation of GABA-ergic inhibition on the nigro-striatal dopaminergic neurones produced by baclofen diminishes after 90 minutes. We propose that the reversal of catalepsy by baclofen is a result of the reinstatement of impulse flow in the nigro-striatal dopaminergic neuronal system. As a result the high concentrations of endogenous dopamine that have accumulated during the first 90 min are released, resulting in a reversal of the cataleptogenic effect of α-FPT.

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