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A role for 5-hydroxytryptamine in the GABA-mimetic potentiation of α-flupenthixol-induced catalepsy in the rat

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1 α-Flupenthixol (α-FPT)-induced catalepsy in the rat was potentiated by diaminobutyric acid (DABA), an inhibitor of the neuronal high affinity uptake of γ-aminobutyric acid (GABA).

2 The depletion of 5-hydroxytryptamine (5-HT) with *p*-chlorophenylalanine (PCPA) abolished the DABA potentiation of α-FPT-induced catalepsy; this response was restored with 5-hydroxytryptophan.

3 Potentiation of α-FPT-induced catalepsy by clonazepam was significantly reduced by methysergide. Conversely, the potentiation of catalepsy by clomipramine was significantly reduced by picrotoxin.

4 These results are interpreted as evidence supporting a role for 5-HT in modifying the GABA-ergic inhibition of dopaminergic pathways, possibly by regulating the release of GABA.

Introduction

The ability of drugs with proposed γ-aminobutyric acid (GABA)-ergic agonist activity to potentiate neuroleptic-induced catalepsy has been attributed to the enhanced GABA-ergic inhibition of the ascending nigrostriatal dopaminergic pathway (Kaariainen, 1976; Keller, Schaffner & Haefely, 1976; Worms, Willigens & Lloyd, 1978). Evidence for the inhibitory regulation of this dopaminergic pathway by a descending striato-nigral GABA-ergic pathway has been obtained electrophysiologically (Crossman, Walker & Woodruff, 1974), behaviourally (Tarsy, Pycock, Meldrum & Marsden, 1975) and pharmacologically (Cheramy, Nieoullion & Glowinski, 1978).

In addition to this GABA-ergic afferent input to the substantia nigra there is evidence of other distinct afferent inputs, e.g. substance P, (Dray & Straughan, 1976; Cuello, Emson, Del Fiacco, Gale, Iversen, Jessell, Kanazawa, Paxinos & Quik, 1978) and 5-hydroxytryptamine (5-HT) (Fibiger & Miller, 1977; Dray, Davies, Oakley, Tongroach & Velucci, 1978) being amongst the best documented.

In view of the reported modulation of neuroleptic-induced catalepsy by 5-HT (Costall, Fortune, Naylor, Marsden & Pycock, 1975; Fuenmayor & Vogt, 1979) the current investigation was performed to evaluate whether procedures affecting 5-HT-ergic systems in any way modified the ability of GABA-ergic drugs to potentiate neuroleptic-induced catalepsy.

Methods

All experiments were performed on female Wistar rats weighing 120–150 g. The drug dosages are expressed in terms of the free base. All drugs, except clonazepam, were dissolved in distilled water although 5-hydroxytryptophan (5-HTP) required some gentle heating. Clonazepam was suspended in a 1% solution of Tween 80. Injection volumes were 1 ml/kg for all drugs except diaminobutyric acid (DABA) where the injection volume was increased to 2 ml/kg. All drugs were given intraperitoneally (i.p.).

The number of animals referred to in the legends represents the total number of animals that received the appropriate treatment collected over several weeks. This approach takes into account any day to day variability that may occur in the evaluation of catalepsy. All results were analysed by a non-parametric multivariate test (Mantel & Valand, 1970).

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Assessment of catalepsy

Catalepsy was measured in a black perspex chamber by placing the front limbs of the animal over an 8 cm high horizontal bar and recording the duration that the animal maintained this enforced position. The cataleptic state was considered over, when all four feet of the animal were on the floor of the chamber. A duration of 0–10 s was scored as 0; 10 s–1 min as 1; 1–2 min as 2; 2–3 min as 3; 3–4 min as 4; over 4 min as 5. Each observation of catalepsy lasted for a maximum of 4 min.

Catalepsy was recorded each day starting at 10 h 00 min, for a total period of 6 h, at 30 min intervals for the first 2 h and thereafter 60 min intervals, in a temperature controlled and sound-proofed room.

The effect of diaminobutyric acid on the cataleptogenic activity of α-flupenthixol and its interaction with 5-hydroxytryptamine

Control animals received distilled water whereas test animals were given DABA 478 mg/kg (2.5 mmol/kg). Both these injections were given 19 h before the administration of α-flupenthixol (α-FPT) 0.2 mg/kg. These dosages were chosen from the results of previous experiments where the dose-response relationship of α-FPT and DABA had been evaluated (Williams & Davies, 1979). Any intrinsic cataleptogenic activity for DABA was evaluated in a separate group by injecting distilled water in place of α-FPT in DABA-pretreated animals.

Depletion of 5-HT was produced by pretreating test animals with three consecutive daily doses of *p*-chlorphenylalanine (PCPA) 100 mg/kg (Koe & Weissman, 1966). Each injection was given at 09 h 00 min. This regimen has produced, in our hands, a 90% decrease in total brain 5-HT (unpublished observation). Control animals received distilled water in place of PCPA. Six hours after the final administration of PCPA or distilled water all animals received DABA 478 mg/kg. Nineteen hours later, i.e. at 10 h 00 min on day 4, all animals received α-FPT 0.2 mg/kg and catalepsy was evaluated.

Further groups of animals were depleted of 5-HT and given DABA as above, then at 09 h 00 min and 09 h 30 min on day 4 test animals were given the peripheral decarboxylase inhibitor, benserazide 50 mg/kg, and 5-HTP 50 mg/kg respectively, whereas control animals received benserazide and distilled water in place of 5-HTP. At 10 h 00 min each animal was given α-FPT, 0.2 mg/kg, and catalepsy evaluated.

The effect of methysergide on clonazepam potentiation of α-flupenthixol-induced catalepsy

Test animals were given methysergide, 5 mg/kg, at 09 h 00 min whereas control animals received distilled water. Thirty minutes later animals of both groups received clonazepam, 10 mg/kg, followed again 30 min later by α-FPT, 0.2 mg/kg. Any intrinsic cataleptogenic activity for methysergide or clonazepam was tested for in separate groups by giving methysergide and clonazepam alone and evaluating catalepsy over a 6 h period.

The effect of picrotoxin on clomipramine potentiation of α-flupenthixol-induced catalpsy

Test animals were given picrotoxin, 0.1 mg/kg. Control animals received distilled water; 30 min later animals from both groups were given clomipramine, 15 mg/kg, followed a further 30 min later by α-FPT, 0.2 mg/kg. Any intrinsic cataleptogenic activity that either clomipramine or picrotoxin may have possesed was evaluated.

Drugs

The drugs used and their sources, were as follows: α-flupenthixol (Lundbeck & Co., Copenhagen, Denmark); methysergide (Sandoz); clonazepam (Roche); clomipramine (Ciba-Geigy); 5-HTP, DABA, PCPA and picrotoxin (Sigma Chemical Co.).

Results

The effect of diaminobutyric acid on the cataleptogenic activity of α-flupenthixol and its interaction with 5-hydroxytryptamine

Figure 1 clearly illustrates that DABA, 478 mg/kg, 19 h prior to α-FPT, 0.2 mg/kg, significantly potentiated ($P<0.001$) the cataleptogenic activity of α-FPT. DABA (478 mg/kg) followed 19 h later by distilled water resulted in no catalepsy. The depletion of 5-HT produced by PCPA significantly reduced the ability of DABA to potentiate α-FPT-induced catalepsy. However, despite the 5-HT depletion, the catalepsy that was developed was not significantly different from that produced by α-FPT alone.

Figure 2 shows that the administration of 5-HTP, 50 mg/kg, given together with 50 mg/kg of benserazide, restored the ability of DABA to potentiate α-FPT-induced catalepsy of 5-HT depleted animals.

The effect of methysergide on clonazepam potentiation of α-flupenthixol-induced catalepsy

Methysergide, 5 mg/kg, 30 min before the administration of clonazepam, 10 mg/kg, significantly inhi-

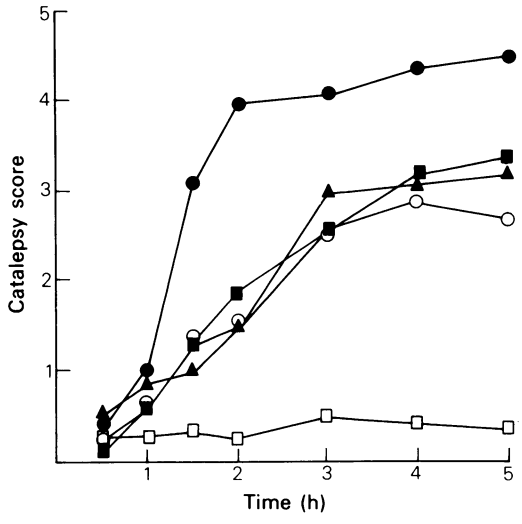

Figure 1 The effect of diaminobutyric acid (DABA) on α-flupenthixol (α-FPT)-induced catalepsy in both normal rats (●) and in animals depleted of 5-hydroxytryptamine (5-HT) (▲). DABA (478 mg/kg, 2.5 mmol/kg) was given i.p. 19 h before α-FPT (0.2 mg/kg i.p., $n = 15$). (■) Control animals received distilled water 19 h before α-FPT ($n = 14$). Depletion of 5-HT was achieved with *p*-chlorophenylalanine (PCPA) 100 mg/kg daily for 3 days; 6 h following the last PCPA injection animals received DABA (478 mg/kg), 19 h later these animals were then given α-FPT (0.2 mg/kg, $n = 11$). (○) The effect of PCPA pretreatment on α-FPT-induced catalepsy ($n = 15$). (□) DABA (478 mg/kg) had no intrinsic cataleptic activity when given 19 h before testing ($n = 5$). Mean values given. Statistical analysis: (●) vs (■): $P < 0.001$; (○) vs (■): not significant.

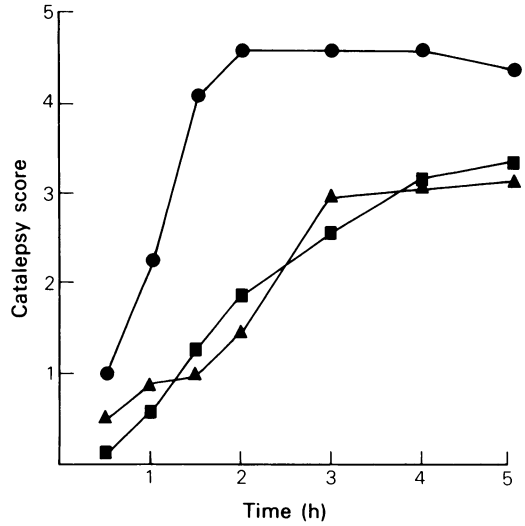

Figure 2 The effect of 5-hydroxytryptophan (5-HTP) on the potentiation by diaminobutyric acid (DABA) of α-flupenthixol (α-FPT)-induced catalepsy in 5-hydroxytryptamine (5-HT)-depleted animals. 5-HT depletion was carried out as described in Figure 1 (●). Eighteen hours after DABA (478 mg/kg) and 60 and 30 min before α-FPT (0.2 mg/kg) the animals received benserazide (30 mg/kg) i.p. and 5-HTP (50 mg/kg) i.p. respectively ($n = 9$). (▲) Control animals received distilled water in place of 5-HTP ($n = 11$). Mean values given. (■) α-FPT ($n = 14$). Statistical analysis: (●) vs (▲): $P < 0.001$.

bited the potentiation of α-FPT-induced catalepsy by clonazepam (Figure 3). Both clonazepam and methysergide showed no intrinsic cataleptogenic activity.

The effect of picrotoxin on clomipramine potentiation of α-flupenthixol-induced catalepsy

The potentiation of α-FPT-induced catalepsy by clomipramine, 15 mg/kg, shown in Figure 4, was significantly blocked by the preadministration of picrotoxin, 0.1 mg/kg.

The degree of α-FPT-induced catalepsy in animals pretreated with picrotoxin, 0.1 mg/kg, was not significantly different from that produced by α-FPT alone. However, larger doses of picrotoxin, 0.25 and 0.5 mg/kg, significantly reduced the catalepsy (results not given). Both clomipramine and picrotoxin showed no intrinsic cataleptogenic activity.

Discussion

The potentiation of neuroleptic-induced catalepsy by GABA-mimetic drugs has been related to the latter's enhancement of GABA-ergic inhibition of the ascending nigro-striatal dopaminergic pathway (Keller *et al.*, 1976). The striato-nigral GABA-ergic input to the substantia nigra is primarily considered to exert an inhibitory effect upon the ascending nigro-striatal dopaminergic pathway (Yoshida & Precht, 1971; Gale & Guidotti, 1976), although more recent studies have implicated a more complex and diverse involvement (Dray, Fowler, Oakley, Simmonds & Tanner, 1977; Cheramy *et al.*, 1978). DABA which has been demonstrated both *in vitro* and *in vivo* to inhibit GABA uptake (Iversen & Johnston, 1971; Sutton & Simmonds, 1974) has been shown in the present work to potentiate α-FPT-induced catalepsy. A similar effect of DABA on haloperidol-induced catalepsy has been reported by Worms *et al.* (1978). The administration of DABA alone produced no catalepsy, indicating that the induction of catalepsy was primarily the result of the blockade of striatal postsynaptic dopamine receptors by the neuroleptic

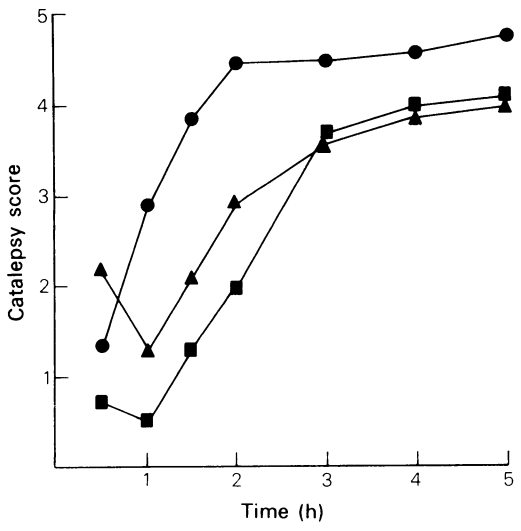

Figure 3 The effect of clonazepam and methysergide on α-flupenthixol (α-FPT)-induced catalepsy. (●) Clonazepam (10 mg/kg i.p.) was given 30 min before α-FPT (0.2 mg/kg, i.p.; $n=10$). (▲) Methysergide (5 mg/kg i.p.) was given 30 min before clonazepam (10 mg/kg i.p.) and 60 min before α-FPT (0.2 mg/kg i.p.; $n=10$). (■) α-FPT (0.2 mg/kg i.p.; $n=10$). Mean values given. Statistical analysis: (●) vs (▲): $P<0.01$.

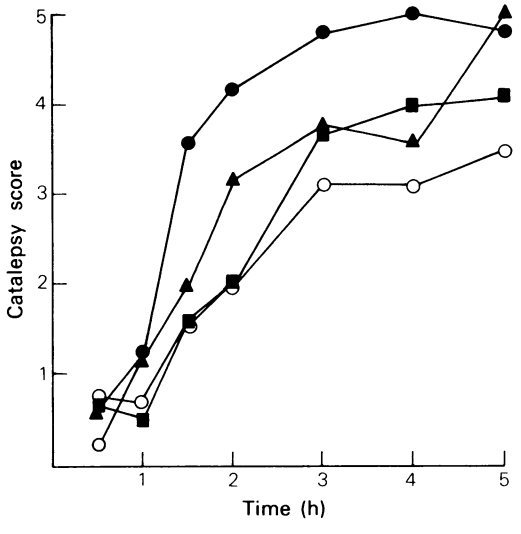

Figure 4 The effect of picrotoxin and clomipramine on α-flupenthixol (α-FPT)-induced catalepsy. (●) Clomipramine (15 mg/kg i.p.) was given 30 min before α-FPT (0.2 mg/kg i.p.; $n=5$). (○) Picrotoxin (0.1 mg/kg i.p.) was given 30 min before clomipramine (15 mg/kg) and 60 min before α-FPT (0.2 mg/kg; $n=15$). (▲) Picrotoxin (0.1 mg/kg) plus α-FPT (0.2 mg/kg; $n=5$). (■) α-FPT (0.2 mg/kg; $n=10$). Mean values given. Statistical analysis: (●) vs (■): $P<0.001$; (●) vs (○): $P<0.01$; (■) vs (▲): not significant.

(Hornykiewicz, 1973; Consolo, Ladinsky & Bianchi, 1975).

Previous reports have indicated that impairment of the 5-HT-ergic system attenuated the intensity of neuroleptic induced catalepsy (Costall *et al.*, 1975; Fuenmayor & Vogt, 1979). However, in the work reported here, the depletion of 5-HT produced by preadministration of the tryptophan-5-hydroxylase inhibitor, PCPA, did not affect the cataleptogenic activity of α-FPT. It did, however, significantly block the ability of DABA to potentiate α-FPT-induced catalepsy, suggesting that 5-HT may in some way regulate the GABA-ergic inhibition of dopaminergic systems. The possible importance of 5-HT in the GABA-ergic potentiation of neuroleptic-induced catalepsy is further emphasised by the restoration of the DABA potentiation of α-FPT-induced catalepsy in 5-HT-depleted animals by the 5-HT precursor, 5-HTP.

If 5-HT releases GABA, it would be anticipated that in an animal with an impaired 5-HT system, this release would be significantly reduced, perhaps to such an extent that even the presence of DABA would be insufficient to produce sufficient synaptic levels of GABA to inhibit dopaminergic pathways (e.g. in the nigra). The possibility exists that DABA may release GABA from neurones. Simon, Martin & Kroll (1974) showed that DABA increased the efflux of [^{3}H]-GABA from synaptosomal preparations; however, increasing external GABA concentrations had a similar effect. It is thus difficult to evaluate whether the release of [^{3}H]-GABA following DABA was the result of displacement of the transmitter from the synaptosomal fraction or was due to an increase in external GABA concentration following blockade of re-uptake by DABA. Regardless of the method whereby DABA brings about an increase in the synaptic GABA concentration, it appears that 5-HT may regulate the release of GABA. In support of this, Mayer & Straughan (1981) have shown that the effects of 5-HT on hypothalamic neurones were blocked by bicuculline or picrotoxin. These results were interpreted by the authors to mean that either 5-HT indirectly released GABA and that the consequent inhibitory effects were blocked by the antagonists, or that 5-HT acted directly on the postsynaptic membrane at the same receptor-complex as GABA.

Based on the premise that 5-HT releases GABA, it was predicted that 5-HT receptor blockers should reduce any GABA-ergic potentiation of α-FPT-induced catalepsy. Clonazepam, like other benzodiazepines, has been reported to facilitate GABA-ergic transmission (Polc, Möhler & Haefely, 1974; Haefely, Kulcsar, Möhler, Pieri, Polc & Schaffner,

1975), and was thus used to potentiate α-FPT-induced catalepsy. If then the release of GABA is impaired, as we predict, by the blockade of 5-HT receptors, then the ability of endogenously released GABA to potentiate α-FPT-induced catalepsy, in clonazepam pretreated animals would be removed. Indeed, the 5-HT antagonist, methysergide, significantly blocked clonazepam-induced potentiation of catalepsy. These results with clonazepam are in contrast to the view expressed by Di Chiara, Porceddu, Morelli, Mulas & Gessa, (1979) who stated that drugs which potentiated GABA-ergic transmission should have an anti-cataleptic effect, and that this effect was mediated via a GABA-ergic nigro-thalamic pathway.

Balsara, Jadhav & Chandorkar, (1979) showed that the 5-HT uptake inhibitor, clomipramine, potentiated haloperidol-induced catalepsy. We postulated that clomipramine would enhance the release of GABA indirectly by increasing the 5-HT concentration in the synaptic cleft. This increased GABA release would then potentiate the α-FPT-induced catalepsy and this effect would be blocked by the GABA receptor blocker, picrotoxin. As the results showed, this potentiation of catalepsy by clomipramine was blocked with picrotoxin. That the effect of clonazepam could be blocked by a 5-HT antagonist, methysergide, and that the effect of clomipramine, could be blocked by the GABA antagonist, picrotoxin, is further evidence for an interaction between GABA and 5-HT.

Overall the results suggest that 5-HT-ergic mechanisms may regulate the activity of dopaminergic pathways via an indirect effect on the release of GABA. Taleisnik, Celis & Tomatis (1973/74) have postulated a similar 'circuit' for the release of melanocyte stimulating hormone (MSH). They suggested that a 5-HT neurone regulates the release of GABA which in turn inhibits the catecholamine-containing (? dopaminergic) neurone involved in the release of MSH.

Possible sites of interaction between the transmitters involved in catalepsy can only be surmised from the results presented in our study, as all drugs were given systemically and some of these drugs may have an action at more than one site, possibly in the periphery as well as in the central nervous system. Taking into account this proviso it is considered that the action of these drugs on catalepsy is in the central nervous system. The three probable central sites of action, i.e. substantia nigra, striatum or thalamus, all have been implicated in catalepsy, and all have the necessary neuronal innervation to support the hypothesis of 5-HT/GABA interaction in catalepsy. Evidence supporting the substantia nigra as the primary site of action is provided by the decrease of striatal homovanillic acid (HVA) levels following the injection of 5-HT into the nigra, while injection of a 5-HT antagonist into the same site increases striatal HVA levels (Straughan & James, 1978). It has also been shown that the intra-nigral administration of PCPA increased striatal dopamine turnover (Tanner, 1978). Thus, there is good evidence for a regulatory effect of 5-HT on ascending dopaminergic pathways from the nigra. In what manner this regulation is achieved is at present a matter of conjecture. It may be that the afferent 5-HT-ergic innervation to the substantia nigra from both medial and dorsal raphe nuclei (Dray, Gonye, Oakley & Tanner, 1976; Dray *et al.*, 1978) may regulate the release of GABA from the terminals of the striato-nigral GABA-ergic pathway which in turn affect ascending dopaminergic neurones. *In vitro* release studies are now being undertaken in an attempt to resolve this possibility. Indeed, histological studies suggest that 5-HT nerve terminals make axo-dendritic contacts with cells in the zona reticulata of the substantia nigra and that these are closely related to GABA nerve endings (Straughan & James, 1978).

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