POSSIBLE INVOLVEMENT OF GABA_A RECEPTOR SITES IN CATALEPSY

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ABSTRACT

The present work was performed to show the possible interaction of GABA_A and GABA_B receptors in catalepsy. The following results were obtained:

1- Muscimol (MUS), a GABA_A agonist, induced catalepsy. This effect was dose-dependent. Baclofen (BAC), a GABA_B agonist, had no effect in this respect.

2- Catalepsy induced by muscimol was potentiated by pretreatment of animals with bicuculline (BIC), a GABA_A antagonist, while pretreatment of animals with picrotoxin (PIC), another GABA_A antagonist, did not change the response.

3- The cataleptogenic effect of a-flupenthixol (a-FPT), a neuroleptic which is a potent cataleptogenic drug, was also increased by bicuculline pretreatment. A-flupenthixol, in animals pretreated with picrotoxin, induced a small but significant increase in catalepsy.

4- Muscimol catalepsy may be due to GABA inhibitory effect of the drug upon dopaminergic function, while potentiation of cataleptogenic effect of a-flupenthixol or that of muscimol by bicuculline may be exerted through release of GABA from GABAergic nerve endings.


INTRODUCTION

It has been shown that neuroleptics produce catalepsy. The dopaminergic system in striatum is thought to be associated with motor function. Therefore drugs which decrease the dopaminergic activity cause catalepsy in laboratory animals.14 Catalepsy induced by neuroleptics is mediated through direct blockade of dopamine receptors.6-22 Many workers have proposed that GABA-ergic neurones originating in the striatum and terminating in the substantia nigra exert an inhibitory influence upon nigro-striatal dopaminergic neurones.1-10 Amino-oxyacetic acid (AOAA) which increases cerebral levels of GABA, potentiated haloperidol-induced catalepsy.14 There are also reports of change in the cataleptic effect of a-flupenthixol, a neuroleptic of the thioxanthene group by baclofen. It has been shown that baclofen potentiates the catalepsy of a-flupenthixol for the first 90 min, but at all times after 90 min the degree of...
catlepsy was significantly decreased. The ability of drugs with proposed GABA-ergic agonist properties to potentiate neuroleptic-induced catalepsy has been attributed to the enhanced GABA-ergic activity in inhibition of nigrostriatal dopaminergic pathway. GABA receptor sites on peripheral autonomic nerve terminals and in mammalian brain slices have been described and classified as GABA_A and GABA_B. The existence of GABA_A subtypes is also suggested. The present investigation was performed to show the possible interaction of GABA_A and GABA_B receptors in catalepsy.

METHOD AND MATERIALS

Male albino rats weighing 150-200 g were used. The rats were housed in groups of 7 rats with access to food and water. Catalepsy was measured by placing the forepaws of the animal over an 8 cm high horizontal bar and recording the duration (in seconds) that the animal maintained this posture. Catalepsy was evaluated every 30 min for 2 h following drug administration. Results were analysed by student's t-test.

Drugs: The following drugs were used: baclofen (Ciba-Geigy), muscimol (Fluka Ag. Chem.), picrotoxin (Sigma), (+) -bicuculline (Sigma), and α-flupenthixol (Lundbeck, France). All drugs were prepared immediately before use. The drugs were dissolved in distilled water except for (+) -bicuculline that was first dissolved in one drop of acetic acid and diluted with distilled water. Administrations were achieved intraperitoneally. Bicuculline was injected 30 min and picrotoxin 15 min before muscimol or α-flupenthixol.

RESULTS

The time course of the cataleptogenic effect of muscimol (MUS) is shown in Fig. 1. In rats, the intraperitoneal (I.P.) injection of different doses of MUS (2, 3, and 4 mg/kg) induced catalepsy. The effect was evident 30 min after drug administration and its duration and intensity increased with the dose. Baclofen (BAC; 2.5, 5, and 7.5 mg/kg, I.P.) did not produce catalepsy (not represented).

The effects of bicuculline (BIC) and picrotoxin (PIC) on cataleptogenic activity of MUS are shown in Fig. 2. The BIC (3 mg/kg, I.P.) 30 min prior to administration of a dose of 2 mg/kg of MUS potentiated the drug catalepsy, while PIC (2 mg/kg, I.P.) 15 min before MUS administration did not change MUS cataleptic effect.

Fig. 3 shows the dose-response curve of cataleptogenic effect of α-flupenthixol (α-FPT). α-FPT (0.2, 0.4, and 0.8 mg/kg, I.P.) was given to rats. The catalepsy induced was dose-dependent.

![Fig. 1. Time course of the catalepsy produced by intraperitoneal administration to rats of MUS. (A) 2; (B) 3; and (C) 4 mg/kg. Ordinate: duration of catalepsy (sec); abscissae: time (min) after injection of MUS. Each point is the mean of at least 7 observations. Vertical bars indicate the S.E. mean.](image)

![Fig. 2. The effect of BIC or PIC on MUS-induced catalepsy. Rats were injected intraperitoneally with MUS (○, 3 mg/kg), BIC (△, 3 mg/kg) plus MUS (3 mg/kg, 30 min after) or PIC (■, 2 mg/kg) plus MUS (3 mg/kg, 15 min after). Ordinate: duration of catalepsy (sec); abscissae: time (min) after injection of MUS. Each point is the mean of 7 observations. Vertical bars indicate the S.E. mean. ***p<0.02, ****p<0.01, *****p<0.001 different from MUS treated rats.](image)

Effects of GABA_A antagonists BIC and PIC on catalepsy induced by α-FPT is shown in Fig. 4. BIC (3 mg/kg, I.P.) 30 min prior to administration of a dose of 2 mg/kg of α-FPT showed a marked cataleptogenic response in pretreated rats. PIC (2 mg/kg, I.P.) pretreatment of animals made a
small potentiation of a-flupenthixol-induced catalepsy.

DISCUSSION

The striatal dopaminergic system is thought to be involved in motor function. Therefore, drugs which decrease dopaminergic activity cause catalepsy. The descending striatonigral GABAergic pathway has been suggested as exerting an inhibitory action on the dopaminergic nigrostriatal tract. GABA receptor sites were divided into two types of GABA \(_A\) and GABA \(_B\) receptor sites. The existence of subtypes of GABA \(_A\) receptors has also been described. \(I, 2, 3\) I. P. injection of MUS, a GABA \(_A\) agonist with high affinity for GABA \(_A\) receptors, induced catalepsy in a dose-dependent manner. These results agree with the inhibitory effect of GABA-ergic system upon dopaminergic nigrostriatal pathway proposed by others. \(4, 5, 6\) In contrast, I. P. injection of BAC, a GABA \(_A\) agonist, did not induce catalepsy. From these results, one may conclude that the cataleptogenic effect of MUS was induced through a GABA \(_A\) receptor stimulation. Some workers found that BAC potentiates a-FPT-induced catalepsy. \(4, 5, 6\) It has been shown that BAC enhances GABA release and displaces (\(3^H\))-GABA from conventional binding sites in brain. \(7, 8\) Therefore, the potentiation of cataleptic state of a-FPT by BAC may be produced through GABA release and activation of GABA \(_A\) receptors. \(9\) Similar mechanism may be proposed for AOAA which increases cerebral levels of GABA and potentiates the haloperidol-induced catalepsy. \(10\)

Pretreatment of animals with PIC, another GABA \(_A\) antagonist, \(11\) potentiated cataleptogenic effect of a-FPT or that of MUS. There is evidence showing that BIC (but not PIC) releases the GABA from brain slices. \(12\) Therefore, the potentiation of MUS or a-FPT-induced catalepsy by BIC in our experiments may be due to presynaptic blockade of GABA neurons and consequent release of GABA from GABA nerve endings.

Pretreatment of animals with PIC, another GABA \(_A\) antagonist, \(13\) induced a small but significant increase in cataleptic effect of a-FPT. PIC does not release GABA and some experiments suggest that this drug enhances the striatal dopamine release. \(14, 15\) These may show why the effect of BIC on catalepsy is different from that of PIC.

In conclusion, while involvement of GABA \(_A\) receptor sites in catalepsy is possible, more experiment is needed to elucidate the exact mechanism.

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REFERENCES


