

Basic Science In Medicine

POSSIBLE INVOLVEMENT OF GABA_A RECEPTOR SITES IN CATALEPSY

A. SADEGHI-LOUYEH* AND V. SIMONIAN**

From the Department of Physiology and Pharmacology,** Tehran University of Medical Sciences, Tehran,
Islamic Republic of Iran.*

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 α -flupenthixol (α -FPT), a neuroleptic which is a potent cataleptogenic drug, was also increased by bicuculline pretreatment. α -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 α -flupenthixol or that of muscimol by bicuculline may be exerted through release of GABA from GABAergic nerve endings.

MJIRI, Vol. 7, No. 3, 179-182, 1993.

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^{11,12,13,19} exert an inhibitory influence upon nigro-striatal dopaminergic neurones.^{1,20} Amino-oxyacetic acid (AOAA) which increases cerebral levels of GABA, potentiated haloperidol-induced catalepsy.¹⁶ There are also reports of change in the cataleptic effect of α -flupenthixol, a neuroleptic of the thioxanthene group by baclofen. It has been shown that baclofen potentiates the catalepsy of α -flupenthixol for the first 90 min, but at all times after 90 min the degree of

Correspondence to: Dr. A. Sadeghi-Louyeh, Department of Physiology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

catalepsy was significantly decreased.¹⁰ 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 nigro-striatal dopaminergic pathway.^{16,17,25} GABA receptor sites on peripheral autonomic nerve terminals and in mammalian brain slices have been described and classified as GABA_A and GABA_B.³ The existence of GABA_A subtypes is also suggested.⁵ 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 before the administration 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.

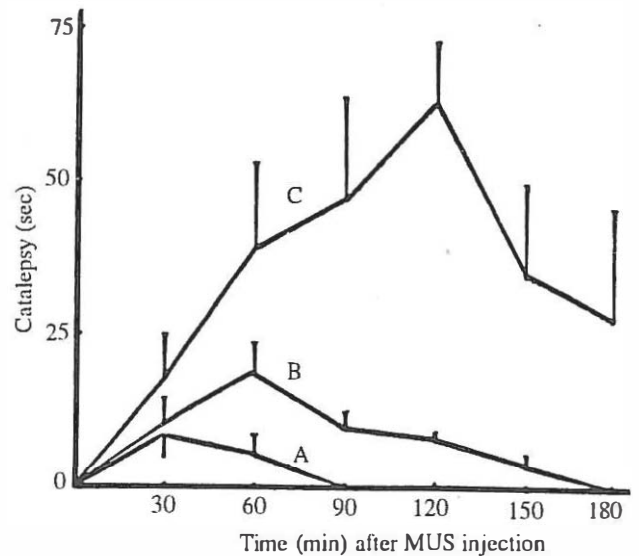


Fig. 1. Time course of the catalepsy produced by intraperitoneal administration to rats of MUS. (A) 2; (B) 3; and (C) 4 mg/kg. Ordinate: duration of catalepsy (sec), abscissae: time (min) after injection of MUS.

Each point is the mean of at least 7 observations. Vertical bars indicate the S.E. mean.

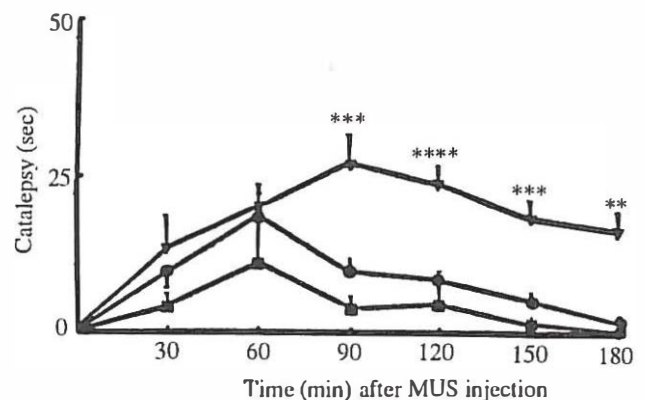


Fig. 2. The effect of BIC or PIC on MUS-induced catalepsy. Rats were injected intraperitoneally with MUS (●, 3 mg/kg), BIC (▼, 3 mg/kg) plus MUS (3 mg/kg, 30 min after) or PIC (■, 2 mg/kg) plus MUS (3 mg/kg, 15 min after). Ordinate: duration of catalepsy (sec); abscissae: time (min) after injection of 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.

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

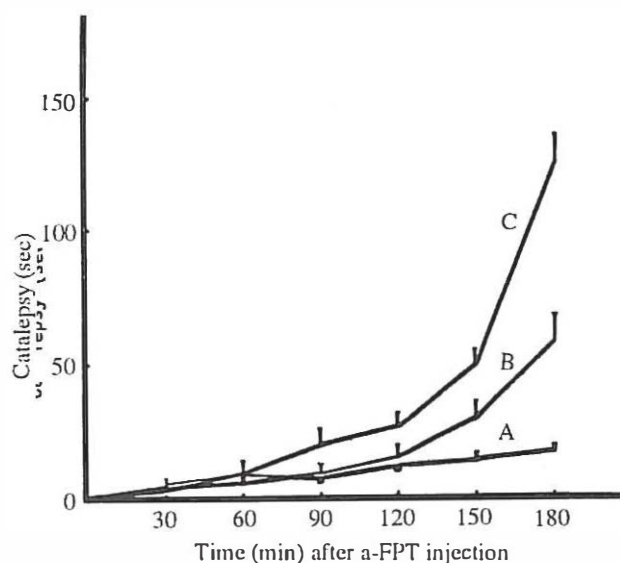


Fig. 3. Catalepsy caused by different doses of a-FPT. Rats were injected intraperitoneally with a-FPT (A) 0.2, (B) 0.4, and (C) 0.8 mg/kg.

Ordinate: duration of catalepsy (sec); abscissae: time (min) after injection of a-FPT.

Each point is the mean of at least 6 observations. Vertical bars indicate the S.E. mean.

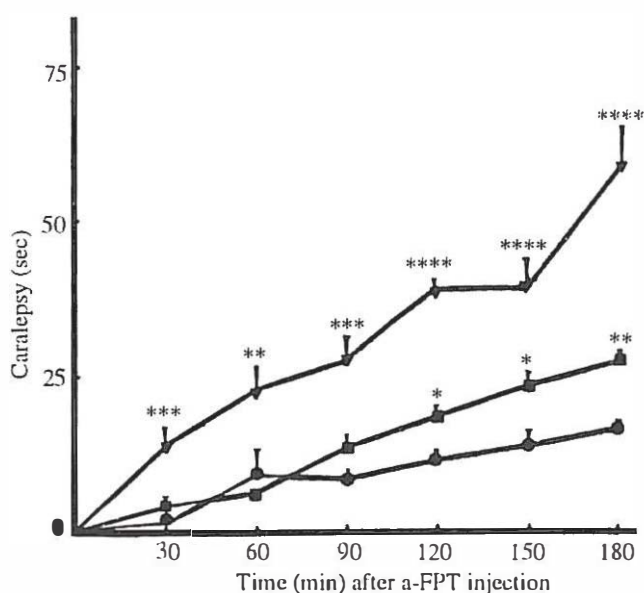


Fig. 4. The effect of BIC or PIC on a-FPT-induced catalepsy. Rats were injected intraperitoneally with a-FPT (●, 0.2 mg/kg), BIC (▼, 3 mg/kg) plus a-FPT (0.2 mg/kg, 30 min after), or PIC (■, 2 mg/kg) plus a-FPT (0.2 mg/kg, 15 min after).

Ordinate: duration of catalepsy (sec); abscissae: time (min) after injection of a-FPT.

Each point is the mean of 7 observations. Vertical bars indicate the S.E. mean.

* $p < 0.05$, ** $p < 0.02$, *** $p < 0.01$, **** $p < 0.001$ different from a-FPT treated animals.

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.¹⁴ The descending striatonigral GABA-ergic pathway^{1,12,13,19} has been suggested as exerting an inhibitory action on the dopaminergic nigrostriatal tract.^{1,20}

GABA receptor sites were divided into two types of GABA_A and GABA_B receptor sites.³ The existence of subtypes of GABA_A receptors has also been described.⁵

I. P. injection of MUS, a GABA_A agonist with high affinity for GABA_A and low affinity for GABA_B receptors,⁵ 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.^{7,20} In contrast, I.P. injection of BAC, a GABA_B agonist,^{4,5,20} 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 potentiated a-FPT-induced catalepsy.¹⁰ It has been shown that BAC enhances GABA release¹⁸ and displaces (3H)-GABA from conventional binding sites in brain.²³ Therefore, the potentiation of cataleptic state of a-FPT by BAC may be produced through GABA release and activation of GABA_A receptors.¹⁰ Similar mechanism may be proposed for AOAA which increases cerebral levels of GABA²⁴ and potentiates the haloperidol-induced catalepsy.¹⁶

Pretreatment of animals with BIC, a GABA_A antagonist,^{8,9} 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.¹⁵ 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,²¹ 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.²⁷ 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.

ACKNOWLEDGEMENTS

We wish to thank Miss T. Hosseini-Nia for her assistance

in analysis of data and Ciba-Geigy (Basle, Switzerland) for supply of baclofen.

REFERENCES

- Anden NE, Stock G: Inhibitory effect of gamma-hydroxybutyric acid on the dopamine cells in the substantia nigra. *Naunyn-Schmiedeberg's Arch Pharmacol* 279: 89-92, 1973.
- Bartholini G, Stadler H: Evidence for an intrastriatal GABAergic influence on dopamine neurons of the cat. *Neuropharmacology* 16: 343-7, 1972.
- Bowery NG, Doble A, Hill DR, Hudson AL, Shaw JS, Turnbull MJ, Warrington R: Bicuculline-insensitive GABA receptors on peripheral autonomic nerve terminals. *Eur J Pharmacol* 71: 53-70, 1981.
- Bowery NG, Hill DR, Hudson AL: Characteristics of GABA_B receptor binding sites on rat whole brain synaptic membranes. *Br J Pharmacol* 78: 191-206, 1983.
- Bowery NG, Price GW, Hudson AL, Hill DR, Wilkin GP, Turnbull MJ: GABA receptor multiplicity: visualization of different receptor types in the mammalian CNS. *Neuropharmacology* 23: 219-31, 1989.
- Carlsson A, Lindquist M: Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol et Toxicol* 20: 140-4, 1963.
- Cheramy A, Nieouillon A, Glowinski J: GABAergic processes involved in the control of dopamine release from nigrostriatal dopaminergic neurons in the cat. *Eur J Pharmacol* 48: 281-95, 1978.
- Curtis DR, Duggan AW, Felix D, Johnston GAR: GABA, bicuculline, and central inhibition. *Nature (Lond)*, 226: 1222-4, 1970.
- Curtis DR, Duggan AW, Felix D., Johnston GAR, and McLennan H: Antagonism between bicuculline and GABA in the cat. *Brain Res* 33, 57-73, 1971.
- Davies JA, Williams J: The effect of baclofen on a flupenthixol-induced catalepsy in the rat. *Br J Pharmacol* 62: 303-5, 1978.
- Fonnum F, Grofova, Rinvik E, Storm-Mathisen J, Walberg F: Origin and distribution of glutamate decarboxylase in the substantia nigra of the cat. *Brain Res* 71: 77-92, 1974.
- Fonnum F, Gottesfeld Z, Grofova I: Distribution of glutamate decarboxylase, choline acetyltransferase, and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatoentopeduncular, and striatonigral GABAergic fibers. *Brain Res* 143: 125-38, 1978.
- Hattori T, McGeer PL, Fibiger HC, McGeer EG: On the source of GABA-containing terminals in the substantia nigra. Election microscopic autoradiographic and biochemical studies. *Brain Res* 54, 103-14, 1973.
- Hornykiewicz O: Dopamine in the basal ganglia. Its role and therapeutic implications (Including the clinical use of L-dopa). *Brit Med Bull* 29: 172-8, 1973.
- Johnston GAR, Mitchel JF: The effect of bicuculline, metazol, picrotoxin, and strychnine on the release of (³H)-GABA from rat slices. *J Neurochem* 18: 2441-6, 1971.
- Kaarianien I: Effects of aminooxyacetic acid and baclofen on the catalepsy and on the increase of mesolimbic and striatal dopamine turnover induced by haloperidol in rats. *Acta Pharmacol Toxicol* 39: 393-400, 1976.
- Keller HH, Schaffner R, Haefely W: Interaction of benzodiazepines with neuroleptics on central dopamine neurons. *Naunyn-Schmiedeberg's Arch Pharmacol* 294: 1-7, 1976.
- Kerwin R, Pycocock C: Baclofen (-p-chlorophenyl-gamma-aminobutyric acid) enhances (³H)-gamma-aminobutyric acid (³H-GABA) release from rat globus pallidus in vitro. *J Pharm Pharmacol* 30, 622-627, 1978.
- Kim JS, Bak JJ, Hassler R, Okada Y: Role of gamma-aminobutyric acid (GABA) in the extrapyramidal motor system. 2. Some evidence for the existence of a type of GABA-rich strio-nigral neurons. *Exp Brain Res* 14: 95-104, 1971.
- Racagni G, Bruno F, Cattabeni F, Maggia, DI, Giulio AM, Parenti M, and Groppetti A: Functional interaction between rat substantia nigra and striatum: GABA and dopamine interrelation. *Brain Res* 134: 353-8, 1977.
- Ticik MK, Maksay: Convulsant/depressant site of action at the allosteric benzodiazepine-GABA receptor-ionophore complex. *Life Sci* 33: 2363-75, 1983.
- Van Rossum JM: The significance of dopamine receptor blockade for the mechanism of action of neuroleptic drugs. *Archs Int Pharmacodyn Exp Ther* 283-63, 1966.
- Waddington JL, Cross AJ: Baclofen and muscimol: behavioral and neurochemical sequelae of unilateral intranigral administration and effects of ³H-GABA receptor binding. *Naunyn-Schmiedeberg's Arch Pharmacol* 306: 275-80, 1979.
- Wallach DP: Studies on the GABA pathway-I. The inhibition of gamma-aminobutyric acid-alpha ketoglutaric acid transaminase in vitro and in vivo by U-7524 (aminooxyacetic acid). *Biochem Pharmacol* 5: 323-31, 1961.
- Worms P, Willigens MT, Lloyd KO: GABA involvement in neuroleptic-induced catalepsy. *J Pharm Pharmacol* 30: 716-8.