EFFECT OF ETHOSUXIMIDE ON DOPAMINERGICALLY MEDIATED BEHAVIOURS

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Summary : Pretreatment with ethosuximide, a drug of choice for petit mal epilepsy, was found to inhibit the conditioned avoidance response in rats and the traction response in mice and to antagonise methamphetamine induced stereotyped behaviour in rats. Our results, which indicate that ethosuximide is capable of inhibiting the dopaminergically mediated behaviours, are in agreement with the recent reports stating that ethosuximide exerts central dopamine receptor blocking activity.

Key words : ethosuximide, methamphetamine, conditioned avoidance response, traction response, stereotyped behaviour

INTRODUCTION

Ethosuximide, the drug of choice for petit mal epilepsy (14), is reported to induce catalepsy in mice by blocking post-synaptic striatal dopamine receptors (8). As dopaminergic mechanisms are involved in the maintenance of conditioned behaviour (2, 5) and in induction of amphetamine stereotypy (11, 12), we decided to investigate the effect of ethosuximide on conditioned avoidance response (CAR) and methamphetamine-induced stereotyped behaviour (SB) in rats. Further, as the traction response in mice is selectively inhibited by dopamine receptor blocking drugs (4, 7) we have also studied the effect of ethosuximide on the traction response in mice.

MATERIALS AND METHODS

Male albino rats and mice, weighing between 100 to 180 *g* and 20 to 30 *g* respectively, were used for the study. The animals were kept on a standard diet and tap water *ad libitum*. Each animal was used once only. All observations were made between 10.00 and 16.00 hr at 27 to 30°C in a noiseless, diffusely illuminated room.

The drugs used were ethosuximide (Parke-Davis), chlorpromazine hydrochloride (May and Baker), haloperidol ('Serenace' injection, Searle) and methamphetamine

hydrochloride ('Methedrine' injection, Burrroughs Wellcome). Ethosuximide (ETH) and chlorpromazine (CPZ) were dissolved in distilled water while haloperidol (HAL) and methamphetamine (MAMP) injection solutions were diluted to required strength with distilled water. Except for ETH and HAL doses refer to the salt. In rats, all drugs except ETH, were injected in a volume of 0.2 *ml*/100 *g* body weight while ETH was injected in a volume of 0.5 *ml*/100 *g* body weight. In mice, all drugs were injected in a volume of 0.1 *ml*/10 *g* body weight. All drugs were administered intraperitoneally. For each dose 10 animals were used. Control groups received requisite volume of distilled water intraperitoneally.

Conditioned avoidance response (CAR) in rats :

Effect on CAR was studied in trained rats by the technique of Cook and Weidley (1). Both control and drug treated groups were tested for CAR 30 min after the injection. The drug effect on CAR was expressed as the percentage of animals which failed to climb the pole on hearing the buzzer but did climb the pole in response to the electric shock.

Traction response in mice :

Control and drug treated groups were tested for the traction response by the method of Courvoisier *et al.* (4) at 60 min time interval after the injection. The response was said to be inhibited when the animal was unable to draw itself up to touch the wire within 5 sec of placement.

The ED_{50} of the drug for inhibiting the CAR and the traction response was computed by the method of Miller and Tainter (10).

Methamphetamine induced stereotyped behaviour (SB) in rats :

Effect of ETH pretreatment on MAMP induced SB was studied by the method of Costall *et al.* (3). Control groups received distilled water followed 30 min later by MAMP injection. Drug-treated groups received either ETH or HAL followed 30 min later by MAMP. 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 10 min intervals for 4 hr according to the following scoring system : 0 ; short lasting period of locomotor activity but no stereotyped behaviour ; 1 : discontinuous sniffing, constant exploratory activity ; 2 : continuous

sniffing and small head movements, periodic exploratory activity; 3 : continuous sniffing and small head movements, discontinuous gnawing, biting or licking and very brief periods of locomotor activity and 4 : continuous gnawing, biting or licking, no exploratory activity and occasional backward locomotion.

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

RESULTS

In doses of 100 to 400 *mg/kg*, ETH induced a state of sedation without loss of righting reflex or apparent change in muscle tone and in a dose-dependent manner inhibited the CAR in rats and traction response in mice and antagonised MAMP-induced SB in rats. Doses beyohd 400 *mg/kg* tended to produce motor incoordination and ataxia.

1. Effect on CAR in rats :

$ED_{50} \pm$S.E.M. of ETH for inhibiting the CAR was 154.9 *mg*$\pm$8.2 while that of CPZ and HAL were 4.07 *mg*$\pm$0.14 and 0.38 *mg*$\pm$0.02 respectively. ETH was, on a weight basis, about 38 and 400 times less potent than CPZ and HAL respectively, in inhibiting the CAR.

2. Influence on traction response in mice :

$ED_{50} \pm$S.E.M. of ETH for inhibiting the traction response was 144.5 *mg*$\pm$8.5 while that of CPZ and HAL were 5.62 *mg*$\pm$0.30 and 0.69 *mg*$\pm$0.04 respectively. ETH was, on a weight basis, about 25 and 200 times less potent than CPZ and HAL respectively, in inhibiting the traction response.

3. Effect on methamphethamine-induced SB in rats :

Pretreatment with 50 *mg/kg* of ETH did not significantly affect the intensity of MAMP stereotypy. However, pretreatment with 100, 200 and 400 *mg/kg* of ETH and 0.25 *mg/kg* of HAL was found to significantly decrease the intensity of MAMP stereotypy. Further, pretreatment with 400 *mg/kg* of ETH and 0.25 *mg/kg* of HAL completely abolished the SB induced by 5 *mg/kg* dose of MAMP (Table I). On a weight basis ETH appears to be 1600 times less potent than HAL in abolishing MAMP stereotypy.

TABLE I : Effect of ethosuximide and haloperidol on methamphetamine-induced stereotyped behaviour in rats.

Study	Treatment dose mg/kg	Intensity score Mean±S.E.M.
I 1.	MAMP 5	2.8 ± 0.13
2.	ETH 50 + MAMP 5	2.4 ± 0.16
3.	ETH 100 + MAMP 5	1.9 ± 0.10*
4.	ETH 200 + MAMP 5	1.1 ± 0.10**
5.	ETH 400 + MAMP 5	0
6.	HAL 0.25 + MAMP 5	0
II 1.	MAMP 6	3.7 ± 0.15
2.	ETH 50 + MAMP 6	3.4 ± 0.16
3.	ETH 100 + MAMP 6	2.9 ± 0.10*
4.	ETH 200 + MAMP 6	2.0 ± 0.00**
5.	ETH 400 + MAMP 6	0.9 ± 0.10**
6.	HAL 0.25 + MAMP 6	0.8 ± 0.13**

*$P<0.01$; **$P<0.001$. Numerals following the drugs indicate their doses (*mg/kg*).

DISCUSSION

Westerink *et al.* (13) have recently provided biochemical evidence for a functional blockade of striatal and mesolimbic dopamine receptors by ethosuximide in the rat brain, while Jadhav *et al.* (8), on the basis of beavioural studies, have recently reported that ethosuximide is capable of blocking post-synaptic striatal dopamine receptors.

CAR is a dopamine-mediated response (2, 5) and the inhibition of CAR by neuroleptics like chlorpromazine and halperidol, has been attributed to blockade of post-synaptic dopamine receptors in the nigro-striatal dopaminergic system (9). Amphetamine-induced SB, considered to result from activation of post-synaptic striatal dopamine receptors by released dopamine, is also effectively antagonised by the dopamine receptor blocking drugs, chlorpromazine and haloperidol (11, 12). As ethosuximide is reported to block post-synaptic striatal dopamine receptors (8, 13), it was expected to and, indeed, was found to inhibit CAR and to antagonise methamphetamine stereotypy in rats. Further, the traction response in mice, which is selectively inhibited by the dopamine receptor blocking drugs (4, 7), was also inhibited by ethosuximide.

Thus, our findings, taken along with those of Westerink *et al.* (13) and Jadhav *et al.* (8) suggest that ethosuximide is capable of blocking transmission in the nigro-

striatal dopaminergic system. Our conclusion is also in agreement with the clinical observation of Goldensohn *et al.* (6) regarding the occurence of parkinsonian symptoms in association with ethosuximide therapy.

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