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EFFECT OF TAURINE, ALONE OR IN COMBINATION WITH METHAMPHETAMINE ON AVOIDANCE BEHAVIOR IN RATS

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ABSTRACT

The effects of taurine and methamphetamine on condi— tioned avoidance response (CAR) in rats were factorially assessed. The effects of taurine were also studied on the locomotor activity in rats. Taurine at a high dose (200 mg/kg) suppressed both avoidances and escape responses and it caused brief sedation in rats. Methamphetamine (1 mg/kg), administered after taurine was able to reverse the effects of taurine on avoidance and escape tasks. There was no significant interaction between taurine and methamphetamine on avoidance behaviour. However, a significant interaction between them was obtained on the escape response, suggesting a common mechanism for the two variables on the escape response, which probably involves their opposite effects on brain catecholamines. A small dose of taurine (50 mg/kg) potentiated the enhancement of methamphetamine on CAR acquisition. The mechanism of this potentiation could not be deduced from the present study.

INTRODUCTION

High levels of taurine exist in different regions of the brain. There is some evidence that this amino acid may function as a neurotransmitter or neuromodulator in the CNS (Cooper et al., 1982). In vitro studies has shown that taurine may decrease the release of neurotransmitters like noradrenaline, acetylcholine and GABA from slices of brain cortex and isolated nerve endings (Kuriyama et al., 1978; Pasantes-Morales and Moran, 1981; Namina et al., 1983). Recently, it has also been shown that taurine antagonizes the release of dopamine from rat striatal synaptosomes (Arzate et al., 1986).

The role of the central catecholaminergic and cholinergic systems in the processes of learning and memory is now well documented. Although taurine exists in large quantities in the brain, studies of its central actions are few. The present study is primarily aimed at studying the role played by taurine in the learning process. Drugs like the amphetarines, which cause the release of catecholamines, are likely to be antagonized by taurine. It is, therefore, decided to study the interaction between taurine and methamphetamine in the process of learning. The amphetamines are

known to facilitate various learned responses (Heart and Whalen, 1963; Kulkarni, 1968; Castellani, 1974) and their effects are suppressed by catecholamine depletors like reserpine or a-methyl-p-tyrosine (Seiden and Carlsson, 1963; Bracs et al., 1982).

MATERIALS AND METHODS

Subiects:

Male naive Sprague-Dawley rats, obtained from the King Saud Univesity, College of Pharmacy Animal Care Centre, were used. The animals weighed 250-3009, and they had free access to commercial diet and tap water except during the experiment.

Acquisition of conditioned avoidance response (CAR):

A computerized reflex conditioning system (model Reflex- 16/Apple-Columbus Instruments) was used. Each shuttle box is equipped with a loudspeaker with adjustable sound intensity, light bulbs, animal location sensors and a stainless steel bar grid on the cage floor to deliver electric shock and to adjust shock intensity.

The CAR acquisition test consisted of one session of 100 (massed) trials for each rat. Each subject was placed in the shuttle box and allowed 5 mm of free exploration before the first trial was started. Each trial commenced with the buzzer (CS) which remained on for 10 sec. Simultaneously with the cessation of the CS, the shock (US) was delivered via the grid floor. The US was left on until the rat moved to the opposite compartment of tfle tox or until the predetermined cutoff time was reached. If the subject moved to the opposite compartment of the box during the CS interval, the response was scored as an avoidance; if the subject responded while the shock was being presented, the response was scored as an escape. The intertrial interval was 35 sec and the shock level was 1 mA.

Forty eight rats were randomly assigned to six groups of 8 animals each. Two groups were pretreated with saline (2 ml/kg, i.p.), another two groups were prtreated with taurine (50 mg/kg, i.p.) and the remaining two groups were pretreated with taurine (200 mg/kg, i.p.) One group of each pair was administered methamphetamine (1 mg/kg, s.c.) whereas the other group was injected with saline (2 ml/kg, s.c.) at 30 mm after the pretreatments. For each group, results were expressed as the mean percentage avoidance responses. The mean percentage escape responses, were calculated using the formula (escapes/(lOO-avoidanoes)J %.

Locomotor Activity:

Locomotor activity was recorded using an activity meter (Optovarimex, Columbus). Groups of 4 animals each were administered i.p. with saline, taurine (50 mg/kg) or taurine (200 mg/kg) and each rat was immediately placed in the activity cage. The activity counts were recorded automatically every 10 min for 1 h following the administration of drug or saline.

Drugs:

Taurine (Fluka, Switzerland) and D-N--methamphetamine hydrochloride (E. Merck) were dissolved in 0.9% physiological saline. They were administered in a constant volume of 2 ml/kg. Equivalent volumes of saline were administered to animals of control groups.

Statistics:

The data for the acquisition of CAR were evaluated by analyses of variance (Winer, 1971). Differences between means were evaluated by Newmann-Kuels procedure. Mann Whitney U-test was used to evaluate the locomotor activity counts.

RESULTS

Acquisition of CAR:

The results of avoidance and escape respondings of rats were separately analysed by a 2 x 3 analysis of variance. These data are presented in Fig.l and Fig.2, respectively.

Fig.l shows per cent avoidances as a function of taurine dosage. The taurine dosage variable produced a highly significant effect ($F = 8.7$, $df = 2/42$, $P < 0.01$). Also the saline and methamphetamine variable was highly significant ($F = 12.27$, $df = 1/42$, $P < 0.01$). The interaction between the two variables was not significant ($F = 1.81$, df 2/42). Test on means using Newmann-Kuels procedure indicated that taurine (50 mg/kg) did not modify, whereas taurine (200 mg/kg) produced a significant decrease in avoidance responding ($P < 0.05$). However, the group pretreated with taurine (50 mg/kg) before methamphetammne (1 mg/kg), showed a significant increase in avoidance responding ($P < 0.01$).

Fig.2 shows per cent escapes as a function of taurine dosage. Analysis of variance on these scores indicated that effects of taurine dosage and those of the saline and methamphetamine variables are statistically significant (F 9.28, df = 2/42, P 0.01); $F = 5.24$, $df = 1/42$, $P < 0.05$, respectively). Also, a highly significant interaction between the two variables was obtained ($F = 9.76$, $df=2/42$, $P < 0.01$). The test on means showed that the taurine (200 mg/kg)! saline group was significantly different from all other groups ($P<0.005$) indicating a low escape responding. The results also

showed that methamphetamine (1 mg/kg) was able to reverse the effect of taurine (200 mg/kg) on escape responding.

Locomotor Activity:

Path doses of taurine caused significant reductions of locomotor activity in rats (Fig. 3). Taurine (200 mg/kg) causd a greater reduction and a more prolonged action than taurine (50 mg/kgY The duration of action of taurine was brief, thus the small dose of taurine was effective during 30 min following its administration, whilst the effect of taurine (200 mg/kg) was sustained for about 40 mm post injection.

DISCUSSION

The results of the present study indicated that a high dose of taurine suppresses both avoidance and escape responses in rats in the CAR procedure. Clearly methamphetamine administered after taurine was able to reverse these effects of taurine. With regard to escape responding, which involves running movements of rats from one compartment to another when an electric shock was delivered (an unconditoned response), there was a statistical interaction between methamphetamine and taurine. This may suggest that the two variables are operating via a common mechanism. It is likely that the catecholaminergic systems, which are believed to play a major role in motor acitivity are involved. The catecholaminergic systems are affected in opposite ways by taurine and methamphetamine. Thus taurine decreases their release (see introduction) whereas methamphetamine causes their release (Moore, 1977). Also, the locomotor activity experiment showed that, in contrast to the known stimulant effects of methamphetamine, the animals were briefly sedated by taurine but remained alert and were able to Jump from the electric shock in the CAR procedure.

The suppression of CAR acquisition by the high dose of taurine was expected because of the brief sedation induced by taurine in animals. Also, it has previously been suggested that the escape task is sensitive to treatments that hinder the organism's ability to sustain artive responses (Anisman et al., 1984). Disruption of the escape reponse by taurine probably affected the sequence of events in the trial and in turn caused reduced acquisition of CAR.

The low dose of taurine caused less sedation than the high dose; it did not modify avoidance responding, but it significantly protentiated methamphetamine effect on CAR acquisition. There was no statistical interaction between methamphetamine and taurine in the avoidance task, therefore it could be suggested at present that the potentiation observed was due to different mechanisms being

set into action by either drug. It is premature to make suggestions as to the mechanisms involved from the data presented in this study. However, it appears that taurine at low doses may have induced anxiety in animals probably via a decreased release of GABA (Namina et al., 1983). It appeared from observation of animals of this particular group in the shuttle box, that they were somewhat anxious, though a measurement of this behaviour was not made. It is assumed that anxiety is tfle substrate for maintaining avoidance behaviour. Thiebot and Soubrie (1981) indicated that benzodiazepines, wnich cause enhancement of GABA—ergic transmission, may improve avoidance learning in the shuttle box when the anxiety level of the animals is too high. The amphetamines had been shown to cause more anticipatory responses in animals after the presentation of buzzer (D'Amato et al., 1968; Cicala, 1969) which provide greater opportunity for reinforcement of avoidance response. It is likely that the anxiety induced by taurine may have increased the anticipatory reponses of methamphetamine, hence the potentiation of the effect of methamphetamine on CAR acquisition. The role played by taurine in anxiety is currently investigated in this laboratory.

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