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EFFECTS OF L-TRYPTOPHAN AND L-METHIONINE ON ACTIVITY IN THE RAT

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1 The effects of an intraperitoneal dose of 20 mg/kg L-tryptophan and doses of 100 and 150 mg/kg of L-methionine were investigated on activity in the rat.

2 Activity was measured by a time sampling behaviour categorization procedure, and began 15 min after compound administration, lasting for a total of one hour.

3 Total active behaviour in the first half hour was reduced after 20 mg/kg tryptophan, 100 or 150 mg/kg methionine. Only 20 mg/kg tryptophan led to a significant reduction in active behaviour during the second half hour.

4 Administration of 100 mg/kg methionine plus 20 mg/kg tryptophan, and 150 mg/kg methionine plus 20 mg/kg tryptophan had no discernible effect on activity.

5 The results draw attention to the role of another amino acid in the modification of the behavioural effects of tryptophan.

Introduction

There have been a number of recent investigations of the effects of various amino acids on behaviour. Many of these investigations have concentrated on the essential amino acids tryptophan (e.g. Modigh, 1973; Hingtgen & Aprison, 1975) and methionine (e.g. Beaton, 1975), and have often involved administration of relatively large quantities, in relation to normal dietary intake.

Both amino acids are of considerable potential behavioural interest. Tryptophan is metabolized along several pathways, which include the formation of tryptamine and 5-hydroxytryptamine (5-HT). 5-HT is implicated in a wide range of behavioural processes such as hunger regulation, pain sensitivity, etc. Changes in blood tryptophan have been shown to be associated with changes in brain 5-HT (Wurtman & Fernstrom, 1975), but whilst such central changes are suggestive, they do not necessarily imply appreciable behavioural effects (Grahame-Smith, 1973). Methionine has been suggested to have a possible role in the aetiology of some forms of schizophrenia (Osmund & Smithies, 1952) where its properties as a methyl donor have been emphasized.

In general, both amino acids have been reported to reduce motor activity. The dose of tryptophan found to achieve this effect has varied between 0.7 mg/kg (Brown, 1960) and 800 mg/kg (Modigh, 1973) after intraperitoneal injection. However, as in numerous other investigations of effects on activity, this variation may in part be a function of the methods used for recording activity.

Taylor, Goudie & Williams (1973), Goudie & Taylor (1974) and Taylor, Goudie, Mortimore & Wheeler (1974) have reported a technique for time sampling activity in rats. A modification of this technique is described here and was used to investigate the effects on activity of a single dose of 20 mg/kg L-tryptophan, and of 100 and 150 mg/kg L-methionine, both singly and in combination with tryptophan.

Methods

Male Wistar albino rats were used, housed individually, and weighing approximately 300 grams. The subjects were housed under normal lighting conditions with exposure to food and water *ad libitum*. An experimental group was made up of 7 randomly chosen rats. Six experimental groups were used: (1) control—2 injections of vehicle (distilled water); (2) 20 mg/kg tryptophan—tryptophan plus one injection of vehicle; (3) 100 mg/kg methionine and (4) 150 mg/kg methionine—appropriate dose of methionine plus an injection of vehicle; (5) 100 mg/kg methionine plus 20 mg/kg tryptophan and (6) 150 mg/kg methionine plus 20 mg/kg tryptophan—appropriate injections of both compounds. All compounds were administered in a

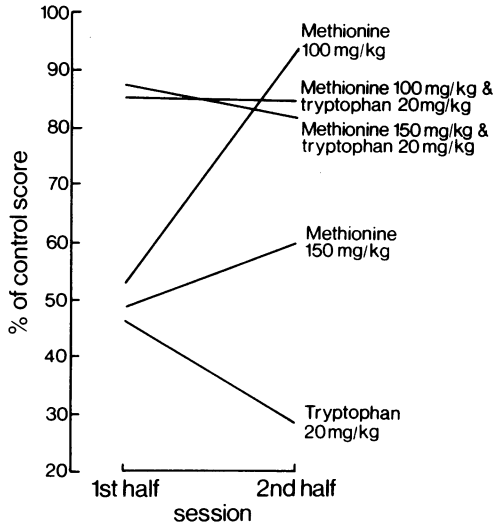

Figure 1 Active behaviour of rats after injections of tryptophan, methionine or both amino acids during the first and second half sessions expressed as a percentage of control values.

volume of 2 ml/kg by intraperitoneal injection, and were made up in distilled water. The pH of all solutions administered was approximately 7.

Observations were conducted between 12 h 00 min and 18 h 00 min on successive days. Immediately after injection, rats were individually placed in an evenly illuminated open field (45 cm × 45 cm) where their behaviour was observed and recorded for 1 min intervals every 5 min, beginning 15 min after injection. A time sampling 'all-or-nothing' system of recording activity was used, based on Taylor *et al.* (1974) and Goudie & Taylor (1974). The occurrence of any of the following behaviours was recorded during the 1 min observation period: rearing, walking, sniffing, grooming, immobility (see Taylor *et al.*, 1973, for details of behaviours). Frequency of occurrence of the behaviours within the 1 min interval was not recorded. The summation of the categories rearing and walking were defined as 'active' behaviours. Observations were conducted until 75 min post injection.

Results

Figure 1 shows the active behaviour observed during the first half (30 min) and second half (30 min) sessions, expressed as a percentage of control values. Both doses of methionine and the dose of tryptophan used, when compared to controls, led to a significant reduction in total active behaviour for the first half of the sessions (Mann-Whitney U test: $P < 0.05$). Only tryptophan remained significantly different from control during the second half session, although a near significant reduction in the 150 mg/kg methionine group ($P = 0.064$) is apparent. Tryptophan administered with either dose of methionine produced no significant effects on behaviour during either the first or second half session, with no evidence of a dose-response relationship.

No significant differences were found in the incidence of immobile grooming and sniffing behaviours between the various groups. Informal observations of animals revealed no systematic effects, other than a general reduction in activity corresponding to the above differences.

Discussion

The results presented here suggest that a dose of 20 mg/kg L-tryptophan is sufficient to have an effect upon behaviour in terms of a reduction in active categories. Because a smaller dose than that reported here has been shown to increase brain 5-HT (Wurtman & Fernstrom, 1975), it is tempting to suggest that the behavioural effect noted is related to such an increase. 5-HT and its immediate precursor 5-hydroxytryptophan, have been reported to produce behavioural depression in rats (Aprison & Hingtgen, 1966); on the other hand, there is evidence that the effects on motor activity of 5-HT and 5-hydroxytryptophan are at least in part the result of peripheral rather than central factors (e.g. Jacobs & Eubanks, 1974).

Wayner, Ono, Deyoung & Barone (1975) have demonstrated that changes in extracellular reaction potentials of cells in various brain areas can occur when tryptophan and methionine, among other essential amino acids, are administered microelectrophoretically. This introduces the possibility of some relatively direct central action of the amino acids, as well as potential central actions of metabolites e.g. 5-HT.

Methionine at both doses used here produced a reduction in active behaviour during the first half session, of comparable magnitude to that produced by tryptophan; no significant effects were apparent in the second half session, although there is a non-significant suggestion of a dose-related effect, in terms of duration of action in the 150 mg/kg group. The dose levels used here are somewhat lower than those reported by other authors (Bovet, Leathwood, Mauron, Olivero & Satta, 1971; Beaton, 1975). Whilst the specific central action of methionine remains obscure, there is evidence that L-DOPA acts as a competitive inhibitor of methionine uptake by nerve endings in homogenates of rat brains (Baldessarini & Karobath, 1972). Furthermore, methionine appears to reverse the clinical effectiveness of L-DOPA in Parkinsonism (Pearce & Waterbury, 1974). These reports suggest

some interaction between methionine and L-DOPA, which may perhaps mediate some of the behavioural effects described here.

Administration of both compounds together failed to produce any behavioural effects. Neither the dose of methionine nor the length of time after administration appear to be relevant factors, which is surprising in view of their effects when the compounds are administered singly.

Wurtman & Fernstrom (1975) have demonstrated that brain 5-HT and tryptophan levels reflect not only plasma concentrations of tryptophan, but also plasma concentrations of other amino acids. An analagous process might be suggested here, as some form of mutual interference after the administration of tryptophan together with methionine. Whether such interference involves a common transport system, or operates at some other level is not clear. However, these results emphasize the role of another amino acid in the modification of the behavioural effects of tryptophan.

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