by a method based on that of Pasquini & Soto (1972) using n-butanol-water. Following 15 min incubation suspensions were spun down and the resultant pellets resuspended in 1.5 ml 50% sucrose and extracted for 2 h at room temperature with 16 ml n-butanol-water. Experiments showed a large uptake into the organic layer in the ratio 9.7 : 1 compared to partition of organic solvent against an aqueous solution of CPZ of 1 : 1. Extraction of proteolipids from subfractions followed by incubation with ^{3}H-CPZ gave similar results. Subfractions prepared from rats which had been injected with ^{3}H-CPZ (8 mg/kg i.p.) also showed a preferential uptake into the organic layer when partitioned against water in the ratio 12.5 : 1. Phospholipids, phosphatidyl inositol and phosphatidyl ethanolamine in n-butanol-water (Blaustein, 1967) incubated with ^{3}H-CPZ followed by partition against water also gave a similar partition of about 10 : 1 in favour of the organic layer.

These results have led us to believe that the phenomenon of accumulation of CPZ in rat brain subfractions is a solubility effect of the CPZ in the proteolipid of the membranes.

References

BLAUSTEIN, M.P. (1967). Phospholipids as ion exchangers: Implications for a possible role in biological membrane excitability and anesthesia. *Biochim. biophys. Acta*, 135, 653-668.

MARCHBANKS, R.M. & WHITTAKER, V.P. (1967). Some properties of the limiting membrane of synaptosomes and synaptic vesicles. *Abstr. Commun., First Meet., Int. Soc. Neurochem.* (Strasbourg) p. 147.

PASQUINI, J.M. & SOTO, E.F. (1972). Extraction of proteolipid from nervous tissue with n-butanol-water. *Life Sci.*, 11, Part 2, 433-443.

The effect of L-tryptophan on changes in motor activity caused by parachlorophenylalanine

G. CURZON & C.A. MARSDEN*

Department of Neurochemistry, Institute of Neurology, Queen Square, London WC1N 3BG

L-tryptophan administration increases brain 5-hydroxytryptamine (5-HT) turnover without effect on either motor activity (Modigh, 1973) or sensitivity to electric shock (Hole & Marsden, 1975). Intravenous infusion of L-tryptophan into normal human subjects also has relatively little influence on the results of objective psychological tests though EEG changes were noted (Greenwood, Friedel, Bond, Curzon & Lader, 1974). It is possible that L-tryptophan may have more striking effects when 5-HT metabolism is deficient. This would be consistent with the postulated 5-HT defect in depression and the reported beneficial effect of tryptophan on it (Coppen, 1972). We have studied the effect of L-tryptophan on motor activity in rats previously given p-chlorophenylalanine (PCPA) at a dosage that increased activity (Fibiger & Campbell, 1971) while only partially inhibiting 5-HT synthesis.

Male Sprague-Dawley rats (180-200 g) were housed in groups of three under a 12 h light-dark cycle at 24° C. After 4 days the following drug schedule was adopted: (1) PCPA (150 mg/kg i.p.) followed by L-tryptophan (150 mg/kg i.p.) 24 h later. (2) PCPA (150 mg/kg) plus vehicle (2.5% Tween in 0.9% saline) 24 h later. (3) Saline (0.9%) plus L-tryptophan (150 mg/kg) 24 h later. (4) Saline plus vehicle 24 h later. In one experiment L-tyrosine was given instead of L-tryptophan. Motor activity was measured simultaneously in control and treated rats with Animex DSE activity meters. Activity recording was started 15 min after the last injection (at 9.45 or 11.45 h) and continued for 120 minutes. At the end of this period the animals were killed and brain tryptophan, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) measured (Curzon, Joseph & Knott, 1972).

L-tryptophan alone caused no significant change in motor activity while PCPA alone caused a significant increase which was almost completely reversed by L-tryptophan but not by L-tyrosine. L-tryptophan caused increases in brain tryptophan (+545%), 5-HT (+50%) and 5-HIAA (+108%). PCPA altered brain tryptophan by −26%, 5-HT by −59% and 5-HIAA by −66%. L-tryptophan markedly diminished the biochemical effects of PCPA, both 5-HT and 5-HIAA returning towards control values (−19% and −10% respectively). While L-tyrosine caused a significant increase in tyrosine (+76%) there was no significant change in brain tryptophan, 5-HT and 5-HIAA. Similarly, the tryptophan, 5-HT and 5-HIAA values in rats given PCPA were not significantly different from those in rats given PCPA and L-tyrosine.

Fibiger & Campbell (1971) showed that the effects of PCPA on motor activity were reversed

by 5-hydroxytryptophan (5-HTP). However, results with 5-HTP are not clearly interpretable as, unlike tryptophan, it can be decarboxylated to 5-HT in neurones other than those containing 5-HT (Fuxe, Butcher & Engel, 1971). The present finding that tryptophan reverses the effect of PCPA is stronger evidence that 5-HT neurones are involved. Furthermore, the results demonstrate an alteration of behaviour by tryptophan only in 5-HT deficient animals and therefore may be relevant to the effect of tryptophan in depression.

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References

COPPEN, A. (1972). Biogenic amines and affective disorders. *J. Psychiatr. Res.*, 9, 163-175.

CURZON, G., JOSEPH, M.H. & KNOTT, P.J. (1972). Effects of immobilization and food deprivation on rat brain tryptophan metabolism. *J. Neurochem.*, 19, 1967-1974.

FIBIGER, H.C. & CAMPBELL, B.A. (1971). The effect of para-chlorophenylalanine on spontaneous locomotor activity in the rat. *Neuropharmacology*, 10, 25-32.

FUXE, K., BUTCHER, L.L. & ENGEL, J. (1971). DL-5-Hydroxytryptophan-induced changes in central monoamine neurons after peripheral decarboxylase inhibition. *J. Pharm. Pharmac.*, 23, 420-422.

GREENWOOD, M.H., FRIEDEL, J., BOND, A.J., CURZON, G. & LADER, M.H. (1974). The acute effects of intravenous infusion of L-tryptophan in normal subjects. *Clin. Pharmacol. Therap.* 16, 455-464.

HOLE, K. & MARSDEN, C.A. (1975). Unchanged sensitivity to electric shock in L-tryptophan treated rats. *Pharmacol. Biochem. & Behav.* (in press).

MODIGH, K. (1973). Effects of L-tryptophan on motor activity in mice. *Psychopharmacologia*, 30, 123-134.

The effects of lithium, rubidium and caesium on the response of rats to tranylcypromine and α-methyl-*p*-tyrosine given separately or in combination

F.A. JENNER, A. JUDD* & JUDITH PARKER

M.R.C. Unit for Metabolic Studies in Psychiatry, University Department of Psychiatry, Middlewood Hospital, P.O. Box 134, Sheffield S6 1TP

Administration of 20 mg/kg tranylcypromine (Tc) to rats primed for three days with lithium chloride (LiCl) injections produces hyperactivity which is inhibited by para-chlorophenylalanine (Grahame-Smith & Green, 1974b). A similar syndrome is produced by combining L-tryptophan and Tc. This latter response is inhibited by α-methyl-*p*-tyrosine (αmpt) (Grahame-Smith & Green, 1974a). The effect of Tc on LiCl, rubidium chloride (RbCl) or caesium chloride (CsCl) loaded rats is reported here. Rats given LiCl, RbCl or CsCl in their diet (30 mmol/kg dry food) for 14 days and then injected s.c. with 15 mg/kg Tc exhibited marked hyperactivity. All facets of activity do not increase but there is a characteristic continuous locomotion with the body close to the cage floor.

The hyperactivity is greater and of more rapid onset following RbCl than LiCl. This difference was associated with different rates of accumulation of 5-hydroxytryptamine (5-HT), the increases above control values were 46% (Li) and 85% (Rb).

Hyperactivity was inhibited by αmpt (250 mg/kg i.p. 36 h before, plus 150 mg/kg 2 h before, Tc) more effectively following LiCl than RbCl. This combination of αmpt and Tc produced rat brain concentrations of dopamine (DA) significantly below control values in sodium chloride (NaCl) and LiCl pretreated rats but not following RbCl. This suggests that a system which is both 5-HT and DA sensitive is responsible for the hyperactivity.

The increase in brain noradrenaline (NA) concentration following Tc injection was significantly less following RbCl than after NaCl or LiCl. A smaller proportion of NA metabolized by the monoamine oxidase pathway following RbCl treatment could produce this effect. αmpt causes a decrease in rat brain NA concentration which is greater following LiCl or RbCl treatment than after NaCl. This could be due to lithium or rubidium increasing NA 'turnover' rates. All results reported are significant at levels beyond $P = 0.05$.

Previous studies have emphasized the opposite effects of lithium and rubidium on animal activity and brain monoamines. This study shows similar effects on activity when Tc is administered, and both ions increased 5-HT accumulation and NA turnover rates.

The fact that lithium is effective in the treatment of bipolar affective illnesses does perhaps indicate that it has more than one action. Drug-induced hyperactivity in animals has frequently been seen as an analogue to mania, and lithium has often been found to be effective in