20 mg/kg L-TP. The two age groups also reached their maximum 5-HT accumulation at different brain tryptophan concentrations.

Both adult and immature rats exhibited similar behavioural changes following L-TP injection. Activity increased at both ages with increasing L-TP dose up to around 70 mg/kg. This increased activity without an increase in brain 5-HT in immature rats might be due to increased sensitivity postsynaptic to the 5-HT neurones. However, behavioural responses to putative 5-HT agonists (5-methoxy-N, N-dimethyl tryptamine and quipazine) did not reveal any difference between adults and pups.

In 21-day rats pretreated with a peripheral decarboxylase inhibitor (50 mg/kg benzerazide Ro4-4602 15 min before TCP) activity counts at both 35 and 70 mg/kg L-TP were reduced by approximately 50%. This indicates a possible involvement of tryptamine in the immature rat behavioural responses to L-TP as previously suggested for the adult rat (Marsden & Curzon, 1978).

These results, therefore, show that immature rats respond behaviourally in a similar way to adults following L-TP and TCP administration, but that the biochemical correlates of such treatment are different.

References

CURZON, G. & GREEN, A.R. (1970). Rapid method for the determination of 5-hydroxytryptamine and 5-hydroxyindole acetic acid in small regions of rat brain. *Br. J. Pharmac.*, **39**, 653–655.

DENCKLA, W.D. & DEWEY, H.K. (1967). The determination of tryptophan in plasma, liver and urine. *J. Lab. Clin. Med.*, **69**, 160–169.

GRAHAME-SMITH, D.G. (1971). Studies *in vivo* on the relationship between brain tryptophan, brain 5-HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. *J. Neurochem.*, **18**, 1053–1066.

GREEN, A.R. & GRAHAME-SMITH, D.G. (1976). Effects of drugs on the processes regulating the functional activity of brain 5-hydroxytryptamine. *Nature, Lond.*, **260**, 487–491.

MARSDEN, C.A. & CURZON, G. (1978). The contribution of tryptamine to the behavioural effects of L-tryptophan in tranylcypromine treated rats. *Psychopharmacology*, **57**, 71–76.

Backward walking and circling: a behavioural response to concurrent catecholamine and 5-hydroxytryptamine release

G. CURZON, J.C.R. FERNANDO & A.J. LEES

Department of Neurochemistry, Institute of Neurology, 33 John's Mews, London WC1N 2NS

Amphetamine, fenfluramine and p-chloroamphetamine at high dosages cause backward walking and circling in rats (Taylor, Goudie, Mortimore & Wheeler, 1974; Growdon, 1977). Bizarre behaviour of this kind is of particular interest as a possible animal model for amphetamine psychosis. It also occurs when animals are given many other drugs with hallucinogenic properties (Schneider, 1968; Smythies, Johnstone, Bradley, Benington, Morin & Clark, 1967). In this study we have obtained evidence for the roles of dopamine (DA) and 5-hydroxytryptamine (5-HT) in the mediation of backward walking and circling.

Male Sprague-Dawley rats (180–200 g) were housed three to a cage and behaviour scored for 1 h after i.p. injection of drugs using the method of Taylor *et al.* (1974) modified to include 5-HT dependent behaviours described by Trulson & Jacobs (1976). (+)-Amphetamine (15 mg/kg) caused backward walking and circling which were significantly increased by L-tryptophan (50 mg/kg) and decreased by the inhibitor of 5-HT synthesis p-chlorophenylalanine (200 mg/kg), by the 5-HT receptor blockers methergoline (1 mg/kg) by the 5-HT receptor blockers metergoline (1 mg/kg) and cyproheptadine (10 mg/kg), by fluoxetine (10 mg/kg) (which selectively inhibits uptake of drugs into 5-HT neurones) and by the dopamine receptor blockers α-flupenthixol (0.2 mg/kg) and pimozide (25 mg/kg).

Amphetamine (5 mg/kg), fenfluramine (5 mg/kg, 10 mg/kg) and p-chloroamphetamine (5 mg/kg, 10 mg/kg) when given alone did not cause backward walking and circling but these behaviours did occur when amphetamine (5 mg/kg) was given together with either fenfluramine (5 mg/kg) or p-chloroamphetamine (5 mg/kg). The two latter drugs also caused various behavioural changes characteristic of 5-HT release (Trulson & Jacobs, 1976) which were unaffected by amphetamine (5 mg/kg). This suggests that (unlike backward walking or circling) these behaviours are not enhanced when the activation of catecholamine receptors is increased above physiological levels. Fenfluramine and p-chloroamphetamine markedly decreased rearing, gnawing and licking induced by amphetamine.

There is evidence that many drugs which cause hallucinations in man and backward walking and circling in laboratory animals also (either directly or indirectly) activate both DA and 5-HT post-synaptic receptors. The present results suggest the possibility that these effects are together responsible for the above behavioural changes in animals.

References

GROWDON, J.H. (1977). Postural changes, tremor, and myoclonus in the rat immediately following injections of

p-chloroamphetamine. *Neurology*, **27**, 1074–1077.
SCHNEIDER, C. (1968). Behavioural effects of some morphine antagonists and hallucinogens in the rat. *Nature, Lond.*, **220**, 586–587.
SMYTHIES, J.R., JOHNSTONE, V.S., BRADLEY, R.J., BENINGTON, F., MORIN, R.D. & CLARK, L.C. (1967). Some new behaviour-disrupting amphetamines and their significance. *Nature, Lond.*, **216**, 128–129.
TAYLOR, M., GOUDIE, A.J., MORTIMORE, S. & WHEELER, T.J. (1974). Comparison between behaviours elicited by high doses of amphetamine and fenfluramine: implications for the concept of stereotypy. *Psychopharmacologia*, **40**, 249–258.
TRULSON, M.E. & JACOBS, B.L. (1976). Behavioural evidence for the rapid release of CNS serotonin by PCA and fenfluramine. *Eur. J. Pharmac.*, **36**, 149–154.

Long term effects of p-chloroamphetamine on hippocampal 5-hydroxytryptamine release

C.A. MARSDEN

Department of Physiology and Pharmacology, Medical School, Queens Medical Centre, Nottingham, NG7 2UH

ρ-Chloroamphetamine (PCA) produces a long lasting depletion of brain 5-hydroxytryptamine (5-HT) which may be associated with a cytotoxic effect on brain 5-HT neurones (Sanders-Bush & Massari, 1977). An initial effect of PCA however is a rapid and short lasting release of brain 5-HT (Sanders-Bush & Massari, 1977) accompanied by a characteristic behavioural response consisting of forepaw treading, lateral headweaving, hind limb abduction and straub tail (Curzon, Fernando & Marsden, 1978). It is possible to monitor this release in the unrestrained unanaesthetized rat using *in vivo* voltammetry (Marsden, Conti, Strope, Curzon & Adams, 1979). The present communication concerns the long term effects of PCA administration on 5-HT release.

Release was monitored in male Wistar rats (220–280 g) using electrochemical electrodes implanted chronically into the dorsal hippocampus (Adams, Conti, Marsden & Strope, 1978). A potential (+0.7 V) was applied and the current changes which followed oxidation of electroactive compounds by the working electrode were recorded. Behavioural effects were scored using a 0-3 rating scale (Curzon, Fernando & Marsden, 1978).

PCA (5.0 mg/kg i.p.) produced a marked behavioural response ($n = 6$) and a concurrent increase in current (i) values ($n = 4$) which did not occur in rats pretreated with ρ-chlorophenylalanine (200 mg/kg) so probably reflects increased release of 5-HT. When L-tryptophan (50 mg/kg i.p.) was given 30 min before PCA (5 mg/kg) there was a significant increase in both the behavioural score ($P<0.001$) and 5-HT release ($P<0.01$). A second dose of PCA (5 mg/kg) given 24 h after the first significantly reduced the behavioural score and 5-HT release ($P<0.001$) compared to the response produced by the first dose. The behavioural and 5-HT release effects were restored by pretreating rats with L-tryptophan (50 mg/kg) 30 min before the second PCA injection. This result indicates that at 24 h the effects of PCA on 5-HT turnover are still reversible. When the second dose of PCA was given 10 days after the first there was still a significant reduction in both the behavioural score and 5-HT release compared with the response after the first injection. However, L-tryptophan (50 mg/kg) pretreatment failed to restore either the behavioural effects or the release of 5-HT, indicating at this stage that the effects of PCA on 5-HT turnover are largely irreversible. When the MAO inhibitor tranylcypromine (20 mg/kg i.p.) was given in place of L-tryptophan at 10 days the administration of PCA did result in a delayed and very exaggerated behavioural response but only a small increase in current (i) values indicating marked 5-HT receptor stimulation accompanied by relatively low 5-HT release.

The results are consistent with the suggestion that PCA has a long term cytotoxic action on 5-HT neurones and indicate that this may be accompanied by the development of post-synaptic receptor supersensitivity.

References

ADAMS, R.N., CONTI, J., MARSDEN, C.A. & STROPE, E. (1978). The measurement of dopamine and 5-hydroxytryptamine release on CNS of freely moving unanaesthetized rats. *Br. J. Pharmac.* (in press).
CURZON, G., FERNANDO, J.R.C. & MARSDEN, C.A. (1978). 5-hydroxytryptamine: the effects of impaired synthesis on its metabolism and release in rats. *Br. J. Pharmac.*, **63**, 627–634.
MARSDEN, C.A., CONTI, J., STROPE, E., CURZON, G. & ADAMS, R.N. (1979). Monitoring 5-hydroxytryptamine release in the brain of the freely moving unanaesthetized rat using *in vivo* voltammetry. *Brain Research* (in press).
SANDERS-BUSH, E. & MASSARI, V.J. (1977). Action of drugs that deplete serotonin. *Fed. Proc.*, **38**, 2149–2153.