of NA, dopamine (DA) and 5-HT in rat brain was studied during the chronic administration of agents which differ in their patterns of monoamine uptake inhibition. Compounds investigated were desipramine, chlorimipramine, maprotiline, a specific inhibitor of NA uptake (Waldmeier, Baumann, Greengrass & Maitre, 1976), Org 6582 (±-8-chloro-11-anti-aminobenzo-(b)-bicyclo-[3.3.1]-nona-3,6a-(10a)-diene hydrochloride), a specific inhibitor of 5-HT uptake (Sugrue, Goodlet & Mireylees, 1976) and mianserin, an atypical antidepressant devoid of effect on monoamine uptake *in vivo* (Leonard, 1974; Goodlet, Mireylees & Sugrue, 1977).

Male Sprague-Dawley rats weighing 120–150 g at the start of chronic drug administration were used. Drugs (10 mg/kg, i.p.) were injected once daily at noon for 14 days. Twenty-four h after the last injection the probenecid-induced increase in brain 5-hydroxyindoleacetic acid (5-HIAA) concentration and the α-methyl-*p*-tyrosine-induced fall in brain NA and DA contents were measured. In other experiments levels of brain (minus striatum) 3-methoxy-4-hydroxyphenyl-glycol (MHPG), striatal DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and whole brain NA, DA, 5-HT and 5-HIAA were determined using conventional fluorimetric procedures.

The chronic administration of desipramine resulted in a significant increase in both MHPG concentration and in the α-methyl-*p*-tyrosine-induced fall in brain NA content. Chronic mianserin also caused a small, but significant, increase in MHPG levels. Neither desipramine nor mianserin altered synthesis of DA or 5-HT or steady levels of 5-HIAA, DOPAC or HVA. Chronically administered Org 6582 decreased by approx. 40% brain 5-HIAA content and significantly antagonized the probenecid-induced increase in brain 5-HIAA levels. Chronic Org 6582 had no effect on synthesis of NA or DA and on levels of MHPG, DOPAC or HVA. Neither maprotiline nor chloripramin at the dosage regimen employed, altered synthesis of NA, DA or 5-HT or steady state levels of metabolites.

These findings reveal that, in contrast to the acute situation, chronically administered desipramine increases the synthesis of NA in rat brain. Brain 5-HT synthesis is decreased by the chronic administration of the specific 5-HT uptake inhibitor Org 6582. Similar results are seen following the acute administration of the compound. These observations suggest that rat brain 5-hydroxytryptaminergic systems are more resistant than noradrenergic systems to adaptive changes following a prolonged inhibition of monoamine uptake.

References

CARLSSON, A. & LINDQVIST, M. (1978). Effects of antidepressant agents on the synthesis of brain monoamines. *J. Neural Trans.* **43**, 73–91.

GOODLET, I., MIREYLEES, S.E. & SUGRUE, M.F. (1977). Effects of mianserin, a new antidepressant, on the *in vitro* and *in vivo* uptake of monoamines. *Br. J. Pharmac.*, **61**, 307–313.

LEONARD, B.E. (1974). Some effects of a new tetracyclic antidepressant, Org. GB94, on the metabolism of monoamines in the rat brain. *Psychopharmacologia* (Berl.), **36**, 221–236.

SUGRUE, M.F., GOODLET, I. & MIREYLEES, S.E. (1976). On the selective inhibition of serotonin uptake *in vivo* by Org. 6582. *Eur. J. Pharmac.*, **40**, 121–130.

WALDMEIER, P.C., BAUMANN, P., GREENGRASS, P.M. & MAITRE, L. (1976). Effects of clomipramine and other tricyclic antidepressants on biogenic amine uptake and turnover. *Postgrad. Med. J.*, **52** (Suppl. 3), 33–39.

Investigation of food consumption using a dietary self-selection procedure: effects of pharmacological manipulation and feeding schedules

J.E. BLUNDELL & R.A. McARTHUR

Department of Psychology, University of Leeds, Leeds LS2 9JT, U.K.

It is known that pharmacological manipulation of catecholamine (CA) (Leibowitz, 1976) and serotonin (5-HT) systems (Blundell, 1977) may bring about a depression of food intake. These effects have usually been examined by measuring the weight of food consumed by deprived rats allowed access to a single diet. When rats are given the opportunity to self-select particular proportions of protein and carbohydrate from separate diets, it has been reported that drugs known to increase 5-HT metabolism (fenfluramine and fluoxetine) spare protein intake while suppressing total intake in the weanling rat (e.g. Wurtman & Wurtman, 1977). On the other hand amphetamine, which is believed to exert its anorexic actions via CA mechanisms (e.g. Blundell & Latham, 1978), suppressed both protein intake and total food intake. However, it is known that the age of animals and deprivation regimens may affect protein requirements (NAS-NRC, 1978), 5-HT metabolism (Perez-Cruet, *et al.*, 1972) and feeding behaviour (Levitsky, 1970). Accordingly, we have further investigated the effects of various doses of (i) amphetamine and fenfluramine

Table 1 Effect of fenfluramine and (+)-amphetamine on total food intake, protein intake and protein energy percent[1]. Figures represent means of total energy and protein consumed 0–1 h (amphetamine) and 0–4 h (fenfluramine) after drug administration. These intervals correspond to the biologic half-lives of these compounds in the rat. The figures in parentheses represent intake values expressed as a percentage of saline controls

Drug	*Feeding schedule*	*n*	*Dose mg/kg*	*Food consumed (kj) Total energy intake*	*Total protein intake*	*PE%*
Fenfluramine	Free-feeding	10	0.0	104.92	33.84	31.91
			1.0	85.39 (85.10)	28.56 (91.81)	33.42 (108.90)
			2.0	64.22 (63.99)***	19.31 (67.16)*	30.45 (101.52)
			4.0	38.17 (37.21)***	12.01 (39.62)***	30.60 (101.05)
	Deprivation	8	0.0	237.34	51.34	21.74
			1.0	169.62 (73.71)***	46.56 (91.50)	27.45 (123.21)
			2.0	157.24 (66.24)***	43.92 (88.99)	27.59 (132.53)*
			4.0	113.80 (48.33)***	29.05 (57.64)*	24.92 (120.09)
Amphetamine	Free-feeding	10	0.0	40.48	13.64	30.35
			0.5	26.23 (72.01)	4.83 (41.77)***	27.36 (74.45)
			1.0	8.37 (24.32)***	1.48 (11.01)***	17.91 (48.58)**
			2.0	10.18 (27.69)***	0.98 (9.28)***	12.31 (37.54)**
	Deprivation	8	0.0	124.66	32.92	26.02
			0.5	109.73 (99.23)	24.66 (88.67)	22.21 (88.55)*
			1.0	69.91 (68.09)*	17.27 (67.89)*	24.37 (96.81)
			2.0	27.38 (26.58)***	7.32 (30.21)**	22.09 (91.85)

Significantly different from saline control: (paired *t*-test).
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$.

[1] Protein energy per cent (PE%) $= \frac{\text{total protein consumed (g)} \times 16.70 \text{ kj}}{\text{total food consumed (g)} \times 18.08 \text{ kj}} \times 100.$

on dietary self-selection in adult rats under free-feeding and cyclic deprivation regimens.

Adult male rats obtained all their food by self-selecting from two food cups containing iso-caloric powder diets varying in protein inclusion (5 and 45% casein). One group of animals was allowed to feed freely from the diets whilst a second group was allowed access to the diets for only 8 h per day. Three doses of (1) amphetamine and fenfluramine were administered under each feeding schedule, and the amount of diet consumed from each of the two food cups was measured periodically after drug injection.

Table 1 shows that for deprived animals our data are broadly in keeping with the findings of Wurtman & Wurtman. Amphetamine markedly reduced food intake and slightly decreased protein energy per cent, whilst fenfluramine gave rise to an increase in the proportion of protein in the total food consumed (protein sparing effect). However, these effects were altered under free-feeding conditions. Amphetamine produced a striking reduction in protein intake and protein energy percentage, whilst the protein sparing effect of fenfluramine was noticeably diminished. Accordingly, the effect of food deprivation was to enhance the effect of fenfluramine on protein energy per cent. (125.4% vs 103.8%—mean percent change from saline control for 3 doses) and to ameliorate the reduction in protein energy per cent by amphetamine (87.6% vs 53.7%). These data show an interaction between pharmacological manipulation and feeding schedule which is revealed by the animals selection of the proportion of protein in its diet. This interaction may depend upon differences in the activity levels of deprived and free-feeding rats (Collier, Leshner & Squibb, 1969) or differences in brain levels of CA/5-HT (Coscina, Leprohon, Warsh, & Anderson, 1977).

This work was funded by a postgraduate studentship awarded to R.McA. by the Institut de Recherches Servier, France.

References

BLUNDELL, J.E. (1977). Is there a role for serotonin (5-hydroxy-tryptamine) in feeding? *Int. J. Obesity*, **1**, 15–42.

BLUNDELL, J.E. & LATHAM, C.J. (1978). Pharmacological manipulation of feeding behaviour: Possible influence of serotonin and dopamine on food intake. In: *Central Mechanisms of Anorectic Drugs* ed. Garattini, S. & Samanin, R. pp. 83–109. Raven Press, New York.

COLLIER, G., LESHNER, A.I. & SQUIBB, R.L. (1969). Dietary self-selection in active and non-active rats. *Physiol. Behav.* **4**, 79–82.

COSCINA, D.V., LEPROHON, C., WARSH, J.J. & ANDERSON, G.H. (1977). Brain monoamine levels in hypothalamic obese rats who self-select protein and energy intake. Paper read at the Second International Congress on Obesity, Washington D.C.

LEIBOWITZ, S.F. (1976). Brain catecholaminergic mechanisms for control of hunger. In: *Hunger: Basic Mechanisms and Clinical Implications*, ed. Novin, D., Wyrwicka, W. & Bray, G. pp. 1–19 Raven Press, New York.

LEVITSKY, D.A. (1970). Feeding patterns of rats in response to fasts and changes in environmental conditions. *Physiol. Behav.* **5**, 291–300.

NAS-NRC (U.S.A.) (1978). Nutrient requirements of domestic animals, No. 10, Nutrient requirements of laboratory animals. National Academy of Science, Washington, D.C.

PEREZ-CRUET, J., TAGLIAMONTE, A., TAGLIAMONTE, P. & GESSA, G.L. (1972). Changes in brain serotonin associated with fasting and satiation in rats. *Life Sci.* **11**, 31–39.

WURTMAN, J.J. & WURTMAN, R.J. (1977). Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. *Science* **198**, 1178–1180.

Evidence for the release of hippocampal 5-hydroxytryptamine by α-methyltryptamine

C.A. MARSDEN

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

Previous studies have indicated that in the rat the initial behavioural response produced by α-methyltryptamine (10 mg/kg) involves stimulation of 5-hydroxytryptamine (5-HT) receptors following a pre-synaptic action of α-methyltryptamine on 5-HT neurones (Marsden, 1978). In the present study an *in vivo* electrochemical technique for measuring 5-HT release in the unanaesthetised rat (Conti, Strope, Adams & Marsden, 1978; Marsden, Conti, Strope, Curzon & Adams, 1979) has been used to show whether or not the pre-synaptic action of α-methyltryptamine causes an increase in extra-neuronal 5-HT.

The electrochemical activities (oxidation potentials) of 5-HT, tryptamine, α-methyltryptamine and L-tryptophan were determined in 10 ml 1×10^{-3} M solutions of each prepared in 0.1 M phosphate buffer pH 7.4 using linear sweep voltammetry (CV-1A, Bioanalytical Systems-Anachem Ltd). with semi-micro carbon paste working, silver-silver chloride reference and stainless steel auxiliary electrodes. The potential sweep was from 0.0 to 1.2 V at 100 mV/sec. 5-HT was oxidised at about +0.4 V while α-methyltryptamine, tryptamine and L-tryptophan were oxidised at potentials between +0.75 and +0.85 V.

Release of 5HT was monitored in male Wistar rats (240–280 g) using micrographite electrochemical electrodes implanted into the dorsal hippocampus (Conti, *et al.*, 1978). Linear sweep voltammetry (0.0 − +1.0 V at 50 mV/sec) and chronoamperometry (fixed potential +0.6 V applied for 1 sec every 10 min) were used to measure the current changes. Rats injected with saline showed no clear oxidation peaks following a linear potential sweep. However, 45 min after giving α-methyltryptamine (10 mg/kg) there were two peaks clearly visible, one between +0.35 − +0.5 V and the other between +0.75 − +0.85 V. The peak at the higher potential first appeared 10–15 min and the lower peak 30–45 min after injection. The appearance of the peak at the lower potential coincided with the onset of the initial behavioural response. The occurrence of the two peaks suggested that α-methyltryptamine increased the extra-neuronal 5-HT concentration (peak at +0.4 V) following its accumulation in the brain (peak at +0.8 V). If this were so, depletion of brain 5-HT prior to α-methyltryptamine administration would be predicted to prevent the increase in detectable 5-HT and thus the peak at +0.4 V but not to affect the peak at the higher potential. Pretreatment with p-chlorophenylalanine (PCPA, 200 mg/kg i.p.) 24 h before prevented the initial behavioural response produced by α-methyltryptamine and the appearance of the oxidation peak at +0.4 V. There was however also a small reduction in the peak at the higher potential indicating either that PCPA reduced the uptake of α-methyltryptamine into the brain or that α-methyltryptamine released something oxidisable at +0.8 V (e.g. tryptamine). The marked peak at +0.4 V after α-methyltryptamine injection does not simply reflect MAO inhibition as whole brain 5-HT, measured fluorometrically, was only increased by 19% ($n = 6$) 45 min after 10 mg/kg injection. Furthermore, other MAO inhibitors do not produce the same initial behavioural response.

The results support findings relating the initial behavioural response induced by α-methyltryptamine to a pre-synaptic effect on 5-HT neurones leading to increased 5-HT in the synaptic cleft. This may be caused either by release of 5HT or by blockade of 5-HT re-uptake (Horn, 1973) combined with some inhibition of MAO.