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Effects of Manipulations of Peripheral Serotonin on Feeding and Drinking in the Rat

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FLETCHER, P J AND M J BURTON *Effects of manipulations of peripheral serotonin on feeding and drinking in the rat* PHARMACOL BIOCHEM BEHAV **20**(6) 835–840, 1984 —Rats injected peripherally with serotonin showed a dose dependent increase in water intake which was maximal at 2-hours This effect, along with a dose dependent anorexia was also observed in animals eighteen hour food deprived overnight In rats maintained on a 6-hour feeding schedule there was a significant anorectic effect of 5-HT that could be reversed by pretreatment with methysergide but not metergoline However the hyperdipsia was not apparent in these animals due to prandial drinking by control animals The optimal dose of 5-HT for producing an anorexic response produced only a transient conditioned taste aversion to a novel solution in a sensitive 2-bottle choice test On the other hand a high dose of 5-HT, and 3 mg/kg fenfluramine produced sustained aversions These results are discussed with regard to a possible peripheral role for 5-HT in the control of food intake

Feeding Drinking Peripheral serotonin Serotonin antagonists Conditioned taste aversion Gastric emptying

SEROTONIN (5-HT) has been implicated in the central control of feeding for twenty years or more (for reviews see [1,11]). Although 95% of the serotonin in the body is found in the periphery the anoretic action of serotonin agonist drugs has usually been interpreted in terms of modulation of cell systems arising from the midbrain raphe system [1,11]. Attempts to demonstrate a peripheral role of 5-HT in feeding using 5-hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, in conjunction with a peripheral decarboxylase inhibitor have generally produced equivocal results [2]. Although some reviewers have not ruled out the possibility of a role for peripheral 5-HT in feeding it is only recently that several lines of evidence have emerged suggesting that both serotonin and serotoninergic drugs may have anoretic effects arising from peripheral actions Peripheral injections of serotonin produce anorexia [19] and hyperdipsia [14], this latter effect can be blocked by the serotonin antagonist methysergide and appears to involve the renin-angiotensin system [25] Other authors have shown that animals in which the central anoretic actions of fenfluramine are blocked by lesions of the midbrain raphe system will nonetheless show anorexia to fenfluramine if tested ad lib [7]. The proposed explanation of this effect was that fenfluramine acts peripherally to decrease stomach clearance and that the retention of food in the stomach leads to longer intermeal intervals.

Since peripherally injected serotonin is believed not to cross the blood brain barrier [18] it is of interest to investigate whether its anoretic actions depend upon activation of serotonin receptors and are therefore blockable by serotonin antagonists, how the observed hyperdispia interacts with food intake, and whether the explanations advanced for the peripheral action of fenfluramine have any validity in this case

METHOD

EXPERIMENT 1 SEROTONIN EFFECTS ON CONSUMMATORY BEHAVIOURS

Procedure

Thirty adult male Lister hooded rats (300–420 g) were used. The rats were group housed and maintained on a 12-hour light-dark cycle. Food and water were available at all times. On the days of testing, 2 hours after the onset of the light phase rats were divided into 5 groups of 6 rats each, and placed in individual cages with access to water for 1-hour in the first experiment. The rats were then injected with 0.5, 1 0, 2 0 or 4.0 mg/kg 5-HT or saline (SC), and replaced in the cage with a preweighed bottle of water. Water intake was measured by reweighing the bottle, to 0.1 g, at 0.5, 1, 2 and 3 hours post-injection. Ten days after the above experiment the same animals were food deprived for eighteen hours and then injected as described above. The rats were then placed in individual cages with preweighed amounts of food and water. Intakes were determined by weighing the food and water at 0.5, 1, 2, and 3 hours post-injection.

Results

Analyses of variance involving dose of 5-HT and time as factors were carried out on the cumulative intake data (Table 1) When rats were presented with water alone the 5-HT produced a dose dependent increase in water intake, $F(4,25)=30.8$, $p<0.001$, with significant increases at 1, 2 and 3 hours, but not at 30 minutes. Both the main effect of time and the dose/time interaction were significant, $F(3,75)=190$, $p<0.001$ and $F(12,75)=8.2$, $p<0.001$ respectively. Similarly, in food deprived rats a significant effect of 5-HT on

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TABLE 1

THE EFFECTS OF DEPRIVATION STATE (DEP) ON 5-HT INDUCED CHANGES IN CUMULATIVE WATER AND FOOD INTAKES

Dep	Measure	Time	5-HT mg/kg 0	0 5	1 0	2 0	4 0
Ad-Lib	Water (ml)	0 5 hr	0 5 (0 1)	0 6 (0 1)	0 9 (0 13)	0 8 (0 11)	1 2 (0 14)
		1 hr	0 8 (0 13)	1 3 (0 17)	1 9 (0 17)	2 7† (0 6)	3 1† (0 2)
		2 hr	1 3 (0 16)	2 1 (0 3)	3 2† (0 4)	4 3† (0 32)	4 8† (0 3)
		3 hr	1 7 (0 18)	2 5 (0 22)	4 1† (0 4)	4 8† (0 23)	5 1† (0 2)
18 hr Food Dep	Water (ml)	0 5 hr	1 5 (0 67)	2 2 (0 49)	1 4 (0 53)	1 7 (0 35)	2 4 (0 51)
		1 hr	3 2 (0 84)	3 8 (0 6)	3 4 (0 47)	5 6 (0 33)	5 5† (0 75)
		2 hr	5 1 (0 89)	5 4 (0 62)	6 6 (0 84)	8 8† (0 34)	9 5† (1 0)
		3 hr	5 6 (0 85)	7 2 (0 78)	7 7 (0 82)	9 6† (0 29)	10 8† (0 84)
18 hr Food Dep	Food (g)	0 5 hr	3 7 (0 6)	2 4 (0 64)	1 7 (0 44)	1 0† (0 2)	0 7† (0 1)
		1 hr	4 8 (0 47)	3 3 (0 7)	1 8† (0 44)	1 3† (0 24)	1 1† (0 23)
		2 hr	6 9 (0 5)	5 4 (0 73)	4 7† (0 9)	3 9† (0 4)	3 4† (0 25)
		3 hr	7 4 (0 5)	6 0 (0 72)	6 3 (0 41)	4 9† (0 67)	4 0† (0 16)

Each figure represents the mean and SEM (parentheses) of 6 rats
*Differs from 0 mg/kg 5-HT, $p<0.05$
†Differs from 0 mg/kg 5-HT, $p<0.01$

water intake was observed, $F(4,25)=5.68$, $p<0.01$. The two highest doses of 5-HT caused significant increases in water intake at 1, 2 and 3 hours but not at 30 minutes. The main effect of time and the dose/time interaction were significant, $F(3,75)=212$, $p<0.001$ and $F(12,75)=4.43$, $p<0.001$, respectively. In these latter animals 5-HT also produced a dose dependent reduction of food intake, $F(4,25)=11.1$, $p<0.001$, which was seen at all time periods However by 3-hours only the two highest doses of 5-HT were significantly different from controls. The main effect of time was also highly significant, $F(3,75)=117$, $p<0.001$

Discussion

These results replicate previously reported findings that 5-HT produces a dose dependent increase in water intake in water-replete rats, which is maximal at 2-hours post-injection. Serotonin can produce a simultaneous decrease in food intake, and an increase in water intake. Although both effects occur in the first 2-hours post-injection the time courses differ The anorexia is seen in the first half-hour and is most marked during the first hour, whereas the drinking response is maximal at 2-hours, but does not occur in the first 30 minutes. Comparing the data for the first and second parts of this experiment it can be seen that a higher dose of 5-HT is required for the dipsogenesis to exceed that of control animals when feeding occurs at the same time. In addition the size of the dipsogenic effect appears larger when the animal is given access to water only (although a direct comparison can not be made here). The explanation for this effect is probably the increased prandial water intake of control animals.

The "peripheral" anorectic effects of fenfluramine which occur in free feeding animals may depend upon the rat having a full stomach Typically experiments on anorectic drugs have examined animals on a deprivation schedule, rather

than subjected to overnight deprivation as used here and in a previous study [19]. The following experiments used rats which were habituated to eating their daily ration of food in a 6-hour period. These experiments were also conducted to investigate the effects of 5-HT antagonists on peripheral administration of 5-HT.

EXPERIMENT 2a THE EFFECT OF METHYSERGIDE ON 5-HT INDUCED CHANGES IN FEEDING AND DRINKING

Procedure

Sixteen adult male Lister hooded rats (230–300 g) were individually housed under a 12-hour light-dark cycle. Prior to the experiment rats were habituated to a 6-hour food access period beginning 2 hours after the onset of the light phase until food intakes had stabilised Water was available at all times. In addition for 3 days prior to the experiment rats were given sham injections of saline at times and routes corresponding to subsequent drug injections

The rats were then divided into 2 groups matched on the basis of baseline 6-hour food intakes. One group always received methysergide (3 mg/kg IP), the other group received an equal volume of distilled water. Thirty minutes later all rats were injected with 5-HT (1, 2 or 4 mg/kg SC) or saline. Preweighed amounts of food and water were placed in the cage immediately following the second injection. Food and water intakes were recorded at 1, 2, 4 and 6 hours

Each rat received every dose of 5-HT and saline in a counterbalanced order; and at least 2 drug-free days were allowed between experimental days The dose of methysergide used was derived from a dose response curve in 18-hour food deprived rats. This dose attenuated 5-HT anorexia without suppressing food intake in its own right.

EXPERIMENT 2b THE EFFECTS OF METERGOLINE ON 5-HT INDUCED CHANGES IN FEEDING AND DRINKING

A further 16 adult male Lister hooded rats (240–330 g) were treated in identical fashion to Experiment 2a except that they received metergoline (1 mg/kg IP) or its vehicle (1% ascorbic acid) 3 hours prior to the second injection. This dose was based on previous usage in the literature.

Results 2a

Analysis of variance involving factors of pretreatment and dose of 5-HT showed that 5-HT produced a dose-dependent reduction in food intake at all time intervals measured, smallest $F(3,42)=3.79$, $p<0.05$. This effect was largest during the first hour, $F(3,42)=23\ 9$, $p<0.001$, and is shown in Fig. 1a. A significant main effect of methysergide was observed at 1 and 2 hours post-injection, smallest $F(1,14)=6.02$, $p<0.05$, but not at 4 and 6 hours. However methysergide alone did not significantly alter food intake. There was a significant 5-HT pretreatment interaction only at 1 hour, $F(3,42)=4.07$, $p<0.025$, which can be attributed to the failure of methysergide to affect the anorexia caused by the highest dose of 5-HT. These results indicate that over the first 2-hours of the feeding period methysergide significantly attenuated the anorectic action of 5-HT

Analysis of the water intake data revealed a significant main effect of 5-HT during the first hour, $F(3,42)=7\ 26$, $p<0\ 01$, indicating a dose dependent increase over this time period This main effect failed to reach significance at any of the other time periods examined, largest $F(3,42)=2.64$, $p>0.05$. Neither the main effect of pretreatment, nor the

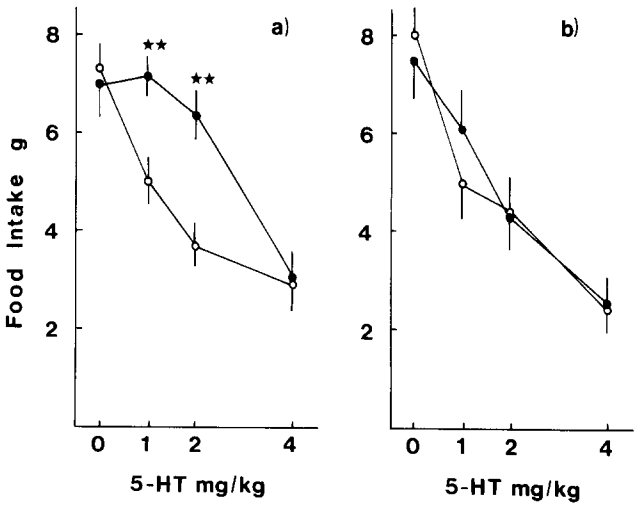

FIG 1. The effects of (a) 3 mg/kg methysergide or (b) 1 mg/kg metergoline pretreatment on the changes in 1-hour food intake induced by various doses of peripherally administered 5-HT In both (a) and (b) filled circles represent antagonist pretreatment and open circles represent vehicle pretreatment Each point represents the mean and SEM of values from 8 rats Two stars, differs from saline pretreatment, $p<0\ 01$

5-HT/pretreatment interaction reached significance at any time period, largest $F(1,14)=2.42$, $p>0.1$ and $F(3,42)=1.59$, $p>0.1$ respectively.

Results 2b

As shown in Fig. 1b the 5-HT produced an identical dose dependent reduction of food intake during the first hour, $F(3,42)=30.6$, $p<0.001$, to that seen in Experiment 2a. This effect was seen at all time periods, smallest $F(3,42)=3.79$, $p<0.05$. Metergoline pretreatment failed to reach significance over the first three time periods, largest $F(1,14)=2.96$, $p<0\ 1$, but was significant over the whole 6-hour period, $F(1,14)=9.73$, $p<0\ 01$ The 5-HT/treatment interaction was not significant at any time period, largest $F(3,42)=1.93$, $p>0.1$.

Analysis of the water intake data revealed that the main effect of 5-HT was not significant at any time period, largest $F(3,42)=2\ 18$, $p>0\ 1$. Similarly both the main effect due to metergoline pretreatment and the 5-HT/pretreatment interaction did not reach significance, largest $F(1,14)=2.83$, $p>0.1$ and $F(3,42)=2.09$, $p>0.1$ respectively

One explanation for metergoline's failure to attenuate the anorectic action of 5-HT may be that the metergoline dose was insufficient, despite being commonly cited as centrally active in blocking 5-HT. Therefore Experiment 2c was undertaken to examine the effects of a range of doses of metergoline against a single dose of 5-HT.

EXPERIMENT 2c THE EFFECTS OF VARIOUS DOSES OF METERGOLINE ON 5-HT INDUCED CHANGES IN FEEDING AND DRINKING

Procedure

A further 16 adult male hooded Lister rats (280–360 g) were used. The procedure was similar to that used in Exper-

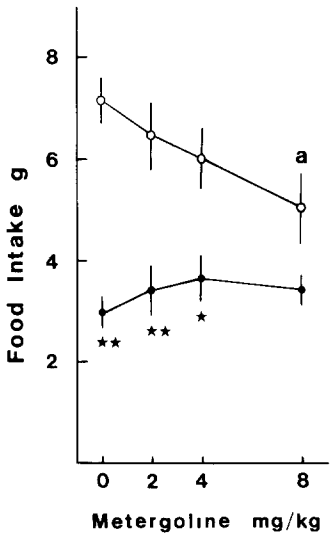

FIG 2 The effects of different doses of metergoline on the change in 1-hour food intake induced by 2 mg/kg 5-HT The 5-HT (filled circles) or saline (open circles) were administered 3-hours after metergoline Each point represents the mean and SEM of values from 8 rats. One star differs from corresponding vehicle treated group, $p<0.05$ Two stars differs from corresponding vehicle treated group, $p<0$ 01 a Differs from vehicle-vehicle group, $p<0$ 01

iment 2b, except that animals were divided into 2 groups of 8 rats on the basis of whether they received an injection of 2 mg/kg 5-HT or saline (SC) following a 3-hour pretreatment with 2, 4, 8 mg/kg metergoline (IP) or its vehicle

Results 2c

The results for the first hour are shown in Fig. 2 The 5-HT significantly reduced food intake during this time period, $F(1,14)=23$ 9, $p<0.001$, but the main effect of metergoline pretreatment did not reach significance, $F(3,42)=2.28$, $p>0.05$. However the 5-HT/pretreatment interaction was highly significant, $F(3,42)=5$ 24, $p<0.01$ Further analysis of this interaction revealed that animals treated with 8 mg/kg prior to 5-HT did not differ from animals treated with 8 mg/kg metergoline alone However this dose of metergoline significantly reduced food intake in its own right No significant differences existed across the 5-HT condition

At all other time periods the main effect of 5-HT was significant, $F(1,14)=13$, $p<0.01$. The main effect of metergoline pretreatment was significant at 2 and 4 hours, smallest $F(3,42)=2.9$, $p<0.05$, which reflected a reduction in food intake by the highest dose of metergoline. At 4 hours a significant 5-HT/pretreatment interaction was detected, $F(3,42)=3.25$, $p<0$ 05, but again this effect can be attributed to the anorexia induced by 8 mg/kg metergoline These results indicate that metergoline pretreatment failed to attenuate 5-HT induced anorexia.

Analysis of the water intake data revealed that 5-HT caused a slight increase in water consumption only at 1-hour, $F(1,14)=4.9$, $p<0.05$ The main effect of metergoline pretreatment, and the 5-HT/pretreatment interaction did not reach significance at any time period, largest $F(3,42)=2.64$ and 1.3 respectively, both $p>0.05$

Discussion

The results of Experiments 2a and 2b show that 5-HT produced a dose-dependent reduction of food intake across 6-hours in food deprived animals, and this effect occurred maximally in the first hour Apart from a transient increase in water intake during the first hour of Experiments 2a and 2c 5-HT failed to affect water intake Nevertheless, 5-HT treated rats maintained their water consumption at control levels. The probable explanation for the failure to detect a significant rise in water consumption consistent with that observed in non-deprived rats is the interaction between 5-HT, and prandial drinking associated with enhanced food intake in response to scheduled food deprivation

Pretreatment with methysergide clearly attenuated the anorectic action of 5-HT during the first 2-hours of the feeding period Metergoline pretreatment did not exert any attenuation even at dose above those which block the anorectic action of serotonergic agonists such as fenfluramine [5,12] and quipazine [20]. Higher doses of metergoline caused a reduction in food intake, possibly due to an interaction with other neurotransmitter systems [24] Both of these antagonists have been reported to have central [16] and peripheral [17] actions but the present results may indicate that methysergide is a more effective antagonist than metergoline at peripheral 5-HT receptors mediating 5-HT anorexia

Taking the 6-hour data into account statistical analysis revealed that methysergide pretreatment did not affect 5-HT anorexia This failure to detect a significant main effect of pretreatment may have been due to data from those rats receiving the highest dose of 5-HT A previous report [3] has demonstrated a biphasic action (a short term inhibition, followed by a long term facilitation) of methysergide on fenfluramine anorexia. The apparent blockade of 5-HT anorexia by 1 mg/kg metergoline (Experiment 2b) over the 6-hour period is equally puzzling, but it is unclear whether this effect is due to a direct action at 5-HT receptors, or a nonspecific action of metergoline itself on food intake

It is possible that the reduction in food intake caused by the peripheral administration of 5-HT is the result of malaise Using a 1-bottle test it has been shown that 2 mg/kg 5-HT does not support a conditioned taste aversion (CTA) [19] Two bottle tests have been shown to be more sensitive in detecting a CTA [10] The following experiment was conducted to examine the effects of 5-HT in this more sensitive paradigm; a fenfluramine group was also included for comparison

EXPERIMENT 3 CONDITIONED TASTE AVERSION

Procedure

Thirty-five adult male Lister hooded rats (190–280 g) were individually housed under a 12 hour light dark cycle. The rats were habituated to 23 5 hours water deprivation with water available in 2 bottles for 10 minutes each morning (1000–1010 a m.) and in 1 bottle for 20 minutes (1500–1520) each afternoon Following the habituation period the rats were presented with 2 bottles of 0.9% saline solution during the morning session Immediately afterwards the rats were divided into 5 groups and given one of 5 pairs of injections: 1 ml/kg saline (SC) followed by 5 ml/kg saline (IP), 1 ml/kg saline (SC) followed by 5 ml/kg 0 15 M LiCl (IP), 2 mg/kg 5-HT

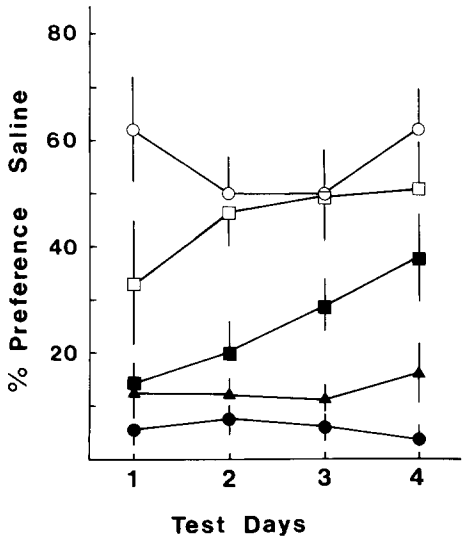

FIG 3 The effects of pairing various agents with a novel solution on the subsequent preference for saline in a 2-bottle choice test Agents used were saline (open circles), 5 ml/kg 0 15 M LiCl (filled circles), 2 mg/kg 5-HT (open squares), 4 mg/kg 5-HT (filled squares) and 3 mg/kg fenfluramine (filled triangles) See text for full procedural details and statistical analysis. Each point represents the mean and SEM of values from 7 rats.

(SC) followed by 5 ml/kg saline (IP), 4 mg/kg 5-HT (SC) followed by 5 ml/kg saline (IP), 3 mg/kg fenfluramine (SC) followed by 5 ml/kg saline (IP). Two injections were given to control for differences in volume and route of injection between the LiCl condition and the other drug conditions. Water was given as normal for that afternoon, and for the day following injections. Four consecutive test days were run, where each rat was given a 2-bottle choice between saline and water during the morning drinking session. The initial position of each bottle was counterbalanced as far as possible within groups and across days, and additionally the positions of the bottles were reversed halfway through the 10 minute session. The intakes of each solution were determined by weighing the bottles before and after the drinking session. Water was available for 20 minutes as usual each afternoon.

The dose of fenfluramine was chosen because previous unpublished work in our laboratory has shown that it produces an approximately equivalent degree of anorexia to 2 mg/kg 5-HT

Results 3

The results are shown in Fig 3 as the preference for saline solution over water (the amount of saline consumed divided by the total amount of fluid consumed, expressed as a percentage). Analysis of variance showed a highly significant effect of groups, $F(4,90)=71.2$, $p<0.001$, but neither the main effect of days nor the groups/days interaction reached significance, $F(3,30)=0.75$, $F(12,90)=1.59$, both $p>0.1$, respectively. Planned comparisons using t-tests were then carried out on each of the 4 test days. It was found that animals which had received LiCl, 4 mg/kg 5-HT, or fenfluramine showed a significantly reduced preference for saline solution in comparison to control animals on all 4 test days (all $p<0.01$). However those animals which had received 2 mg/kg 5-HT were significantly different from controls only on the first test day ($p<0.01$).

Discussion

The 2-bottle choice test has been shown to be a very sensitive paradigm for detecting a conditioned taste aversion (CTA) to a novel flavour [10]. This is demonstrated here by those animals in the LiCl condition, since this dose of LiCl produces a CTA which extinguished rapidly in a 1-bottle test. Therefore it would appear that although the low dose of 5-HT produced a transient CTA on the first day, this is unlikely to explain the anorexia observed in the previous experiments as such a small effect is unlikely to generate the consistent fifty percent reductions in food intake seen across repeated injections of 5-HT in Experiment 2. It is interesting that fenfluramine produced a CTA whereas 2 mg/kg 5-HT did not, despite the fact that the degree of anorexia produced by these agents, at the doses used, is equivalent. The 4 mg/kg dose of 5-HT produced a significant CTA to saline, taken with data from Experiment 2a where methysergide failed to antagonise the anorexia caused by a dose of 4 mg/kg 5-HT, this finding is consistent with the idea that high doses of 5-HT may have widespread actions throughout the body. Observation of the animals given this dose of 5-HT revealed profound sedative effects which were not seen at lower doses: there was also a striking increase in peripheral vasodilation.

GENERAL DISCUSSION

The experiments confirm that peripherally administered serotonin induces a dose dependent anorexia which appears to depend upon the activation of peripheral serotonin receptors, in that the anorexia can be reversed by pretreatment with the serotonin receptor blocker methysergide The action of serotonin occurs in food deprived animals and thus differs from the reported peripheral actions of fenfluramine which only occur if the animal is feeding freely and thus has food in its stomach [7] Further evidence for this dissociation arises from the observed actions of low doses of metergoline which failed to reverse 5-HT anorexia but are reported to block the actions of fenfluramine [5,12]. There is no obvious explanation as to why metergoline and methysergide should differ in their ability to block peripheral 5-HT anorexia. Although metergoline has been reported to be a potent antagonist at central 5-HT receptors [8] there are no obvious differences in their 5-HT actions peripherally that might explain these results.

The causes of the observed anorexia are unclear although there are several obvious possibilities. Fenfluramine even in low doses induces a clear CTA using the more sensitive two bottle test, 5-HT however at least at the lower doses used here does not It seems unlikely that any simple explanation in terms of gastric malaise is appropriate although the validity of conditioned taste aversion as a measure of gastric disturbance has been questioned [22]. We made measurements of gastric contents one hour after a 10 g meal of wet mash (3.3 g dry weight mash) and found that the 5-HT animals retained significantly more than controls. Similar observations have been made of fenfluramine treated animals and slowed gut emptying has been advanced as an explanation of the observed anorexia [7]. Simulations of such reduced emp-

tying using a quantitative model of energy flows [4] reveal that the animals would be expected to take longer rather than shorter meals unless the gut loadings reach the point of activating stomach stretch receptors Since rats can consume far more than 10 g of wet mash it seems unlikely that this is an explanation unless the 5-HT acts to enhance the activity of such stretch receptors It is reported that vagotomy does not alter 5-HT induced anorexia [21] and since stretch reception is normally thought to be mediated by vagal afferents there seems little support for the stretch reception idea. Given the high quantities of 5-HT in enteric cells of the gut [9] some role via smooth muscle modulation of peristalsis remains the most probable explanation

Other alternatives such as the competition with water intake induced by hyperdipsia as a result of activation of the renin-angiotensin system seem unlikely because of the different time course of the two effects Further support for this hypothesis comes from observations of the hyperdipsia in animals given access to food which only slightly exceeds prandial drinking seen in controls One obvious possibility is sedative effects or more subtlely alterations in post-prandial cortical synchronicity such as have been described for cholecystokinin [15] There were no obvious effects at 2 mg/kg of serotonin in either these or in previous studies Since the actions of CCK are blocked by vagotomy [23], and if the previous report that this manipulation does not affect 5-HT anorexia is correct, then it seems unlikely that any explanation in terms of sedation will explain the observed results. The resolution of some of these issues awaits the results of microstructural analyses [6] At the present time it is clear that 5-HT exerts a considerable peripheral anorexia and that this effect will have to be taken into account in considering the actions of serotonergic agonist drugs.

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REFERENCES

1 Blundell, J E Is there a role for serotonin (5-hydroxytryptamine) in feeding? *Int J Obes* **1:** 15–42, 1977
2 Blundell, J. E and C J Latham. Serotonergic influences on food intake Effect of 5-hydroxytryptophan on parameters of feeding behaviour in deprived and free feeding rats *Pharmacol Biochem Behav* **11:** 431–437, 1979
3 Blundell J E , C J Latham and M B Leshem Biphasic action of a 5-hydroxytryptamine inhibitor on fenfluramine-induced anorexia *J Pharm Pharmacol* **25:** 492–494, 1973
4 Booth, D A Prediction of feeding behaviour from energy flows in the rat In *Hunger Models*, edited by D A Booth New York Academic Press, 1978, pp 227–228
5 Borsini, F , C Bendotti, A Aleotti, R Samanin and S Garattini D-fenfluramine and d-norfenfluramine reduce food intake by different serotonin receptors in the rat brain *Pharmacol Res Commun* **14:** 671–678, 1982
6 Burton, M J , S J Cooper and D A Popplewell The effect of fenfluramine on the microstructure of feeding and drinking in the rat *Br J Pharmacol* **72:** 621–633, 1981
7 Davies, R F , J R Rossi, J Panksepp, N J Bean and A J Zolovick Fenfluramine anorexia A peripheral locus of action *Physiol Behav* **30:** 723–770, 1983
8 Fuxe, K , L Agnati and B Everitt Effects of methergoline on central monoamine neurones Evidence for a selective blockade of central 5-HT receptors *Neurosci Lett* **1:** 283–290, 1975
9 Gershon, M D Enteric serotonergic neurons In *Biology of Serotonergic Transmission*, edited by N N Osborne New York John Wiley and Sons Ltd , 1982, pp 363–399
10 Grote, F W and R T Brown Conditioned taste aversions Two-stimulus tests are more sensitive than one-stimulus tests *Behav Res Meth Instrum* **3:** 311–312, 1971
11 Hoebel, B G Pharmacologic control of feeding *Annu Rev Pharmacol Toxicol* **17:** 605–621 1977
12 Jesperson, S and J Scheel-Krugger Evidence for a difference in mechanism between fenfluramine and amphetamine induced anorexia *J Pharm Pharmacol* **25:** 49–54, 1973
13 Kety, S The central physiological and pharmacological effects of the biogenic amines and their correlations with behaviour In *The Neurosciences*, edited by G C Quarton, T Melnechuck and F O Schmitt New York Rockefeller Univ Press , 1967, pp 444–451
14 Kikta, D C , R M Threatte, C C Barney, M J Fregly and J E Greenleaf Peripheral conversion of L-5-hydroxytryptophan to 5-HT induces drinking in rats *Pharmacol Biochem Behav* **14:** 889–893, 1981
15 Mansbach, R S and D N Lorenz Cholecystokinin (CCK-8) elicits prandial sleep in rats *Physiol Behav* **30:** 179–183, 1983
16 Martin, L L and E Sanders-Bush Comparison of the pharmacological characteristics of 5-HT1 and 5-HT2 binding sites with those of serotonin autoreceptors which modulate serotonin release *Naunyn Schmiedebergs Arch Pharmacol* **321:** 165–170, 1982
17 Mawson, C and M Whittington Evaluation of the peripheral and central antagonistic activities against 5-hydroxytryptamine of some new agents *Br J Pharmacol* **39:** 223P, 1970
18 Oldendorf, W H Brain uptake of radiolabelled amino acids amines and hexoses after arterial injection *Am J Physiol* **221:** 1629–1639, 1971
19 Pollock, J D and N Rowland Peripherally administered serotonin decreases food intake in rats *Pharmacol Biochem Behav* **15:** 179–183, 1981
20 Samanin, R , C Bendotti, G Candelaresi and S Garattini Specificity of serotoninergic involvement in the decrease of food intake induced by quipazine in the rat *Life Sci* **21:** 1259–1266, 1977
21 Simansky, K J , K A Bourbonais and G P Smith Abdominal vagotomy reduces the dipsogenic but not the anorexic action of systemic serotonin in rats *Neurosci Abstr* **8:** 605, 1982
22 Smith, G P and J Gibbs Postprandial satiety In *Progress in Psychobiology and Physiological Psychology* vol 8, edited by J M Sprague and A N Epstein New York Academic Press, 1979, pp 179–242
23 Smith, G P , C Jerome, B J Cushin, R Eterno and K J Simanski Abdominal vagotomy blocks the satiety effect of cholecystokinin in the rat *Science* **213:** 1036–1037 1981
24 Spano, P F , G Biggio, M Cassu, G L Gessa, S R Bereggi, S Govoni and M Trabucchi Interaction of metergoline with striatal dopamine system *Life Sci* **23:** 2383–2392, 1978
25 Threatte, R M , M J Fregly, T M Connor and D C Kikta L-5-hydroxytryptophan induced drinking in rats Possible mechanisms for induction *Pharmacol Biochem Behav* **14:** 385–391, 1981