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Effects of Chronic Systemic Administration of 5-HT on Food Intake and Body Weight in Rats

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EDWARDS, S. AND R. STEVENS. *Effects of chronic systemic administration of 5-HT on food intake and body weight in rats.* PHARMACOL BIOCHEM BEHAV 47(4) 865–872, 1994.—The effects of chronic peripheral administration of 5-HT on food intake and body weight was investigated. In normal male Wistar rats, normal female Wistars, obese Zucker males, ovariectomised Wistar females, or normal Wistar males free fed a cafeteria diet, suppression of the creeping weight gain typical of control animals is observed. In females, this effect is not dependent on the local hormonal environment, because intact and ovariectomised females showed similar responses to treatment. One sex difference is that the weight suppressive effect in males is accompanied by an anorectic effect, whereas this anorectic effect is absent in females. Thus, although reduced food intake may partially explain the suppression of weight gain in males, in females it must be due to other, perhaps metabolic, effects. It is possible that these metabolic effects may also occur in males, suggesting one possible explanation of why the effect was typically larger in males than females.

5-Hydroxytryptamine Food intake Anorexia Chronic administration Body weight Rats

THE effects of acute treatment with 5-HT on food intake have now been investigated and documented in some depth. It is known that systemically administered 5-HT, which does not cross the blood–brain barrier (7), and must, therefore, be acting peripherally, produces a dose-dependent anorectic effect (2,5,8) that is not caused by sensorimotor or locomotor disruption or the production of a conditioned taste aversion (8). Furthermore, 5-HT produces the full behavioural sequence of satiety and it has been argued that 5-HT must be considered as a putative peripheral satiety signal (3), although it has recently been reported that 5-HT does not provide an adaquate signal for elicing complete satiety in the absence of postingestive cues, as may occur in rats fitted with an open gastric cannula (11). Also, it has been reported that the anorectic effect of 5-HT is attenuated, though not completely blocked, by the specific peripheral 5-HT_2 antagonist xylamidine, suggesting the involvement of both 5-HT_2 and non-5-HT_2 receptor subtypes in its mediation (2). There has, however, been little or no work on the cumulative effects of chronic systemic administration of 5-HT. Thus, an experiment was initiated to explore the effect of long-term 5-HT administration, with particular reference to effects on food intake and body weight.

Both normal males and females were investigated to explore possible sex differences in response to chronic 5-HT treatment, because sex differences in eating behaviour and weight gain are well documented [e.g., see (6,9,12,13)]. Because the use of anorectic drugs in the clinical domain is likely to be restricted to obese rather than normal weight individuals, three different animal models of obesity were included in the experiment, using genetically obese male Zucker *fa/fa* rats, ovariectomised female rats, and normal male rats allowed to free feed on a varied and highly palatable cafeteria-type diet, to test whether chronic 5-HT treatment produces weight loss in fat rats. The investigation of ovariectomised females has the added advantage that it allows for an estimation of the effect of the sex hormonal environment via a comparison between ovariectomised and intact rats.

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METHOD

Subjects

Five groups of rats were included in the experiment. These were normal male Wistars (197–264 g; $n = 20$), normal female Wistars (162–220 g; $n = 28$), obese male Zuckers (386–533 g; $n = 20$); ovariectomised female Wistars (229–333 g; $n = 20$), and normal male Wistars fed a highly palatable cafeteria diet (334–428 g; $n = 20$). All rats were housed singly with water available ad lib. Ambient temperature was kept at 22°C, and the animals were maintained on a 12 L : 12 D cycle (lights on 0730–1930 h).

Drugs

The drug used was 5.0 mg/kg 5-hydroxytryptamine creatinine sulphate (Sigma), delivered subcutaneously in a 0.9% saline vehicle, at a volume of 0.86 ml/kg.

Procedure

The methodology used was a modified form of that used in previous experiments [e.g., see (2,3,5)]. Before the experiment, the rats were habituated to a restricted feeding regimen for 2 weeks (except the cafeteria-fed group, who were allowed to free feed). Chow was presented at 1430 and removed at 1830. The cafeteria group always had chow available ad lib, and, in addition, were presented each day with three of the following foodstuffs: jam doughnuts, chocolate biscuits, chocolate chip cookies, cornflakes, potato crisps, crackers, chocolate drops. Fresh food was presented to the cafeteria group each day before injection, and the food type was changed every 2 days. Food intake for this group was not measured, because spillage of the food types described was difficult to prevent. For all groups, after the habituation period, the baseline period started. The rats were injected with saline at 1330. For the four groups of rats on the restricted feeding regimen, preweighed food was given at 1430, and reweighed at 1530, 1630, 1730, and 1830, when the feeding period ended and the rats were weighed. The cafeteria group continued to freefeed, and were weighed at 1830. The baseline period was continued for 10 days. Following this, the experimental period began. The procedure was the same as for the baseline period, except that half the rats received saline and the other half 5-HT. The experimental period lasted for 30 days, except for the cafeteria group, where the experimental period lasted for 25 days.

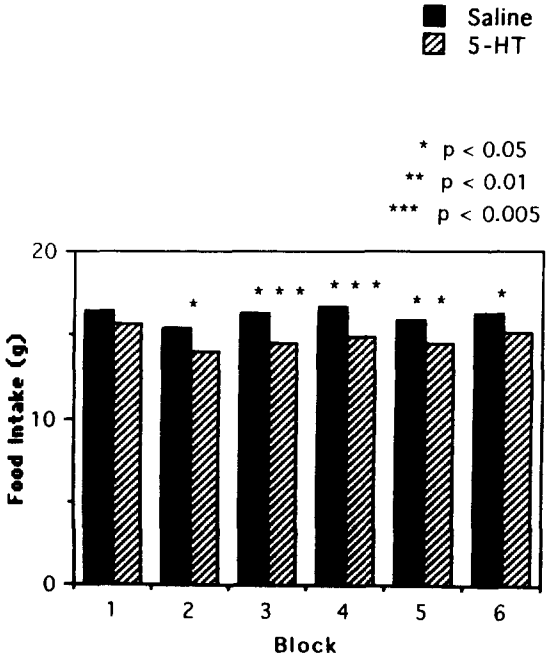

FIG. 1. Mean food intakes across blocks for normal male rats, showing within-block simple main effects between saline- and 5-HT-treated rats.

RESULTS

Normal Males

The 30 treatment days of food intake and body weight data were grouped into six blocks of 5 days and analysed independently using 2 × 6 mixed-design ANOVAs (with treatment and blocks as factors). Figure 1 summarises food intakes; because the analysis showed significant effects of treatment, $F(1, 18) = 8.06, p < 0.05$, and block $F(5, 90) = 16.75, p < 0.0001$, simple main effects were examined for 5-HT vs. saline treatments across blocks. Food intakes did not differ between the two groups in block 1, but the 5-HT group ate significantly less than the saline group in each of the other blocks [block 2: $F(1, 108) = 6.71, p < 0.05$; block 3: $F(1, 108 = 10.91, p < 0.005$; block 4: $F(1, 108) = 10.42, p < 0.005$; block 5: $F(1, 108) = 7.10, p < 0.01$; block 6: $F(1, 108) = 4.74, p < 0.05$]. Pair-wise comparisons, using Tukey's test, were used to further examine the main effect of block (Table 1). It can be seen, from Fig. 1 and Table 1, that food intake varied across blocks for both groups for reasons that are not known. However, as the interaction between treatment and blocks was not significant, it is unlikely that this variation can be attributed to the experimental treatment.

Body weights, expressed as a percentage of mean body weight within a block compared to mean baseline body weight, are shown in Fig. 2. There were significant effects of treatment, $F(1, 18) = 35.95, p < 0.0001$, block, $F(5, 90) = 141.67, p < 0.0001$, and their interaction, $F(5, 90) = 59.40, p < 0.0001$. A simple main effects comparison of 5-HT vs. saline treatments across blocks showed no difference between groups in block 1 ($F < 1$), but the 5-HT group weighed less than the controls in block 2, $F(1, 108) = 12.96, p < 0.001$, block 3, $F(1, 108 = 31.34, p < 0.0001$, block 4, $F(1, 108) = 44.91, p < 0.0001$, block 5, $F(1, 108) = 62.67, p < 0.0001$, and block 6, $F(1, 108) = 80.44, p < 0.0001$. The significant simple main effects of blocks for the saline group, $F(5, 90) = 189.20, p < 0.0001$, and for the 5-HT group, $F(5, 90) = 10.82, p < 0.0001$, were investigated using Tukey's test to make pair-wise comparisons between blocks within each treatment group. For the 5-HT-treated rats, body weights within the first four blocks did not differ, but block 5 weights were significantly greater than weights in blocks 1-3 ($p < 0.05$), and block 6 weights were significantly greater than blocks 1-4 ($p < 0.05$ or better). For rats in the control condition, there were significant differences between all blocks (at least $p < 0.01$ in each case).

Normal Females

Analysis of data on food intake and body weight was carried out as above using 2 × 6 mixed design ANOVAs (with

TABLE 1

SUMMARY TABLE OF PAIR-WISE COMPARISONS FOR FOOD INTAKE BETWEEN BLOCKS (TUKEY'S TEST) IN NORMAL MALE RATS

	Block 2	Block 5	Block 3	Block 6	Block 4	Block 1
Block 2	X	–	s	s	s	s
Block 5	–	X	–	s	s	s
Block 3	s	–	X	–	–	s
Block 6	s	–	–	X	–	–
Block 4	s	s	–	–	X	–
Block 1	s	s	s	–	–	X

Blocks are arranged in ascending order of size of intake across rows and columns. s = Significant difference; upper triangle $p < 0.05$; lower triangle $p < 0.01$.

treatment and blocks as factors). Mean food intakes are illustrated in Fig. 3. Although there was a significant effect of block, $F(5, 130) = 5.70, p < 0.0001$, treatment had no direct effect ($F < 1$) or interactional effect ($F < 1$). Comparisons between pairs of blocks were made using Tukey's test (Table 2). As was true of male rats, there was unsystematic variation across blocks (Fig. 3 and Table 2).

Analysis of food intakes between groups on day 1 of the treatment period was carried out (Table 3), since it has previously been shown that the anorectic effect of 5-HT in males is produced during the first hour of feeding with no evidence of rebound feeding during the latter 3 h of feeding (2). There was a significant main effect of time, $F(3, 78) = 24.47, p < 0.0001$, but no significant main effect of treatment, $F(1, 26) < 1, p > 0.10$. However, the interaction effect was significant, $F(3, 78) = 5.64, p < 0.005$. Analysis of simple main effects of treatment for each hour revealed that food intake was significantly lower in hour 1 for the 5-HT-treated rats, $F(1, 104) = 14.90, p < 0.001$. There were no significant differences in food intake for any other hour. Thus, unlike the case for males, acute 5-HT administration does not appear to elicit a cumulative anorectic effect in females over the 4-h feeding period, as the initial anorectic effect of the first hour is overcome by greater, though individually nonsignificant, food intakes during the latter 3 h.

Body weights are shown in Fig. 4. There were significant effects of treatment, $F(1, 26) = 10.34, p < 0.005$, and block, $F(5, 130) = 9.70, p < 0.0001$, but no significant interaction effect, $F(5, 130) = 2.10, p > 0.05$. There were no differences in body weights between the two groups in block 1, but the 5-HT group had gained less weight than the saline group by block 2, $F(1, 156) = 7.86, p < 0.01$, block 3, $F(1, 156 = 13.52, p < 0.0005$, block 4, $F(1, 156) = 7.90, p < 0.01$, block 5 $F(1, 156) = 10.12, p < 0.005$, and block 6, $F(1, 156) = 9.40, p < 0.005$.

To better understand the effect of blocks, pair-wise comparisons were made using Tukey's test (Table 4). As can be seen from Fig. 3, body weights fell during blocks 3 and 4, after showing an initial gain, and then recovered during blocks 5 and 6. Body weights in block 4 were significantly lower than that in blocks 2, 5, and 6 ($p < 0.01$). Furthermore, body weights in blocks 1 and 3 were significantly lower than in

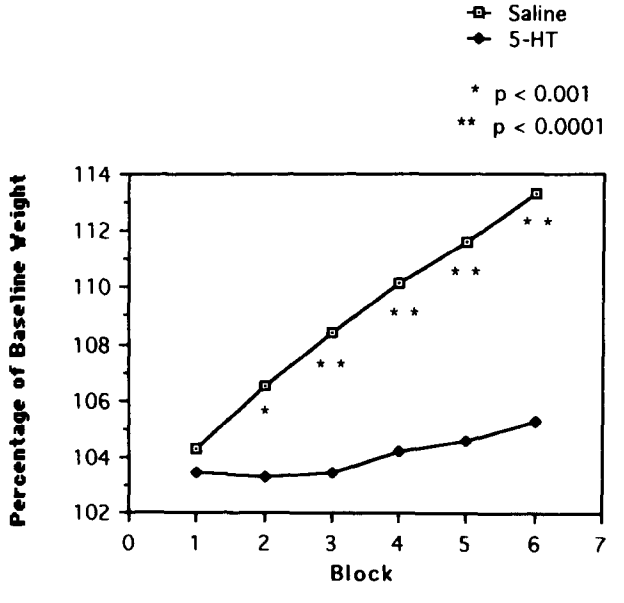

FIG. 2. Body weights across blocks for normal male rats, showing within-block simple main effects between saline- and 5-HT-treated rats.

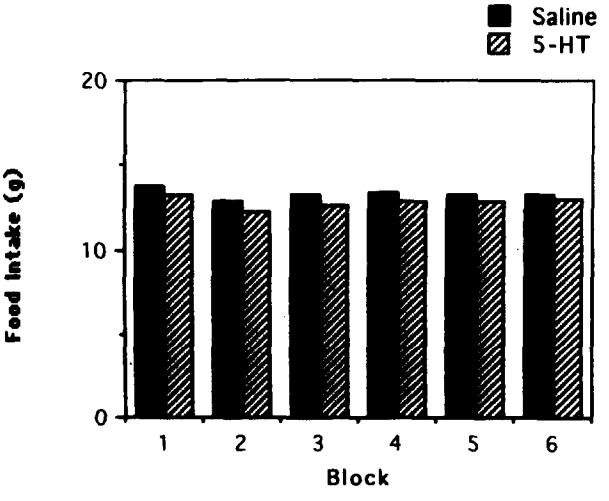

FIG. 3. Mean food intakes across blocks for normal female rats.

TABLE 2

SUMMARY TABLE OF PAIR-WISE COMPARISONS FOR FOOD INTAKE BETWEEN BLOCKS (TUKEY'S TEST) IN NORMAL FEMALE RATS

	Block 2	Block 3	Block 5	Block 4	Block 6	Block 1
Block 2	X	–	–	s	s	s
Block 3	–	X	–	–	–	s
Block 5	–	–	X	–	–	–
Block 4	–	–	–	X	–	–
Block 6	–	–	–	–	X	–
Block 1	s	–	–	–	–	X

Blocks are arranged in ascending order of size of intake across rows and columns. s = Significant difference; upper triangle $p < 0.05$; lower triangle $p < 0.01$.

block 5 ($p < 0.05$). There is no obvious reason for these haphazard variations.

Obese Males

One rat in the control group died, so $n = 9$ for the control group and $n = 10$ for the drug group. Otherwise, analysis of data was carried out as above. Mean food intakes are shown in Fig. 5. There was a significant effect of treatment, $F(1, 17) = 50.85$, $p < 0.0001$, but not of block, $F(5, 85) = 2.26$, $p > 0.05$, nor did they interact, $F(5, 85) = 2.21$, $p > 0.05$. The 5-HT-treated rats ate less than the control animals in each of the blocks, $F(1, 102) > 20, p < 0.0001$ in all six cases).

In the analysis of body weights, which are summarised in Fig. 6, the effects of treatment, $F(1, 17) = 73.51$, $p < 0.0001$, block, $F(5, 85) = 113.00$, $p < 0.0001$, and their interaction, $F(5, 85) = 67.19$, $p < 0.0001$, were significant. The 5-HT group gained less weight than controls in each of the blocks [block 1, $F(1, 102) = 8.51$, $p < 0.005$, block 2, $F(1, 102) = 23.73, p < 0.0001$, block 3, $F(1, 102) = 50.35$, $p < 0.0001$, block 4, $F(1, 102) = 76.10$, $p < 0.0001$, block 5, $F(1, 102) = 121.07$, $p < 0.0001$, and block 6, $F(1, 102) = 153.70, p < 0.0001$]. Also significant were the simple main effects across blocks for the saline group, $F(5, 85) = 167.37$, $p < 0.0001$, and the 5-HT group, $F(5, 85) = 3.75$, $p < 0.005$. These were investigated further by comparing blocks within a treatment condition using Tukey's test. For the saline group, all blocks differed significantly from each other (at least $p < 0.01$ in all cases except for the comparisons of block 3 vs. block 4, and block 5 vs. block 6, where $p < 0.05$). But for the 5-HT-treated group, the only significant differences were between block 1 and other blocks (at least $p < 0.05$ in all cases, except block 1 vs. block 2, where the difference was not significant).

Ovariectomised Females

Analysis of data was carried out as above. Figure 7 summarises food intakes for which there was no effect of treatment ($F < 1$), although there was for block, $F(5, 90) = 6.74$, $p < 0.0001$. In pair-wise comparisons of blocks, food intakes in blocks 3 and 4 were significantly lower than those in the other blocks ($p < 0.01$). No other differences were significant.

Analysis of food intakes between groups on day 1 of the treatment period was carried out (Table 5). There was a significant main effect of time, $F(3, 54) = 9.56$, $p < 0.0001$, but no significant main effect of treatment, $F(1, 18) < 1$, $p > 0.10$, or interaction effect, $F(3, 54) < 1$, $p > 0.10$, was found. Analysis of simple main effects of treatment for each hour was carried out for comparison with the results for normal females above, revealing no significant differences in food intake for any hour. Thus, as was the case for normal females, and unlike the case for males, acute 5-HT administration does not appear to elicit a cumulative anorectic effect in ovariectomised females over the 4-h feeding period. However, normal and ovariectomised females differed in response to acute 5-HT treatment in that the normal, but not ovariectomised, females displayed an anorectic effect in the first hour, even though this was later overcome by rebound effects so that no cumulative anorexia was found.

Mean weights are shown in Fig. 8. Both the effects of treatment, $F(1, 18) = 11.89, p < 0.005$, and blocks, $F(5, 90) = 8.78$, $p < 0.0001$, were significant, as was the interaction between them, $F(5, 90) = 3.03$, $p < 0.05$. The gain in body weight was less in the 5-HT-treated animals than in the controls for block 2, $F(1, 108) = 5.04$, $p < 0.05$, block 4, $F(1, 108) = 6.00$, $p < 0.05$, block 5, $F(1, 108) = 9.42$, $p < 0.005$, and block 6, $F(1, 108) = 23.65$, $p < 0.0001$. There was no simple main effect of blocks for 5-HT-treated

TABLE 3

MEAN FOOD INTAKES FOR DAY 1 IN NORMAL FEMALE RATS

	Hours Post Food Presentation				
Drug	1	2	3	4	Total Intake
Saline	6.07	1.93	2.71	3.07	13.78
5-HT	4.14*	2.43	3.36	3.14	13.07

*$p < 0.001$.

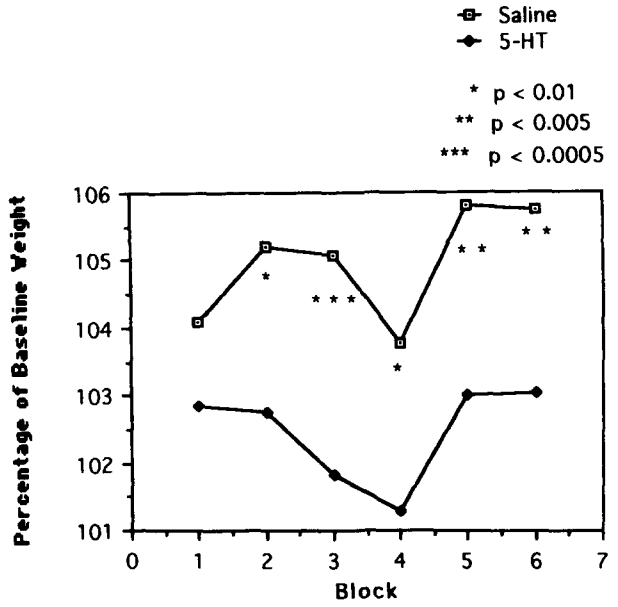

FIG. 4. Body weights across blocks for normal female rats, showing within-block simple main effects between saline- and 5-HT-treated rats.

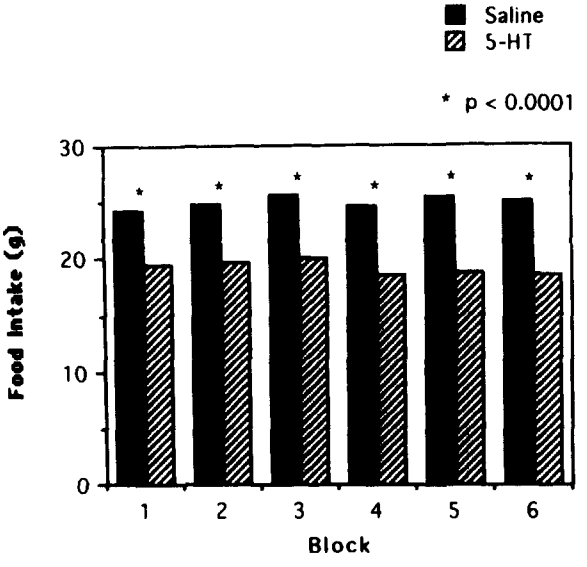

FIG. 5. Mean food intake across blocks for obese male rats, showing within-block simple main effects between saline- and 5-HT-treated rats.

rats ($F < 1$) but there was for the saline group, $F(5, 90) = 11.00$, $p < 0.0001$, where body weights in block 6 were significantly higher than those in blocks 1-3 ($p < 0.01$) and block 4 ($p < 0.05$).

Cafeteria-Fed Males

During the experiment three rats in the drug group died, which left 10 control rats and 7 drug animals. The 25 treatment days of body weight data was grouped in five blocks of 5 days each and analysed using a 2 × 5 mixed design ANOVA (with treatment and blocks as factors). Mean weights are shown in Fig. 9. The effects of treatment, $F(1, 15) = 17.39$, $p < 0.001$, and block, $F(4, 60) = 30.05$, $p < 0.0001$, were significant, as was their interaction, $F(4, 60) = 13.17$, $p < 0.0001$. According to simple main effects analysis, weight changes did not differ significantly between the two groups in block 1 ($F < 1$), but the 5-HT-treated rats gained less weight than the control rats in block 2, $F(1, 75) = 5.08$, $p < 0.05$, block 3, $F(1, 75) = 14.77$, $p < 0.0005$, block 4, $F(1, 75) = 23.19$, $p < 0.0001$, and block 5, $F(1, 75) = 35.34$, $p < 0.0001$. There was also a significant simple main effect of blocks for the saline group, $F(4, 60) = 49.82$, $p < 0.0001$, but not for the 5-HT group, $F(4, 60) = 2.38$, $p > 0.05$. For the saline group, body weights in block 1 were significantly lower than those in all other blocks ($p < 0.01$ in all cases), and body weights in block 5 were significantly higher than those in all other blocks ($p < 0.01$ in all cases).

DISCUSSION

For the normal male rats, it is clear that although both groups of rats grew bigger, the saline-treated rats grew far more than those treated with 5-HT. After 30 days of treatment, the 5-HT-treated rats were 5.3% above their baseline weights compared to 13.3% for the control rats. This difference may be explained by the disparity in food intakes. Except for block 1, the 5-HT-treated rats ate consistently less than the control rats. Interestingly, there was considerable variation in food intake across blocks for both groups of rats. Although

TABLE 4

SUMMARY TABLE OF PAIR-WISE COMPARISONS FOR BODY WEIGHT BETWEEN BLOCKS (TUKEY'S TEST) IN NORMAL FEMALE RATS

	Block 4	Block 3	Block 1	Block 2	Block 6	Block 5
Block 4	X	–	–	s	s	s
Block 3	–	X	–	–	–	s
Block 1	–	–	X	–	–	s
Block 2	s	–	–	X	–	–
Block 6	s	–	–	–	X	–
Block 5	s	–	–	–	–	X

Blocks are arranged in ascending order of size of intake across rows and columns. s = Significant difference; upper triangle $p < 0.05$; lower triangle $p < 0.01$.

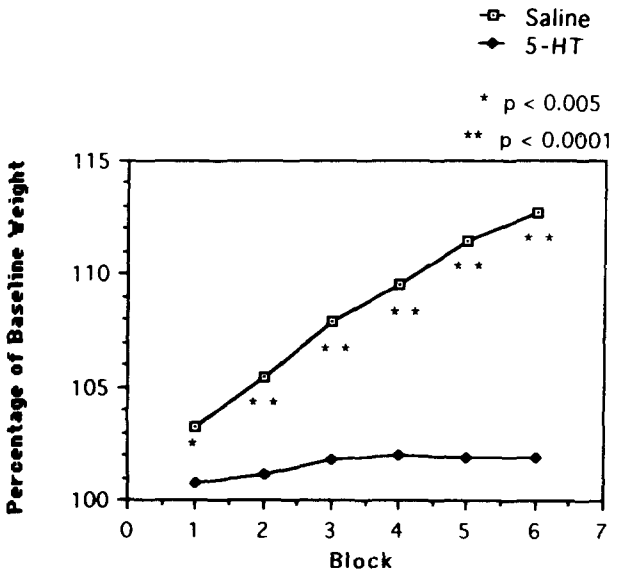

FIG. 6. Mean body weight across blocks for obese male rats, showing within-block simple main effects between saline and 5-HT-treated rats.

the reason for this is unclear, the pattern of variation was the same for both groups so it can not be attributed to the experimental treatment.

It should be noted that chronic 5-HT-treatment suppressed, without entirely abolishing, the creeping weight gain of normal rats in laboratory conditions, rather than inducing weight loss in the rats. The body weights of rats in the 5-HT condition increased in the second half of the experiment; this could represent a rebound or tolerance effect, or the dose of 5-HT used was insufficient to maintain baseline body weight over long periods. The failure to induce weight loss may be because of several factors. First, a 5-HT-induced anorectic effect may never create a negative energy balance at doses that do not provoke nonspecific behavioural effects. Second, there may be resistance to a degree of weight loss which would leave the rats underweight. If this is the case, weight loss may be more likely to occur in genetically obese Zucker rats which could lose more weight without risk of becoming underweight (see below).

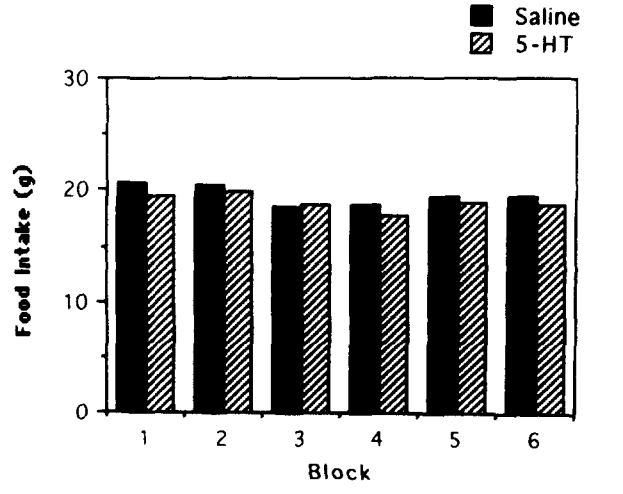

FIG. 7. Mean food intake across blocks for ovariectomised female rats.

For the normal females, the 5-HT-treated rats also gained significantly less weight than the saline rats; thus, by block 6, the 5-HT-treated rats were 3.0% above their baseline weights, compared to 5.7% for the control group. However, this difference in growth cannot be attributed to differences in food intake because there was none. Therefore, the weight depression effect of chronically administered 5-HT in females is differentiated from that in males. A second sex difference is the size of the weight variations. Female control rats gained only 5.7% of baseline weight compared to 13.3% in males, and 5-HT-treated females gained only 3.0% compared to 5.3% in males.

The mechanisms underlying these sex differences is unknown. However, the effect in males seems related to a 5-HT-mediated anorectic effect, since suppression of weight gain was accompanied by reduced food intake. In females, because no anorectic effect was observed, the effect must be mediated by other means such as metabolic changes, or events associated with the oestrus cycle. These possibilities are discussed further below.

For the genetically obese Zucker males, treatment with 5-HT considerably suppressed food intake throughout the treatment period resulting in these rats failing to grow as much as the control group. The obese controls gained 12.7% over baseline weights, compared to only 1.9% for the drug-treated group. The overall pattern of results here, then, is similar to that of the normal males, but the difference in weight gain between control and drug-treated groups is larger in the case of genetically obese Zuckers (10.8%) than normal Wistars (8%).

Once again, the drug-treated rats did not lose weight, they instead showed suppression of the creeping weight gain characteristic of the control group. Although it seems unlikely that resistance to being underweight could account for the failure of 5-HT treatment to induce weight loss, the reasons for obesity in Zucker *fa/fa* rats need to be considered. Their obesity is thought to be associated with metabolic and behavioural alterations including hypercholesterolaemia and hyperlipaemia (1,14), hyperphagia, and underactivity (4). If an alteration of a putative body weight set point is involved, then the failure of the Zucker rat to lose weight under chronic 5-HT treatment may be because a set point is being protected, even though it may be abnormally high.

For ovariectomised females, once again, chronic 5-HT administration prevented the creeping weight gain characteristic of the control group. The 5-HT-treated rats were only 1.7% above their baseline weights by the end of the experiment, compared to 7.8% for the control group. However, as was true of normal females, this cannot be attributed to an anorectic effect because none occurred and, therefore, the lack of any 5-HT-induced anorectic effect in females is not dependant on ovarian hormones.

As with normal male Wistars and genetically obese male Zucker rats maintained on a standard chow diet, the creeping gain in body weight characteristic of rats treated with saline was considerably suppressed in rats chronically treated with 5-HT even though they were free feeding on a highly palatable diet. Whereas control rats gained 8.5% of baseline weight, drug-treated rats gained only 1.8%. For comparison, for normal males, the saline-treated males had gained 11.6% of base-

TABLE 5

MEAN FOOD INTAKES FOR DAY 1 IN OVARIECTOMIZED FEMALE RATS

Drug	Hours Post Food Presentation 1	2	3	4	Total Intake
Saline	8.70	2.80	3.70	5.40	20.60
5-HT	6.90	3.80	3.00	3.90	17.60

line weight after 25 days of treatment, whereas 5-HT treated rats had gained 4.6%. It surprised us that the saline-treated animals eating highly palatable foods, as well as chow, failed to gain weight more rapidly than the controls in Experiment 1. Although we failed to produce any sign of dietary-induced obesity, the effects of 5-HT on body weight in this experiment are of particular importance. The rats were allowed to feed freely throughout the 24-h cycle, suggesting that the 5-HT-induced weight suppressive effect is not dependent on restricted access to food.

Thus, from this experiment, several substantial findings emerge. First, there are sex differences in the reaction to chronic systemic 5-HT administration. In the control condition, both males and females experience a creeping weight gain, and this effect is greatly attenuated by the chronic administration of 5-HT. However, whereas males show a considerable 5-HT-induced anorectic effect which could at least partially account for this failure to accumulate body weight, no such anorectic effect is detectable in females, although the failure to accumulate weight is still evident, albeit at a lower level than in males. It would appear, therefore, that the weight suppression effect in females may be dependent on changes in metabolism. Indeed, a metabolic effect probably also occurs in males, and because this would be concomitant with the anorectic effect of 5-HT, the greater effect in males would be accounted for. A further possibility is that the metabolic effect in females is so large that it triggers a compensatory increase in food intake, thus effectively masking the anorectic effect. These different mechanisms may be mediated via systems influenced by different 5-HT receptor subtypes. Furthermore, whatever aspect (or aspects) of the metabolism of the female may be involved in the mediation of this effect, it does not depend on ovarian hormones, because there was an effect in both ovariectomised and intact females. Although the effect of 5-HT may be slightly more pronounced in ovariectomised females than in intact females (see Figs. 4 and 8), the difference between the two sets of animals was not large. Thus, ovarian hormones in adult females are not responsible for the difference in male and female reaction to chronic 5-HT treatment. However, it is possible that sex hormones acting during a critical developmental period are implicated in whatever metabolic factor or factors are involved. The metabolic factors in question remain unknown, but one possibility is serotonergic involvement in diet-induced thermogenesis, known to be important in energy balance (10), implying the involvement of brown adipose tissue.

Second, a common feature of chronic 5.0 mg/kg 5-HT treatment, in both sexes, is that it does not produce weight

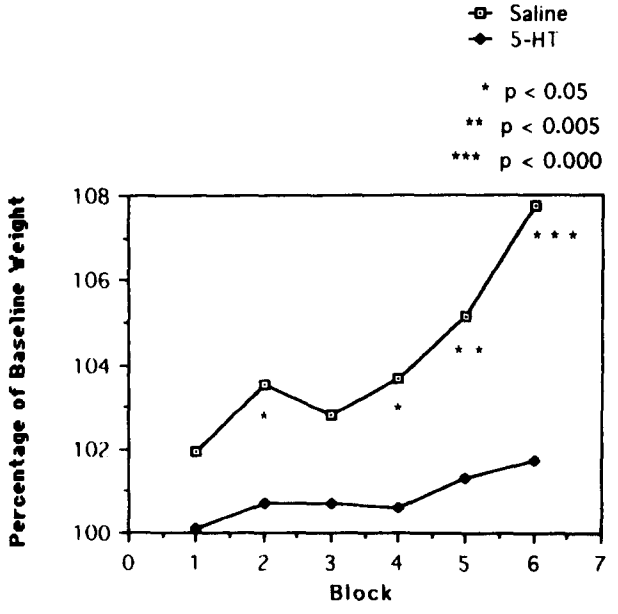

FIG. 8. Mean body weights across blocks for ovariectomised female rats, showing within-block simple main effects between saline- and 5-HT-treated rats.

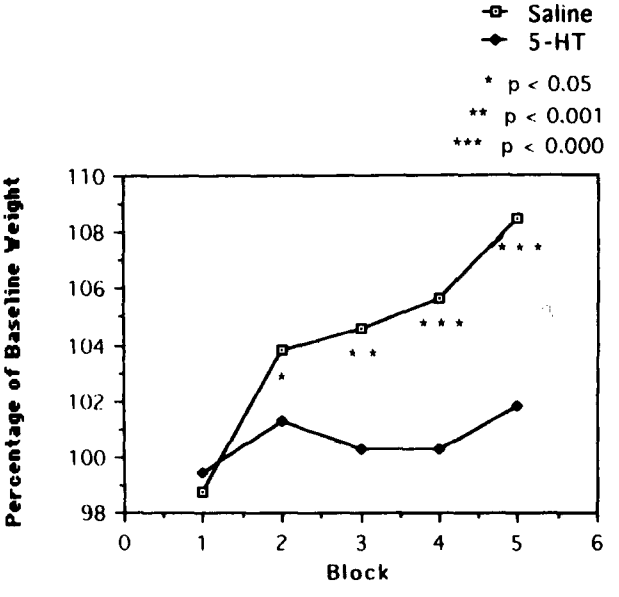

FIG. 9. Mean body weight across blocks for cafeteria diet males, showing within-block simple main effects between saline- and 5-HT-treated rats.

loss, but rather suppresses the creeping weight gain found in all sets of rats in the control condition. Once again, however, the roles of different 5-HT receptor subtypes remain unclear.

Third, no evidence has been found here for any rebound or tolerance effects to the chronic systemic administration of 5-HT. Although the creeping weight increase in normal males was not entirely eliminated, it is unclear whether this can be attributed to rebound effects. However, the body weight data do not show an initial weight loss, or even a complete suppression of weight gain, followed by weight gain; instead, weight is gained slowly throughout the treatment period. Of course, administration of 5-HT for longer than 30 days may provide evidence for a greatly delayed rebound effect.

In conclusion, when 5-HT is administered systemically to rats, whether normal male Wistars, normal female Wistars, obese Zucker *fa/fa* males, ovariectomised Wistar females, or normal Wistar males free fed on a cafeteria diet, a suppression of the creeping weight gain typical of saline-treated animals is observed. In females, this weight suppressive effect is not dependent on the local hormonal environment as determined by the oestrus cycle, because intact and ovariectomised females exhibited similar responses to treatment. However, there is a major sex difference, such that the weight suppressive effect in males is accompanied by a considerable anorectic effect, whereas this anorectic effect is absent in females. Thus, whereas reduced food intake may explain the suppression of weight gain in males, the phenomenon in females must be because of other effects, perhaps metabolic in nature. It is possible that these metabolic effects may also occur in males, suggesting one possible explanation of why the effect was typically larger in males than females. However, what these metabolic effects are is unknown, although a role for 5-HT in diet-induced thermogenesis in brown adipose tissue must be a possibility.

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