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Effects of Repeated Administration of Serotonergic Agonists on Diet Selection and Body Weight in Rats

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LUO, S. AND E. T. S. LI. *Effects of repeated administration of serotonergic agonists on diet selection and body weight in rats.* PHARMACOL BIOCHEM BEHAV 38(3) 495–500, 1991.—Food intake, diet selection and body weight gain were examined in three separate experiments in which rats received saline or one of three serotonergic agonists, dexfenfluramine, RU 24969 and fluoxetine. In all experiments, food was available only in the dark period during which time rats were given simultaneous access to two isoenergetic diets which differed in their protein and carbohydrate content. After habituation to this feeding paradigm and intraperitoneal injections, rats were assigned to control or drug group. Saline or a serotonergic agonist was given to the same rat once daily, 15 min prior to feeding, for six consecutive days. All three agonists (1.5 mg/kg for dexfenfluramine and RU 24969; 3 mg/kg for fluoxetine) caused immediate (first two h of feeding) hypophagia which was accounted for by the selective suppression in intake of the high-carbohydrate-low-protein diet. This selective shift in diet choice was sustained upon repeated exposure. Although the effects of these agonists on daily (12-h) feeding was less pronounced, appetite suppression was due entirely to reduced intake of the high-carbohydrate-low-protein diet. Of the three agonists tested, partial tolerance was observed only after dexfenfluramine. Nevertheless, all three agonists caused comparable declines in weight gain. These results suggest that repeated administration of serotonergic agonists has sustained impacts on food intake, diet choice and weight gain.

5-HT agonists Dexfenfluramine RU 24969 Fluoxetine Chronic Feeding Diet selection Body weight

BASED on pharmacological manipulations, a role for serotonin (5-HT) in the control of food intake has been suggested (4). Many agents which suppress serotonergic neurotransmission are orexigenic (2,9). Conversely, agents which enhance serotonergic neurotransmission are known to be anorexic (5). In addition to affecting food intake, we and others have reported specific changes in food choice after self-selecting rats are treated with selective 5-HT agents. For instance, increases in intake after 8-hydroxy-2-(di-n-propylamino)-tetralin or buspirone, which slow 5-HT turnover, are entirely attributable to increases in intake of diets high in carbohydrate content (22). Such a change in ingestive behavior is the mirror image of that seen in rats with enhanced 5-HT neurotransmission. Tryptophan (21,24), 5-HT (16), fenfluramine (23, 29, 30), fluoxetine (23,29), CGS 10686B (15) and recently RU 24969 (23) have been shown to reduce food intake and selectively reduce the intake of diets high in carbohydrate content. These data support the notion that 5-HT plays a role in diet selection (20).

To further explore the involvement of 5-HT in diet selection, the present study examined food intake, diet selection pattern and body weight change in rats given 5-HT agonists once daily for six consecutive days. Two indirect (dexfenfluramine and fluoxetine) and one direct (RU 24969) agonists were tested. The selection of these agonists was based on three factors. First, after acute administration, all three drugs cause anorexia and selective suppression in intake of high-carbohydrate diets (23). Second, anorectic tolerance has been reported after repeated administration of dexfenfluramine (26) but not fluoxetine (31). Third, little information is available on the chronic effect of RU 24969.

METHOD

Animals

In all experiments, young male Wistar rats (Charles River, Montreal, P.Q.), 140–150 g, were housed individually in hanging stainless steel, wire mesh cages in an environmental chamber, with an ambient temperature of 22 ± 1°C, and 12-hour light-dark cycle (lights on at 0700 h). Water was provided ad lib, but food was available only in the dark period (1900–0700 h) (18).

Diets

Rats were given simultaneous access to two isoenergetic diets (4.25 kcal or 17.78 kJ per gram) which differed in their protein (P) and carbohydrate (C) content. The proportions of other ingre-

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TABLE 1

THE CHRONIC EFFECT OF DEXFENFLURAMINE ON FOOD INTAKE AND SELECTION

	Day 1	2	3	4	5	6
0–1 h						
			Total Food			
SAL	1.9 ± 0.3	2.3 ± 0.3	2.8 ± 0.3	3.0 ± 0.3	2.9 ± 0.3	2.3 ± 0.2
DFF	0.8 ± 0.1*	1.9 ± 0.2	2.1 ± 0.2	1.9 ± 0.2*	2.2 ± 0.2*	1.6 ± 0.3
			HC-LP			
SAL	1.0 ± 0.2	1.7 ± 0.3	1.6 ± 0.2	1.9 ± 0.3	2.1 ± 0.3	1.1 ± 0.2
DFF	0.2 ± 0.1*	0.9 ± 0.1*	0.7 ± 0.2*	0.7 ± 0.2*	1.1 ± 0.2*	0.6 ± 0.2
			LC-HP			
SAL	0.9 ± 0.3	0.6 ± 0.2	1.2 ± 0.3	1.1 ± 0.3	0.8 ± 0.2	1.2 ± 0.2
DFF	0.6 ± 0.1	1.0 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
0–2 h						
			Total Food			
SAL	4.8 ± 0.5	4.1 ± 0.3	5.4 ± 0.4	5.1 ± 0.6	5.2 ± 0.4	4.8 ± 0.5
DFF	1.8 ± 0.2*	2.9 ± 0.3*	2.6 ± 0.3*	2.9 ± 0.4*	3.3 ± 0.4*	3.1 ± 0.3*
			HC-LP			
SAL	2.8 ± 0.4	2.7 ± 0.4	3.6 ± 0.5	3.2 ± 0.4	3.5 ± 0.4	2.9 ± 0.4
DFF	0.6 ± 0.1*	1.5 ± 0.3*	0.9 ± 0.2*	1.3 ± 0.3*	1.4 ± 0.3*	1.3 ± 0.3*
			LC-HP			
SAL	2.0 ± 0.5	1.4 ± 0.4	1.8 ± 0.5	1.9 ± 0.5	1.6 ± 0.3	1.8 ± 0.3
DFF	1.1 ± 0.2	1.4 ± 0.3	1.7 ± 0.2	1.7 ± 0.3	1.8 ± 0.4	1.8 ± 0.3
0–12 h						
			Total Food			
SAL	24.7 ± 0.7	24.6 ± 0.5	26.3 ± 0.6	26.4 ± 0.4	26.5 ± 0.7	26.4 ± 0.7
DFF	21.5 ± 0.5*	23.8 ± 0.8	24.9 ± 0.5	25.2 ± 0.7	24.9 ± 0.7	25.1 ± 0.5
			HC-LP			
SAL	14.8 ± 1.4	16.8 ± 1.7	16.5 ± 1.5	16.0 ± 1.4	17.5 ± 1.2	16.7 ± 1.2
DFF	11.6 ± 1.5	14.0 ± 1.3	14.4 ± 1.4	14.1 ± 1.3	14.5 ± 1.0	14.9 ± 1.2
			LC-HP			
SAL	9.8 ± 1.4	7.8 ± 1.5	9.8 ± 1.4	10.4 ± 1.4	8.9 ± 1.2	9.6 ± 1.1
DFF	9.8 ± 1.3	9.8 ± 1.2	10.6 ± 1.3	11.1 ± 1.2	10.3 ± 1.3	10.1 ± 1.1

Dexfenfluramine (1.5 mg/kg, IP) was injected daily 15 min before food access, cumulative intake in grams.

Mean ± SEM, n≥12.

*$p<0.05$ vs. saline on the same day (ANOVA).

dients (w/w) such as corn oil (10%), mineral mixture (4%, TD-67233) and vitamin mixture (2.5%, TD-67231) were similar in both diets (19). The desired proportion of C and P in a diet was obtained by adjusting the cornstarch and casein content. In the first two experiments (dexfenfluramine and RU 24969), the high-C-low-P (HC-LP) diet contained 78.5% C and 5% P and the low-C-high-P (LC-HP) diet contained 38.5% C and 45% P. To ensure that changes in food choice was not limited to a specific pair of diets, two different diets were used in the third experiment (fluoxetine). In the latter experiment, the HC-LP diet now contained 73.5% C as cornstarch and 10% P as casein, whereas the LC-HP diet now contained 23.5% C and 60% P.

General Procedures

Upon arrival, rats were weighed and placed on experimental diets. The positions of the food cups were alternated daily to control for a possible position preference. Food was presented at 1900 h and removed at 0700 h the following morning, corresponding to the beginning and the end of the dark period, respectively. Rats were allowed to adapt to this feeding schedule and self-selection paradigm for at least two weeks prior to any behavioral testing. During this period all rats were given two or more intraperitoneal injections (0.9% NaCl, 1 ml/kg body weight). This habituation procedure was performed until food intake during the first hour after saline injection was not different from no treatment. Since it would be difficult to detect a reduction in food intake if rats ate little following food presentation, rats that consistently consumed less than 1 g (total food intake) during the first hour (i.e., 1900–2000 h) on baseline and saline treatment days were excluded from the experiments.

TABLE 2

THE CHRONIC EFFECT OF RU 24969 ON FOOD INTAKE AND SELECTION

	Day 1	2	3	4	5	6
0–1 h						
			Total Food			
SAL	2.7 ± 0.3	2.9 ± 0.2	2.8 ± 0.3	2.4 ± 0.3	3.2 ± 0.3	2.9 ± 0.2
RU	1.8 ± 0.3*	1.8 ± 0.3*	1.7 ± 0.2*	1.4 ± 0.3*	2.1 ± 0.3*	1.8 ± 0.3*
			HC-LP			
SAL	1.5 ± 0.4	2.0 ± 0.2	1.5 ± 0.3	1.3 ± 0.4	2.0 ± 0.3	1.7 ± 0.5
RU	0.8 ± 0.2	0.9 ± 0.2*	0.8 ± 0.1*	0.4 ± 0.1*	1.0 ± 0.2*	0.9 ± 0.2
			LC-HP			
SAL	1.2 ± 0.2	0.9 ± 0.2	1.3 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	1.2 ± 0.5
RU	1.0 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.1 ± 0.2	0.9 ± 0.2
0–2 h						
			Total Food			
SAL	4.2 ± 0.4	4.5 ± 0.4	5.6 ± 0.6	4.2 ± 0.9	5.2 ± 0.5	4.6 ± 0.2
RU	2.9 ± 0.4	2.9 ± 0.6	3.3 ± 0.6*	1.9 ± 0.4*	3.3 ± 0.6*	3.1 ± 0.6
			HC-LP			
SAL	2.1 ± 0.4	2.9 ± 0.4	2.7 ± 0.5	2.1 ± 0.6	3.3 ± 0.4	2.7 ± 0.7
RU	1.4 ± 0.4	1.4 ± 0.3*	1.7 ± 0.5	1.2 ± 0.4	2.0 ± 0.4*	1.8 ± 0.4
			LC-HP			
SAL	2.1 ± 0.4	1.6 ± 0.4	2.9 ± 0.9	2.1 ± 0.5	1.9 ± 0.5	1.9 ± 0.5
RU	1.5 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	0.7 ± 0.1*	1.3 ± 0.3	1.3 ± 0.4
0–12 h						
			Total Food			
SAL	23.7 ± 0.8	23.5 ± 1.2	25.5 ± 1.1	23.4 ± 1.0	24.1 ± 0.6	25.5 ± 0.7
DFF	20.4 ± 0.8*	21.1 ± 1.3	20.7 ± 1.8	20.9 ± 0.9	23.9 ± 0.7	23.9 ± 0.9
			HC-LP			
SAL	13.6 ± 1.5	14.0 ± 1.7	14.3 ± 2.0	14.3 ± 1.8	13.7 ± 1.3	16.4 ± 1.8
DFF	9.4 ± 1.8	11.0 ± 1.3	9.7 ± 1.6	9.9 ± 1.7	11.4 ± 0.9	11.9 ± 0.5*
			LC-HP			
SAL	10.1 ± 1.3	9.5 ± 1.5	11.2 ± 1.9	9.2 ± 1.4	10.4 ± 1.1	9.1 ± 1.6
DFF	11.0 ± 1.5	10.2 ± 0.9	11.0 ± 1.2	11.0 ± 1.1	12.5 ± 0.8	12.0 ± 1.2

RU 24969 (1.5 mg/kg, IP) was injected daily 15 min before food access, cumulative intake in grams. Mean ± SEM, n = 8.

*$p<0.05$ vs. saline on the same day (ANOVA).

Design

Three separate experiments were performed. In each experiment naive rats were used for studying food choice after repeated administration of a 5-HT agonist. At the onset of the test, rats were weighed and baseline food intakes were measured. In each experiment, rats were then assigned to one of two groups in such a way so that mean body weight, baseline food intake and selection pattern were matched. Dexfenfluramine (DFF: 1.5 mg/kg), RU 24969 (RU: 1.5 mg/kg) and fluoxetine (FLX: 3.0 mg/kg) were dissolved in saline and were given intraperitoneally (1 ml per kg) once daily at 1845 h for six consecutive days to one group. The other group received saline and served as a control. The dose selected for each of the agonists was based on results of acute experiments (23). Subsequent food intake corrected for spillage, was measured 1, 2 and 12 h later. During the treatment period, body weight was recorded every other day.

Statistics

Data on intake of total food and that of individual diets are given as mean ± SEM. For each experiment, a general linear program of SAS (SAS Institute Inc., Cary, NC) was used to perform two-way analysis of variance (within subject: day effect and between subjects: drug effect) with repeated measures on intake at 1, 2 and 12 h after drug administration. Daily, day to day and overall (6 days) effects of drugs were assessed. Body weight data were analyzed by Student's *t*-test. A probability level of 5% was

TABLE 3

THE CHRONIC EFFECT OF FLUOXETINE ON FOOD INTAKE AND SELECTION

	Day 1	2	3	4	5	6
0–1 h						
	Total Food					
SAL	5.0 ± 0.6	5.0 ± 0.6	4.8 ± 0.7	5.7 ± 0.7	5.5 ± 0.6	5.6 ± 0.7
FLX	3.3 ± 0.2*	4.1 ± 0.2	2.9 ± 0.4*	3.5 ± 0.5*	3.8 ± 0.6	4.1 ± 0.4
	HC-LP					
SAL	3.9 ± 0.7	3.7 ± 0.7	4.3 ± 0.8	4.6 ± 0.7	4.2 ± 0.6	4.5 ± 0.7
FLX	2.3 ± 0.2*	2.9 ± 0.2	2.0 ± 0.3*	2.3 ± 0.4*	3.1 ± 0.5	2.8 ± 0.5
	LC-HP					
SAL	1.1 ± 0.3	1.3 ± 0.3	0.5 ± 0.1	1.1 ± 0.2	1.3 ± 0.3	1.1 ± 0.3
FLX	1.0 ± 0.3	1.2 ± 0.3	0.9 ± 0.3	1.2 ± 0.4	0.7 ± 0.3	1.3 ± 0.4
0–2 h						
	Total Food					
SAL	8.0 ± 0.9	8.6 ± 0.8	6.9 ± 0.9	8.3 ± 1.1	8.1 ± 1.0	8.0 ± 1.1
FLX	6.1 ± 0.3	6.9 ± 0.6	5.4 ± 0.8	5.7 ± 0.9	6.3 ± 1.2	6.8 ± 1.2
	HC-LP					
SAL	6.1 ± 1.1	7.0 ± 1.0	6.0 ± 0.9	7.0 ± 1.1	6.4 ± 1.1	6.4 ± 1.2
FLX	4.2 ± 0.4	4.7 ± 0.5	3.7 ± 0.5*	4.0 ± 0.7*	4.7 ± 0.7	4.6 ± 0.6
	LC-HP					
SAL	1.9 ± 0.3	1.6 ± 0.2	0.9 ± 0.2	1.3 ± 0.2	1.7 ± 0.4	1.6 ± 0.5
FLX	1.9 ± 0.5	2.2 ± 0.6	1.7 ± 0.5	1.7 ± 0.5	1.6 ± 0.5	2.2 ± 0.9
0–12 h						
	Total Food					
SAL	25.8 ± 1.9	26.7 ± 1.7	24.7 ± 1.9	26.2 ± 2.1	25.1 ± 1.5	25.7 ± 2.7
FLX	21.5 ± 1.3	22.9 ± 1.0	20.6 ± 1.3	21.5 ± 1.4	22.4 ± 1.0	21.5 ± 2.2
	HC-LP					
SAL	17.9 ± 1.8	18.9 ± 1.6	18.3 ± 1.7	19.2 ± 2.1	17.1 ± 1.2	19.1 ± 2.4
FLX	14.2 ± 1.5	14.3 ± 1.4	13.2 ± 1.6	14.2 ± 1.7	15.4 ± 1.4	14.1 ± 2.3
	LC-HP					
SAL	7.9 ± 1.1	7.8 ± 0.7	6.4 ± 0.8	7.0 ± 0.8	7.9 ± 0.9	6.6 ± 1.6
FLX	7.3 ± 1.4	8.7 ± 1.5	7.3 ± 1.4	7.3 ± 1.5	7.0 ± 1.6	7.4 ± 1.6

Fluoxetine (3 mg/kg, IP) was injected daily 15 min before food access, cumulative intake in grams (g).

Mean ± SEM, n = 7.

*$p<0.05$ vs. saline on the same day (ANOVA).

taken as the acceptable point of statistical significance (28).

RESULTS

Food Intake and Selection Pattern

Experiment 1: Dexfenfluramine. Food intake and selection after saline and DFF (1.5 mg/kg) treatments are shown in Table 1. The overall effect of DFF was to suppress intake of total food during the first hour of free feeding, $F(1,23)=7.43$, $p<0.02$. This effect was mainly due to a selective reduction in intake from the HC-LP diet, $F(1,23)=10.42$, $p<0.005$, but not from the LC-HP diet, $F(1,23)=0.030$, NS. This selective anorectic effect of DFF was sustained in the second hour of feeding. Thus, in the first two hours of feeding, intake of total food, $F(1,23)=21.17$, $p<0.001$, and intake of the HC-LP diet, $F(1,23)=20.56$, $p<0.001$, were significantly decreased. Intake of the LC-HP diet, $F(1,23)=0.37$, NS, was not affected.

There was a drug × day interaction on 2-h intake of total food. Contrast test indicated that the effect of DFF on day 1 was significantly larger than on day 2, $F(1,23)=12.82$, $p<0.002$, and day 6, $F(1,23)=4.29$, $p<0.05$. Similarly, the effect of DFF on intake of the LC-HP diet was significantly larger on day 1 than on day 2, $F(1,23)=10.61$, $p<0.005$, and day 3, $F(1,23)=7.71$,

TABLE 4

EFFECTS OF DRUG TREATMENT ON BODY WEIGHT GAIN

	Day 1	Day 7	Changes
Saline	267.7 ± 4.4	316.7 ± 6.0	49.0 ± 1.9
DFF	263.1 ± 3.9	303.0 ± 4.9	39.9 ± 1.8*
Saline	268.7 ± 3.9	315.0 ± 5.2	46.3 ± 2.7
RU 24969	261.1 ± 5.9	298.0 ± 7.2	36.9 ± 2.5†
Saline	320.5 ± 15.9	351.0 ± 16.7	30.6 ± 5.0
FLX	307.6 ± 7.9	329.7 ± 7.0	22.1 ± 4.8

Values are in grams. Mean ± sem. All drugs were injected once daily from day 1 to day 6. *$p<0.01$, †$p<0.05$, Student's t-test.

$p<0.01$. Over a 12-h period, DFF tended to suppress total food intake, $F(1,23)=4.14$, $p=0.0536$. The suppression was more severe on day 1 than on days 2 and 3 ($p<0.05$, contrast test). Although intakes from both diets were not significantly affected by DFF, it is apparent that the decrease was due to reduced intake of the HC-LP diet.

Experiment 2: RU 24969. Mean food intake and selection after daily RU (1.5 mg/kg) or saline treatment are given in Table 2. Significant overall drug effect on total food intake was obtained at 1 h, $F(1,14)=10.86$, $p<0.01$ and 2 h, $F(1,14)=9.48$, $p<0.01$. During the first hour of feeding, the suppression of total food intake was mainly caused by a reduction in intake of the HC-LP diet, $F(1,14)=10.56$, $p<0.01$, but not that of the LC-HP diet, $F(1,14)=0.22$, NS. The effect of RU on 2 h intake of the HC-LP diet was close to significant, $F(1,14)=4.54$, $p=0.0514$.

The anorectic effect of RU was sustained for the entire 12-h period. Total food intake was reduced, $F(1,14)=6.34$, $p<0.05$. This reduction was due to decreased intake of the HC-LP diet, $F(1,14)=4.46$, $p=0.0532$. No drug × day interaction was observed at all time periods.

Experiment 3: Fluoxetine. Although the composition of the diet pair is different from those in the first two experiments, FLX produced a selective change in food choice which is consistent with that observed after DFF or RU 24969 (Table 3). FLX decreased total food intake, $F(1,12)=6.41$, $p<0.05$, in the first hour of feeding and the reduction was from the HC-LP diet, $F(1,12)=5.45$, $p<0.05$, but not from the LC-HP diet, $F(1,12)=0.00$, NS. No significant effect of FLX was observed at 2 and 12 h, although intake of the HC-LP diet tended to decrease at 2 h, $F(1,12)=4.06$, $p=0.0668$. Day effect and drug × day interaction were not observed.

Body Weight Change

Changes in body weight over the six-day period are shown in Table 4. Body weight of rats in the first two experiments were similar at the onset of treatment. Weight gains of the DFF and RU 24969 groups were significantly less than (18.6% and 20.3%) their respective control ($t=3.459$, $p<0.01$ and $t=2.514$, $p<0.05$). Older and heavier rats were used in the third experiment. Although rats that received FLX gained 28% less weight than the saline control, the difference was not statistically significant ($t=1.218$). This is due to a larger variation in the initial body weight and weight gain over the six-day period.

DISCUSSION

The results of this study show a sustained immediate anorexia and selective suppression of intake of diets high in carbohydrate content after 5-HT agonists were given by intraperitoneal injection once daily for six consecutive days. On a daily (12-h) basis, the reduction in food intake was attributed entirely to reductions in intake of the HC-LP diet. The effect of the three agonists on weight gain was similar. Rats given 5-HT agonists continued to gain weight but at a slower rate.

Anorexia is known to occur after DFF (10, 11, 25, 27), RU (3,14) or FLX (8, 13, 31) treatment. We had shown earlier that in self-selecting rats, the immediate anorexia is always accompanied by a selective decrease in intake of the HC-LP diet (23). The present data confirm the previous observation and further show that such behavioral phenomenon is high reproducible, even though rats had been exposed to the same drug for five consecutive days. This selective shift in food choice is less apparent over a 12-h period (daily) as drug effects on intakes of both diets were not significant within any of the individual experiments. This is due to a larger between rat variance as compared to the difference in intake induced by the agonists. In this context, power analysis (7) indicates that at least 20 rats per group will be required to show a significant difference (with power = 0.8), if any, in 12-h intake of the HC-LP diet. Only 7 to 12 rats per group were used in each of the experiments. Nevertheless, a consistent trend can be observed throughout. Twelve-hour intake from the HC-LP diet was suppressed after all three 5-HT agonists, whereas 12-h intake from the LC-HP diet was unchanged after FLX but tended to increase after DFF and RU. Thus the reduced food intake over the 6-day period was attributed solely to decreases in intakes from the HC-LP diet.

The study was designed to investigate the effect on body weight by doses of 5-HT agonists which selectively suppressed carbohydrate intake. Based on results of our previous acute study (23), a selective change in carbohydrate appetite is most pronounced when a modest anorexia is induced. Thus doses selected were such that each of the agonists would cause an overall decrease in food intake by 10%. The effect of RU was right on target, whereas DFF and FLX reduced overall intake by 6% and 15%, respectively. The smaller reduction caused by DFF might be related to the development of partial tolerance to the anorectic effect. In this context, it is important to point out that despite a smaller reduction in food intake, rate of weight gain in the DFF group was similar to that of the other two groups. Because the thermogenic effect of fenfluramine is independent of its appetitive effect (17), an elevated metabolic rate might have contributed to the continual decline in weight gain. Two factors might have contributed to the larger decrease in food intake after FLX. First, the 3 mg/kg dose might have produced more potent effects than anticipated. Second, rats in the FLX experiment were older and their baseline intake (first two hours) was much higher.

Tolerance to the anorectic effect was observed in the DFF-treated rats. This is in keeping with results of earlier reports (26,27). The present data, however, suggest that such tolerance is only partial because food intake (2 h) remained significantly suppressed on days 2 to 6. This sustained anorexia was due entirely to the reduction in intake of the HC-LP diet. This is because as tolerance developed, the initial weak effect of DFF on intake of the LC-HP diet basically disappeared. It is not known whether tolerance would eventually develop in the FLX and RU rats if the agonists were administered chronically. In another study, tolerance was not observed after 10 days of FLX administration (31). This is the first report to show the longer term effects of RU 24969.

In the present study, rats in all three experiments exhibited similar baseline (saline days) preference for carbohydrate. Although absolute intake of the HC-LP diet during the first two hours of feeding was higher in the FLX rats (Table 2), carbohydrate preference was offset by a lower carbohydrate content in the LC-HP diet. Thus percent energy selected as carbohydrate from the diet pairs during the first two hours of feeding was 59.5, 58.5

and 59.6 for the DFF, RU and FLX groups, respectively. Despite the fact that the three agonists, at the doses used, were not equipotent in the suppression of total food intake, they were consistent in their effects on diet selection, i.e., a selective suppression in carbohydrate intake.

Many serotonergic agents influence feeding behavior and they act at multiple levels of the serotonergic system. For example, it has been suggested that dexfenfluramine acts via interaction(s) with the 5-$HT_{1\ non\text{-}A}$ receptor subtypes (12). Hyperphagia caused by agents such as buspirone occurs via interaction(s) with the 5-HT_{1A} receptors (6). As these drugs alter appetite through a selective change in intake of diets high in carbohydrate content (15, 21–23, 29, 30), it is likely that the serotonergic system also plays a role in diet selection (1). Whether the same mechanism(s) and site(s) of action are responsible for the control of food intake and diet selection remain to be elucidated. Nevertheless, in view of the sustained changes in food choice and body weight gain after repeated administration of drugs which enhance 5-HT neurotransmission, it would be important to examine the chronic effects of 5-HT_{1A} agonists. Such a study is currently underway in our laboratory.

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