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Failure of Serotonin Antagonist Pizotifen to Stimulate Feeding or Weight Gain in Free-Feeding Rats

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SWIERGIEL, A. H. AND G. PETERS. *Failure of serotonin antagonist pizotifen to stimulate feeding or weight gain in free-feeding rats.* PHARMACOL BIOCHEM BEHAV **35**(1) 61–67, 1990.—The serotonin antagonist pizotifen (BC-105) is prescribed as an appetite and weight enhancer (Mosegor®—Wander, also commercialized under brand names Sanmigran® or Sandomigran®—Sandoz, Switzerland) for anorectic and convalescent humans. There has been, however, difficulty in demonstrating any orexigenic effect of pizotifen in laboratory animals. In the present report, the influence of chronic administration of pizotifen (0.1–30.0 mg/kg b.wt. per day, SC) on food intake and body weight gains was studied in rats given a standard diet (SD—energy content 14.5 kJ/g, 9% fibre), and in rats either habituated to a low energy content, carbohydrate-free diet (DD—7.3 kJ/g, 45% fibre), or given the DD after habituation to the SD. Pizotifen failed to increase food intake or weight gain. Nor did it shorten a period of initial depression of intake of the unfamiliar DD. On the contrary, pizotifen seemed to diminish food intake and weight gain in rats fed the low energy content diet. Since it has been reported that other 5-HT antagonists, e.g., cyproheptadine, methysergide, and ritanserin can enhance feeding, it is of some interest that pizotifen failed to affect food intake or weight gain in rats. The results suggest that the effects of pizotifen (and, possibly, of serotonin) in rats may differ from those in man. The possibility that feeding in the rat is mediated by 5-HT_1 rather than 5-HT_2 receptors is discussed.

Pizotifen BC-105 Appetite Food intake Anorexia Rat Serotonin 5-HT

PIZOTIFEN (BC-105) is used as an appetite and body weight enhancer (Mosegor®—Wander) in humans [(15,19); and see Swiss Pharmacopoeia, 1986, p. 877]. Pizotifen is a relatively specific serotonin (5-HT) antagonist (21) with a higher binding affinity for the 5-HT_2 than for 5-HT_1 receptors (10,22). Its supposed mechanisms of action is via 5-HT competitive occupancy of the 5-HT_2 binding sites and blockade of 5-HT transmission (27,30) and it is assumed that both peripheral and central serotonergic mechanisms can be manipulated by its administration. Recent evidence suggests that an increase in serotonin-mediated neural transmission depresses feeding (12). Consequently, pizotifen is thought to stimulate food intake by antagonizing the feeding suppressive effects of endogenous serotonin.

Orexigenic effects of pizotifen, however, have only been observed, though not adequately proved to occur, in the anorectic and underweight human patients [(15, 19, 30); and R. Kenzelmann of Wander Pharma Switzerland, personal communication], and in cats, dogs and tree shrews [(21); and Kenzelmann, personal communication]. Increase in appetite and calorie intake in man has been reported after administration of another serotonin antagonist, cyproheptadine (25,29) and almost never after other 5-HT antagonists, methysergide and metergoline [(12); but see (28)], and there has been some difficulty in confirming this effect in animals, particularly in the rat (9, 12, 17). In fact, it has been observed recently that cyproheptadine does not stimulate feeding in rats at all, whereas methysergide, metergoline and ritanserin can increase food intake only under particular testing conditions (9).

Considering the possible key role of peripheral as well as central serotonergic systems in the control of appetite, macronutrient selection and energy balance (4, 26, 33), and the fact that the laboratory rat is usually an animal of choice in pharmacological studies of ingestive behavior, the present experiments were designed to elucidate the properties of pizotifen as a serotonin-related food intake stimulant in rats.

In medicine, pizotifen is administered to stimulate general appetite and to increase total calorie intake rather than to affect the intake of a single meal or a particular diet or macronutrient. On the other hand, the use of pizotifen as an appetite stimulant is widely publicized in developing countries, in which large parts of the population subsist on very low caloric density food. Therefore, in the present study, two diets of different caloric density were used with an aim to observe effects of pizotifen on ingestion of both amounts of food and energy.

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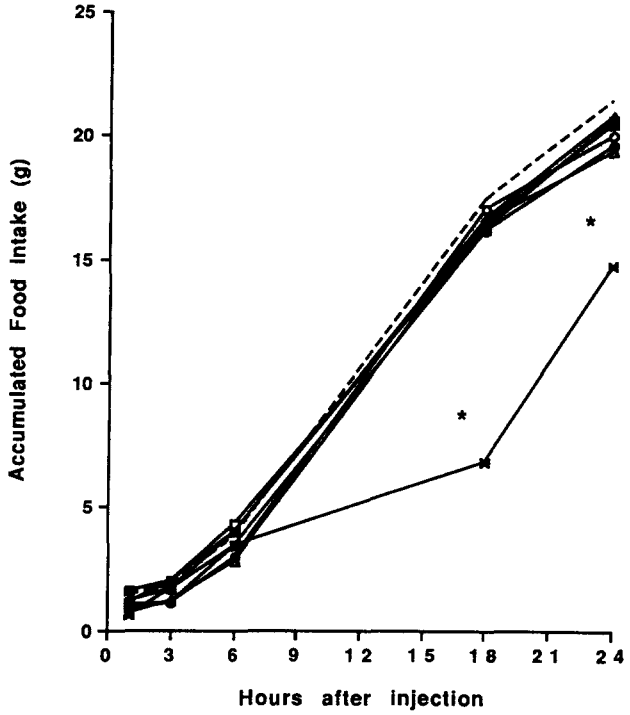

FIG.1. Effect of a single SC injection of pizotifen on accumulated intake of a standard diet in nonfasted rats. Control: saline injection (dashed line); pizotifen (mg/kg): 0.1 (open circles); 0.3 (open triangles); 1.0 (open squares); 3.0 (closed circles); 5.0 (closed triangles); 10.0 (closed squares); 30.0 (asterisks). The results are shown as mean values. N = 6 per group, save 30.0 mg/kg where N = 3. *Different from the control, $p<0.001$, *t*-test.

METHOD

Animals

Experimentally naive male rats (Wistar-Swiss) were habituated to the laboratory animal facilities and different diets for several weeks. By the time of drug administration the rats weighed about 300 g. The animals were housed singly and had access to food and water throughout the experiment. A 0600–1800 light/dark cycle was maintained.

Diets

The pelleted diets were custom-made by NAFAG, Switzerland. The standard diet (SD) was regular NAFAG No. 900 composed of purified ingredients: 26% protein (casein calcium—vitamin free), 44.7% carbohydrate (corn and wheat starch, sugar), 5.2% fat (soya oil), 9.3% crude fibre (mainly cellulose), 4.8% minerals and vitamins, 10% water, and provided 14.5 kJ/g of feed energy. The diluted diet (DD) was NAFAG No. 909 modified with an aim to dilute caloric content of the standard diet by 50%. This was achieved by removing all carbohydrate and adding a considerable amount of nonnutritive fibre. The diluted diet was thus composed of the same components as the SD, but in proportion of 29% protein, 5.5% fat, 47.3% fibre, 8.2% minerals, vitamins and bentonit, 10% water, and provided 7.3 kJ/g of energy. Fresh diets and water were provided daily and spillage, if any, accounted for when calculating food and water intake.

Drugs

Pizotifen (BC-105) (Sandoz) is a tricyclic benzocycloheptathiophene derivative with a side chain resembling that of cyproheptadine. It was suspended in sterile 0.9% NaCl to inject in a final volume of 1 ml/kg body weight. The drug was injected subcutaneously (SC) always at 0900. Previous pharmacokinetic studies (30) suggest that a single dose of BC-105 is effective for at least 24 hours from the moment of injection or oral intake. Control groups received physiological saline in a volume of 1 ml/kg.

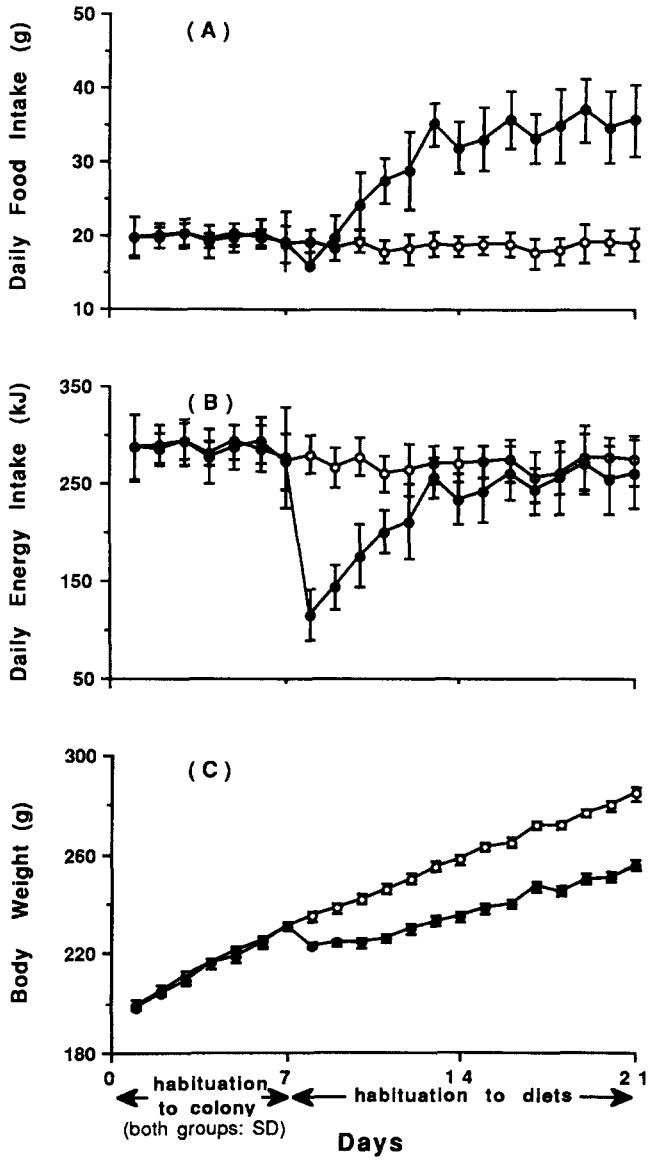

FIG. 2. Daily food (A) and energy (B) intake and body weight (C) of rats maintained on standard (SD—open symbols) or diluted (DD—solid symbols) diet. The results are shown as mean ± SEM. N = 24 per group.

Experiment 1

This experiment examined the effects of several single doses of pizotifen on intake of a standard diet over a single 24-hr period. Forty-two rats were used. Each animal was assigned randomly to one of seven groups (n = 6). A wide range of doses of 0.1 to 10.0 mg/kg was employed since there were no previous data available

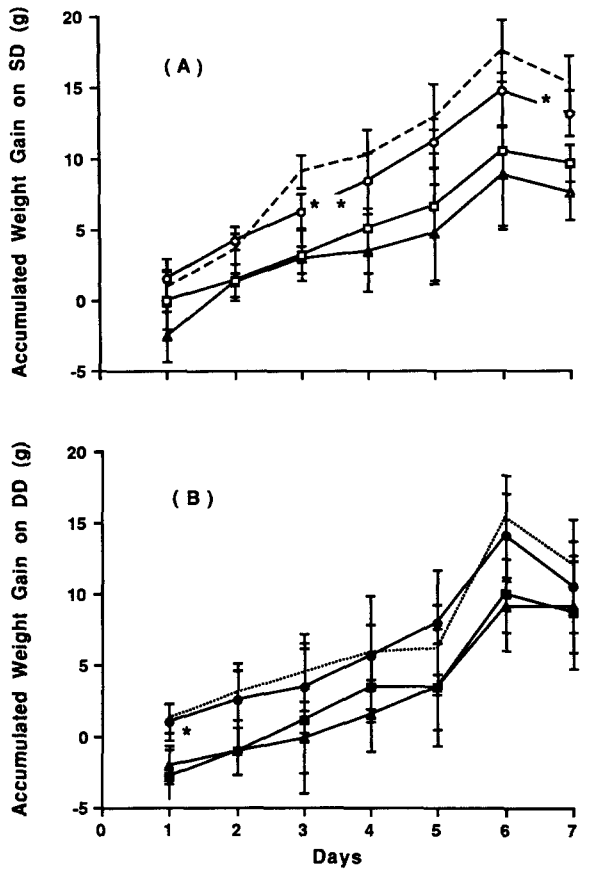

FIG. 3. Effect of daily SC injections of pizotifen on accumulated weight gain on standard diet (A, open symbols) or diluted diet (B, solid symbols). Control: saline injections (dashed line for SD and dotted line for DD); pizotifen (mg/kg): 0.1 (circles); 0.3 (triangles); 1.0 (squares). The results are shown as mean ± SEM. N = 6 per group. *,**Different from the control, $p<0.05$, 0.01, respectively, F-test.

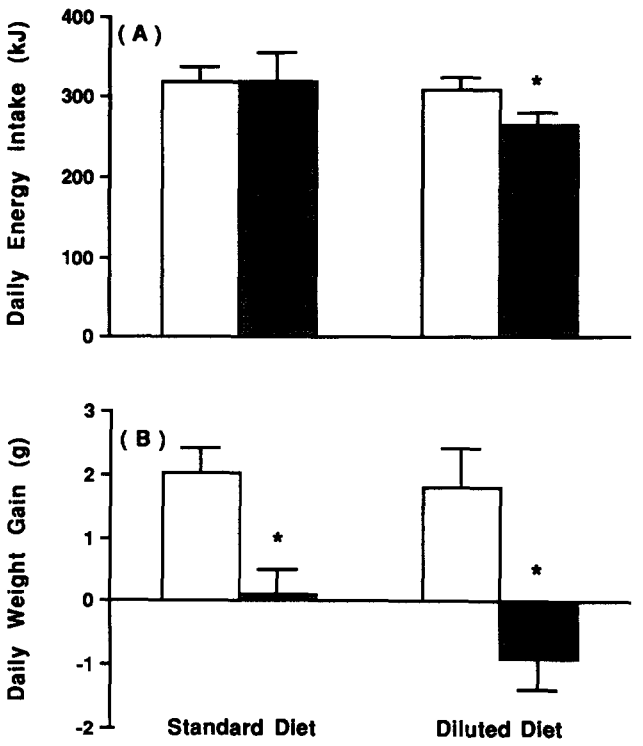

FIG. 4. Effect of six daily SC injections of 1.0 mg/kg of pizotifen (solid columns) on mean daily energy intake (A) and body weight gain/loss (B). Control: saline injections (open columns). The results are shown as mean ± SEM. N = 6 per group. *Different from the control, $p<0.05$, t-test.

concerned with the effects of pizotifen on food intake in rats. Group 1 received physiological saline (SC) and served as a control. Groups: 2, 3, 4, 5, 6, and 7 received 0.1, 0.3, 1.0, 3.0, 5.0 and 10.0 mg/kg of BC-105, respectively. Food intake was measured 1 hour, 3 hours, 6 hours, 18 hours (including 12 hours of dark phase) and 24 hours after drug administration. Since forty-five animals were available for this experiment, three spare rats were given a massive dose of 30 mg/kg of pizotifen and their food intake was observed.

Experiment 2A

This experiment was designed to examine daily food and energy intakes and body weight gains in rats fed either standard or diluted diet. Forty-eight rats were randomly divided into two groups: standard diet group (SD), and diluted diet group (DD). For seven days both groups were fed the standard diet (period of habituation to a colony), and for the next fourteen days (period of habituation to the diets) the SD group continued with the standard diet, whereas the DD group was fed the diluted diet.

Experiment 2B

This experiment studied the effects of three doses of pizotifen on 1) intake of familiar, either standard or diluted diet, and on 2) body weight. Forty-eight rats that had previously been habituated to the respective diets for at least 14 days (from Experiment 2A) were used. They were divided into eight groups (n = 6). Groups 1 (SD) and 5 (DD) received saline and served as the control groups. Groups 2, 3, 4 (SD) and 6, 7, 8 (DD) received 0.1, 0.3, 1.0 mg/kg of pizotifen, respectively, daily for seven days. The effect of 1.0 mg/kg of pizotifen was observed once more in the additional twenty-four rats habituated to either the standard or diluted diets, and in this case pizotifen or saline were administered for six consecutive days.

Experiment 3

This experiment examined the effects of three doses of pizotifen on intake of an unfamiliar diet and body weight gains. The rats habituated to the colony and maintained on laboratory chow UAR A04-France (12.12 kJ/g; 17% protein, 58.7% carbohydrate; 3% fat; 4.3% fibre; 5% minerals and vitamins; 12% water) were given for the first time either an unfamiliar, standard diet (SD) or unfamiliar diluted diet (DD). Forty-eight rats divided into the SD and DD groups (n = 24) were further subdivided into eight groups (n = 6). Groups 1 and 5 received saline, and groups, 2, 3, 4 (DD) and 6, 7, 8 (SD) received 0.1, 0.3, 1.0 mg/kg of pizotifen, respectively, for seven consecutive days.

Data Analysis

Daily and accumulated food, energy and water intakes, and

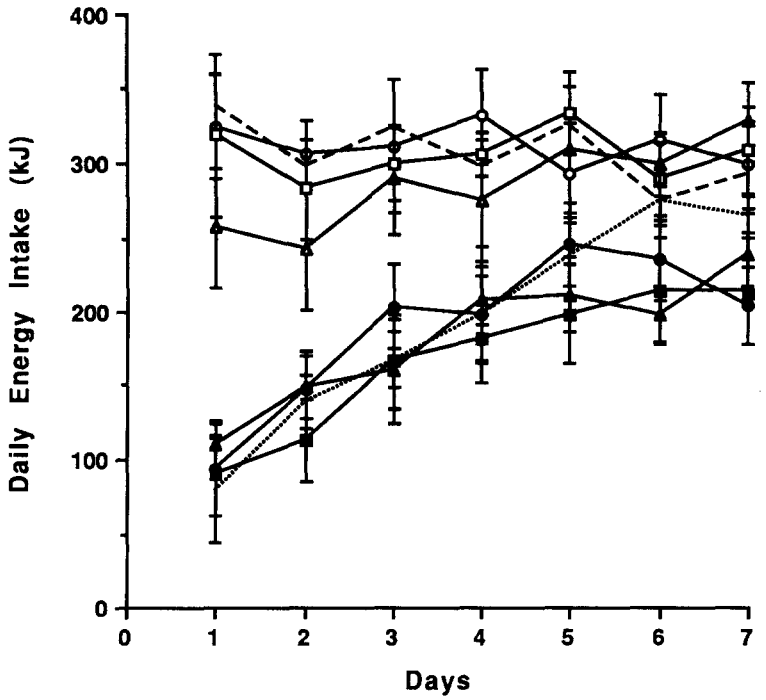

FIG. 5. Effect of daily SC injections of pizotifen on daily energy intake in rats fed unfamiliar standard diet (open symbols) or unfamiliar diluted diet (solid symbols). Control: saline injections (dashed line for SD and dotted line for DD); pizotifen (mg/kg): 0.1 (circles); 0.3 (triangles); 1.0 (squares). The results are shown as mean ± SEM. N = 6 per group.

body weight gains were analyzed by a one- or two-way ANOVA, followed by unpaired *t*-tests for a priori designed comparisons between a control group and a drug group.

RESULTS

In none of the experiments did pizotifen stimulate appetite or body weight gains in rats. Nor did it shorten the period of initial depression of intake of unfamiliar food.

Experiment 1

Pizotifen had no significant (at $p = 0.05$) effect on food intake, and rather tended to depress intake of a standard diet in comparison with physiological saline treatment (Fig. 1). The 30 mg/kg dose of pizotifen significantly depressed food intake 18 and 24 hr after drug administration ($p<0.001$).

Experiment 2A

No differences, in daily or accumulated, 7-day food and energy intakes, or body weight gains were observed between the groups during the period of habituation to the colony (Fig. 2). Feeding the rats with diluted diet resulted in an initial depression of energy intake and body weight loss. By the fifth day of the habituation the DD rats increased intake of the diluted diet (Fig. 2A) so that they ingested the same amount of energy as the rats fed the standard diet (Fig. 2B). They also reached the daily body weight gains observed in the rats fed the standard diet, but they maintained the lower body weight ($p<0.001$) than that displayed by the SD rats (Fig. 2C).

Experiment 2B

There was no significant effect of chronic administration of pizotifen on intake of the familiar standard diet or the familiar diluted diet. In terms of energy intake all groups of rats ingested similar daily or 7-day accumulated amount of kilojoules, although doses of 0.3 and 1.0 mg/kg of pizotifen appeared to diminish energy intake in the DD on days 1 and 7 of treatment. Pizotifen significantly and dose-dependently depressed daily body weight gain in rats fed the SD on day 3, $F(3,20) = 5.408$, $p<0.01$, and significantly depressed their accumulated 7-day body weight gain, $F(3,20) = 3.172$, $p<0.05$ (Fig. 3A). Pizotifen depressed daily weight gain on day 1 in rats fed the DD, $F(3,20) = 3.173$, $p<0.05$, and tended to depress their accumulated body weight gain (Fig. 3B). Doses of 0.3 and 1.0 mg/kg were equally most effective in depressing body weight.

The additional observation of the effect of 1.0 mg/kg dose of pizotifen confirmed that while pizotifen did not significantly affect intake of the standard diet (Fig. 4A), it nevertheless depressed daily body weight gain (Fig. 4B). Repetition demonstrated once more that pizotifen could decrease intake of the diluted diet (Fig. 4A) ($p<0.05$) and strongly depressed body weight gain ($p<0.05$) (Fig. 4B).

Experiment 3

There was no statistically significant effect of pizotifen on accumulated 7-day energy intake in the unfamiliar SD or DD, although on particular days pizotifen appeared to affect intake. Changes, however, were inconsistent and bidirectional (Fig. 5). On the first day of treatment pizotifen tended to depress intake of the SD, while the same dose seemed to stimulate intake of the unfamiliar DD. On the last two days of treatment control rats maintained on the SD ate less than those injected with pizotifen while the situation with animals fed the DD was just the opposite.

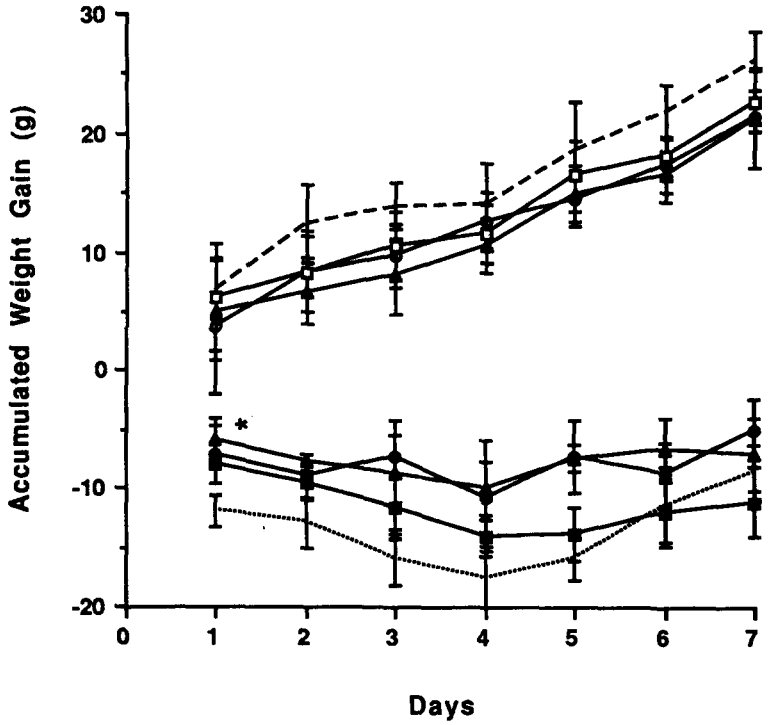

FIG. 6. Effect of daily SC injections of pizotifen on daily weight gain on unfamiliar standard diet (A, open symbols) or unfamiliar diluted diet (B, solid symbols). Control: saline injections (asterisks); pizotifen (kg/mg): 0.1 (circles); 0.3 (triangles); 1.0 (squares). The results are shown as mean ± SEM. N = 6 per group. *Different from the control, $p<0.01$, F-test.

Pizotifen had no consistent effect on daily or 7-day accumulated weight gain in rats fed the SD or DD (Fig. 6). Only on the first day of treatment it diminished significantly the loss of body weight, $F(3,20)=6.030$, $p<0.01$, in rats maintained on the DD.

Water Intake

Water intake was correlated with amount of food ingested and the food/water intake ratio was maintained at 0.9 for both diets. Pizotifen did not appear to affect this relationship. Increased intake of the diluted diet was accompanied by increased drinking, and any changes in water intake appeared to be secondary to changes in amount of food ingested.

DISCUSSION

Pizotifen administered in a wide range of doses had no stimulating effect on food intake or body weight gain in free-feeding rats. Also, the drug-treated animals did not seem to make a distinction between a diet high in carbohydrates and calories and a diet low in energy content and carbohydrate free. As discussed earlier, it has been difficult to demonstrate increases in food intake with 5-HT antagonists. However, if the assumption that the activation of 5-HT receptors inhibits food intake is true, than the converse should hold: 5-HT receptor blockade should facilitate feeding. Very rare observations support this notion: cyproheptadine has been reported to increase eating and body weight (2,13), and methysergide increases eating (5,9), but only in meal-fed rats. A recent study by Fletcher (9) very convincingly questions the capacity of cyproheptadine to increase food intake in rats. It is quite intriguing that pizotifen and cyproheptadine are marketed as effective appetite and body weight stimulants (Mosegor®—Wander; Periactin®—Merck Sharp & Dohme, respectively) and weight gain is observed as a side effect for methysergide (Sansert®—Sandoz) in the course of treatment for migraine (16). Yet, increased intake in rats after these drugs is the exception rather than the rule.

Although one cannot exclude the possibility that the doses of pizotifen used in the present experiments were outside the pharmacologically effective range for the rat, this seems implausible. Chemically, pizotifen closely resembles cyproheptadine. Cyproheptadine has been similarly dosed when reported to increase food consumption in rats (2,13). Also, doses 2.5–10.0 mg/kg b.wt. of pizotifen administered peripherally affected centrally mediated conditioned cardiovascular responses in rabbits (14). Moreover, 30.0 mg/kg b.wt. of pizotifen was effective in Experiment 1, clearly exerting a depressing effect on food intake. Even though there are well recognized theoretical and methodological reasons why an increase in food intake is more difficult to demonstrate than anorexia (4), these should be of little significance in long-term experiments where accumulated food intakes and weight gains are recorded. Therefore, failure to observe stimulating effects of pizotifen in rats was not likely to be caused by a dosage miscalculation or an inappropriate experimental protocol. Orexigenic action of pizotifen reported in humans, but not observed in rats, thus requires a careful consideration of the serotonin-dependent changes in ingestive behavior.

A possible explanation of the inability of pizotifen to increase food intake in rats is provided by the recent paper by Fletcher (9). The author reports that methysergide, metergoline and ritanserin, but not cyproheptadine, can increase food intake, but only in rats that fed to satiety immediately prior to drug treatment. When the

antagonists were administered before the beginning of a single meal animals showed, at certain doses, a suppression of feeding. The results point out that the conditions of testing/satiety can be critical to observe intake-enhancing effects of 5-HT antagonists. Serotonin antagonists could increase food intake by allowing resumption of eating through an elimination of the state of satiety that follows the ingestion of a large meal.

Another explanation of the failure of pizotifen (and other 5-HT_2 antagonists) to augment feeding in rats is that the animals' 5-HT_2 receptors may not mediate serotonergic inhibition of feeding, or that they are relatively less important in this respect than in humans. Therefore, a serotonin antagonist acting predominantly on 5-HT_2 receptors could not facilitate feeding by counteracting serotonergic depression of appetite. Evidence comes from comparison of the effects of two 5-HT antagonists on the anorectic effects of D-fenfluramine: metergoline, that is a competitive antagonist of 5-HT, with similar in vitro affinity for both 5-HT_1 and 5-HT_2 receptors (10,12), and ritanserin, a potent and selective 5-HT_2 receptor antagonist (10). Metergoline (5-HT_1 and 5-HT_2 occupancy) prevents the anorectic effect of D-fenfluramine or 5-HT, whereas ritanserin (5-HT_2-only receptors blocker) does not (24). This observation may suggest that in the rat 5-HT_1, rather than 5-HT_2 receptors mediate inhibitory effects of serotonin on feeding, although this interpretation is occasionally contested (23) and conflicts with the report that low doses of ritanserin can elicit feeding under the conditions described by Fletcher (9). Moreover, evidence accumulates that within the 5-HT_1-subtype of receptors, the 5-HT_{1A} receptor mediates increased food intake, while the 5-HT_{1B} receptor is exclusively responsible for anorexia elicited by serotonergic agonists (7,8). Depression of food consumption evoked by injection of 5-HT into the hypothalamic paraventricular nucleus can be blocked only by the general receptor antagonists—metergoline, methysergide and cyproheptadine that act, inter alia, on the 5-HT_{1B} receptors and not by the selective 5-HT_2 receptor antagonist, ritanserin (24,32). Effects observed after administration of trifluoromethylphenylpiperazine (TFMPP) also suggest that the role of 5-HT_2 receptors in rats may be marginal as far as feeding is concerned. Although TFMPP is generally considered as an agonist of the 5-HT_{1B} receptor (10), paradoxically it acts also as pure antagonist of the 5-HT_2 receptor in the rat's brain and may be able to antagonize completely effects of serotonin mediated by the 5-HT_2 sites (27). However, a decrease, rather than increase, in food intake in rats is reported after administration of TFMPP (11), further arguing against the possibility of stimulating food intake in rats by a 5-HT_2 antagonist. Considering that the 5-HT_{1B} receptor seems to occur only in rodents and not in humans (18), it may be that its feeding-related role is fulfilled by a 5-HT_2 receptor in humans. Therefore, pizotifen, that preferentially binds to 5-HT_2 sites, could counteract serotonergic inhibition of feeding more effectively in man than in rodents.

The above argument suggests yet another possible interpretation of the varying effects of pizotifen, namely that the role of the serotonergic system in the modulation of appetite differs between species. Although not well documented in the case of feeding regulation, this notion can be supported by the examples derived from other regulated systems. In the cats, dogs and primates (the species in which pizotifen has been reported to increase feeding) centrally administered 5-HT causes a rise in body temperature. In the rat, 5-HT action is quite opposite and causes a fall in body temperature (3). In the cats and dogs 5-HT is reported to be a blood pressure depression agent (1). In contrast, in the rats and rabbits 5-HT is a pressor agent (20). The effects of serotonergic manipulations on body temperature or blood pressure are quite complex and, of course, the present results cannot be explained adequately in terms of interspecies differences with regard to temperature or cardiovascular regulation. However, the possibility of the different effects of serotonergic manipulations on feeding in various species is further supported by the recent observation that the 5-HT_{1B} receptor, which is clearly involved in feeding, appears to be rodent specific, and absent in humans (18).

Finally, it is noteworthy that all three marketed serotonin antagonists, pizotifen, cyproheptadine and methysergide, have also been long established as migraine prophylactic drugs and display antianxiety effects in animals (6). It may well be, therefore, that their orexigenic action in humans is only secondary to other clinical, nonappetite related, effects.

ACKNOWLEDGEMENTS

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