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Effects of Gastrin-releasing Peptide$_{1–27}$ on Taste Responses in the Rat

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Abstract

Gastrin-releasing-peptide$_{1–27}$ (GRP) has been implicated in the regulation of satiety and appetite in numerous paradigms. However, the specific site and mode of action of this gut–brain peptide has not been elucidated. The following experiment examined the effects of GRP on taste responses to sucrose in the behaving rat. A brief-exposure, multi-bottle gustometer was used to provide rats with momentary access to six different concentrations of sucrose in a single test session. This procedure has been used previously, resulting in monotonically increased licking behavior as concentrations of sucrose increase. Differing injection procedures were employed such that rats were tested immediately after i.p. injection or 5 min after i.p. injection of 5 nmol/kg body wt of GRP. Results indicate that GRP does reduce the oral reinforcing properties of sucrose, but the effect is transient, diminishing significantly within 5 min after injection.

Key words: brief-exposure tests, curve-shift, gut peptides, satiety

Introduction

The term 'satiety' refers to the factors that contribute to the termination of a meal and the lengthening of time intervals between meals. If increased food intake leads to the development of certain eating disorders, such as obesity or bulimia nervosa, then an understanding of the normal mechanisms that control the size and frequency of meals is essential to the treatment of such disorders. Though knowledge of these mechanisms is still limited, uncovering the complex physiology involved in satiety has progressed steadily over the past 25 years (Blundell, 1984), in large part due to the discovery of certain peptides released by the gut in response to ingested food (Gibbs and Smith, 1984). Work in this area continues to accelerate, with particular interest focusing on a small group of these integrative peptides that link the gastrointestinal tract and brain (Hobel, 1985). These peptides have been shown to act both by their release into the gastrointestinal system (peripheral action) and via direct actions in certain brain areas (central action) (Gibbs and Smith, 1992).

One mammalian peptide in particular, gastrin-releasing peptide$_{1–27}$ (GRP), has been extensively studied because it has a demonstrated effect on limiting meal sizes and increasing the intervals between meals (Thaw, 1994). GRP has been shown to be involved in regulating satiety in several paradigms such as sham feeding, *ad libitum* feeding, feeding deprivation schedules, operant conditioning procedures and with various species including rats, mice, hamsters, pigs, non-human primates and humans (Gibbs *et al.*, 1979; Gibbs and Smith, 1980, 1992; Kulkosky *et al.*, 1982; Smith *et al.*, 1982; Hsiao and Spencer, 1983; Woods *et al.*, 1983; Wiener *et al.*, 1984; Babcock *et al.*, 1985; Mindell *et al.*, 1985; Morley *et al.*, 1985; Ladenheim and Ritter, 1988; Flynn, 1989; Thaw, 1994). Though there is little doubt that this peptide is involved in satiety, the mechanisms by which it acts and even its site of action are not completely understood (Kirkham *et al.*, 1991). However, several other manipulations that induce satiety in rats, such as i.v. injections of glucose, insulin and glucagon, and the induction of gastric distention (Glenn and Erickson, 1976; Giza and Scott, 1983, 1987), have been shown to be associated with changes in taste sensitivity. Also, stomach distention and nutrient infusions have been shown to modify taste-elicited activity in nerves from the tongue and stomach, as well as neurons in the hindbrain (NST) (Brush and Halpern, 1970; Glenn and Erickson, 1976; Giza and Scott, 1983, 1987) and this has led to modifications of human ratings of taste pleasantness (Cabanac, 1971). It has been postulated that changes in gustatory sensibility may accompany the inhibition of food intake produced by the administration of certain gut peptides (Giza *et al.*, 1990). Support for this comes from studies examining the effects of the gut peptide cholecystokinin on palatability that have shown significant decreases in ingestive responses to sucrose solutions (Waldbillig and O'Callaghan, 1980; Waldbillig and Bartness, 1982; Bartness and Waldbillig, 1984; Eckel and Ossenkopp, 1994). Thus, GRP may exert its satiating effects, in part,

through a taste mechanism as well (Gosnell and Hsiao, 1984; Giza *et al.*, 1990; Flynn, 1995).

Flynn (Flynn, 1995) has examined the effect of GRP on taste using taste reactivity tests developed earlier (Grill and Norgren, 1978). He found various concentrations of GRP to reduce the mean ingestive responses, though not significantly, to a single test concentration of sucrose. Flynn also examined effects with respect to NaCl (Flynn, 1995). He reported no reliable changes in taste reactivity to 0.5 M NaCl in rats on sodium-restricted or normal diets. It may be that NaCl ingestion patterns after GRP administration affect only low concentrations (0.01 or 0.05 M for example) not tested in his procedure. If it is the case that only certain concentrations of solutions are affected by GRP, this provides the necessity to test a variety of concentrations, including sucrose solutions.

To test the hypothesis that GRP affects the oral reinforcing properties of particular concentrations of sucrose, behavioral changes in taste perception following injections of GRP into the peritoneal cavity of the intact rat were examined in the behaving animal. Since the efficacy and speed of action of this peptide was not known with respect to effects on taste, injections of the peptide were administered either immediately before testing or 5 min prior to testing. Given the brief half-life of GRP, it was postulated that the peptide would exert its effect immediately (Bloom *et al.*, 1983; Knigge *et al.*, 1984). Using brief-exposure taste tests (described below), rats were allowed to sample sucrose solutions from any one of eight individual sipper tubes for 30 s. Baseline measures of sucrose licking behavior were recorded (no injection) and followed by testing using sucrose as the tastant with each subject receiving a single injection of either 0.9% NaCl in distilled water (saline control), or 5 nmol/kg body wt GRP dissolved in saline and administered either immediately before testing or 5 min prior to testing. The dose of GRP used for these studies was chosen for two main reasons. First, 5 nmol/kg body wt represents a dose of GRP that reliably increases the inter-meal interval in freely feeding rats (Thaw *et al.*, 1998). This increased latency between meals is an indication of satiety and provides evidence that such a dose of GRP is sufficient to produce the desired effect of increased satiety. Since the present study was concerned with elucidating a role for the taste system as one of the potential mechanisms of action for the satiety effects of GRP, it was necessary to make use of a concentration of GRP that has been determined to affect satiety. Smaller doses of GRP injected peripherally have not led to reliable effects on satiety (Thaw *et al.*, 1998). The second main reason for choosing 5 nmol/kg body wt GRP concerns the fact that the present study set out to examine taste-related behaviors. The dose of GRP used in this study has not been implicated in producing malaise or conditioned taste aversions following peripheral injections into the peritoneal cavity (Gibbs, 1985). However, larger doses of GRP and other bombesin-related peptides have been implicated as potentially leading to malaise in rats (Deutsch, 1980; Deutsch and Parson, 1981). Using the modest dose chosen for this study, results provide evidence that the oral reinforcing properties of sucrose are reduced in the behaving rat following peripheral administration of GRP.

Materials and methods

Subjects

Ten male Sprague–Dawley rats (200–250 g; Harlan-Teklad) were used as subjects. Rats were housed individually in standard polycarbonate cages. The animal room was maintained at 20 ± 2°C on a 12 h:12 h light:dark cycle, with lights off at 07.00. Rats were maintained at all times on water and laboratory rodent diet (Teklad LM-485), with no deprivation of any kind. The testing apparatus was housed in a room directly adjacent to the animal room. All rats were tested during the dark phase. The room housing the testing apparatus was illuminated with a 25 W red light.

Procedure

Rats were tested individually using a multi-bottle gustometer similar to that described previously (Smith, 2000). Any one of eight individual sipper tubes was presented to a rat for brief periods of time. Postingestinal cues were minimized due to the minute volume of fluid consumed (0.005 ml/lick). Thus, the rats' responses were directed by the stimulating properties of the solutions tested. The dependent measures produced (total licks, latency to lick and inter-lick intervals) provided indications of the sensory experience of the rat. In this way it was possible to determine each rat's baseline behavior to various tastant concentrations and then compare them to behavioral data obtained following injections of control and GRP solutions.

Training

Rats were trained to lick from the eight sipper tubes by filling each tube with 0.25 M sucrose and presenting them in random order until all eight tubes had been sampled during a single training session. A computer-controlled shutter was used to block or allow access to the sipper tubes that protruded through a small hole on the back wall of the apparatus. Each rat received 5–8 days of consecutive training until they all responded immediately to the presentation of each tube. During this training period, access to each tube was limited to 30 s. The 30 s access time began with the rat's first lick on a tube. Once the access time expired there was an additional 30 s delay before the next tube was presented. However, if a rat did not lick a tube within 100 s, the next tube in the series was presented. The apparatus training sessions were followed by collection of baseline data on a variety of sucrose solutions and water. Six of the eight available tubes were filled with sucrose concentrations of 0.03, 0.06, 0.125, 0.25 and 0.5 M or water and were randomly presented twice each during a single test session.

Table 1 Injection procedure for saline, GRP immediate injection and GRP 5 min delay injection

Injected	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Rat nos 3, 4, 6, 8, 10	Saline	GRP	Saline	GRP, 5 min delay	Saline	GRP	Saline	GRP, 5 min delay
Rat nos 1, 2, 5, 7, 9	GRP, 5 min delay	Saline	GRP	Saline	GRP, 5 min delay	Saline	GRP	Saline

Testing

Baseline data were collected for four consecutive days, followed by eight consecutive days of testing using the same procedure and including peptide or control injections. GRP solutions were prepared such that 5 nmol of GRP was contained in each milliliter of solution. Rats received a single i.p. injection of either saline or 5 nmol/kg body wt GRP using a sterile 1 cm^3 syringe with a 26 gauge needle. With this method, each rat received the same relative amount of GRP, though the total volume injected varied according to body wt. The rats were placed into the testing apparatus either immediately following injection or 5 min post-injection and the various tubes were presented in random order twice for a total of 12 presentations per test session. The eight testing days consisted of counterbalanced injections in which half of the subjects received saline and half received a GRP injection. The injection solution was alternated each day to provide 48 h between any two GRP injections. Each GRP injection procedure was employed twice (Table 1). The testing procedure required ~15 min to complete for each rat and there was no significant difference in time to complete the test between the three conditions (16.2, 14.5 and 15.7 min for saline, GRP and 5 min delay GRP, respectively). After a completed test session the apparatus was cleaned with distilled water and the next rat was placed in the apparatus.

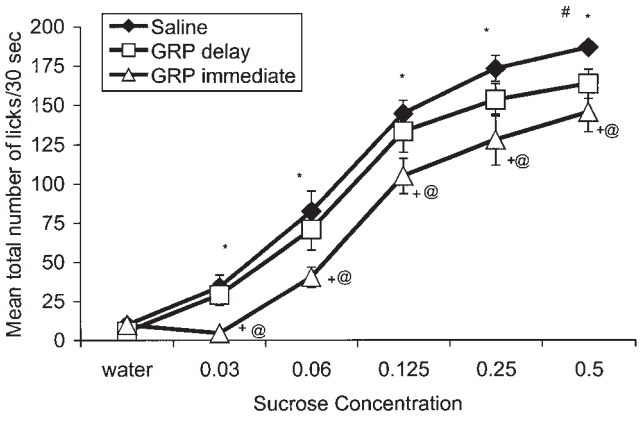

Figure 1 Comparison of mean total number of licks (+SE) on sucrose solutions following injections of saline, 5 nM GRP and 5 nM GRP with a 5 min delay before testing. *Significant difference ($P < 0.05$) between groups using a repeated-measures ANOVA [$F(2,18) = 9.67$, 4.32, 6.25, 11.68 and 17.52 for 0.5, 0.25, 0.125, 0.06 and 0.03 M sucrose, respectively. #Significant difference between saline and 5 min delay GRP injection using Fisher's LSD one-tailed *post hoc* test ($t = 2.25$; $P < 0.05$). +Significant difference ($P < 0.05$) between immediate and 5 min delayed GRP injection using Fisher's LSD one-tailed *post hoc* test ($t = 1.75$, 1.98, 2.69, 3.09 and 4.05 for 0.5, 0.25, 0.125, 0.06 and 0.03 M sucrose, respectively). @Significant difference ($P < 0.05$) between saline and immediate GRP injection using Fisher's LSD one-tailed *post hoc* test ($t = 4.01$, 3.34, 3.86, 4.37 and 4.99 for 0.5, 0.25, 0.125, 0.06 and 0.03 M sucrose, respectively).

Results

Data analysis

The dependent variable of interest was the total number of licks on each sucrose concentration. Results from this laboratory as well as others have demonstrated a monotonically increasing curve for sucrose licking behavior in the rat, i.e. the higher the concentration of sucrose, the more licks in brief exposure taste tests, up to 1 M (Spector *et al.*, 1990; Thaw, 2001). Data from the baseline days were compared to saline injection data using repeated-measures analysis of variance (ANOVA) to determine if the injection procedure itself led to behavioral changes. No significant differences were found [$F(1,9) = 0.04$; $P = 0.77$]. Data collected following saline injections were then compared to the two GRP injection procedures using repeated-measures ANOVA for each concentration tested and Fisher's LSD *post hoc* test to determine the effectiveness of the two GRP injection procedures. Each rat received two presentations of each solution during a single test session and both GRP injection procedures were administered twice, while the saline procedure was administered between each GRP test session. Therefore, the means for each concentration were calculated for each rat and used to conduct the repeated-measures ANOVA. Results indicated a significant decrease in the total number of licks on the 0.5, 0.25, 0.125, 0.06 and 0.03 M sucrose concentrations following GRP injections [$F(2,18) = 9.67$, $F(2,18) = 4.32$, $F(2,18) = 6.25$, $F(2,18) = 11.68$ and $F(2,18) = 17.52$, respectively; $P < 0.05$]. Even more interesting was the finding that these significant differences were attributable to the immediately tested group for all concentrations, with the exception of 0.5 M sucrose that led to significantly reduced licking in both GRP injection conditions (Fisher's LSD *post hoc* test, $t = 2.25$ for saline versus 5 min delay GRP; $P < 0.05$; Figure 1). In fact, the immediately injected GRP results were significantly different from the 5 min delay GRP injections for all sucrose solutions, but not water (Fisher's LSD *post hoc* test, $t = 1.75$,

1.98, 2.69, 3.09 and 4.05 for 0.5, 0.25, 0.125, 0.06 and 0.03 M sucrose, respectively; $P < 0.05$; Figure 1). Given that each concentration was presented twice during each 15 min test session, it was even possible to identify changes in the effectiveness of the GRP as the test progressed. For example, the mean number of licks on each sipper tube was nearly identical when comparing the first and second presentations of sucrose concentrations following saline injections. However, the mean number of licks that occurred during the first series of sucrose solutions was notably less than the number of licks for the second presentation with both GRP injection procedures, indicating a decrease in the effectiveness of the GRP in reducing licking behavior as time progressed during testing. Using a matched *t*-test, the first series of sucrose solutions for both GRP injection procedures resulted in significant differences in total licks for 0.125, 0.06 and 0.03 M sucrose ($t = 2.29$, 1.85, and 2.96, respectively; $P < 0.05$; Figure 2). Using the same test, the second series of sucrose presentations following the immediate GRP injection procedure was compared to the first series of sucrose solutions following the 5 min delay GRP procedure (Figure 3). It was not surprising to find no significant differences between these two sets of data, since in both cases ~5 min had elapsed since the GRP had been injected.

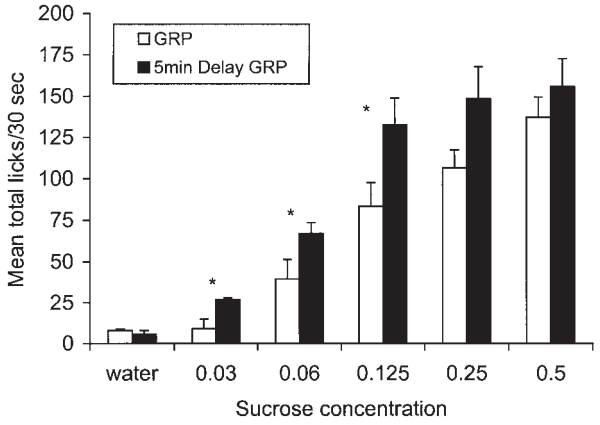

Figure 2 Comparison of mean total number of licks (+SE) on first presentation of sucrose solutions following injections of 5 nM GRP and 5 nM GRP with a 5 min delay before testing. *Significant difference ($P <$ 0.05) between immediate and 5 min delayed GRP injection using matched

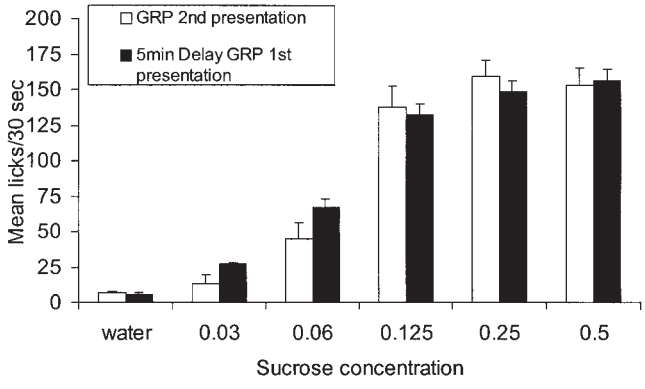

Figure 3 Comparison of mean total number of licks (+SE) on second presentation of sucrose solutions following injections of 5 nM GRP and first presentation of sucrose solutions following 5 nM GRP with a 5 min delay before testing. No significant differences were found.

The mean latency to begin licking and the inter-lick interval for each concentration of sucrose were also examined (Tables 2 and 3). There were no significant differences in the mean time elapsed before initiating the first lick on any of the solutions tested, nor were there any significant differences in the inter-lick intervals for any of the solutions presented (including water).

Discussion

The above results demonstrate that peripheral injections of GRP lead to significant reductions in licking behavior of sucrose solutions using brief-exposure taste tests. These effects are more pronounced when rats are tested immediately after injection as opposed to testing after a 5 min post-injection delay. Also, the ability of GRP to reduce licking behavior decreases within the test sessions described here, supporting the hypothesis that the effects of GRP on taste rapidly diminish. Prior studies have shown that the rate of licking solutions containing sucrose increases in a predictable fashion as the concentration of the sucrose increases when using brief-exposure tests (Davis, 1973, 1996; Cagan and Maller, 1974). These monotonically increasing curves allow investigators to infer the palatability or oral reinforcing properties of the solutions. Also, by using tests

Table 2 Mean latency (s) to first lick for water and solutions of sucrose (M) after i.p. injections of saline, GRP and GRP with a 5 min delay before testing

	Sucrose solution					
	0.00	0.03	0.06	0.125	0.25	0.5
Saline	4.77	7.65	8.42	7.69	8.9	5.05
GRP	6.88	8.73	11.77	5.84	5.44	5.89
GRP, 5 min delay	5.23	7.11	8.93	7.02	5.16	4.81

Table 3 Mean inter-lick interval (ms) for water and solutions of sucrose (M) after i.p. injections of saline, GRP and GRP with a 5 min delay before testing

	Sucrose concentration					
	0.00	0.03	0.06	0.125	0.25	0.5
Saline	148.67	137.98	140.26	155.35	159.03	157.79
GRP	148.50	159.00	147.91	158.22	160.36	155.48
GRP with 5 min delay	150.94	144.73	138.28	148.56	151.29	160.47

of brief duration the post-ingestive effects of calorically dense solutions is minimized. This allows for the behaviors to be directed by the taste of the solution more than by the metabolic effects that occur with accumulation of nutrients in the stomach or intestines. The results of this study show that specific decreases in licking produce a curve that is shifted downward following GRP injections. Curve-shift studies by Weingarten and others (Sakic *et al.*, 1996; Weingarten *et al.*, 1996) indicate that such changes in behavior can be interpreted as reductions in the oral reinforcing properties of sucrose. In fact, the similarity in results of this study and Weingarten's study, which used sham feeding, further supports the effectiveness of the brief-exposure taste test as a way to collect behavioral data guided specifically by taste. Of course, more general effects of GRP on behavior, such as locomotor or oromotor changes, may be contributing to the decreases in licking behavior observed. This is unlikely for three main reasons. First, Flynn (Flynn, 1995) found no differences in ingestive or aversive responses to sucrose solutions following peripheral injections of GRP and saline in rats using a taste reactivity test. Notable deficits in oromotor responses would certainly have been detected with this procedure. Secondly, GRP does not reduce sham feeding (Smith *et al.*, 1997). Rats that received GRP injections just prior to being given access to 0.2 M sucrose solutions behaved similarly to saline-injected rats. Specifically, GRP-injected rats licked a stainless steel sipper tube consistently during a 30 min access period. In contrast, when these same subjects had their cannulae closed, GRP led to a 44% decrease in real feeding. This clearly demonstrates a lack of a generalized motor effect of GRP in reducing licking behavior. Other studies comparing the effects of cholecystokinin and bombesin-like peptides on licking behaviors revealed no changes in licking characteristics with bombesin-like peptide injections, though cholecystokinin injections did alter several licking behaviors (Hsiao and Spencer, 1983). Finally, the results from this study reveal no substantial changes in the latency to initiate licking or the inter-lick interval for any concentrations of sucrose or for any of the injection procedures. Decreases in the latency to initiate licking may have implicated generalized decreases in motor activity or even mild malaise as possible sources of reduced licking behavior. Since rats had to make a volitional movement to get into place to lick the tubes presented, deficits in motor ability would have been evident in the time it took each rat to orient into the proper position. Inter-lick intervals have been noted previously as a microstructural measure that tends to remain constant in taste-elicited behaviors (Davis and Smith, 1988). Thus, a lack of change in the inter-lick interval can be used to support the hypothesis that the procedure employed for this experiment reflects changes in the oral reinforcing properties of sucrose following administration of GRP.

The finding of more pronounced changes in licking behavior immediately after injection of GRP compared to results following a 5 min delay between GRP injection and testing are important. First, this demonstrates an immediate effect of GRP on the taste-elicited behaviors of rats sampling sucrose solutions. Reductions in the hedonics or palatability of sugar solutions have already been established for another gut peptide (cholecystokinin) that has a demonstrated satiety effect (Waldbillig and Bartness, 1982; Eckel and Ossenkopp, 1994). Similar reductions in taste responses may now be noted for GRP. Given the inhibition of feeding behavior observed with GRP injections (Gibbs *et al.*, 1994; Rushing *et al.*, 1996; Thaw *et al.*, 1998), it can be argued that GRP-induced satiety may rely in part on reductions in the hedonics or palatability of ingested nutrients. Secondly, the change in behavior reported here is significantly larger as compared to the taste reactivity test conducted by Flynn (Flynn, 1995). Two possible reasons for this discrepancy emerge. The two tests (taste reactivity and brief exposure) are either not comparable or the time elapsed between the administration of GRP and testing may have differed. The comparability of the two tests has not yet been fully established; however, studies using cholecystokinin have produced similar results in both taste reactivity tests (Eckel and Ossenkopp, 1994) and brief-exposure tests (Waldbillig and Bartness, 1982; Weingarten *et al.*, 1996). Therefore, the issue of time elapsed between injections of GRP and testing may be more critical. Few data are presently available adequately to address the effect of immediate versus delayed testing of GRP on feeding and taste. However, physiological reports indicate that GRP has a relatively brief half-life of disappearance of <3 min (Bloom *et al.*, 1983; Knigge *et*

al., 1984). The effects of GRP on feeding behavior are not currently assumed to be influenced by the timing of administration, likely due to GRP inducing release of other factors such as gastrin, which do not reach maximum levels until nearly 15 min post-GRP injection (Knigge *et al.*, 1984). Yet the taste responses reported here are clearly related to temporal factors. The timing of GRP administration and subsequent testing of its behavioral effects should be observed carefully in subsequent studies. Lastly, the similarity in licking behaviors of sucrose solutions for the second series of solutions following GRP injections and the first series of solutions following a 5 min delay after GRP injection represent the relative speed with which the effect of GRP on taste diminishes. Specifically, the first sucrose solutions encountered by the subjects immediately after GRP administration showed severely reduced lick totals. By the second presentation of each sucrose concentration, the effects of GRP were already reduced substantially, though not significantly. The same pattern of decreased effectiveness is seen within the test sessions of the 5 min delay GRP injection procedure. Though there is an overall effect of reduced licking following the 5 min delay procedure, the majority of decreased lick totals occurred during the first presentation of sucrose solutions. The second presentation of solutions results in lick totals more similar to results following saline injections than GRP injections. Taken together, the findings presented here demonstrate a decrease in the orosensory-guided responses to sucrose following peripheral GRP administration, though the effect diminishes within a matter of minutes after initial injection. Thus GRP may act, in part, by decreasing the oral reinforcing properties of food as a mechanism of action to reduce caloric intake.

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