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7-OH-DPAT selectively reduces intake of both chow and high fat diets in different food intake regimens

John-Andrews M. McQuade, Stephen C. Benoit, Stephen C. Woods, Randy J. Seeley*

Department of Psychiatry, University of Cincinnati, P.O. Box 670559, Cincinnati, OH 45267-0559, USA

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Abstract

Mesolimbic dopaminergic system activation correlates with ingestive behavior in numerous feeding regimens. DA release is enhanced by food intake following deprivation, amount of food consumed, and the palatability of the food consumed. The dopamine-3 receptor (D3-R) has a limited expression pattern that is restricted largely to the mesolimbic dopaminergic system. The D3-R has been hypothesized to inhibit DA-mediated reward, locomotion and motivation. To test the potential for an inhibitory role of the D3-R on food intake, we administered the D3-R agonist 7-OH-DPAT (5, 10 and 50 μg/kg ip) to rats that had ad libitum access to standard rodent chow (3.41 kcal/gm, 0.51 kcal/gm from fat) or a preferable, high fat (HF) (4.4 kcal/gm, 1.71 kcal/gm from fat). In the second set of experiments we administered 7-OH-DPAT (10, 50 and 100 μg/kg) to rats that had access to chow or HF diet for only 3 h per day (meal fed). In the third set of experiments we administered 7-OH-DPAT (10 and 50 μg/kg) to rats that had access to chow or HF diet after a 21-h food restriction. The 10 and 50 μg/kg doses significantly, but equally reduced intake of chow and HF diet in animals that were ad libitum fed. In animals that were meal-fed the dose response was effectively shifted to the right and the 10 μg/kg dose was ineffective at reducing intake. The 50 and 100 μg/kg doses significantly but equally reduced intake of both diets. In animals that were 21-h restricted and had access to chow both the 10 and 50 μg/kg doses were ineffective at reducing intake. However, in animals that had access to HF diet, 7-OH-DPAT dose-dependently reduced intake. These results support a potential role for the D3-R in ingestive behavior particularly in situations that involve a significant learned component.

Keywords: Food intake; Dopamine; D3-Receptor; High-fat diets

1. Introduction

The catecholiminergic neurotransmitter dopamine (DA) has been implicated in a variety of reinforcement and reward paradigms utilizing psychostimulants and natural rewards, such as food or water (see reviews, Koob, 1992; Spanagel and Weiss, 1999). DA release and metabolism has been monitored in the shell of the nucleus accumbens (NAcc) and has been demonstrated to be elevated by a variety of rewards (Hernandez and Hoebel, 1988; Mirenowicz and Schultz, 1996; Richardson and Gratton, 1996; Hajnal and Norgren, 2001). Feeding is one behavior that appears to be influenced by DA release. DA release is elevated in the nucleus accumbens (NAcc) of animals maintained at reduced body weight (Hernandez and Hoebel, 1988), access to a preferred, HF diet (Wilson et al., 1995; Martel and Fantino, 1996a,b) on a restricted feeding schedule (Radhakishun et al., 1988), conditioned responding for food (Hernandez and Hoebel, 1988), 20-min access to sucrose (Hajnal and Norgren, 2001) or after a short food deprivation (Yoshida et al., 1992; Westerink et al., 1994). The dopamine-1 and dopamine-2 receptor (D1 and D2-R) have been investigated as to their role in mediating the effects of DA using available selective drugs (Sidhu et al., 1986; Protais et al., 1994). D1 and D2-R antagonists reduce intake of sucrose and standard rodent chow in feeding paradigms (Schneider et al., 1986; Smith and Schneider, 1988; Muscat and Willner, 1989; Terry and Katz, 1992; Hsiao and Smith, 1995; Lutz et al., 2001).

* Corresponding author. Tel.: +1-513-558-6664; fax: +1-513-558-8990.
E-mail address: Randy.Seeley@uc.edu (R.J. Seeley).

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The D3-R has recently received attention for its potential role in locomotor behavior, reward-related behaviors, psychosis and Parkinson's disease (Levant, 1997; Joyce, 2001; Richtand et al., 2001). D3-Rs (protein and mRNA) are expressed predominantly in limbic brain (olfactory tubercle, shell of the nucleus accumbens and islands of Calleja) regions vital to a range of motivated behaviors (Richtand et al., 1995; Levant, 1998; Gurevich and Joyce, 1999; Diaz et al., 2000). It is hypothesized that activation of the D3-R functionally opposes D1/D2-R activation at the cellular level (Diaz et al., 1994; Ridray et al., 1998) and with regard to behavior (Sigala et al., 1997; Schwartz et al., 1998; Richtand et al., 2001). Pharmacological manipulation of the D3-R utilizing the mildly selective D3-R agonist, 7-OH-DPAT, has been shown to reduce consumption of 3% sucrose (Gilbert and Cooper, 1995). When assessed directly in a conditioned reward paradigm (Sutton et al., 2001), a progressive ratio schedule for food or intracranial self-stimulation (Depoortere et al., 1996), 7-OH-DPAT reduced responding at lower doses and increased responding at a higher dose. Moreover, the D3-R mutant mouse has been demonstrated to develop an enhanced conditioned place preference to amphetamine (Xu et al., 1997). The fact that D3-Rs are localized to mostly limbic regions suggests that low doses of 7-OH-DPAT may activate a D3-R mediated inhibition of reward-related behaviors.

Given the potential linkage between the D3-R and reward-related behaviors, we sought to determine the effect of 7-OH-DPAT on food intake. In particular, release of DA in the accumbens is enhanced with exposure to preferred foods. Thus, we hypothesized that 7-OH-DPAT acting on postsynaptic D3-R would reduce food intake but do so more potently in rats offered a preferred high-fat (HF) diet compared to standard laboratory chow. Further, Salamone (1992) and others have hypothesized that a critical distinction for understanding the function of DA is that DA antagonists more easily disrupt behaviors that involve significant learned components opposed to behaviors that do not (Salamone, 1992). Thus, we also tested the ability of 7-OH-DPAT to reduce food intake in a number of different food intake paradigms that differed in their reliance on learned food intake responses. If correct, we would expect 7-OH-DPAT to more effectively reduce food intake in paradigms that emphasized learned food intake responses.

2. Methods

2.1. Animals

All procedures were approved by the Institutional Animal Care and Use Committee at the University of Cincinnati. Male Long–Evans (Harlan, IN) weighing 200–250 g were housed individually in a vivarium with a 12:12-h light–dark schedule. The temperature of the room was maintained at 25 °C. All animals had ad libitum access to water. Animals used in ad libitum experiments had free access to standard rodent chow (Teklad, 3.41 kcal/g, 0.51 kcal/g from fat) or HF diet (Dyets, PA, 4.41 kcal/g, 1.71 kcal/g from fat). Animals used in meal-feeding experiments were restricted to 3 h of food access per day. Similarly, two groups of animals were established, animals with only 3 h access to chow or HF per day. Access to food began at lights out (1300 h) and ended 3 h later (1600 h). During the 3-h access period animals had ad libitum access to the food and water. Twenty-one hour food restricted animals were divided into two groups as in the other two experiments. Twenty-one hour restricted animals had ad libitum access to chow or HF diet until the restriction began. Animals were only restricted once a week for the duration of the experiment.

2.2. Drugs

The D3-R agonist 7-OH-DPAT ((±)-7-Hydroxy-dipropylaminotetralin HBr) (RBI, MA) was dissolved in 0.9% NaCl.

2.3. Experimental procedure

2.3.1. Ad libitum, meal-fed, and 21-h restricted dose response curves

Animals were maintained on chow or HF for at least 1 month prior to the ad libitum experiment. Doses of 7-OH-DPAT used in the ad libitum experiment were 0, 5, 10, 50, 100 μg/kg, subcutaneous. All doses were given in an order that was counterbalanced across subjects. On the day of injection, food was removed 2 h prior to the injection to equalize gastric contents. Injection of drug or saline preceded lights out and replacement of food by 15 min. Food intake was monitored for 3 h postinjection. Animals in the meal-feeding experiment were meal-fed chow or HF for a period of at least 3 weeks prior to experimentation. Doses of 7-OH-DPAT used in the meal feeding experiment were 0, 10, 25, 50 μg/kg sc. On experimental days, animals were injected with saline or drug 15 min prior to lights out and replacement of food. Twenty-one hour restricted animals were maintained on chow or HF for at least 2 weeks prior to experimentation. Animals began the restriction period 3 h into the dark cycle. Animals were injected with 0, 10, 50 μg/kg sc, 15 min prior to lights out on the following day. Food was returned when the lights went off. In all three experiments food intake was monitored at 30, 60, and 180 min.

2.4. Statistical analysis

Food intake analysis was done using repeated-measures analysis of variance (ANOVA) with factors of diet, drug and time. Drug dose was performed as a within-subjects design in every experiment. When appropriate, post hoc

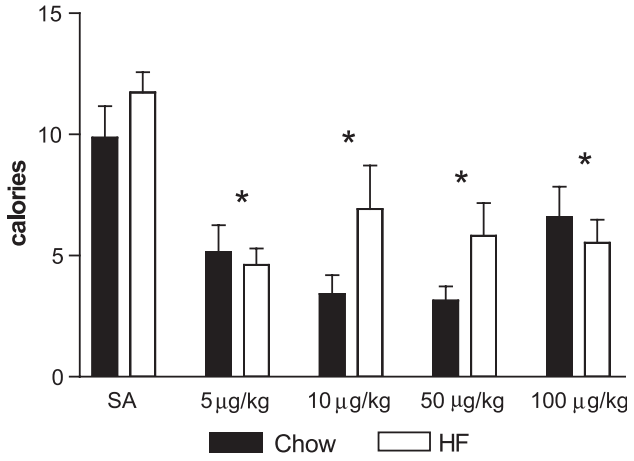

Fig. 1. Mean caloric intakes at 60-min of ad libitum animals (calories), chow (filled bars) and HF (clear bars) following intraperitoneal administration of either saline (SA) or 7-OH-DPAT (5,10, 50, and 100 µg/kg). * $P<.05$ compared to saline intake.

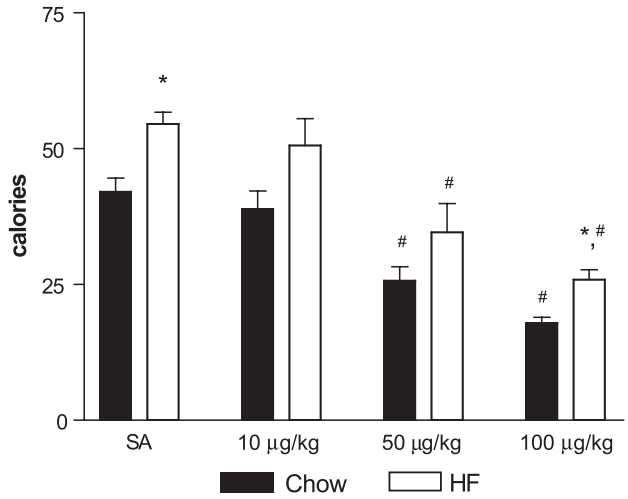

Fig. 2. Mean caloric intake at 60-min by meal fed animals, chow (filled bars) and HF (clear bars), following intraperitoneal administration of either saline (SA) or 7-OH-DPAT (10, 50, and 100 µg/kg). * $P<.05$ relative to chow, within dose; # $P<.05$ compared to saline intake.

analyses were performed using the least squares difference (LSD) test.

3. Results

3.1. 7-OH-DPAT, dose–response curves

3.1.1. Ad libitum

Administration of the D3-R agonist, 7-OH-DPAT, to animals in an ad libitum feeding schedule potently reduced food intake over the time course analyzed (Fig. 1). The data is normalized to calories per gram of chow or HF. The three-way ANOVA revealed an overall interaction of Diet × Drug × Time [$F(8,216)=2.17$; $P<.05$]. There was a main effect of drug on chow intake [$F(4,56)=11.58$; $P<.05$ and HF intake, $F(4,52)=12.83$; $P<.05$]. Post hoc analyses revealed that each dose significantly suppressed intake compared to saline ($P<.05$) (Table 1). Both 5 and 10 µg/kg doses of 7-OH-DPAT [$F(2,54)=5.30$; $P<.05$ and $F(2,54)=5.07$; $P<.05$] significantly reduced intake, as revealed by a three-way ANOVA (Drug × Diet × Time). ANOVA did not reveal a significant result with the other doses tested. Two-way ANOVA (Drug × Diet) revealed a trend for the 5µg/kg dose to differentially reduce intake of chow versus HF [$F(1,27)=2.15$; $P<.07$]. There was a trend at 10 µg/kg and 50 µg/kg to differentially affect intake of chow versus HF diet, $P=.07$ (Fig. 1).

3.1.2. Meal fed

Administration of 7-OH-DPAT to animals in a meal-feeding paradigm also potently reduced food intake [$F(6,108)=2.42$; $P<.05$] (Fig. 2). The low dose, 10 µg/kg, that was effective in reducing intake in the ad libitum paradigm was ineffective at reducing intake in the meal-fed animals with access to chow (Fig. 2). The other comparable doses of 50 and 100 µg/kg equally reduced intake in each intake paradigm. Interestingly, the higher doses assessed did reduce the intake of HF diet more then chow but only at the 3-h time points ($P<.05$) (Table 2).

Table 1
Mean (± S.E.M.) caloric intake over time of ad libitum fed animals

	Saline	5 µg/kg	10 µg/kg	50 µg/kg	100 µg/kg
30 min					
HF	10.9 ± 0.95[a]	2.77 ± 0.50 *	4.68 ± 1.42 *	4.45 ± 1.31 *	3.39 ± 0.84 *
Chow	7.61 ± 0.90[b]	3.52 ± 0.90 *	2.29 ± 0.76 *	2.06 ± 0.49 *	2.81 ± 0.49 *
60 min					
HF	11.7 ± 0.84	4.61 ± 0.69 *	6.91 ± 1.81 *	5.82 ± 1.35 *	5.53 ± 0.94 *
Chow	9.86 ± 1.30	5.15 ± 1.10 *	3.41 ± 0.77 *	3.14 ± 0.58 *	6.58 ± 1.27 *
180 min					
HF	13.7 ± 1.29	12.1 ± 1.76	13.7 ± 2.20	10.1 ± 2.29	7.75 ± 1.49 *
Chow	14.5 ± 1.52	10.6 ± 1.56 *	9.61 ± 1.25 *	8.30 ± 1.21 *	10.3 ± 1.67 *

Letters indicate difference between diets ($P<.05$).
* At least $P<.05$ relative to saline.

Table 2
Mean (± S.E.M.) caloric intake over time of meal-fed animals

	Saline	10 μg/kg	50 μg/kg	100 μg/kg
30 min				
HF	44.4 ± 2.49[a]	40.0 ± 3.69[a]	23.4 ± 3.82 *	18.6 ± 1.32 *,[a]
Chow	29.7 ± 2.35[b]	29.4 ± 2.17[b]	18.5 ± 2.45 *	10.7 ± 1.17 *,[b]
60 min				
HF	54.6 ± 2.10[a]	50.6 ± 4.95	34.6 ± 5.29 *	25.1 ± 1.82 *,[a]
Chow	42.1 ± 2.52[b]	38.9 ± 3.28	25.7 ± 2.61 *	17.9 ± 1.04 *,[b]
180 min				
HF	101.5 ± 4.97[a]	89.9 ± 7.59	73.7 ± 4.64 *	52.0 ± 4.18 *
Chow	76.9 ± 4.34[b]	74.0 ± 4.97	65.1 ± 2.84 *	55.4 ± 3.25 *

Letters indicate difference between diets ($P<.05$).
* At least $P<.05$ relative to saline.

3.1.3. Twenty-one hour food restriction

Administration of 7-OH-DPAT to animals that were 21-h food restricted reduced caloric intake of the preferable, HF diet without effect in animals with access to chow [Diet × Drug, $F(2,26)=5.80$, $P<.05$, Fig. 3]. Post hoc analyses revealed at 30 min the 50 μg/kg dose of 7-OH-DPAT significantly reduced intake of the HF diet ($P<.05$). Both doses of 7-OH-DAPT (10 and 50 μg/kg) significantly reduced intake of the HF diet at 60 min ($P<.05$). None of the doses of 7-OH-DPAT had an effect on chow intake (Table 3).

3.2. Percent of saline intake

Fig. 4A (chow) and B (HF) represents the data from the common doses (saline, 10 μg/kg, and 50 μg/kg) of all feeding regimens as percent saline intake. Since each feeding regimen elicited differing levels of caloric intake and we were interested in comparing across regimens the data are represented as a percent of the intake consumed after saline treatment. The four-way ANOVA did not reveal an overall interaction [$F(4,116)=0.38$, *ns*]. A two-way ANOVA did

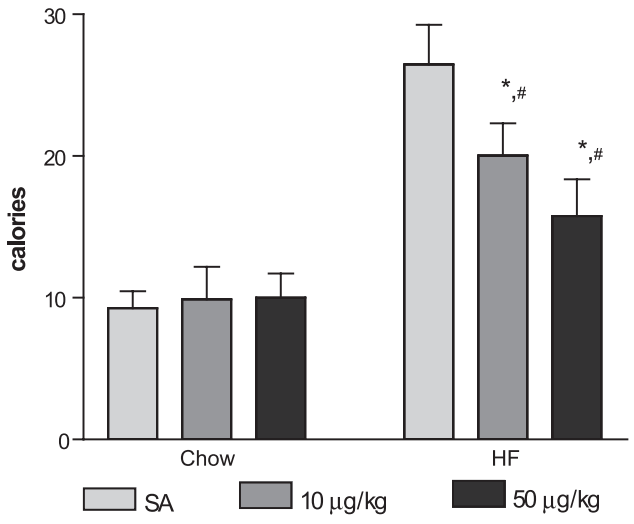

Fig. 3. Mean caloric intake at 60 min by 21-h food restricted animals following intraperitoneal administration of saline (SA) (grey bars), 10 μg/kg (dark grey), and 50 μg/kg (black) 7-OH-DPAT. * $P<.05$ relative to saline; # $P<.05$ relative to chow, within dose.

Table 3
Mean (± S.E.M.) caloric intake over time by meal-fed animals (ad libitum, 21-h restricted)

	Saline	10 μg/kg	50 μg/kg
30 min			
HF	22.1 ± 3.49[a]	17.9 ± 2.27[a]	13.6 ± 2.45 *,[a]
Chow	7.72 ± 0.93[b]	7.83 ± 1.64[b]	8.00 ± 1.89[b]
60 min			
HF	26.5 ± 2.80[a]	20.1 ± 2.27 *,[a]	15.8 ± 2.60 *,[a]
Chow	9.25 ± 1.22[b]	9.90 ± 2.28[b]	10.0 ± 1.89[b]
180 min			
HF	50.1 ± 4.32[a]	40.2 ± 3.88 *,[a]	41.1 ± 3.75[a]
Chow	24.7 ± 2.74[b]	27.9 ± 2.86[b]	26.2 ± 1.90[b]

Letters indicate difference between diets ($P<.05$.)
* At least $P<.05$ relative to saline.

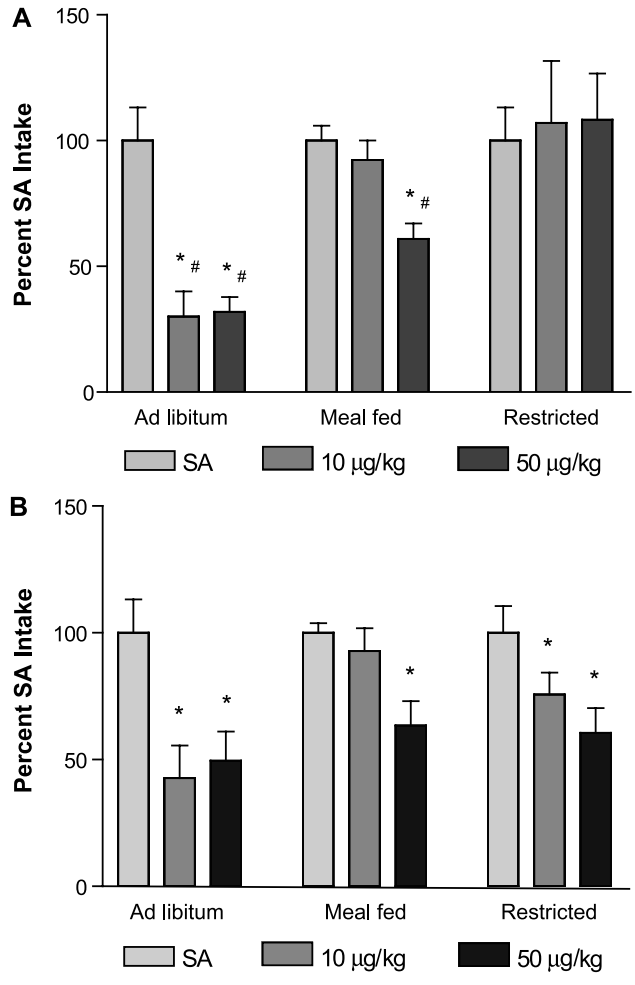

Fig. 4. (A) Percent saline intake of chow at 60 min in each of the three feeding regimens. * $P<.05$ relative to saline within each feeding regimen; # $P<.05$ within the dose of drug across the feeding regimens. (B) Percent saline intake of HF diet at 60 min in each of the three feeding regimens. * $P<.05$ relative to saline within each feeding regimen.

Table 4
Mean (± S.E.M.) body weight of rats on either diet on each of the three experimental regimens at the start of each experiment

	Ad libitum	Meal-fed	Food deprived
Chow	483.3 (± 8.3)	378.2 (± 11.8)	445.7 (± 13.3)
High-fat diet	518.6 (± 0.2)	456.6 (± 9.9)	486.6 (± 23.6)

reveal an interaction of Regimen × Drug [$F(4,116) = 10.3$, $P < .05$]. In addition, there was also an overall main effect of drug [$F(2,116) = 36.2$, $P < .05$]. Post hoc analysis indicated both the 10 and 50 μg/kg doses dose-dependently reduced intake of chow with respect to regimen ($P < .05$) (Fig. 4A). In contrast, there were no significantly different effects of these doses across regimen in animals with access to HF (Fig. 4B; see also data in Table 4).

4. Discussion

The results of this study indicate 7-OH-DPAT differentially reduces food intake with respect to feeding regimen and dose. The dose–response results did not confirm the initial hypothesis that 7-OH-DPAT selectively attenuates intake of the HF diet. We initially assessed D3-R activation in animals with ad libitum access to chow or a preferred, HF diet. Pretreatment with 7-OH-DPAT potently reduced intake of chow and HF equally at all doses tested, except 5 μg/kg which mildly reduced intake of HF diet more then chow at 30 min. There was a trend for 10 and 50 μg/kg to differentially reduce intake of HF diet and chow but this effect did not reach significance. When animals were meal-fed (3 h of access each day that could be predicted) the dose–response curve used to assess 7-OH-DPAT mediated disruption of intake was shifted to the right. The first effective significant reduction in intake in this feeding regimen was at a dose of 50 μg/kg. In this feeding regimen there were no significant differential effects of 7-OH-DPAT on diet. When animals were food restricted for 21 h, similarly to the meal-fed animals, but could not predict when food would be returned, none of the doses tested (10 and 50 μg/kg) significantly reduced intake of chow. In contrast, 7-OH-DPAT dose-dependently reduced intake of the preferable, HF diet in this feeding regimen.

Several issues potentially complicate the interpretation of these data. First, most dopamine drugs can have influences on motor behavior that may cause reductions in food intake that do not reflect a specific role in this motivated behavior. Given that 7-OH-DPAT was most effective in the ad libitum paradigm argues against a simple motor interpretation of these data. Moreover, in the deprived paradigm, the effect of 7-OH-DPAT was seen only in the animals consuming the HF diet. Nonspecific motor effects on food intake would be predicted to influence food intake equivalently on both diets.

Second, the selectivity of 7-OH-DPAT for the D3-R is highly dependent on dose. When locomotor behavior is used as the dependent measure, low doses appear to be specific to the D3-R but higher doses also activate D2-R as evidenced by 7-OH-DPAT influences in mice with targeted disruption of the D3-R (Levant et al., 1996). It is possible that doses that influence food intake are not selective for the D3-R and thus an important contribution of activation of D2-R cannot be ruled out.

Third, animals given access to diets containing differing amounts of fat gradually displayed a divergence in body weight, as expected. Despite the fact that doses were calculated on a per kilogram basis, we cannot completely eliminate potential pharmacokinetic explanations since we cannot account for possible differences in drug metabolism based on body weight or feeding regimen. Overall, in the dose–response curve set of experiments there was little effect of diet, only a significant effect of the drug on food intake. Thus, we concluded heavier (HF-fed) animals are not any more or less sensitive to administration of 7-OH-DPAT.

Finally, when any drug is given to animals and reductions in food intake are demonstrated, it is difficult to eliminate the possibility that it is the result of aversive properties of the drug. Consistent with that hypothesis, a dose of 100 μg/kg of 7-OH-DPAT produces a conditioned taste aversion (Bevins et al., 1996). However, the doses used in the current studies are considerably lower than those shown to produce a taste aversion. Further, the complicated nature of the differences in ability of 7-OH-DPAT across diets and paradigms do not support the hypothesis that the anorexic effects are secondary to its aversive effects.

Nevertheless, the differential ability of 7-OH-DPAT to influence food intake in the different regimens is intriguing. We initially hypothesized that intake of a preferred high-fat diet would be more readily influenced by 7-OH-DPAT compared to the less preferred chow diet. Clearly this prediction was not borne out in the data for both the ad libitum and meal-fed regimens where 7-OH-DPAT was equally effective on both diets. Thus, consumption of a highly preferred diet is not inherently more dependent on a 7-OH-DPAT sensitive circuit. Interestingly, in the paradigm where rats are deprived for 21-h and then given access to either chow of HF diet, 7-OH-DPAT was much more effective at disrupting HF than chow intake. This outcome implies a critical role for dopamine receptors in the much higher caloric intakes consumed by rats exposed to HF diet after a fast but not in the lower caloric intake in rats exposed to chow. Clearly this lower calorie consumption is sufficient to replenish the current metabolic needs of the animal and thus our conclusion is that the 7-OH-DPAT-sensitive circuit is not critical to animals responding to these metabolic needs.

The second issue is that within a specific dietary condition, the response to 7-OH-DPAT was different depending on the paradigm. While all of the paradigms had rats consuming food at the onset of the dark, they differ in the levels of metabolic need and the degree to which the

responses are conditioned. Both the meal fed and 21-h deprived paradigms involve significant periods of food deprivation while the ad libitum paradigm does not. Within the chow-fed group, however, the level of deprivation could not predict the response to 7-OH-DPAT since it was effective in the meal-fed and not in animals that were simply deprived.

Both the meal-fed and ad libitum paradigms share the fact that rats are conditioned to eat at a specific time. In the case of the meal-fed paradigm, that time is dictated by the time of access while it is determined by the rat in the ad libitum paradigm. The role for learning in the meal-feeding paradigm is clear since it take almost 2 weeks before rats are sufficiently conditioned to manage to consume sufficient calories to maintain their body weight. Ad libitum fed animals tend to take their largest meal at lights out (LeMagnen and Tallon, 1966). The onset of the dark phase can provide the animals a conditioned stimulus to initiate a meal (Woods and Strubbe, 1994). It has been argued that rats become conditioned to eat their largest meal at the onset of the dark phase which allows them to anticipate large nutrient influx and mount anticipatory responses to lessen potential deleterious effects of the homeostatic disturbance induced by those nutrients (Woods and Strubbe, 1994). In this scheme, conditioned cues elicit numerous physiological changes (e.g., cephalic insulin secretion) that allow relatively large meals to be consumed. Salamone (1992) has hypothesized that dopamine signaling is most critical to learned behaviors rather than unconditioned behaviors and cites the fact that dopamine release is larger during conditioned responding and various dopamine antagonists are more effective at disrupting conditioned rather than unconditioned responding. Thus, one interpretation of these data is that 7-OH-DPAT acting on postsynaptic D3-Rs disrupts food intake behavior in both the ad libitum and meal-fed paradigms because both involve significant conditioned responses.

The difficulty with that interpretation is that 7-OH-DPAT does reduce intake in the HF-fed rats in the deprivation condition. One way to resolve this discrepancy is to hypothesize that the much higher caloric intakes of rats accustomed to eating HF diets than rats accustomed to eating chow after the same deprivation period relies importantly on learned responses. After all, rats spend several weeks on the HF diet prior to the experiment and it is reasonable that rats learn a great deal about the postingestive consequences of the diet that may enable them to eat larger quantities. In this scenario, the reason that rats after a fast eat nearly double the calories of the HF diet and the reason why intake can be disrupted by 7-OH-DPAT is the same, both depend on significant conditioned responses.

This manuscript documents a previously unreported finding of the D3-R agonist 7-OH-DPAT on food intake. While the initial dose–response curve results did not support the hypothesis that 7-OH-DPAT would have differential effects on feeding with respect to diet, interesting results emerged that both the diet and the feeding regimen influence the anorexic response to 7-OH-DPAT. We suggest that 7-OH-DPAT may have differential effects on feeding through the acquisition of behavior associated with learned responses and conditioning.

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