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Differential actions of dopamine receptor antagonism in rats upon food intake elicited by either mercaptoacetate or exposure to a palatable high-fat diet

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Abstract

Selective dopamine receptor antagonists have been shown to reduce food intake of rats under such regulatory challenge conditions as food deprivation and 2-deoxy-D-glucose-induced glucoprivation, and under such palatable conditions as acute exposure to sucrose solutions. Food intake is increased following either pretreatment with the free fatty acid oxidation inhibitor, mercaptoacetate (MA), or acute exposure to a palatable high-fat source. The present study examined whether equimolar doses (50–800 nmol/kg, sc) of either the selective D_1 receptor antagonist, SCH23390, or the selective D_2 receptor antagonist, raclopride, would alter food intake elicited by either MA (70 mg/kg, ip) or acute exposure to a high-fat diet (67% ground rat chow, 33% vegetable shortening). SCH23390 significantly and dose-dependently reduced MA-induced feeding with the two higher (400 and 800 nmol/kg) doses eliminating this response after the first 2 h and the two lower (50 and 200 nmol/kg) doses preventing the occurrence of significant MA-induced feeding. Raclopride eliminated MA-induced feeding at the highest dose, and produced dose-dependent reductions at lower doses. A different pattern of dopamine antagonist effects emerged for high-fat intake. The identical dose range of SCH23390 failed to alter high-fat intake. In contrast, whereas the highest (800 nmol/kg) dose of raclopride significantly reduced high-fat intake after 1 h, the middle (200 and 400 nmol/kg) doses of raclopride significantly increased high-fat intake after 2 h. These data are discussed in terms of the modulatory actions of dopamine upon food intake, of the differential actions of dopamine receptor subtypes upon intake under challenge and palatable conditions, and of the potential participation of presynaptic and postsynaptic receptor populations in these responses.

Keywords: Dopamine; D_1 receptor; D_2 receptor; SCH23390; Raclopride; Mercaptoacetate; High-fat diet; Food intake

1. Introduction

The neural control of food intake is dependent upon a number of factors, including the homeostatic state of the animal and the type of ingested food. Among a large number of bioactive neurotransmitters and neuropeptides, dopamine has exercised a long-standing role in the mediation of ingestion, particularly in reinforcement mechanisms related to food and water intake (Agmo et al., 1993, 1995; Berridge and Robinson, 1998; Nakajima, 1989). Dopamine acts at multiple receptors (D_1–D_5) with two distinct receptor superfamilies termed D_1 and D_2 (see review: Gingrich and Caron, 1993). There is considerable overlap in the localization of both types of these receptors in the brain as revealed by autoradiographic techniques (e.g., Boyson et al., 1986). Selective dopamine receptor antagonists have been developed that bind specifically and selectively at D_1 (SCH23390: Christensen et al., 1984; Iorio et al., 1983; Sidhu et al., 1986) and D_2 (raclopride: Kopp et al., 1992; Protais et al., 1994) receptors. Each of these antagonists is intimately involved in reducing the ability of rewarding stimuli to control responding (see reviews: Beninger and Miller, 1998; Beninger et al., 1987; Berridge and Robinson, 1998; Nakajima, 1989; Willner et al., 1990). This is best seen in the ability of both dopamine receptor antagonists to dose-dependently reduce sucrose intake (Schneider et al., 1986a,b, 1990; Smith, 1995; Yu et al., 2000a,b). Moreover, both D_1 and D_2 antagonists are also capable of reducing

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food intake under regulatory challenge conditions including food deprivation (Ferrari et al., 1992; Gilbert and Cooper, 1985; Hobbs et al., 1994; Martin-Iverson and Dourish, 1988; Rusk and Cooper, 1989) and 2-deoxy-D-glucose-induced glucoprivation (Berthoud and Mogenson, 1977; Schaefer et al., 1994).

The purpose of the present study is to investigate the role of dopamine receptor subtype antagonists in ingestive situations related to fat metabolism and fat intake. Feeding (Langhans and Scharrer, 1987; Ritter and Taylor, 1989, 1990; Scharrer and Langhans, 1986) can be elicited by lipoprivation induced by the free fatty acid oxidation inhibitor, mercaptoacetate (MA: thioglycolic acid; Bauche et al., 1981, 1983). MA activates several brain regions involved in ingestive behavior including increased c-fos immunoreactivity in the nucleus tractus solitarius, the central nucleus of the amygdala and the parabrachial nucleus (Ritter and Dinh, 1994). Feeding and increased c-fos activation are reduced by subdiaphragmatic vagotomy and capsaicin treatment (Langhans and Scharrer, 1987; Ritter and Taylor, 1989, 1990; Ritter and Dinh, 1994; Ritter et al., 1994). Lesion studies reveal a similar pattern of critical sites at which damage reduced the magnitude of MA-induced feeding including the area postrema, nucleus tractus solitarius, parabrachial nucleus and central amygdala (Bird et al., 1983; Calingasan and Ritter, 1993; Ritter and Hutton, 1995). Dietary history of low, medium- or high-fat diets can influence the potency of MA-induced feeding (Singer-Koegler et al., 1996), and MA increases carbohydrate and protein intake in macronutrient preference studies (Singer et al., 1998). Pharmacological studies have demonstrated that MA-induced feeding can be reduced by general and selective opioid and adrenergic antagonists, as well as by dopaminergic and serotonergic agonists (Garosi et al., 1995; Stein et al., 2000). Insofar as dopaminergic agonists are concerned, both D-amphetamine and lisuride, at doses that promote anorexia, significantly reduced MA-induced feeding (Garosi et al., 1995). It should be noted that dopamine receptor agonists and antagonists can produce decreases in feeding under a variety of ingestive situations (Arneric et al., 1982; Barzaghi et al., 1973; Blundell and Latham, 1978; Heffner et al.,1977; Hobbs et al., 1994; Salamone, 1986, 1988; Schaefer et al., 1994; Willner et al., 1985; Wise and Colle, 1984; Wise and Raptis, 1986), presumably through different modulatory mechanisms of action. Therefore, the first goal of the present study was to examine whether either the D_1 antagonist, SCH23390, or the D_2 antagonist, raclopride, significantly and dose-dependently altered MA-induced feeding.

Evidence has suggested a correlation between dopamine and fat intake (e.g., Routh et al., 1990; Weatherford et al., 1991; Zimmer et al., 1998, 2000). Another means by which dopamine can be evaluated for its role in regulation of fat is to examine whether selective D_1 and D_2 receptor antagonists alter the increased intake observed following exposure to a palatable high-fat source. Using the sham-feeding technique in adult and preweanling rats, Smith et al. have demonstrated that corn oil induces intake (Ackerman et al., 1992; Mindell et al., 1990; Smith and Greenberg, 1991), and that the D_1 antagonist, SCH23390, and the D_2 antagonist, raclopride, each dose-dependently decreased corn oil intake in sham-feeding rats in a 30-min test (Weatherford et al., 1988, 1990). A solid high-fat diet constitutes another palatable source of fat intake, increasing intake after brief (2 h) exposure to the stimulus (Islam and Bodnar, 1990; Sclafani, 1978). The second goal of the present study was to examine whether equimolar doses of SCH23390 and raclopride significantly altered this form of high-fat intake over a 2-h time course.

2. Methods

2.1. Subjects and baseline protocol

Separate groups of 20 male albino Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA, 250–275 g) were used for the MA and high-fat protocols. Both groups were housed individually in wire mesh cages, and were maintained on a 12-h light (0700 hours): 12-h dark (1900 hours) cycle with Purina rat chow and water available ad libitum.

2.2. MA protocol

This group of rats was tested at 4–8 h into the light cycle during which rats consume minimal amounts of food. Preweighed pellets (+0.1 g) were placed directly on the floor of the wire mesh cage to optimize accessibility. Cumulative intakes were assessed after 1, 2 and 4 h, adjusting for spillage that was collected on paper under the cage. Baseline measures were collected until rats stopped novelty feeding, and displayed expected low levels of intake. Rats typically took three to five sessions to meet this requisite criterion. Following these baseline determinations, the rats were given intraperitoneal injections of mercaptoacetic acid (70 mg/kg, thioglycolic acid, Sigma, St. Louis, MO) dissolved in distilled water, and intake was assessed as described above. Eighteen of the 20 rats displayed significant feeding in response to this dose of MA, and continued in the paradigm in two groups matched for the magnitude of MA-induced food intake. One group was given the D_1 antagonist, SCH23390, at ascending subcutaneously administered doses of 50, 200, 400 and 800 nmol/kg, followed by the D_2 antagonist, raclopride at descending doses of 800, 400, 200 and 50 nmol/kg, while the other group received raclopride in ascending doses of 50, 200, 400 and 800 nmol/kg followed by SCH23390 at descending doses of 800, 400, 200 and 50 nmol/kg to control for potential order effects. MA (70 mg/kg, ip) was administered 30 min after antagonist treatments. A minimum of 72 h elapsed between succeeding antagonist injection conditions.

2.3. High-fat protocol

After 1 week of acclimation to the laboratory, this group of rats was exposed for 2 h each day at 3–5 h into the light cycle to a food cup containing a preweighed high-fat diet (67% ground Purina rat chow, 33% vegetable shortening (Pathmark); 5.5 kcal/g: 11.3% protein, 61.3% fat, 27.4% carbohydrate) in their cages. Intake (+0.1 g) was measured after 1 and 2 h. The rat chow was removed during these testing sessions and was returned after testing; water was available ad libitum during testing. All rats were weighed at 1-week intervals. Rats were considered adjusted to the high-fat diet if they consumed a minimum of 2 g each day for 2 consecutive days. Most rats met this criterion typically within 2–3 days, but all satisfied the criterion by 10 days of exposure.

Following baseline procedures, all rats received a vehicle control condition (0.9% normal saline, 1 ml/kg, sc) and 20 min thereafter were exposed to the high-fat diet with intake measured after 1 and 2 h. All rats displayed normal high-fat intake that failed to differ from the baseline criterion following vehicle treatment (data not shown). Two subgroups of rats were matched for vehicle-induced high-fat intakes. The first subgroup received the D_1 receptor antagonist, SCH23390, at ascending doses of 50, 200, 400 and 800 nmol/kg, while the second subgroup received the D_2 receptor antagonist, raclopride, at ascending doses of 50, 200, 400 and 800 nmol/kg. Both antagonists were dissolved in 0.9% normal saline and administered subcutaneously at a concentration of 1 ml/kg. Intervals between injections were typically 72 h to allow clearance of these reversible antagonists. Twenty minutes after each injection, high-fat intake was again assessed after 1 and 2 h. To insure control of potential order effects, the order of injections were counterbalanced across and within the subgroups in that each initially received vehicle, an ascending series of injections of one of the antagonists, a descending series of the other antagonist and a final vehicle treatment.

2.4. Statistics

Repeated-measures one-way analyses of variance were performed to examine alterations in cumulative chow intake among control, MA and the different antagonist–MA conditions after 1, 2 and 4 h, as well as to examine alterations in high-fat intake among vehicle and antagonist conditions after 1 and 2 h. Dunnett comparisons ($P<.05$) examined whether MA and individual doses of the antagonists paired with MA significantly altered intake relative to control values, and also examined whether individual doses of the antagonists paired with MA significantly altered intake relative to MA alone. In the high-fat protocol, Dunnett comparisons were performed to determine significant drug dose effects relative to vehicle treatment.

3. Results

3.1. SCH23390, raclopride and MA-induced intake

Significant differences were observed in food intake among control and the different MA conditions after 1 [$F(9,153)=6.22$, $P<.0001$], 2 [$F=5.93$, $P<.0001$] and 4 h [$F=3.67$, $P<.0003$]. Fig. 1 displays the expected significant increase in food intake following MA relative to vehicle control values after 1 and 2 h. With respect to D_1 receptor antagonist actions of SCH23390, a significant time-dependent and dose-dependent reduction in MA-induced feeding was observed such that the higher 400 and 800 nmol/kg doses of SCH23390 eliminated MA-induced feeding after 1 and 2 h (Fig. 1, upper panel), and prevented significant increases in MA-induced feeding after 4 h (data not shown). The two lower (50 and 200 nmol/kg) doses of SCH23390 paired with MA prevented the expression of significant MA-induced feeding across the time course. With respect to D_2 receptor antagonist actions of raclopride, a significant time-dependent and dose-dependent reduction in MA-induced feeding was also observed such that the highest 800 nmol/kg dose of raclopride eliminated MA-induced feeding after 1 and 2 h (Fig. 1, lower panel), and prevented significant increases in MA-induced feeding after 4 h (data not shown). The two middle (200 and 400 nmol/

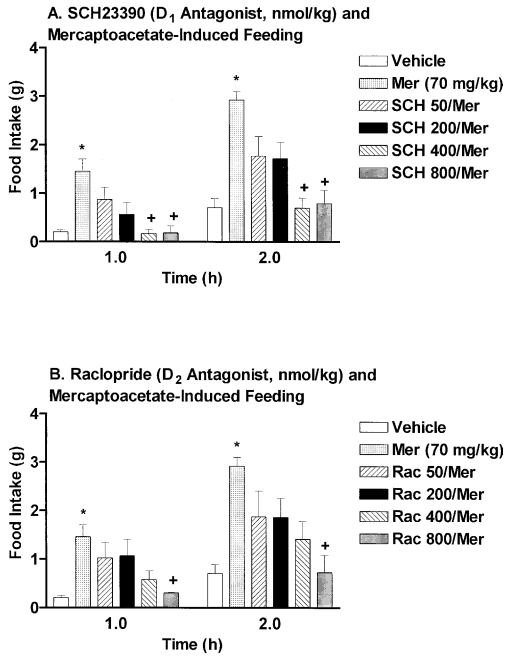

Fig. 1. Alterations in food intake (g, +S.E.M.) as a function of subcutaneous pretreatment of equimolar doses of either D_1 (SCH23390, upper panel) or D_2 (raclopride, lower panel) antagonists followed by MA over the first 2 h of a 4-h time course. The asterisks denote significant differences in MA-induced feeding relative to corresponding vehicle control values, and the crosses denote significant differences in intake following antagonist–MA combinations relative to MA alone (Dunnett comparisons, $P<.05$).

kg) doses of raclopride paired with MA prevented the expression of significant MA-induced feeding across the time course. Pairing of the lowest (50 nmol/kg) dose of raclopride with MA resulted in significant increases in intake after 4 h (data not shown).

3.2. SCH23390 and high-fat intake

Significant differences failed to be observed in high-fat intake following vehicle and SCH23390 treatments after 1 [$F(4,76) = 2.12$, ns] and 2 h ($F = 1.32$, ns). The top panel of Fig. 2 summarizes the failure of SCH23390 to significantly alter high-fat intake after 1 and 2 h.

3.3. Raclopride and high-fat intake

Significant differences were observed in high-fat intake following vehicle and raclopride treatments after 1 [$F(4,76) = 6.09$, $P < .0003$] and 2 h ($F = 6.61$, $P < .0001$). Dunnett comparisons revealed a biphasic and time-dependent effect of raclopride-induced actions upon high-fat intake. The bottom panel of Fig. 2 illustrates that the highest (800 nmol/kg), but not the three lower raclopride dose significantly decreased high-fat intake after 1 h; this suppressive effect dissipated after 2 h. In contrast, the middle (200 and 400 nmol/kg) doses of raclopride significantly increased high-fat intake after 2 h with non-significant increases noted after 1 h (Fig. 2, bottom panel). The lowest dose of raclopride was without effect at any time point.

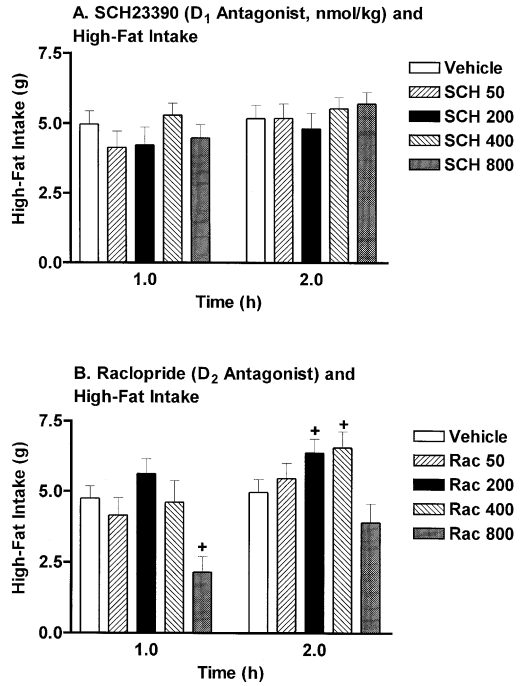

Fig. 2. Alterations in high-fat intake (g, +S.E.M.) as a function of systemic administration of different equimolar doses of either the D_1 antagonist, SCH23390 (upper panel) or the D_2 antagonist, raclopride (lower panel) over a 2-h time course. The crosses denote significant changes in high-fat intake (Dunnett comparisons, $P < .05$) relative to corresponding vehicle values.

4. Discussion

4.1. Dopamine receptor antagonism and MA-induced intake

The respective abilities of the selective dopamine receptor antagonists acting at D_1 (SCH23390) and D_2 (raclopride) receptor subtypes to dose-dependently reduce MA-induced feeding extends the types of regulatory challenge conditions under which these receptors play an important role. Thus, both antagonists also reduced food intake following such regulatory challenges as food deprivation (Ferrari et al., 1992; Hobbs et al., 1994; Koechling et al., 1988) and 2-deoxy-D-glucose-induced glucoprivation (Berthoud and Mogenson, 1977; Schaefer et al., 1994). A previous study (Garosi et al., 1995) found that pretreatment with the dopamine receptor agonists, D-amphetamine and lisuride, each significantly reduced MA-induced feeding, raising the question as to why dopamine receptor agonists and dopamine receptor antagonists both exert the same effects on this form of ingestive behavior. First, it should be noted that dopamine receptor agonists also produce significant reductions in deprivation-induced feeding (Gilbert and Cooper, 1985; Hobbs et al., 1994; Martin-Iverson and Dourish, 1988; Rusk and Cooper, 1989) and glucoprivic feeding (Schaefer et al., 1994) to the same degree and with the same relative potency as dopamine receptor antagonists. That agonists and antagonists of a specific dopaminergic receptor subtype (e.g., D_1 or D_2) produce similar directions of effects upon a given behavior suggests that they may be acting at different sites and/or different mechanisms related to the behavior. Such a view is consistent with similar patterns observed for dopamine effects in the mediation of the negatively reinforcing aspects of addiction (Wise and Bozarth, 1987), the positively reinforcing aspects of addiction (Stewart et al., 1984; Wise and Bozarth, 1987) and the incentive-sensitization theory of addiction (Robinson and Berridge, 1993). Therefore, specifically for MA-induced feeding, it appears that either overstimulation of dopamine receptors with direct or indirect agonists, or blockade of dopamine receptors with selective antagonists reduce MA-induced feeding through a perturbation of normal dopaminergic transmission in sites related to MA-induced feeding such as the central nucleus of the amygdala (Ritter and Hutton, 1995).

This modulatory role for dopamine in mediating MA-induced feeding constitutes only one aspect of other anatomical and neurochemical controls over this ingestive response. Thus, the use of c-fos immunocytochemistry, as well as selective lesion studies have identified the nucleus tractus solitarius, area postrema, the central nucleus of the amygdala and the parabrachial nucleus as sites mediating

MA-induced feeding (Bird et al., 1983; Calingasan and Ritter, 1993; Ritter and Dinh, 1994; Ritter and Hutton, 1995). Garosi et al. (1995) found that agonists at serotonergic receptors and antagonists at α_2-adrenergic receptors each reduce MA-induced feeding. Further, galanin terminals in the area postrema and nucleus of the solitary tract also appear to be involved in MA-induced feeding (Koegler and Ritter, 1998). A recent study in our laboratory (Stein et al., 2000) found that μ, δ and κ opioid receptors are all involved in the mediation of MA-induced feeding through the abilities of general and selective opioid antagonists and antisense oligodeoxynucleotides directed against each opioid receptor clone to reduce this response. The lack of pharmacological specificity mediating the ingestive effects of MA is not surprising given the complex afferent, modulatory and efferent signals required for the successful completion of this important regulatory response.

4.2. Dopamine receptor antagonism and high-fat intake

In addition to the above-cited effects upon intake under regulatory challenges, previous studies showed that D_1 and D_2 receptor antagonists are capable of reducing sucrose intake (Schneider et al., 1986a,b, 1990; Smith, 1995; Yu et al., 2000a,b). Further, rats tested under sham-feeding conditions, which minimizes postingestive intake and depends upon the orosensory components of the ingestive stimulus, displayed significant dose-dependent decreases in intake of a palatable corn-oil solution following D_1 and D_2 receptor antagonists (Weatherford et al., 1988, 1990). Therefore, it was hypothesized that SCH23390 and raclopride should dose-dependently reduce intake of a solid high-fat diet in real-feeding rats. These hypotheses were not fully confirmed in the present study. The D_1 antagonist, SCH23390, failed to significantly alter high-fat intake with the 50 and 200 nmol/kg doses slightly, but not significantly, reducing intake after 1 h. Equimolar doses of the D_2 antagonist, raclopride produced a biphasic effect upon high-fat feeding with the highest 800 nmol/kg dose significantly though transiently reducing high-fat intake after 1 h, and the middle 200 and 400 nmol/kg doses significantly increasing high-fat intake after 2 h. These unexpected findings emphasize the significance of the environmental and physiological circumstances and type of ingestate in determining the effects that D_1 and D_2 antagonists have on their ability to modulate ingestive responses to a palatable diet.

The reductions in intake of sucrose or a combined sucrose–saccharin solution by both SCH23390 and raclopride have been observed in both real-feeding and sham-feeding rats with a similar potency and magnitude (Schneider et al., 1986a; 1989; Yu et al., 2000a,b), suggesting that these antagonists are exerting their effects by acting on the orosensory characteristics of the palatable carbohydrate stimulus. Indeed, both antagonists equipotently block the expression of flavor preferences conditioned by the sweet taste of sucrose in real-feeding (Hsiao and Smith, 1995) and sham-feeding (Yu et al., 2000a,b) rats. Similarly, the increased intake of a high-fat corn oil diet appears to be driven by the palatable orosensory characteristics of the ingestate (Ackerman et al., 1992; Mindell et al., 1990; Smith and Greenberg, 1991), and this response is decreased by a similar dose-dependent dose range of D_1 and D_2 antagonists in sham-feeding rats (Weatherford et al., 1988, 1990). Why then would a different pattern of antagonist results be observed with intake of a solid high-fat diet in real-feeding rats? Part of the answer may be explained by the different pattern of results of dopaminergic antagonists on the acquisition and expression of preferences conditioned by intragastric sucrose infusions. In contrast to the dose-dependent and equipotent decreases in the expression of flavor preferences conditioned by the sweet taste of sucrose in sham-feeding rats by D_1 and D_2 antagonists (Yu et al., 2000a,b), D_1 and D_2 antagonists affect the expression of preferences conditioned by intragastric sucrose infusions only at high doses that may also interfere with motor performance (Azzara et al., 2000). Further, whereas neither SCH23390 nor raclopride affect the acquisition of flavor preferences conditioned by sucrose in sham-feeding rats (Yu et al., 2000b), the former, but not the latter, blocks the acquisition of preferences conditioned by intragastric sucrose infusions (Azzara et al., 2000), suggesting differential dopaminergic modulation of orosensory and postingestive consequences of the simple carbohydrate. The present finding of a lack of D_1 antagonist effects and a biphasic action of D_2 antagonism upon solid high-fat intake in real-feeding rats suggests that overall (orosensory + postingestive) activation of ingestion is mediated differently by dopamine antagonists than activation of one component (e.g., sham-feeding: Weatherford et al., 1988, 1990).

One complicating interpretative factor in analyzing dopamine receptor antagonist-induced reductions in behavioral studies is the potential involvement of sensori-motor dysfunction (e.g., Pecina et al., 1997). Therefore, one cannot conclusively tell whether the dopamine antagonists are reducing the reinforcement or hedonic qualities of the stimulus, or whether subtle sensori-motor deficits are impairing the animal's performance. However, the present experiments used equimolar doses of both antagonists that previously produced dose-dependent reductions in sucrose intake in sham-feeding and real-feeding rats, in corn oil intake in sham-feeding rats and in those regulatory challenge responses to deprivation as well as glucoprivic and lipoprivic stimuli (Berthoud and Mogenson, 1977; Ferrari et al., 1992; Garosi et al., 1995; Gilbert and Cooper, 1985; Hobbs et al., 1994; Martin-Iverson and Dourish, 1988; Rusk and Cooper, 1989; Schaefer et al., 1994; Schneider et al., 1986a,b, 1989, 1990; Weatherford et al., 1988, 1990; Yu et al., 2000a,b). If each and every one of these effects were due to sensori-motor deficits, then one would expect a similar pattern of effects upon high-fat intake in real-feeding rats. That SCH23390 failed to alter high-fat intake at any of the doses in this range strongly suggests that the reductions noted for this antagonist in the other paradigms were due to antagonist-induced alterations in the specific hedonic or

reinforcement process. Further, that raclopride enhanced high-fat intake in the present paradigm strongly suggests that the reductions noted for this antagonist at these doses in the other paradigms were again due to antagonist-induced alterations in the specific hedonic or reinforcement process.

The ability of a high (800 nmol/kg) raclopride dose to reduce solid-high-fat intake in real-feeding rats is consistent with previously described D_2 antagonist actions upon the different forms of food intake described above. It is of interest to determine or at least propose the mechanism(s) of action by which raclopride significantly stimulated fat intake over the first hour of high-fat intake at lower antagonist doses. Dopamine receptors are found at both presynaptic and postsynaptic sites (see review: Langer, 1997), and it appears that the D_2 receptor subtype predominates at the presynaptic autoreceptor site (see review: White, 1996), which was confirmed in D_2 receptor-deficient mice (L'hirondel et al., 1998). D_2 receptor agonists often have a dose-dependent biphasic functional action, suggesting that low doses preferentially stimulate autoreceptors and thereby decreasing dopamine release (e.g., Henry et al., 1998; Pitts et al., 1995). Dopamine release has been shown to be a consequence of exposure to ingestive stimuli, particularly palatable stimuli, including fat sources (Bassareo and DiChiara, 1999; Martel and Fantino, 1996a,b; Westerlink et al., 1994, 1997). One potential mechanism by which raclopride would stimulate high-fat intake in real-feeding rats is that low doses of this antagonist would preferentially block presynaptic dopamine autoreceptors, thereby disinhibiting these synapses, allowing further dopamine release in response to the high-fat stimulus, and thereby increasing intake. Pucak and Grace (1994) have demonstrated that systemic administration of the D_2 antagonist, sulpiride increased firing rates of dopamine neurons through such autoreceptor disinhibition. Further testing of this hypothesis should particularly examine raclopride's dose-dependent actions upon high-fat intake following intracerebral administration into sites displaying food-stimulated dopamine release such as the shell region of the nucleus accumbens. In any case, these differential effects indicate that overall concepts implicating dopamine in reinforcement mechanisms related to food and water intake and dopamine antagonists in reducing the ability of rewarding stimuli to control responding (see reviews: Agmo et al., 1993, 1995; Beninger and Miller, 1998; Beninger et al., 1987; Berridge and Robinson, 1998; Nakajima, 1989; Willner et al., 1990) should be modified and reconsidered in light of these data.

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