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ORIGINAL INVESTIGATION

Selection of sucrose concentration depends on the effort required to obtain it: studies using tetrabenazine, D_1, D_2, and D_3 receptor antagonists

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Abstract
Rationale Low doses of dopamine (DA) antagonists and accumbens DA depletions reduce food-reinforced instrumental behavior but *do not* impair primary food motivation, causing animals to reallocate behavior away from food-reinforced tasks with high response requirements and select less effortful alternatives. *However, it is uncertain if this same pattern of effects would occur if sucrose was used as the reinforcer.*
Objectives These experiments studied the impact of DA depletion and antagonism on performance of an effort-related choice task using sucrose as the reinforcer, as well as sucrose consumption, preference, and taste reactivity tests.
Methods The effects of DA manipulations were assessed using a task in which rats chose between lever pressing on a fixed ratio 7 schedule for 5.0 % sucrose versus freely consuming a less concentrated solution (0.3 %).
Results The DA depleting agent tetrabenazine shifted effort-related choice, decreasing lever pressing for 5.0 % sucrose but increasing intake of the concurrently available 0.3 % sucrose. Tetrabenazine did not affect sucrose appetitive taste reactivity, or sucrose consumption or preference, in free consumption tests. The D_1 antagonist ecopipam and the D_2 antagonist haloperidol also shifted choice behavior at doses that did not alter sucrose consumption or preference. In contrast, sucrose preexposure reduced consumption across all conditions. D_3 antagonism had no effects.
Conclusions D_1 and D_2 receptor blockade and DA depletion reduce the tendency to work for sucrose under conditions that leave fundamental aspects of sucrose motivation (intake, preference, hedonic reactivity) intact. These findings have implications for studies employing sucrose intake or preference in animal models of depression.

Keywords Motivation · Anergia · Anhedonia · Dopamine · Decision making · Depression

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Introduction

Motivation is a multifaceted process, with directional aspects that select specific stimuli toward which behavior is targeted, and activational aspects that enable animals to perform with the vigor or persistence necessary for instigating and sustaining actions that obtain those stimuli (Cofer and Appley 1964; Salamone 1988, 1992; Salamone et al. 1997). Organisms are capable of making vigorous instrumental responses in order to gain access to significant stimuli, and their behavior can reflect a selection process, in which the value of a stimulus (e.g., taste of a food) relative to the cost of obtaining it (e.g., nature of the instrumental response) is an important determinant of behavioral output. Considerable evidence shows that interference with dopamine (DA) transmission alters activational aspects of motivated behavior, while leaving other aspects (e.g., appetite, primary food motivation, or reinforcement) relatively unaffected (Ungerstedt 1971; Rolls et al. 1974; Koob et al. 1978; Salamone et al. 1991, 1993; Baldo et al. 2002; Salamone and Correa 2002). Several lines of research implicate DA, particularly in nucleus accumbens, as a critical component of the brain circuitry regulating exertion of effort and effort-related decision making (Salamone and Correa 2002,

2012; Salamone et al. 1991, 2003, 2005, 2007; Vezina et al. 2002; Wakabayashi et al. 2004; Barbano and Cador 2006, 2007; Cagniard et al. 2006; Phillips et al. 2007; Floresco et al. 2008; Mai et al. 2012; Cocker et al. 2012; Trifilieff et al. 2013).

Studies of effort-related choice behavior typically offer animals multiple paths to obtain reinforcement, which involve cost/benefit trade-offs related to the work requirements for obtaining the reinforcer versus the value of the reinforcing stimulus. Several procedures have been developed for assessment of effort-related decision making; typically, these offer choices between high effort options leading to highly valued reinforcers versus low effort/low reward options. In animal studies, such tasks include a T-maze barrier crossing task (Salamone et al. 1994; Mott et al. 2009; Mai et al. 2012; Pardo et al. 2012), effort discounting (Floresco et al. 2008; Bardgett et al. 2009), and operant procedures offering choices between responding on ratio schedules for preferred reinforcers versus approaching and consuming a less preferred food (Salamone et al. 1991, 2002; Randall et al. 2012, 2014; Sommer et al. 2014). Across multiple tasks, the effects of DA antagonism and accumbens DA depletion have been to shift choice behavior, decreasing selection of the high effort option and increasing selection of the concurrently available low effort choice (Salamone et al. 2007; Salamone and Correa 2012). For example, using a concurrent choice task in which rats can lever press on a fixed ratio 5 (FR5) schedule for preferred high carbohydrate Bio-serv pellets versus approaching and feeding upon concurrently available but less preferred lab chow, it has been shown that systemic or intra-accumbens DA antagonism, as well as accumbens DA depletions, reduce lever pressing but increase consumption of the freely available less preferred lab chow (Cousins et al. 1994; Nowend et al. 2001; Sink et al. 2008; Worden et al. 2009; Nunes et al. 2010; Salamone et al. 1991, 2002; 2009; Koch et al. 2000). Similar reductions in DA transmission did not affect food consumption or food preference in parallel feeding tests (Salamone et al. 1991; Koch et al. 2000; Nunes et al. 2013), and the effects of DA antagonism or depletion on concurrent lever pressing/chow feeding tasks did not resemble the effects of reinforcer devaluation by prefeeding (Salamone et al. 1991; Nunes et al. 2013) or appetite suppressant drugs (Salamone et al. 2002; Sink et al. 2008; Randall et al. 2012, 2014).

Natural palatable rewards such as food and sweet solutions have been used to study DA transmission in the accumbens (Westerink et al. 1997; Roitman et al. 2004). Many studies have shown that sweet taste stimulation can act as a powerful natural reward (Sclafani and Nissenbaum 1987; Levine et al. 2003; Yamamoto 2003). Thus, by using fluids containing different sucrose or saccharine concentrations, researchers have assessed the role of DA in motivational and emotional processes (Ikemoto and Panksepp 1996; Treit and Berridge 1990; Cannon and Palmiter 2003; Cannon and Bseikri 2004). Taste reactivity after oral administration of sucrose is a widely used measure of the emotional reaction to sucrose, and numerous studies have demonstrated that accumbens DA does not mediate these affective reactions (Treit and Berridge 1990; Peciña et al. 1997; see also Berridge and Robinson 1998; Smith et al. 2011). In contrast, some researchers use sucrose consumption or preference as a marker of "hedonia" (i.e., the experience of pleasure), and therefore, manipulations that reduce sucrose consumption or preference are said to produce "anhedonia" (Orsetti et al. 2007; Bai et al. 2014; Hurley et al. 2014).

The present work was undertaken to examine the role of DA in effort-related choice behavior using an adaptation of the concurrent lever pressing/chow feeding procedure originally developed by Salamone et al. (1991). Most of the previous research has been focused on solid food as the reinforcer. However, in the present experiments, we evaluated selection of palatable fluid concentrations of sucrose (5.0 vs 0.3 % *w/v*). Sucrose was chosen as the reinforcer because of the widespread use of sucrose intake and preference tests for studies related to animal models of anhedonia and depression (Orsetti et al. 2007; Bai et al. 2014; Hurley et al. 2014). In the present conditions, animals must press the lever under a FR7 schedule to have access to the 5.0 % sucrose solution, while having concurrent free access to the 0.3 % sucrose solution during the session. The same sucrose concentrations were also used in parallel experiments in which both solutions were given to animals under free access (i.e., no lever pressing requirements). These free access experiments were used to evaluate DA involvement in the directional aspect of motivation under conditions of little or no effort demand and can provide information about possible palatability alterations after DA antagonism. On these two different tasks, we evaluated the effect of the DA depleting agent tetrabenazine, a selective vesicular monoamine transporter-inhibitor for VMAT-2 (Zheng et al. 2006; Fasano and Bentivoglio 2009), which has been shown to deplete accumbens DA and alter effort-related choice behavior in tasks using food reinforcers (Nunes et al. 2013; Randall et al. 2014). Additionally, we also evaluated the effect of tetrabenazine on taste reactivity to the freely available preferred solution (5.0 % sucrose). Because tetrabenazine reduces transmission at both DA D1 and D2 family receptors (Nunes et al. 2013), additional experiments evaluated the effects of selective antagonists for D_1, D_2, and D_3 receptors. Previous research has focused mostly on D_1 and D_2 receptors, but less is known about the potential role of D_3 receptors in effort-based decision making. As an additional control experiment, we evaluated the impact of letting animals satiate on both sucrose solutions before the experimental sessions started.

Materials and methods

Animals

Adult male Sprague-Dawley rats (Janvier, France) were housed in pairs in a colony maintained at 23 °C with 12-h light/dark cycles (lights on at 8:00 h). Rats (N=104) weighed 190–240 g at the beginning of the study; they were initially water restricted, and after the first day of training, they were fed supplemental water to maintain a moderate level of water restriction throughout the study (20 ml/day/rat), with chow available ad libitum in the home cages. Despite water restriction, rats gained weight normally throughout the experiment. All animals were under a protocol approved by the Institutional Animal Care and Use Committee of Universitat Jaume I, and all experimental procedures complied with European Community Council directive (86/609/EEC). All efforts were made to minimize animal suffering and to reduce the number of animals used.

Pharmacological agents

All drugs were administered intraperitoneally (IP). Tetrabenazine (Tocris Bioscience) was dissolved and sonicated in 20 % DMSO which was dissolved in 0.9 % saline (pH= 4.5). SCH39166 (ecopipam; (6aS-trans)-11-Chloro-6,6a,7,8, 9, 13b-hexahydro-7-methyl-5H-benzo[d] aphtha[2,1-b]azepin-12-ol hydrobromide) (Tocris Bioscience), a highly selective D_1 receptor antagonist (Alburges et al. 1992), was dissolved in a 0.2 % tartaric acid solution (pH= 4.0), which was also used as the vehicle control. Haloperidol (Sigma Quimica C.O), a relatively selective DA D_2 receptor antagonist, was dissolved in 0.2 % tartaric acid solution (pH=4.0), which also was used as the vehicle control. GR103691 (Tocris Bioscience), a DA antagonist with high affinity to D_3 receptor (Audinot et al 1998), was dissolved and sonicated in 20 % DMSO/physiological saline solution (pH=4.5).

Doses of tetrabenazine, ecopipam, and haloperidol used for the experiments were based upon previous research (Sink et al. 2008; Worden et al. 2009; Nunes et al. 2013) and on pilot studies. The specific doses of each drug were selected in order to be high enough to produce a robust shift from lever pressing to free intake, but low enough not to produce a general disruption of behavior. The doses of tetrabenazine used were lower than those used to produce tremulous jaw movements or catalepsy (Podurgiel et al. 2013). The dose range chosen for the D_3 antagonist was based upon doses listed in published behavioral studies involving IP administration in rats (Gerlach et al. 2011; Clifford and Waddington 1998).

Apparatus and testing procedures

Operant chambers (28 cm×23 cm×23 cm; Med Associates Inc., St. Albans, VT) were used for the concurrent FR7/free sucrose procedure experiments. Sucrose (Sigma Quimica C.O) solutions were dissolved in tap water for oral consumption. The chambers were equipped with a retractable lever that was located on the right side of the wall (2 cm above the floor), and when the ratio was completed, it triggered the entry of a retractable graduated cylinder tube with rubber stopper and a stainless steel sipper spout with double ball bearings to prevent leakage, on the same wall (5 cm above the grid floor). This tube contained 5.0 % *w*/*v* sucrose solution. The opposite wall contained a drinking spout (0.3 % *w*/*v* sucrose), which was not retractable. All chambers were housed in sound-attenuated enclosures with exhaust fans that masked external noise. Electrical inputs/outputs of each chamber were controlled by an IBM compatible PC (Med-Associates software).

Concurrent FR7/free sucrose Operant sessions occurred once a day for 5 days/week. Animals were trained to lever press for access to a 5.0 % sucrose solution. Rats were initially trained for 4 days to lever press on a FR1 reinforcement schedule: during 3 days, sessions lasted 30 min with the 5.0 % sucrose dispenser available for 30, 15, and 5 s progressively every time the lever was pressed. On the 4th day, the session was reduced to 15 min, and the 5.0 % sucrose dispenser was available for 5 s after each lever press. These conditions were used for the rest of the experiment. For the second phase of training, rats were shifted for 2 days to a FR5 schedule, after which the rats were shifted to FR7 (5 days/week, 2 weeks). Rats were then trained on the concurrent FR7/free 0.3 % sucrose procedure. With this task, 0.3 % sucrose was freely available on the opposite side of the chamber during the FR7 sessions. At the end of the session, rats were immediately removed from the chamber, and sucrose intake was determined by measuring the remaining fluids in both graduated cylinder tubes. Rats were trained for two more weeks, until they attained stable levels of baseline lever pressing (i.e., consistent responding over 200 lever presses per 15 min during the last 5 days), after which drug testing began. Every day, rats received supplemental water (20 ml/animal) in the home cage.

Two-bottle free sucrose drinking paradigm Animals were individually placed during 15 min in new home cages (20 cm× 45 cm×25 cm) where two graduated cylinder tubes containing 0.3 and 5.0 % sucrose drinking solutions were placed separated 10 cm apart for 5 days/week. To control for possible side preferences, the left-right positions of the tubes were randomly assigned to different rats. In order to train these groups in a similar way to the operant groups, rats were initially exposed to the 5.0 % sucrose concentration (30 min, for 3 days) after which 0.3 and 5.0 % sucrose were concurrently present during

15-min sessions for 3 weeks before testing started. At the end of the session, rats were immediately removed from the chamber, and sucrose intake was determined by measuring the remaining fluid. Rats received supplemental water (20 ml/day/rat) in the home cage.

For the pre-exposure condition, animals were trained as described above, and the day before the test, they had ad libitum access to 5 and 0.3 % sucrose and water, for 24 h in their home cage. Then, animals were exposed to an operant session (FR7/free sucrose choice) during which sucrose intake and lever presses were registered. In a parallel experiment, additional animals were exposed to free two-bottle sessions after pre-exposure.

Taste reactivity tests A voluntary sucrose drinking procedure was used, similar to that used in other experiments (Peciña et al. 1997; Ward et al. 2012). Rats were individually placed in new home cages for 15 min with a bottle containing a solution of sucrose (5.0 % *w/v*) for several days before the drug test started. The test day, two video cameras placed in different angles were used to videotape the rats' face, mouth, and body. Behavioral analysis was done in slow motion (1/10 of actual speed) by two observers blind to drug treatment conditions. Averages of the scores from the two observers were obtained for every animal and variable. Because animals were allowed to move freely and detailed oral movements were difficult to register, positive reactions were scored by recording the number of paw licks, and aversive reactions were assessed by forelimb flails and head shakes (Berridge 2000). In addition, latency and frequency to approach and drink the sweetened solution were also registered. Neutral oral movements are mouth movements required to drink the solution that do not involve explicit rhythmic tongue protrusions along the midline or lateral tongue protrusions defined as hedonic by Reynolds and Berridge (2002). Every intake bout was defined as the moment in which animals started to drink until they stopped without removing the tongue from the spout.

Experiments

Within-group designs were used, in which each rat received all drug doses in their particular experiment in a randomly varied order (one treatment per week, with none of the treatment sequences repeated across different animals in the same experiment). Baseline (i.e., nondrug) sessions were conducted 4 additional days per week. The specific treatments and testing times for each experiment are listed below.

Experiment 1 Effect of introducing free low sucrose concentration concurrently available in the operant chamber on lever pressing behavior. As described above, animals were trained under a FR7 schedule until a stable baseline on lever pressing was achieved (2 weeks). The low free access sucrose 0.3 % concentration was introduced and training proceeded (two more weeks). Lever pressing for the 5.0 % concentration was registered before and after introducing the alternative fluid. Animals in operant experiments 4, 5, and 6 were used to study the impact of the free sucrose choice on lever pressing (N=30).

Experiment 2 Effect of the DA depleting agent tetrabenazine on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effect of tetrabenazine on concurrent FR7/free sucrose choice. On the test day, trained rats (N=9) received the following tetrabenazine doses: 0.0, 0.5, 0.75, and 1.0 mg/kg (90 min before testing) and lever pressing and sucrose intake of 5.0 or 0.3 % concentration were assessed.
2. Effect of tetrabenazine on free access two-bottle sucrose choice. On the test day, trained rats (N=10) received the following tetrabenazine doses: 0.0, 0.5, 0.75, and 1.0 mg/kg (90 min before testing) and free sucrose intake of 5.0 or 0.3 % concentration were assessed.
3. Effect of tetrabenazine on taste reactivity after 5.0 % sucrose consumption. Trained rats (N=8) received tetrabenazine doses of 0.0 and 1.0 mg/kg (90 min before testing) in different weeks.

Experiment 3 Effect of pre-exposure to sucrose solutions on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effect of pre-exposure to sucrose on FR7/free sucrose choice. Animals (N=8) were trained as previously described. During 24 h before being tested in the FR7/free sucrose choice, rats had ad libitum water, 5.0 and 0.3 % sucrose solutions in their home cages. After the operant session, lever pressing and sucrose intake of 5.0 or 0.3 % concentration were assessed.
2. Effect of pre-exposure to sucrose on free access two-bottle sucrose choice. Animals (N=9) had ad libitum water, 5.0 and 0.3 % sucrose solution in their home cages during 24 h previous to being tested in the free choice paradigm. Sucrose intake of 5.0 or 0.3 % concentrations was assessed after the session ended.

Experiment 4 Effect of the D_1 antagonist ecopipam (SCH 39166) on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effect of different doses of the D_1 antagonist ecopipam (SCH-39166) on concurrent FR7/free sucrose choice. On the test day, trained rats (N=10) received the

following ecopipam doses: 0.0, 0.05, 0.1, and 0.2 mg/kg (30 min before testing).

2. Effect of different doses of the D_1 antagonist ecopipam (SCH-39166) on free access two-bottle sucrose choice. On the test day, trained rats (N=10) received the following ecopipam doses: 0.0, 0.05, 0.1, and 0.2 mg/kg (30 min before testing).

Experiment 5 Effect of the D_2 antagonist haloperidol on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effect of different doses of the D_2 antagonist haloperidol on FR7/free sucrose choice. On the test day, trained rats (N=10) received the following haloperidol doses: 0.0, 0.025, 0.05, and 0.1 mg/kg (50 min before testing).
2. Effect of different doses of the D_2 antagonist haloperidol on free access two-bottle sucrose choice. On the test day, trained rats (N=10) received the following haloperidol doses: 0.0, 0.025, 0.05, and 0.1 mg/kg (50 min before testing).

Experiment 6 Effect of the D_3 antagonist GR103691 on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effect of different doses of the D_3 antagonist GR103691 on FR7/free sucrose choice. On the test day, trained rats (N=10) received the following GR103691 doses: 0.0, 0.5, 1.0, and 2.0 mg/kg (30 min before testing).
2. Effect of different doses of the D_3 antagonist GR103691 on free access two-bottle sucrose choice. On the test day, trained rats (N=10) received the following GR103691 doses: 0.0, 0.5, 1.0, and 2.0 mg/kg (30 min before testing).

Statistical analyses

For the operant experiments, the dependent variables (total number of lever presses, ml of 5.0 % sucrose reinforcer consumed, average intake of 5.0 % sucrose per reinforcer delivered (i.e., ml of 5.0 % sucrose consumed/number of ratios completed), and total consumption of the 0.3 % sucrose solution) from the 15-min sessions were analyzed with repeated measures of analysis of variance (ANOVA). For the two-bottle consumption and preference tests, repeated measures ANOVA was used to analyze intake of the 5.0 and 0.3 % sucrose solution, as well as the relative preference for 5.0 % sucrose (intake of 5.0 % sucrose divided by total intake, ×100 to express as a percent). Latency to begin drinking was also recorded, and square root transformations were used to normalize variance in the latency data before being analyzed. When the overall ANOVA was significant, nonorthogonal planned comparisons using the overall error term were used to compare each treatment with the vehicle control group (Keppel 1991, pp 165-170). For these comparisons, α level was kept at 0.05 because the number of comparisons was restricted to the number of treatments minus one. STATISTICA 7 software was used for statistical analysis of the data. All data were expressed as mean±SEM, and significance was set at $p<0.05$.

Results

Experiment 1 Effect of introducing free low sucrose concentration concurrently available in the operant chamber on lever pressing behavior. Introducing freely available 0.3 % sucrose solution in the chamber temporarily reduced lever pressing for 5.0 % sucrose solution reinforcement. Repeated measures ANOVA showed a significant overall effect of introducing 0.3 % sucrose on lever pressing ($F(10,290)=7.33$, $p<0.01$). Planned comparisons yielded significant differences between the last day of FR7 alone and the following 2 days of free 0.3 % sucrose concurrently available ($p<0.01$) (see Fig. 1). Thus, the presence of a new sucrose source in the operant cage produced a transient shift in behavior that disappeared by the third day.

Experiment 2 Effect of the DA depleting agent tetrabenazine on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

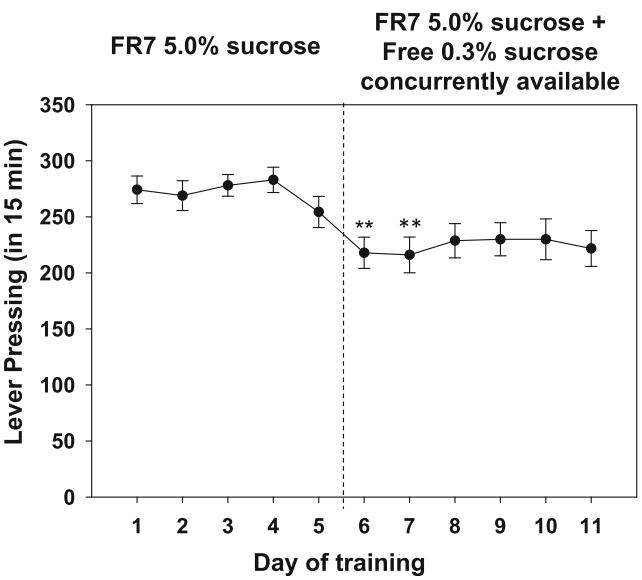

Fig. 1 Effect of introducing a spout providing free 0.3 % sucrose on lever pressing performance. Mean (±SEM) number of lever presses in 15 min. **$p<0.01$ significantly different from the last day with no concurrent 0.3 % sucrose available

1. The effects of tetrabenazine on performance of the concurrent FR7/free sucrose choice procedure are shown in Fig. 2a–d. The ANOVA for repeated measures indicated that tetrabenazine significantly reduced lever pressing ($F(3,24)=5.15$, $p<0.01$), and total intake of the 5.0 % sucrose reinforcer ($F(3,24)=6.88$, $p<0.05$), but had no effect on the average intake per reinforcer delivered ($F(3,24)=0.167$, n.s.). However, tetrabenazine produced a significant increase in the intake of the freely available 0.3 % sucrose solution ($F(3,24)=6.79$, $p<0.01$). Planned comparisons showed that tetrabenazine significantly reduced lever pressing at the two highest doses, 0.75 mg/kg ($p<0.05$) and 1.0 mg/kg ($p<0.01$) compared to vehicle, as well as reducing intake of the 5.0 % sucrose reinforcer (0.75 mg/kg, $p<0.05$, and 1.0 mg/kg, $p<0.01$) compared to vehicle, but significantly increased 0.3 % sucrose intake at all doses tested ($p<0.01$).
2. The effect of tetrabenazine on free access sucrose intake is shown in Fig. 2e, f. Repeated measures ANOVA yielded no effects on intake of either the 5.0 % ($F(3,27)=1.11$, n.s.) or 0.3 % sucrose solutions ($F(3,27)=0.09$, n.s.) and did not alter percent preference for the 5.0 % solution over the 0.3 % solution (mean±SEM=vehicle, 98.46±0.80; 0.5 mg/kg tetrabenazine, 98.39±0.82; 0.75 mg/kg

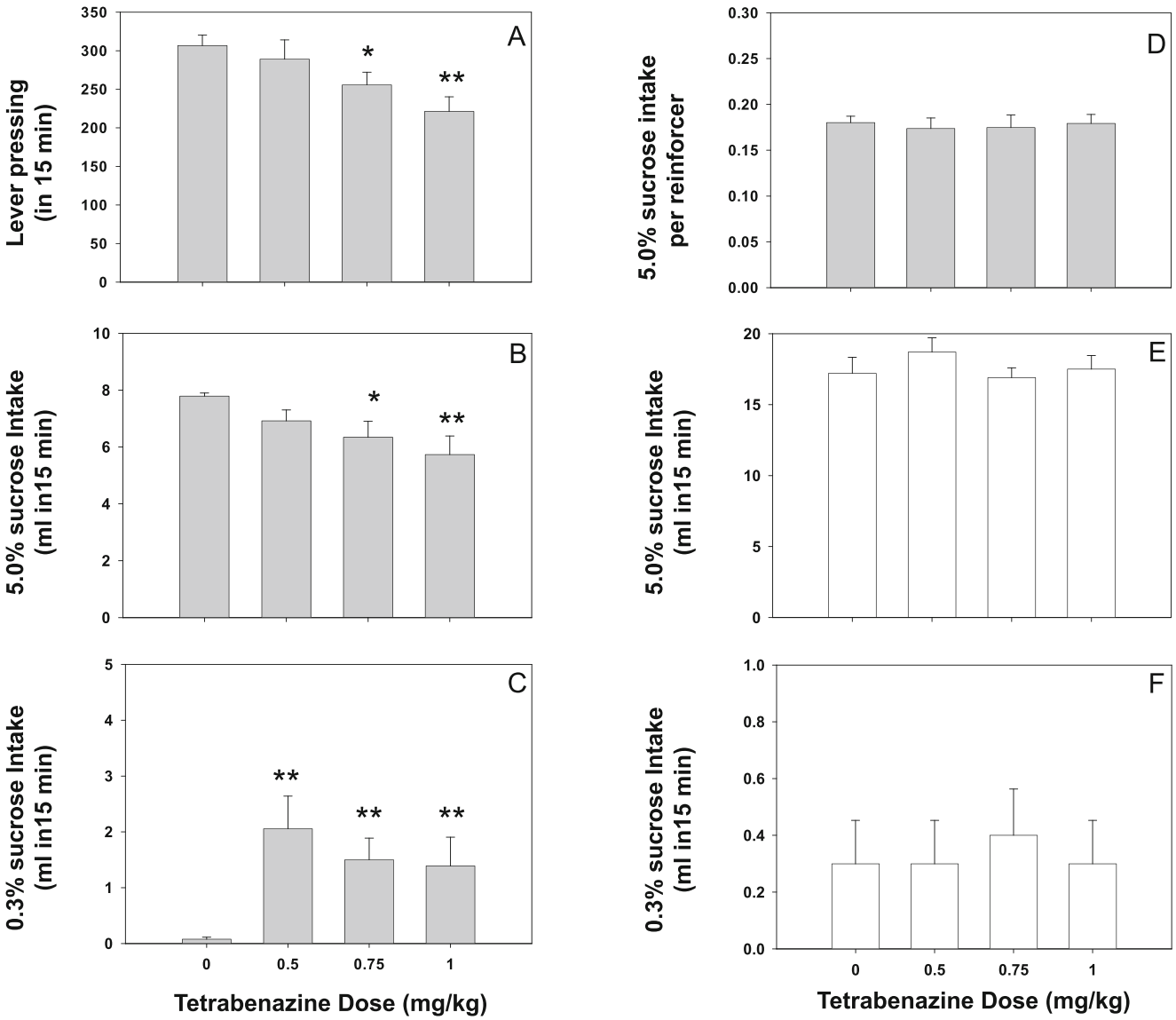

Fig. 2 **a**–**d** Effect of tetrabenazine (0.0, 0.5, 0.75, and 1.0 mg/kg) on performance of the concurrent FR7/free sucrose choice task; **a** lever presses, **b** intake of the 5.0 % sucrose reinforcer, **c** 0.3 % sucrose intake, and **d** intake of 5.0 % sucrose per reinforcer delivered. **e**, **f** Effect of tetrabenazine on performance in the two-bottle free choice task; **e** 5.0 % sucrose intake and **f** 0.3 % sucrose intake. Data are expressed as mean (±SEM) number of lever presses or ml consumed in 15 min. *$p<0.05$, **$p<0.01$ significantly different from vehicle

tetrabenazine, 97.94±0.85; 1.0 mg/kg tetrabenazine, 97.34±0.87; (F(3,27)=0.1, n.s.).

3. The effect of tetrabenazine on taste reactivity to 5.0 % sucrose intake is shown in Table 1. Animals showed no aversive responses (forelimb flails and head shakes) under either condition (vehicle or tetrabenazine). Repeated measures ANOVA showed no tetrabenazine effect on the number of hedonic paw licking responses ($F(1,7)=0.05$, n.s.). Neutral oral movements ($F(1,7)=0.78$, n.s.) were not different between vehicle and tetrabenazine treatments. However, although latency to sucrose intake did not reach statistical significance ($F(1,7)=3.13$, n.s.), tetrabenazine significantly increased frequency of intake (i.e., number of bouts; $F(1,7)=8.78$, $p<0.05$).

Experiment 3 Effect of pre-exposure to sucrose solutions on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Figure 3a–d shows the effect of pre-exposing animals to both concentrations of sucrose 24 h before the concurrent FR7/free sucrose choice test was performed. Repeated measures ANOVA indicated that pre-exposing animals produced a significant decrease in lever pressing ($F(1,7)=10.63$, $p<0.05$) and intake of the 5.0 % sucrose reinforcer ($F(1,7)=18.40$, $p<0.01$), as well as intake per reinforcer delivered ($F(1,7)=9.22$, $p<0.05$). There was a trend toward a reduction of intake of the 0.3 % sucrose solution induced by pre-exposure ($F(1,7)=4.84$, $p=0.064$), but it failed to reach significance with the ANOVA, probably because of a floor effect. Thus, nonparametric analysis (Wilcoxon T) was performed, which showed that pre-exposure did significantly suppress intake of the 0.3 % sucrose solution ($n=8$, $T=1$, $p<0.05$).

Table 1 Taste reactivity responses after free access 5.0 % sucrose solution consumption in vehicle or tetrabenazine (1.0 mg/kg) treated rats

	Vehicle	Tetrabenazine (1.0 mg/kg)
Paw licking (***apetitive***)	2.6 ± 1.0	3.0 ± 1.0
Forelimb flails (***aversive***)	0.0	0.0
Head shakes (***aversive***)	0.0	0.0
Oral movements (***neutral***)	32.8 ± 8.5	39.8 ± 9.4
Intake Latency (seconds)	103.5 ± 45.9	24.5 ± 5.4
Intake Frequency (number of bouts)	15.3 ± 2.3	21.0 ± 3.2*

Mean (±SEM) number of hedonic paw licking responses, neutral oral movements, latency to first intake bout in seconds, and number of intake bouts

*$p<0.05$ significantly different from vehicle

2. The effect of pre-exposing the animals to reduce sucrose motivation, on free access sucrose intake, is shown in Fig. 3e, f. Similar to the operant behavior experiment, the ANOVA indicated that pre-exposing animals to sucrose significantly reduced intake of the 5.0 % sucrose solution ($F(1,8)=64$, $p<0.01$) and had no effect on 0.3 % sucrose intake ($F(1,8)=0.00$, n.s.) since the level of intake was already very low. There was no significant change in percent preference for the 5 % solution (mean±SEM=control, 98.82±0.79; pre-exposure, 96.21±2.83; (F(1,8)=0.69, n.s.).

Experiment 4 Effect of the D_1 antagonist ecopipam (SCH 39166) on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. The effects of ecopipam on the FR7/free sucrose choice procedure are shown in Fig. 4a–d. Like tetrabenazine, ecopipam shifted effort-related choice behavior. Repeated measures ANOVA indicated that ecopipam significantly reduced lever pressing ($F(3,27)=10.05$, $p<0.01$) and intake of the 5.0 % sucrose reinforcer ($F(3,27)=15.04$, $p<0.01$), but did not affect intake per reinforcer delivered ($F(3,27)=0.41$, n.s.). In contrast, ecopipam significantly increased intake of the freely available 0.3 % sucrose solution ($F(3,27)=6.22$, $p<0.01$). Planned comparisons showed that ecopipam significantly reduced lever pressing at the doses of 0.1 mg/kg ($p<0.05$) and 0.2 mg/kg ($p<0.01$) compared to vehicle, as well as reducing intake of the 5.0 % sucrose reinforce at the same doses ($p<0.01$) compared to vehicle and, significantly increased 0.3 % sucrose intake at the doses of 0.1 and 0.2 mg/kg ($p<0.01$).
2. Figure 4e, f shows the effect of ecopipam on free access sucrose intake. Repeated measures ANOVA yielded no effects on 5.0 % sucrose intake ($F(3,27)=0.40$, n.s.) or 0.3 % sucrose intake ($F(3,27)=0.40$, n.s.), and there were no effects on sucrose preference (mean±SEM percent preference for 5 %=vehicle, 98.13±0.66; 0.05 mg/kg ecopipam, 98.14±0.64; 0.1 mg/kg ecopipam, 97.81±1.44; 0.2 mg/kg ecopipam, 98.00±0.53; ($F(3,27)=0.03$, n.s.).

Experiment 5 Effect of the D_2 antagonist haloperidol on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. Effects of haloperidol in the FR7/free sucrose choice procedure are shown in Fig. 5a–d. Haloperidol also shifted effort-related choice behavior. Repeated measures ANOVA showed that this drug produced significant reductions in lever pressing ($F(3, 27)=17.98$, $p<0.01$) and intake of

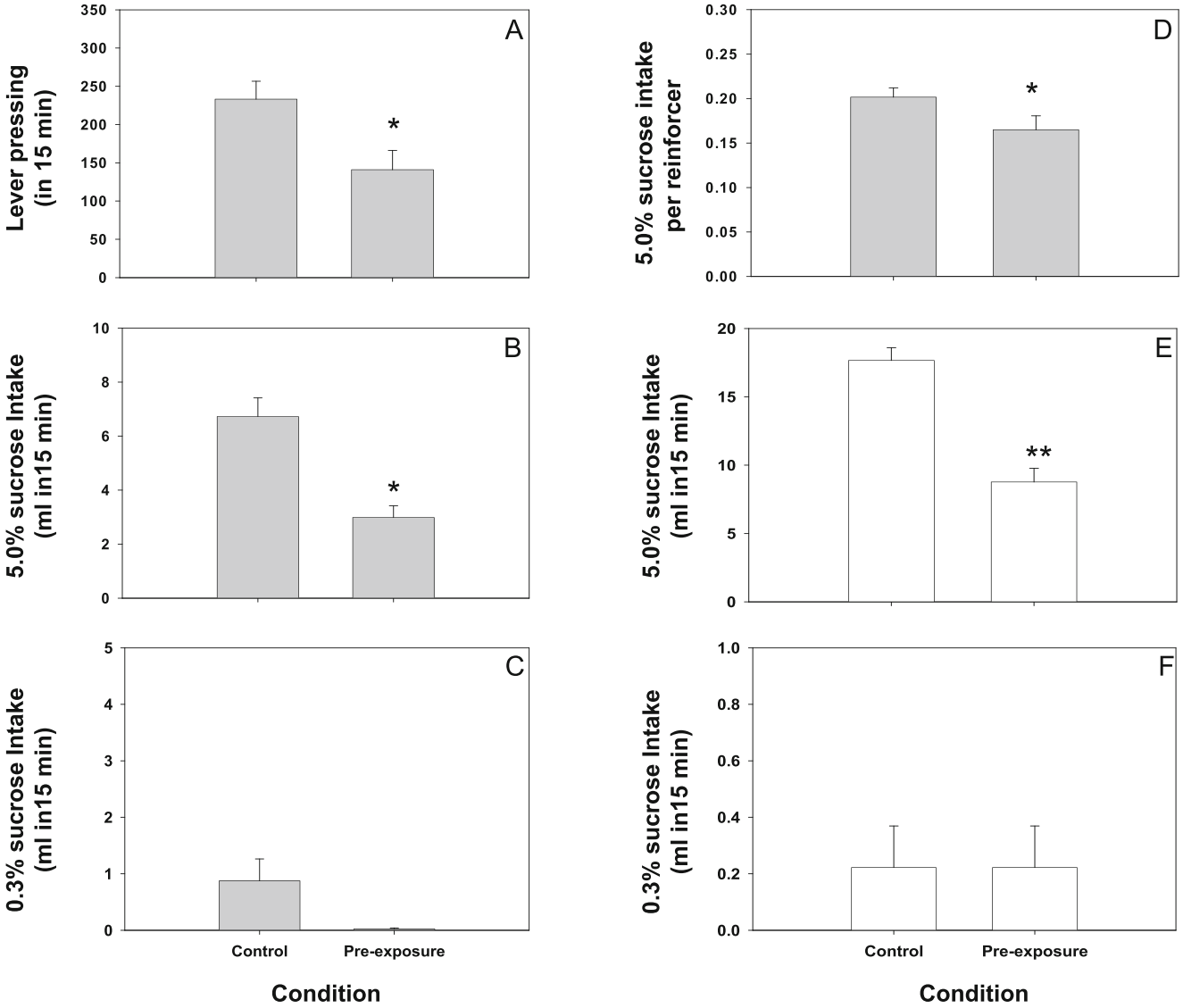

Fig. 3 **a**–**d** Effect of sucrose pre-exposure on performance of the concurrent FR7/free sucrose choice task; **a** lever presses, **b** intake of the 5.0 % sucrose reinforcer, **c** 0.3 % sucrose intake, and **d** intake of 5.0 % sucrose per reinforcer delivered. **e**, **f** Effect of sucrose pre-exposure on performance in the two-bottle free choice task; **e** 5.0 % sucrose intake and **f** 0.3 % sucrose intake. Data are expressed as mean (±SEM) number of lever presses or ml consumed in 15 min. *$p<0.05$, **$p<0.01$ significantly different from control condition

the 5.0 % sucrose reinforcer ($F(3,27)=16.35$, $p<0.01$), and also produced a trend toward a change in the intake of the 5.0 % sucrose per reinforcer delivered ($F(3,27)=2.89$, $p<0.06$), which was due to a slight increase in intake per reinforcer at the 0.05-mg/kg dose relative to the other conditions. As with tetrabenazine and ecopipam, haloperidol significantly increased consumption of the concurrently available 0.3 % sucrose solution ($F(3,27)=6.22$, $p<0.01$). Planned comparisons revealed significant differences between vehicle and the two highest doses of haloperidol (0.05 and 0.1 mg/kg, $p<0.01$) on lever pressing, on intake of the sucrose reinforcer ($p<0.05$ and $p<0.01$, respectively), and also a significant difference between vehicle and 0.1 mg/kg ($p<0.01$) on intake of the freely available 0.3 % sucrose solution.

2. Figure 5e, f shows the effects of haloperidol on free access sucrose intake. Repeated measures ANOVA yielded no effects on free access 5.0 % sucrose intake ($F(3,27)=0.41$, n.s.) or 0.3 % sucrose intake ($F(3,27)=0.64$, n.s.), and no change in preference (mean±SEM percent preference for 5 %=vehicle, 96.78±1.14; 0.025 mg/kg haloperidol, 97.81±0.78; 0.05 mg/kg haloperidol, 96.69±0.92; 0.1 mg/kg haloperidol, 96.78±0.95 ($F(3,27)=0.38$, n.s.)).

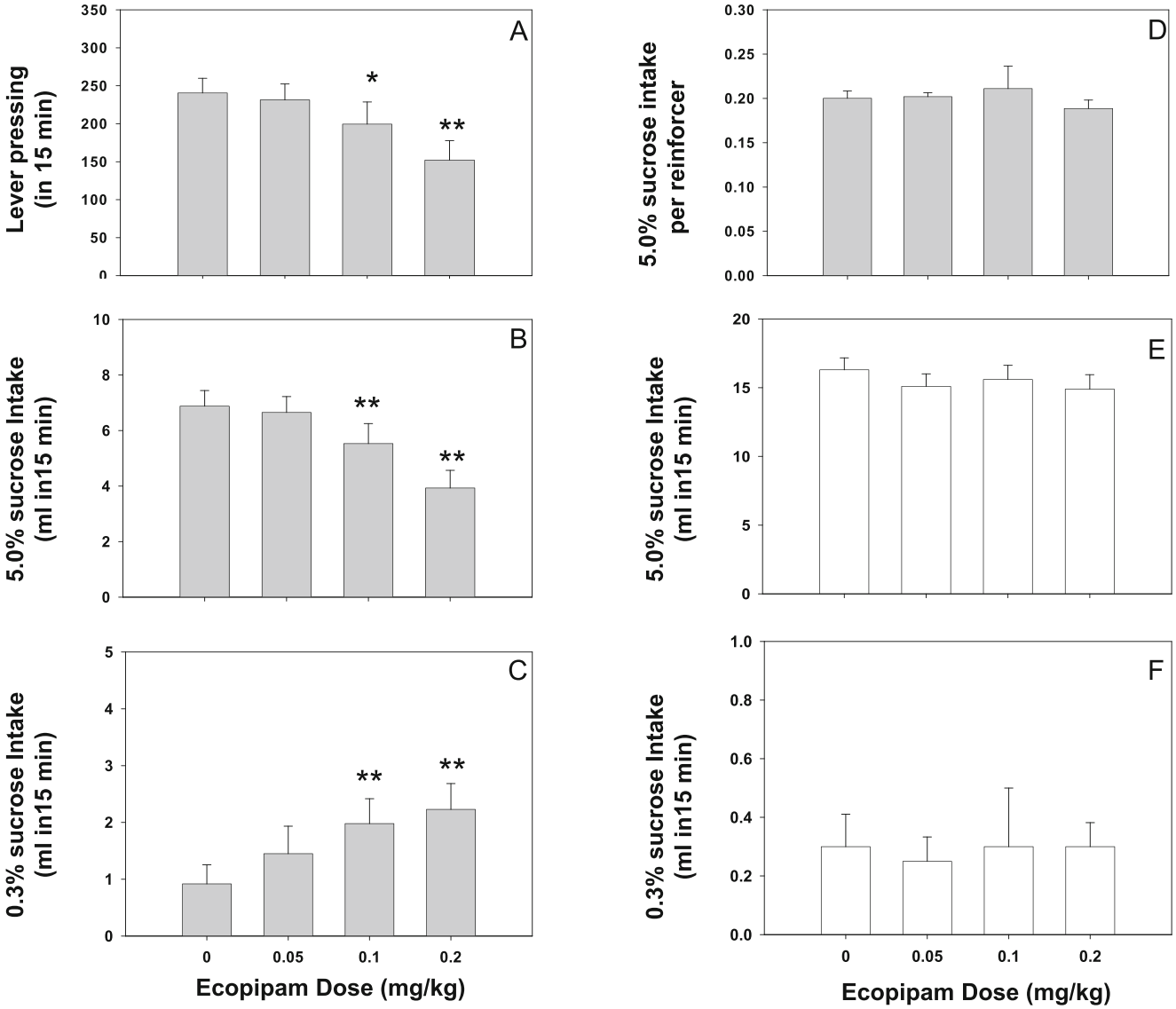

Fig. 4 **a**–**d** Effect of ecopipam (0.0, 0.05, 0.1, and 0.2 mg/kg) on performance of the concurrent FR7/free sucrose choice task; **a** lever presses, **b** intake of the 5.0 % sucrose reinforcer, **c** 0.3 % sucrose intake, and **d** intake of 5.0 % sucrose per reinforcer delivered. **e**, **f** Effect of ecopipam on performance in the two-bottle free choice task; **e** 5.0 % sucrose intake and **f** 0.3 % sucrose intake. Data are expressed as mean (±SEM) number of lever presses or ml consumed in 15 min. *$p<0.05$, **$p<0.01$ significantly different from vehicle

Experiment 6 Effect of the D_3 antagonist GR103691 on performance of concurrent FR7/free sucrose choice procedure and free sucrose intake tests.

1. The effect of different doses of the D_3 antagonist GR103691 on the FR7/free sucrose choice procedure are shown in Fig. 6a–d. Repeated measures ANOVA showed that there were no significant effects on lever pressing ($F(3,27)=1.98$, n.s.), intake of the 5.0 % sucrose reinforcer ($F(3,27)=1.21$, n.s.), average intake per reinforcer ($F(3,27)=1.09$, n.s.) or intake of the free 0.3 % sucrose solution ($F(3,27)=2.19$, n.s.).
2. The effect of GR103691 on free sucrose intake is shown in Fig. 6e, f. Repeated measures ANOVA yielded no effects on intake of either the 5.0 % ($F(3,27)=0.91$, n.s.) or 0.3 % sucrose solutions ($F(3,27)=0.42$, n.s.), and no change in preference (mean±SEM percent preference for 5 %=vehicle, 97.72±0.94; 0.05 mg/kg ecopipam, 97.43±0.86; 0.5 mg/kg ecopipam, 98.31±0.87; 0.1 mg/kg ecopipam, 97.69±0.95 ($F(3,27)=0.26$, n.s.)).

Discussion

The present experiments evaluated the effects of the VMAT-2 inhibitor tetrabenazine, as well as DA antagonists with different selectivity profiles, on effort-related choice behavior using

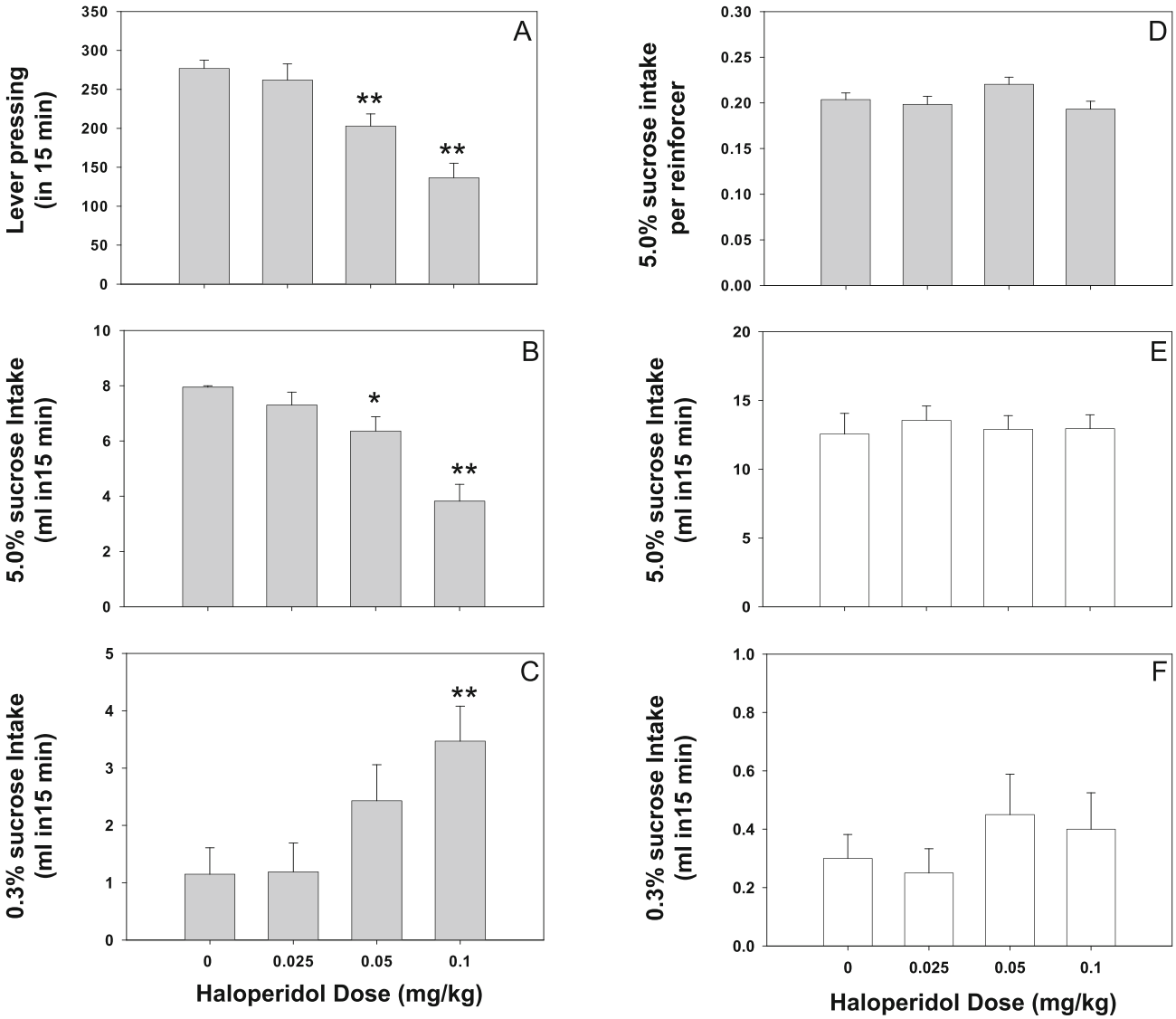

Fig. 5 **a**–**d** Effect of haloperidol (0.0, 0.025, 0.05, and 0.1 mg/kg) on performance of the concurrent FR7/free sucrose choice task; **a** lever presses, **b** intake of the 5.0 % sucrose reinforcer, **c** 0.3 % sucrose intake, and **d** intake of 5.0 % sucrose reinforcer per reinforcer delivered. **e**, **f** Effect of haloperidol on performance in the two-bottle free choice task; **e** 5.0 % sucrose intake and **f** 0.3 % sucrose intake. Data are expressed as mean (±SEM) number of lever presses or ml consumed in 15 min. *$p<0.05$, **$p<0.01$ significantly different from vehicle

sucrose as a reinforcer, as well as intake and preference of sucrose solutions of different concentrations. A concurrent lever pressing/intake task was adapted from previous procedures using solid foods (Salamone et al. 1991, 2002), which allowed animals to choose between lever pressing on an operant FR7 schedule for a preferred reward (in this case 5.0 % sucrose) versus approaching and consuming a freely available but less preferred reward (0.3 % sucrose). Sucrose has been extensively used for the study of emotional reactivity and for the study of the hedonic value of rewards (Peciña et al. 1997; Martinez-Hernandez et al. 2012). However, no previous studies have used sucrose reinforcement of lever pressing for the study of effort-based decision making. Additional experiments assessed the effects of tetrabenazine and DA antagonists on preference and consumption of the high and low sucrose concentrations in free intake tests. Moreover, in parallel control experiments, a reduced motivational state was established by allowing the animals to become satiated during pre-exposure to both types of sucrose solutions, which led to devaluation of the sucrose reinforcer.

In the first group of studies, tetrabenazine was used to produce transient DA depletions. TBZ inhibits VMAT-2, and thus blocks vesicular storage of monoamines, but its greatest effects at low doses are on DA in the striatal complex (Pettibone et al. 1984; Tanra et al. 1995; Guay 2010). Nunes et al. (2013) demonstrated that 0.75 mg/kg TBZ reduced extracellular DA in accumbens core by about 75 %, and also altered DA-related signal transduction at D1 and D2 family

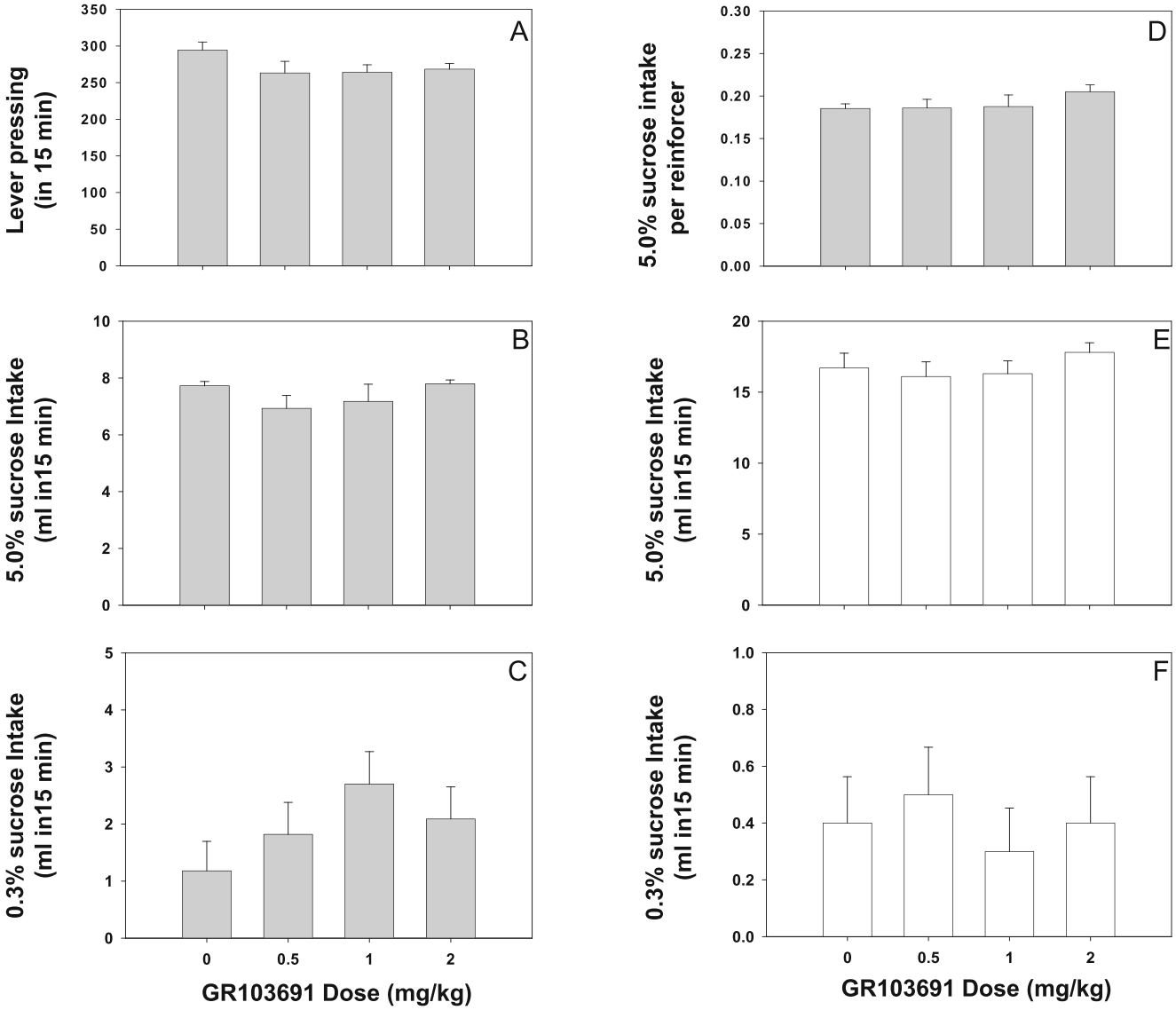

Fig. 6 **a**–**d** Effect of GR103691 (0.0, 0.5, 1.0, and 2.0 mg/kg) on performance of the concurrent FR7/free sucrose choice task; **a** lever presses, **b** intake of the 5.0 % sucrose reinforcer, **c** 0.3 % sucrose intake, and **d** intake of 5.0 % sucrose reinforcer per reinforcer delivered. **e**, **f** Effect of GR103691 on performance in the two-bottle free choice task; **e** 5.0 % sucrose intake and **f** 0.3 % sucrose intake. Data are expressed as mean (±SEM) number of lever presses or ml consumed in 15 min

receptors in accumbens, as marked by expression of phosphorylated DARPP-32. In the present studies with rats tested on the concurrent FR7/free sucrose choice task, tetrabenazine dose dependently decreased lever pressing for 5.0 % sucrose, while increasing intake of the concurrently available 0.3 % sucrose solution. Although tetrabenazine also decreased intake of the 5.0 % sucrose reinforcer, this was totally dependent upon the reduction in lever pressing and the lower number of reinforcers delivered, as the average intake per reinforce delivered was completely unaffected. Moreover, parallel studies with free drinking access to sucrose solutions showed that no dose of tetrabenazine modified sucrose preference or the volume consumed of the sucrose solutions, and taste reactivity studies showed that behavioral reactivity to voluntarily consumed sucrose was not altered. In addition, the pattern of sucrose intake did not reflect a motor impairment or lack of interest in sucrose, since animals that received tetrabenazine showed reduced latency to initiate drinking, and engaged more frequently in sucrose drinking. Taken together, these data indicate that tetrabenazine-induced decreases in lever pressing reinforced by 5.0 % sucrose were not due to changes in sucrose consumption, preference, discrimination, primary or unconditioned motivation, or hedonic reactivity. Thus, tetrabenazine-treated animals remained directed toward the acquisition and consumption of sucrose, but reallocated their behavior away from lever pressing and toward the less effortful option (i.e., drinking higher amounts of the 0.3 % solution). These effects of tetrabenazine are similar to those

reported in studies of effort-related choice using solid food reinforcers and other behavioral procedures (Nunes et al. 2013; Randall et al. 2014; Yohn et al. 2014).

Previous research has shown that tetrabenazine reduces accumbens DA transmission at D_1 and D_2 family receptors (Nunes et al. 2013). To identify which subtype of DA receptor is implicated in the observed effects of tetrabenazine in rats responding on the concurrent FR7/free sucrose task, selective antagonists acting on D_1, D_2, and D_3 receptors were also tested. Ecopipam (SCH39166, D_1 antagonist) and haloperidol (D_2 antagonist) dose dependently shifted effort-related choice, decreasing lever pressing for 5.0 % sucrose but increasing consumption of the 0.3 % sucrose solution. Previous work has shown that systemic or intra-accumbens injections of the D_1-family antagonists SCH23390, SKF83566, and ecopipam (Cousins et al. 1994; Nowend et al. 2001; Salamone et al. 2002; Sink et al. 2008; Worden et al. 2009; Nunes et al. 2010; Randall et al. 2014), as well as the D_2 DA antagonists haloperidol, raclopride, and eticlopride (Salamone et al. 1991, 2009; Cousins et al. 1994; Koch et al. 2000; Randall et al. 2014), all decreased lever pressing and increased chow intake in rats responding on concurrent lever pressing/chow feeding choice tasks.

In contrast, the D_3 antagonist GR103691 did not produce changes in any of the behaviors evaluated, either in the operant procedure or in the free choice situation. Little is known about the behavioral effects of this D_3 antagonist. When injected directly into the basolateral amygdala, GR103691 produced anxiolytic effects at doses that did not affect locomotion or rearing (Diaz et al. 2011). In a range of doses from 0.008 to 1.0 mg/kg IP, GR103691 did not affect parameters such as locomotion, rearing, grooming, sniffing, or eating in rats (Clifford and Waddington 1998). The range of doses used in the present experiments (0.5–2.0 mg/kg, IP) was expanded relative to these other papers, but still, no effect was observed. Although other D_3 antagonists (YQA14 and SB-277011A) have been shown to reduce drug seeking in operant procedures (Song et al. 2014; Higley et al. 2011), the only other study that has assessed the role of a D_3 antagonist on effort-based decision making used a single dose of U99194, and in that study, there were no alterations of choice in rats tested on a T-maze barrier climbing paradigm (Bardgett et al. 2009).

Like tetrabenazine, ecopipam and haloperidol failed to decrease intake of the sucrose reinforcer when expressed as intake per reinforcer delivered and did not affect sucrose consumption and preference at doses that shifted effort-related choice behavior. Furthermore, the effects of tetrabenazine, ecopipam, and haloperidol differed substantially from those produced by sucrose pre-exposure. Allowing animals to satiate on sucrose devalued the sucrose reinforcer and reduced primary motivation for sucrose. Thus, when rats were tested on the concurrent FR7/free sucrose task, pre-exposure reduced sucrose reinforced lever pressing and attenuated intake of the 5.0 % sucrose per reinforce delivered, but failed to increase consumption of 0.3 % sucrose, in fact reducing intake of the low concentration of sucrose to essentially nothing (Fig. 3). Moreover, when pre-exposed rats were tested on the two-bottle free access test, they showed substantially reduced consumption of 5.0 % sucrose. This pattern of effects demonstrates that administration of tetrabenazine, and low doses of D1 or D2 antagonists, were not reducing lever pressing because of reductions in the reinforcement value of sucrose. Furthermore, this conclusion is consistent with the results of Ikemoto and Panksepp (1996), who reported that a dose of the DA antagonist flupenthixol that slowed sucrose reinforced running in an alleyway had no effect on sucrose consumption. Thus, it does not seem tenable to maintain that reductions in sucrose reinforced behavior induced by interference with DA transmission should be interpreted as being due to reduced "reward" or "anhedonia."

In general, it would be useful to exercise caution in labeling the effects of drugs, lesions, genetic or environmental conditions as "anhedonia" simply because they affect sucrose reinforced responding, sucrose intake, or sucrose preference. With dopaminergic agents, one important factor is dose. For example, although intra-accumbens injections of 12–40 μg of the DA antagonists SCH 23390 and raclopride were reported to reduce sucrose intake (Schneider et al. 1992; Smith 1995), those doses are 12–40 times higher than the doses of these drugs (1.0 μg) at which intra-accumbens injections were reported to suppress lever pressing (Nowend et al. 2001). In addition, there are problems in extrapolating from sucrose reinforced responding, consumption or preference to "hedonia", which is, strictly speaking, an emotional response. A number of factors other than changes in pleasurable emotions could be mediating the effects of drug manipulations on sucrose-motivated behavior. For example, DA antagonist-induced deficits in sucrose intake are accompanied by several oral motor impairments (i.e., changes in lick duration, force and efficiency, lap volume, and tongue extension; Fowler and Mortell 1992; Das and Fowler 1996). Because the effects of DA antagonists on sucrose consumption interact with the height of the spout, Hsiao and Chen (1995) suggested that the effects of DA antagonism on sucrose drinking could be viewed as indicating a reduced effort for obtaining the sucrose (Hsiao and Chen 1995). Muscat and Willner (1989) suggested that the effects of DA antagonism on sucrose consumption could be interpreted as a lack of sensorimotor responsiveness. Considerable work from Berridge and colleagues has demonstrated that systemic administration of DA antagonists, as well DA depletions in whole forebrain or nucleus accumbens, do not blunt appetitive taste reactivity for sucrose (Berridge and Robinson 1998, 2003; Berridge 2007; Berridge and Kringelbach 2008). Moreover, microinjections of amphetamine into nucleus accumbens, which elevate extracellular DA, did not enhance appetitive taste reactivity for sucrose

(Smith et al. 2011). Finally, this caution should extend to studies involving animal models of depression. Although it has become commonplace to describe any change in sucrose intake or preference as reflecting "anhedonia," which can be therefore be used to model anhedonia in humans, this is highly problematic. Anhedonia in depression is a concept that is undergoing considerable revision, especially in light of studies showing that depressed people do not show altered performance on the sweet taste test, which is a measure of hedonic reactivity in humans (see reviews by Treadway and Zald 2011; Pizzagalli 2014). People with major depression do show impairments in estimation, anticipation, and recall of reinforcing stimuli, reduced willingness to exert effort, and an uncoupling of behavioral activation and hedonic reactivity processes (Salamone et al. 2006, 2007; Treadway and Zald 2011; Treadway et al. 2012; Pizzagalli 2014), but it does not seem that measures of sucrose intake or preference are the best ways to model these dysfunctions (Markou et al. 2013).

In summary, interference with DA, D1, and D2 receptor transmission by administration of tetrabenazine or DA antagonists can reduce the tendency to work for sucrose under conditions that leave fundamental aspects of sucrose motivation (intake, preference, discrimination, hedonic reactivity) intact. This work highlights the complex and subtle nature of the motivational impairments induced by interference with DA transmission and may have implications for studies of the effort-related motivational and psychomotor symptoms of depression and other disorders (Salamone et al. 2007; Treadway et al. 2012; Gold et al. 2013; Barch et al. 2014).

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