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ORIGINAL INVESTIGATION

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Role of nucleus accumbens dopamine D_1 and D_2 receptors in instrumental and Pavlovian paradigms of conditioned reward

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Abstract *Rationale:* This study investigated the role of nucleus accumbens dopamine D_1 and D_2 receptors in two different paradigms of conditioned reward. *Objective:* We addressed the question whether accumbal dopamine is important for the motor or for the motivational components of reward. *Methods:* We compared the effects of intra-accumbal infusion of the dopamine D_1 receptor antagonist SCH23390 (0.3, 1.0, 3.0 µg) and the D_2 receptor antagonist sulpiride (0.3, 1.0, 3.0 µg) on conditioned lever pressing for food, with the effects on the inhibition of the startle response by a conditioned reward signal. *Results:* Both the D_1 and the D_2 antagonist dose-dependently attenuated conditioned lever pressing for reward under a fixed-ratio of responding and increased the consumption of freely available lab chow. However, the preference for freely available pellets, and the attenuation of the startle response in the presence of a conditioned stimulus predicting reward were not impaired by blockade of accumbal dopamine receptors. *Conclusions:* Our data support the idea that dopamine in the nucleus accumbens is necessary for instrumental response selection in the context of reward rather than for the mere motor performance of behavior or for the evaluation of the hedonic properties of rewarding stimuli.

Key words Acoustic startle response · Dopamine · Nucleus accumbens · Reward · SCH23390 · Sulpiride

Introduction

The nucleus accumbens septi (NAC) is an important element of the neuronal circuitry mediating reward-related processes. The NAC receives excitatory glutamatergic afferences from cortical and limbic brain regions and projects, via the ventral pallidum, to premotor and motor centers of the brain (Mogenson et al. 1993). This anatomical-physiological characteristic qualifies the NAC to function as an interface between motivation and action (Robbins and Everitt 1996; Kalivas and Nakamura 1999). The NAC also receives a dopaminergic input from the ventral tegmental area which has been implicated in the regulation of reward (Chen 1993). However, since dopamine (DA) in the NAC is also involved in aversive conditioning tasks (Wilkinson et al. 1998; Young et al. 1998), the assumption of a sole involvement of the mesoaccumbal DA system in reward-related processes is not tenable. Therefore, it is more likely that accumbal DA generally acts to increase the salience of stimuli.

The role of DA in the NAC in the regulation of reward-related behavior has been thoroughly studied during the past 25 years, and most researchers would agree with the notion that DA regulates reward-related behavior. However, since most behavioral tests for reward use motor activation as the operational variable for the assessment of reward, it is difficult to distinguish motivational functions of NAC DA from sensorimotor effects. Therefore, it is still debated how exactly DA in the NAC acts to increase the behavioral relevance of stimuli in the context of reward (Salamone et al. 1997; Schultz 1997; Berridge and Robinson 1998; Spanagel and Weiss 1999). There is evidence indicating that DA codes for the unpredictability, and, hence, for the novelty of a stimulus, thereby enhancing its relevance as a reward signal (Schultz 1997). It is also possible that DA acts to allocate stimulus-processing capacities of the NAC according to the significance of the stimuli (Redgrave et al. 1999). Recently, it was proposed that the NAC acts to bias the information-processing capacities of the NAC towards a certain processing routine, so as to activate reward-related behavior if the benefit of a response is worth the cost of that response (Salamone et al. 1997). Another concept proposes that the DA system is necessary for the attribution of incentive salience to previously neutral stimuli (Berridge and Robinson 1998). All of

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these concepts imply that the NAC has the capacity to somehow estimate the behavioral importance of stimuli.

The aim of the present study was to compare the effects of microinfusions of the DA D_1 receptor antagonist SCH23390 and the DA D_2 receptor antagonist sulpiride on the performance of rats in a fixed ratio schedule of reinforcement task with the performance in a non-instrumental paradigm of reward, the attenuation of the acoustic startle response (ASR) in the presence of a conditioned reward-stimulus.

A food-choice procedure was developed by Salamone and colleagues (1991), where the animals have the choice between lever pressing for palatable food-pellets and the consumption of freely available lab chow. In this task, it has been shown that NAC DA-depletion or systemic administration of DA antagonists results in a change of the rats' behavioral strategy: while the rats usually prefer lever pressing and the consumption of food pellets, even under relatively demanding fixed ratios of responding, the blockade or destruction of mesoaccumbal DA leads to an impairment of lever pressing. However, these treatments did not affect the primary motivation to consume food, because the rats still ate more of the lab chow under these conditions (Salamone et al. 1991; Sokolowski and Salamone 1998). These findings have been interpreted in the sense that NAC DA is not necessary for the motivation to consume food but rather for the execution of a behavioral response under conditions where a cost-benefit analysis has to be made by the rat, on the basis of the cost of the response and the value of the reward (Cousins and Salamone 1994). It is unclear, however, which subtype of DA receptors mediates this phenomenon of response selection.

The ASR is a fast response to a sudden noise pulse and can be regarded as a protective behavior (Koch 1999). The magnitude of the ASR is attenuated in an appetitive context both in humans (Lang 1995) and in rats (Schmid et al. 1995). This latter phenomenon of reward-attenuated startle (RAS) has also been termed pleasure-attenuated startle. Here, the ASR is reduced in the presence of a conditioned stimulus that has previously been paired with a reward, such as sucrose and corn flakes. Since the motivational aspects of conditioned reward are measured by *attenuation* rather than by *reinforcement* of a motor behavior, RAS serves as a cross-species model to measure reward related affect. RAS can been explained by a state-dependent suppression of the ASR due to negative motivational priming (Dickinson and Dearing 1979). According to this concept, the positive motivation of reward-expectancy interacts with the brain sites that mediate aversive responses and thereby suppresses the ASR. RAS was reduced if the mesoaccumbal DA system was lesioned with 6-OHDA before the conditioning (Koch et al. 1996), suggesting that DA in the NAC plays a role in the acquisition or expression of RAS. However, it is unclear which DA receptor subtypes in the NAC regulate RAS.

The present paper sought to investigate the role of DA D_1 and D_2 receptors in the NAC in an instrumental response task (food-choice procedure) and in a non-instrumental, passive test (RAS) for the hedonic quality of reward-related stimuli.

Materials and methods

Animals

Eighty-one naive male Wistar rats (Charles River, Sulzfeld, Germany) were kept in groups of five or six rats in standard Makrolon cages in a climatized vivarium under a continuous 12 h light/12 h dark cycle (lights on at 0700 hours). They received tap water ad libitum and were maintained on a bodyweight of 250–300 g through restricted feeding of 12 g rodent chow/rat per day. The rats were handled daily before and after surgery. The experiments were done in accordance with ethical guidelines for the use of animals for experiments and were approved by the local animal care committee (Regierungspräsidium Tübingen, ZP 4/96).

Surgery

The rats were anesthetized with chloral hydrate [420 mg/kg intraperitoneally (IP)] and placed in a stereotaxic frame with the incisor bar set 5 mm above the interaural plane. The skull was exposed and stainless steel guide cannulae (22 gauge) were implanted bilaterally aiming at the NAC (3.4 mm rostral, ±1.5 mm lateral and 7.2 mm ventral of bregma; Pellegrino et al. 1979). The cannulae were fixed to the skull with three anchoring screws and dental acrylic cement. After surgery the cannulae were fitted with stylets to prevent them from clogging. The rats were allowed 3 days to recover from surgery.

Drugs

The DA D_1 receptor antagonist SCH23390 (Research Biochemicals Inc., Natick, Mass., USA) was dissolved in distilled water and administered in doses of 0.3 µg/0.5 µl, 1.0 µg/0.5 µl and 3.0 µg/0.5 µl; saline infusions served as control. The DA D_2 receptor antagonist (*S*)-(–)-sulpiride (Research Biochemicals) was dissolved in saline with a drop of glacial acetic acid. The pH was adjusted to 6–7 with NaOH. Sulpiride was administered in doses of 0.3 µg/0.5 µl, 1.0 µg/0.5 µl and 3.0 µg/0.5 µl; saline infusions served as control. Two groups of rats received either SCH23390 or sulpiride. The drugs were infused through 27-gauge stainless steel injection cannulae connected with a length of flexible PVC-tubing to two 1-µl syringes. The rate of infusion was 0.1 µl/30 s (+60 s dwell time of the cannulae). A within-subjects design was applied and each rat received only one of four treatments per day counterbalanced according to a Latin-square. Between each test day the rats were retrained as described below and received no drug treatment. The mixed D_2/D_1 DA receptor antagonist haloperidol (Haldol Janssen, Neuss, Germany) was administered systemically (0.1 mg/kg IP) in control experiments for the food-choice test.

Apparatus and testing procedures

Operant chamber

Tests of lever pressing for pellets and chow eating were conducted in an operant chamber (24×28×28 cm; Operant Behaviour System, TSE, Bad Homburg, Germany). Before surgery, the rats were trained to lever press for 45 mg pellets (Bioserve Inc., Frenchtown, USA; contents: 61% carbohydrates, 19% proteins, 5% fat. 3.6 kcal/g) on a continuous reinforcement (CRF) schedule (one 30-min session per day). After 3 days, a fixed-ratio 5 (FR5) schedule of reinforcement (five lever presses for one pellet) was introduced. The rats were maintained on the FR5 schedule for 2 weeks.

Then they were implanted with guide cannulae as described above. After surgery, the rats were retrained on a FR5 schedule with a glass bowl containing 15–20 g standard lab chow available on the floor of the operant chamber, until their rate of lever pressing was similar to the pre-surgery levels. Then the effects of SCH23390 and sulpiride on the food-choice test were assessed. Five minutes before the test, the rats received microinfusions of 0.3 µg/0.5 µl, 1.0 µg/0.5 µl and 3.0 µg/0.5 µl SCH23390 (n=11) or sulpiride (n=9) into the NAC. Each rat of a group received one of the four treatments per day according to a counterbalanced Latin-square design. During the 30-min test session, 15–20 g standard lab chow was freely available in a glass bowl on the floor of the operant chamber. The total number of lever presses and the amount of food (pellets and lab chow, corrected for spillage) consumed was measured for each rat.

Several control experiments were performed with naive rats in order to compare our data with those first reported by Salamone et al. (1991). First, we tested the effect of the DA antagonist haloperidol (0.1 mg/kg IP) on the food-choice in a CRF schedule. Second, we tested the effect of 0.1 mg/kg haloperidol on food preference when both pellets and lab chow were freely available in a standard Makrolon cage for 10 min on 3 days. Both control tests were also performed with rats receiving intra-accumbal infusions of SCH23390 and sulpiride. Third, it was tested whether intra-NAC infusion of SCH23390 or sulpiride impairs lever pressing in the operant chamber when no lab chow was present.

Reward-attenuated startle

Three days after surgery, the rats were food and water deprived and tested for their ASR magnitudes in the presence of a white light (15 W). The ASR was measured 5 min after placing the rat in a wire mesh cage (20×10×12 cm) mounted on a piezoelectric accelerometer inside a sound-attenuated chamber. Acoustic startle stimuli (30 white noise pulses, 100 dB SPL, 20 ms duration including 0.4 ms rise/fall times) were delivered through a loudspeaker at an interstimulus interval of 30 s. A continuous white background noise of 55 dB SPL was presented throughout the experimental session. The ASR amplitude was calculated from the difference between the maximum voltage output of the accelerometer during 80 ms after and during 80 ms before the onset of the acoustic startle stimulus. After measuring the pre-conditioning ASR magnitude, the rats were subjected to a Pavlovian conditioning training to associate a neutral stimulus (15 W white light) with the presentation of sucrose solution and palatable food (corn flakes). The rats were acclimatized for 5 min to a dark conditioning chamber (40×22×30 cm), then they received 4 ml sucrose solution (10%) and 1 g of corn flakes during 4 min in the presence of light. Then the light was switched off, and the food and sucrose dishes were removed. This dark phase without food and sucrose lasted 5 min. A total of 21 pairings of the conditioned stimulus (CS) with the unconditioned stimulus were performed during 3.5 days. The amount of food and sucrose consumed was enough for the rats to maintain an average body weight equal to 85% of the free-feeding level. After conditioning the ASR was measured again in the presence of light (post conditioning ASR). The rats were divided in 2 groups that received either 0.3 µg/0.5 µl, 1.0 µg/0.5 µl and 3.0 µg/0.5 µl SCH23390 (n=11) or the same concentrations of sulpiride (n=11) into the NAC immediately before placing them into the ASR test cages. Saline infusions served as controls. Each rat of a group received one of the four treatments per day according to a counterbalanced Latin-square design. Between 2 test days the rats received no drugs, but were retrained for RAS to prevent extinction.

The following control experiments were performed. First, we examined whether habituation of the ASR due to repeated testing might have confounded the effect of DA antagonists. Eight rats were implanted with guide cannulae aiming at the NAC and tested for their ASR magnitude 3 days later. Then they were pseudo-conditioned (i.e. they were placed in the conditioning chamber as described above and were exposed to the light and received flakes and sucrose solution afterwards in the home cage) and then tested on 4 days for their ASR magnitude in the presence of the light. They received intra-NAC saline infusions immediately before testing on each day with 1 day of pseudo-conditioning between each test. Then the ASR magnitudes of the 4 different test days were grouped in a randomized way, as if they would correspond to a randomized schedule of drug treatment. As a second control, the effects of intra-NAC SCH23390 and sulpiride (3.0 µg/0.5 µl) on the ASR magnitude in unconditioned rats (n=8) was measured.

Histology

After completion of the behavioral tests the rats were killed by an overdose of pentobarbital, their brains were removed and immersion-fixed in 0.1 M phosphate buffer containing 8% paraformaldehyde and 20% sucrose. Frontal sections were cut on a freezing microtome and Nissl stained with thionin. The injection sites in the NAC were examined under a light microscope and drawn onto plates taken from the brain atlas of Paxinos and Watson (1986).

Statistical analysis

Data were analyzed using repeated measures ANOVA followed by Tukey's t-tests for pairwise post-hoc comparisons. The mean ASR amplitudes before and after conditioning were compared with Student's t-tests.

Results

Operant chamber

The injection sites of SCH23390 and sulpiride were localized in the core and shell regions of the NAC of the rats tested in the food-choice tests and in the control experiments (Fig. 1). The effects of DA antagonists in the food-choice tests are illustrated in Fig. 2. Infusion of the DA D_1 receptor antagonist SCH23390 into the NAC dose-dependently reduced lever pressing and consumption of food pellets [$F(3,30)=19.9$, $P<0.001$] and lead to a significant increase in the consumption of lab chow [$F(3,30)=8.0$, $P<0.001$]. The D_2 receptor antagonist sulpiride also significantly reduced the operant responding for food pellets [$F(3,23)=4.1$, $P<0.05$] and increased the consumption of lab chow [$F(3,23)=3.7$, $P<0.05$].

In a control experiment, rats (n=6) had to press a lever for pellets under a FR5 schedule of reinforcement in the *absence* of lab chow in the operant chamber. Here, it was found that 1.0 and 3.0 µg SCH23390, but not sulpiride, reduced lever pressing [$F(4,20)=10.0$, $P<0.001$, Table 1]. In a further control experiment where the rats (n=5) had free access to both food pellets and lab chow (for 10 min on 3 days), they showed a clear preference for food pellets after intra-NAC infusion of saline or after 3.0 µg SCH23390 or 3.0 µg sulpiride (Table 2). This is supported by an ANOVA computing no significant treatment effect on the consumption of pellets [$F(2,8)=1.0$, $P>0.4$] or chow [$F(2,8)=1.6$, $P>0.3$]. A similar control experiment (Table 2) was performed 30 min after systemic application of haloperidol (0.1 mg/kg IP). Here again, rats (n=9) always preferred food pellets. However, haloperidol significantly in-

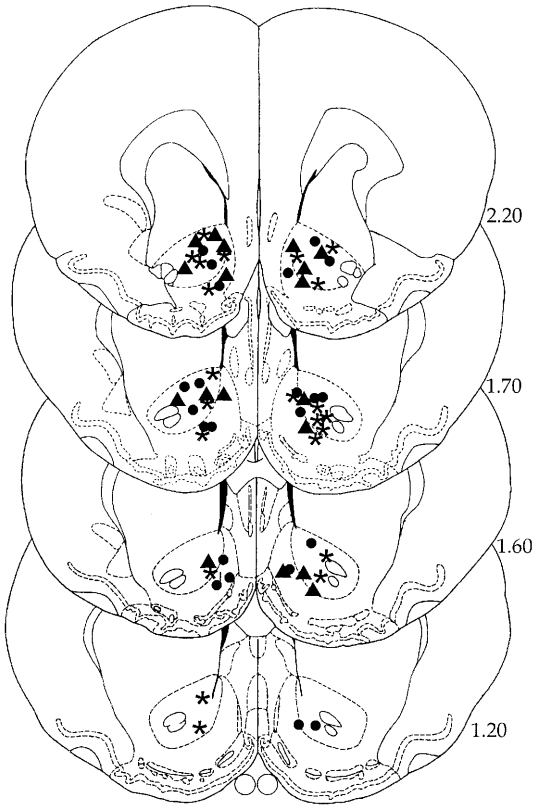

Fig. 1 Frontal sections through the rat forebrain (Paxinos and Watson 1986) showing the injection sites of SCH23390 (●) and sulpiride (▲) in the NAC of rats tested in the food-choice test. *Asterisks* indicate the injection sites of both drugs in control experiments. The *numerals* indicate the distance (mm) rostral from bregma

creased the consumption of lab chow and reduced the amount of food pellets eaten (Student's *t*-test, $P<0.01$). In agreement with previous findings (Salamone et al. 1991), the systemic administration of 0.1 mg/kg haloperidol significantly reduced the consumption of pellets (from 9.6±1 g to 4.1±1.2 g) and increased the consumption of lab chow (from 1.1±0.4 g to 2.9±0.5 g) of rats ($n=11$) under a CRF schedule (Student's *t*-test, $P<0.01$ for each comparison).

Reward-attenuated startle

The injection sites of SCH23390 and sulpiride were localized in the core and shell regions of the NAC of the rats tested in the RAS tests and in the control experiments (Fig. 3). The magnitude of the ASR was signifi-

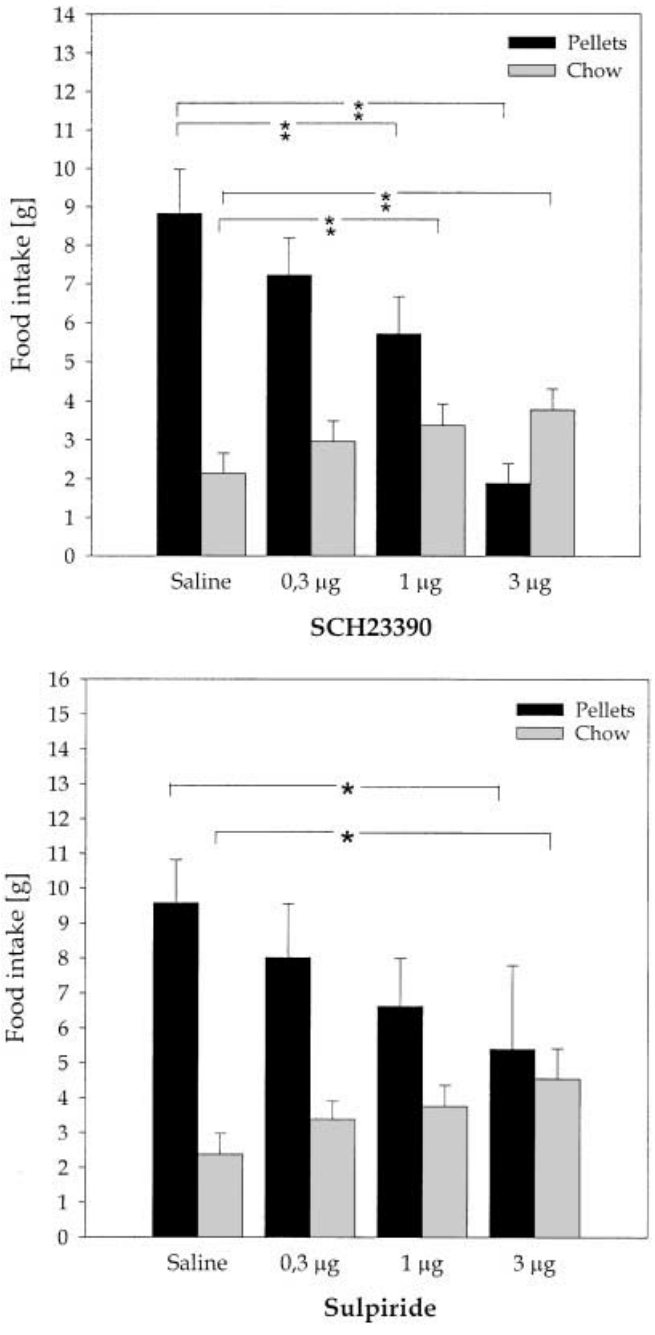

Fig. 2 Bar diagram illustrating the effects of SCH23390 and sulpiride on food intake (pellets and chow) in the operant chamber. *$P<0.05$, **$P<0.01$, ANOVA followed by Tukey *t*-tests for pairwise comparisons

Table 1 Effects of SCH23390 and sulpiride in the NAC on lever pressing for food pellets in the absence of freely available lab chow. Data are mean numbers of lever pressings±SEM

Saline	1.0 µg SCH23390	3.0 µg SCH23390	1.0 µg sulpiride	3.0 µg sulpiride
608±62	466±60[a]	148±42[b]	667±128	556±102

[a] Significant difference between 1.0 and 3.0 µg SCH23390, $P<0.05$
[b] Significant difference between saline and 3.0 µg SCH23390 $P<0.01$; ANOVA followed by Tukey's *t*-test, $n=6$)

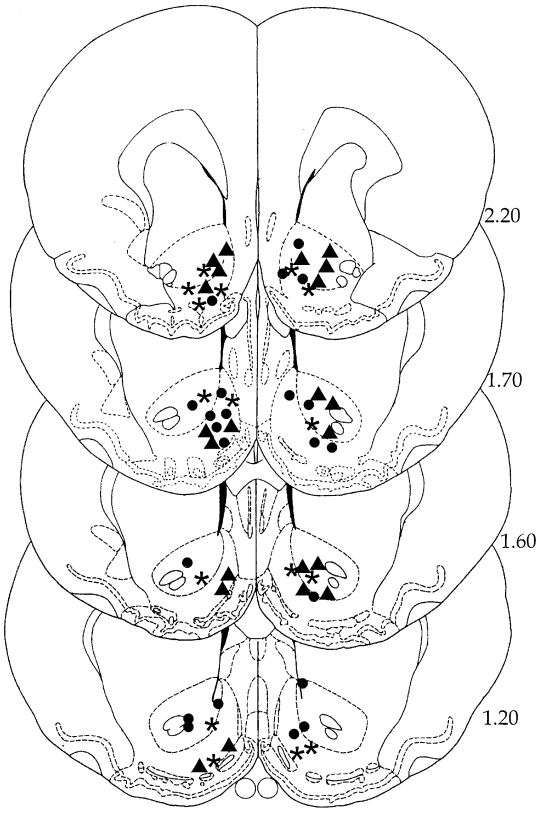

Fig. 3 Frontal sections through the rat forebrain (Paxinos and Watson 1986) showing the injection sites of SCH23390 (●) and sulpiride (▲) in the NAC of rats tested in the RAS test. *Asterisks* indicate the injection sites of both drugs in control experiments. The *numerals* indicate the distance (mm) rostral from bregma

Table 2 Effect of intra-NAC infusion (n=5) of 3.0 µg SCH23390 or 3.0 µg sulpiride, and of systemic application of 0.1 mg/kg haloperidol (n=9) on food intake in a food-choice test where pellets and lab chow were freely available. Data are mean weight of consumed food (g)±SEM

	Pellets	Chow
Saline (intra-NAC)	10.1±0.7	0.0±0.2
SCH23390	8.6±0.7	0.2±0.1
Sulpiride	9.4±1.1	0.1±0.1
Saline (IP)	8.6±0.6	0.2±0.1
Haloperidol	6.5±0.6	0.8±0.2

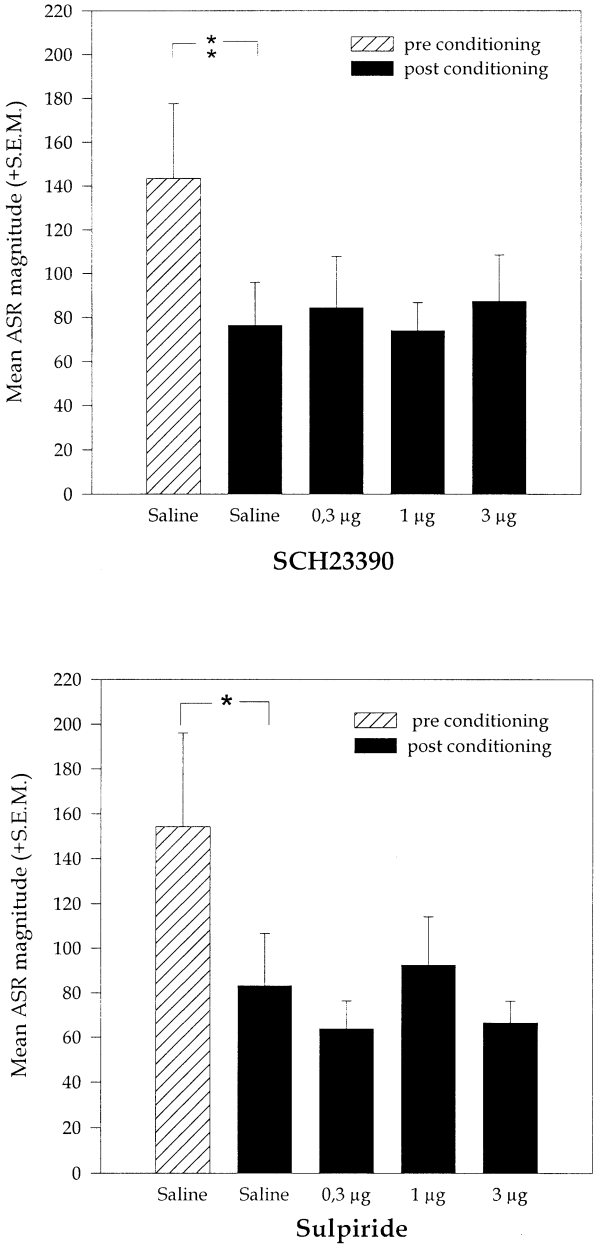

Fig. 4 Bar diagram illustrating the effects of SCH23390 and sulpiride on the magnitude of the ASR before (*hatched bars*) and after (*black bars*) training the rats to associate light with reward (*P<0.05, **P<0.01, Student's t-tests)

cantly reduced in the presence of a light conditioned stimulus predicting reward, both in the SCH23390 group (n=11, Student's t-test, P<0.01) and in the sulpiride group (n=11, Student's t-test, P<0.05). However, neither SCH23390 [F(3,30)=0.31, P=0.8] nor sulpiride [F(3,30)=1.8, P=0.2] reduced this RAS effect (Fig. 4).

Repeated testing of rats after pseudoconditioning did not significantly affect the magnitude of the ASR (n=8, ANOVA, P>0.8, data not shown). Another control experiment revealed that intra-NAC of 3.0 µg SCH23390 or 3.0 µg sulpiride did not affect the magnitude of the ASR in unconditioned rats (n=8, ANOVA, P>0.3, data not shown).

Discussion

We here show that blockade of DA receptors in the NAC with the DA receptor antagonists SCH23390 and sulpiride impair instrumental responding for food. Since this treatment at the same time increased the consumption of freely available lab chow, these data indicate that blockade of NAC DA does not impair the primary motivation ("hunger") in this task, but rather leads to a change in the behavioral strategy of the rats. It is unclear why the increase in the consumption of lab chow is not similar to

the decrease of the amount of food pellets eaten by the rats after DA receptor blockade (Fig. 2).

DA receptor blockade in the NAC shifted response selection towards low effort behavior. Similar results were seen after systemic administration of the DA antagonist haloperidol. The notion that NAC DA is not necessary for the hedonic experience of reward is further supported by the finding that the DA antagonists did not prevent the attenuation of the ASR in the presence of a reward-related conditioned stimulus. These data directly support and extend previous behavioral work (Salamone et al. 1991; Cousins and Salamone 1994) and are consistent with neurochemical data showing that DA release in the NAC is more related to response selection in the context of reward rather than for the approach and consumption of the natural reward (Salamone et al. 1994; Richardson and Gratton 1996).

An extensive recent study has shown that the NAC core and shell subregions are differentially involved in the mediation of conditioned reinforcement (Parkinson et al. 1999). In the present study, we did not attempt to distinguish between the drug effects of injection sites in the core or shell region of the NAC because an injection volume of 0.5 µl will spread about a distance of 1 mm^3 (Routtenberg 1972) probably blurring regional effects of DA receptor antagonists on the behavioral performance. However, a recent lesion study has shown that the core region of the NAC is particularly important for instrumental responding for reward in a food-choice test under an FR5 schedule of reinforcement (Sokolowski et al. 1998).

Interestingly, both the DA D_1 receptor antagonist and the D_2 receptor antagonist affected food-choice behavior in our study. Previously, it has been suggested that the D_1 receptor may be more important than the D_2 receptor for the mediation of conditioned reward (Sutton and Beninger 1999). Consistent with this, in the present study the D_1 receptor antagonist SCH23390 had a slightly more pronounced effect in the food-choice test than the D_2 receptor antagonist sulpiride. However, the control experiment where rats had to press the lever for pellets in the absence of freely available lab chow, showed that lever pressing under these conditions is also reduced by D_1 receptor blockade. This indicates that SCH23390, at least in higher doses, also affected lever pressing per se and did not only affect response selection in the food-choice situation. Notwithstanding a slightly stronger effect of SCH23390, the observation that both D_1 and D_2 receptor antagonists affected the rats food-choice behavior suggests a synergy between D_1 and D_2 receptors in the NAC in the control of reward-related behavior. This is consistent with previous studies showing that either DA D_1 and D_2 receptor antagonists (Wolterink et al. 1993) or agonists (Ikemoto et al. 1997) attenuated reward-related behavior. Interestingly, the preference for the palatable food pellets in a free choice test is not affected by blockade of accumbal DA receptors, suggesting that the gustatory and perhaps hedonic evaluation of the food is also not dependent upon DA release in the NAC.

The attenuation of the ASR in the presence of a reward-predicting cue has previously been shown to be reduced by pre-training 6-OHDA lesions of the NAC (Koch et al. 1996). Here, we show that NAC DA is not involved in the expression of RAS when the DA receptor blockade occurs after conditioning. Hence, we conclude that in the RAS paradigm, mesoaccumbal DA is necessary for the acquisition but not for the retrieval of the conditioned response in the presence of the CS. Control experiments have shown that RAS is not due to long-term habituation of the ASR due to repeated testing. We assume that RAS is due to negative motivational priming whereby a hedonic emotion suppresses aversive response (Lang 1995). RAS was not affected by DA D_1 or D_2 receptor antagonists in the NAC administered in doses that clearly attenuated operant responding for reward. This supports the contention that NAC DA does not mediate the affective motivational component of reward.

Taken together, our findings support the idea that NAC DA is not necessary for the motivational aspects of reward but rather for response selection in the context of reward, where the potential benefits of responding has to be weighed against the energetic demands of this response (Salamone et al. 1997).

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