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The tachykinin NK_3 receptor antagonist SR142801 blocks the behavioral effects of cocaine in marmoset monkeys

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Abstract

Brain neuropeptide transmitters of the tachykinin family are involved in the organization of many behaviors. However, little is known about their contribution to the behavioral effects of drugs of abuse. Recently, the tachykinin NK_3 receptor, one of the three tachykinin receptors in the brain, was shown to attenuate the acute and chronic behavioral effects of cocaine in rats. In order to test if these findings can be generalized to primates we investigated the role of the tachykinin NK_3 receptor in the acute behavioral effects of cocaine in marmoset monkeys (*Callithrix penicillata*) using a figure-eight maze procedure. Animals were pretreated with the tachykinin NK_3 receptor antagonist, (*R*)-(*N*)-[1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-*N*-methylacetamide (SR142801; 0, 0.02, 0.2, 2.0 mg/kg, i.p.), and received either a treatment with cocaine (10 mg/kg, i.p) or saline (i.p.). Cocaine increased locomotor activity and aerial glance behavior, but reduced exploratory and bodycare activities, scent marking and terrestrial scanning behavior. A sensitivity analysis revealed that two responder types can be differentiated in relation to the occurrence of a hyperlocomotor response to cocaine. SR142801 blocked the actions of cocaine on several behaviors dose-dependently for each responder type, respectively. There was no effect of SR142801 alone on any behavior measured. These data suggest that the tachykinin NK_3 receptor contributes to the individual behavioral response to cocaine in marmoset monkeys. Having no behavioral effects on its own, but blocking the cocaine effects, might suggest the tachykinin NK_3 receptor antagonist, SR142801, as a potential treatment of cocaine addiction in humans.

Keywords: Cocaine; Tachykinin NK_3 receptor; SR 142801; Marmoset; Behavior; Sensitivity

1. Introduction

Neuropeptides belonging to the tachykinin family are characterized by having the common C-terminal sequence Phe-X-Gly-Leu-Met-NH_2. Five mammalian tachykinins have so far been identified, namely substance P, neurokinin A, neurokinin B, neuropeptide K and neuropeptide γ. Three distinct G protein-coupled receptors, tachykinin neurokinin1 (NK_1), NK_2 and NK_3, have been characterized. Tachykinin NK_1 and NK_3 receptors are widely distributed in the brain, while the tachykinin NK_2 receptors are found in restricted areas. Substance P, neurokinin A and neurokinin B have higher binding affinity to tachykinin NK_1, NK_2 and NK_3 receptors, respectively, but all the neurokinins bind to all three tachykinin NK receptors (Regoli et al., 1994; Massi et al., 2000; Hökfelt et al., 2001). Compelling evidence suggests that tachykinin NK_3 receptors are involved in memory-, anxiety- and reinforcement-related processes (Hasenöhrl et al., 1990, 1992; Huston et al., 1993; Krappmann et al., 1994). Recently it was shown in rats that the tachykinin NK_3 receptor also mediates the acute as well as the chronic behavioral effects of cocaine (Jocham et al.,

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submitted for publication). However, the findings in rats may not automatically generalize to humans due to the considerable species differences in tachykinin NK_3 receptors between humans and rats (Emonds-Alt et al., 1995; Nguyen-Le et al., 1996).

Cocaine is a potent pharmacological reinforcer and drug of abuse (Vanderschuren and Everitt, 2004). Already the acute application of cocaine causes complex behavioral patterns in humans and animals, including hyperlocomotion, and the suppression of grooming and eating behavior (Müller et al., 2003). Cocaine can induce not only euphoria in humans (Breiter et al., 1997; Volkow et al., 1997) but also anxiety, as shown in rodent studies (Yang et al., 1992; Rogerio and Takahashi, 1992). However, the acute effects of cocaine as well as the liability to develop cocaine addiction differ considerably between individuals (Hooks et al., 1991; Homberg et al., 2002; Deroche-Gamonet et al., 2004). Non-human primates with their complex general behavioral repertoire (Stevenson and Poole, 1976; King et al., 1988; Barros et al., 2004a) and distinguished response profiles to psychostimulants provide a valuable model in the transition from rodents to humans. Even small effects of psychostimulants can, thus, be dissected, identifying high and low hyperlocomotor responding animals, and revealing complex differences in the whole response pattern (Mello et al., 2005).

In this study, we investigate the role of the tachykinin NK_3 receptor in the behavioral effects of cocaine in non-human primates (*Callithrix penicillata*) using a figure-eight maze procedure. In line with a previous study on the acute behavioral effects of a low potency psychostimulant (Mello et al., 2005), we asked whether there are also different responder types for cocaine in non-human primates, and how tachykinin NK_3 receptor antagonism affects them. According to our findings in rats we hypothesized that pharmacological antagonism of the tachykinin NK_3 receptor with the non-peptide tachykinin NK_3 receptor antagonist, (*R*)-(*N*)-[1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-*N*-methylacetamide (SR142801), will not have behavioral effects on its own, but should attenuate the acute behavioral effects of cocaine. Furthermore, we expected responder type differences also after cocaine treatment in monkeys, and a differential influence of tachykinin NK_3 receptor antagonism.

2. Materials and methods

2.1. Subjects

Twelve adult black tufted-ear marmosets (*C. penicillata*, five males and seven females) were used as subjects. Animals weighed 280–405 g at the beginning of experiments. Before and during the experiment all animals were socially housed in separate male/female groups in indoor/outdoor cages (2 × 1.3 × 2 m) of the same colony room (not all members of the housing colony were tested in this experiment). Maintenance and testing of subjects were performed at the Primate Center, University of Brasilia. Except during the 20-min test periods, food and water were available ad libitum. All procedures were approved by the Animal Ethics Committee of the Institute of Biology, University of Brasilia, and followed the 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1996).

2.2. Drugs

The tachykinin NK_3 receptor antagonist SR142801 ((*R*)-(*N*)-[1-[3-[1-benzoyl-3-(3,4-dichlorophenyl)piperidin-3-yl]propyl]-4-phenylpiperidin-4-yl]-*N*-methylacetamide, Sanofi-Synthelabo, Montpellier, France) was suspended in 0.01% Tween 80 (Sigma-Aldrich, USA) in distilled water and injected i.p. in the doses of 0, 0.02, 0.2, and 2 mg/kg. The dose range was based on previous behavioral experiments investigating the effects of SR142801 in rats (Jocham et al., submitted for publication) with regards to the species differences between rats and primates (Emonds-Alt et al., 1995; Nguyen-Le et al., 1996). Cocaine (Sigma, USA) was dissolved in 0.9% physiological saline and injected i.p. in a dose of 0 and 10 mg/kg. The injection volume was 2 ml/kg for SR142801 and 1 ml/kg for cocaine.

2.3. Apparatus

Testing was conducted in a figure-eight continuous maze (Barros and Tomaz, 2002). The maze consisted of a rectangular field (125 × 103 × 35 cm) suspended 1 m from the floor and divided into five arms by two holes and barriers, forming a continuous figure-eight maze (Fig. 1). The apparatus, made of 4-mm transparent glass on a metal frame support, was divided into two segments (front and back chambers) by a concrete visual barrier (147 × 8 × 218 cm). The back chamber consisted of an arm (125 × 30 × 35 cm) with a central guillotine-type door. The latter formed the start compartment. The front chamber had three parallel arms (40 × 25 × 35 cm), 25 cm apart, ending in a common perpendicular arm (125 × 25 × 35 cm). Both chambers were interconnected through holes in the visual barrier at each of the three parallel arms.

2.4. Procedure

All animals were habituated to the maze and the transport cage (35 × 20 × 23 cm) prior to the beginning of the experiment. All subjects were submitted to one more 20-min habituation trial

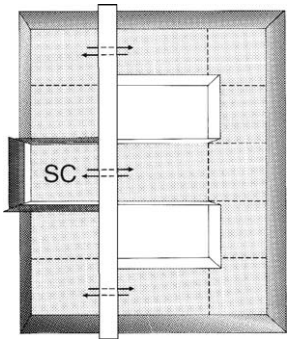

Fig. 1. Top view of the figure-eight continuous maze used for testing (SC indicates the start compartment; for a detailed description, see text).

in the figure-eight maze, which showed stable and, thus, a well habituated activity compared to the last maze exposure. Following the habituation trial, two test sessions were spaced 4 weeks apart. In the first session the effects of SR142801 plus saline were tested, while in the second session the effects of SR142801 in combination with cocaine were evaluated.

In each session, four pseudo-randomly assigned treatment trials were performed with each subject, with a wash out period of 72 h between the treatments. As a pretreatment the animals received an i.p. injection of SR142801 (0, 0.02, 0.2 and 2 mg/kg). After the pretreatment the animals were returned to the home cage for 30 min before they received an i.p. injection of 10 mg/kg cocaine or saline. Immediately following the treatment the animal was released into the maze's start compartment, thus commencing a 20-min trial. Barriers from this compartment were promptly removed upon the animal's exit, permitting free access to the whole apparatus. After the session, the subject was returned to its home environment in the transport cage. Treatments and order of subjects were pseudo-randomly assigned for each test day. Video cameras were used for online monitoring, and all trials were recorded for later behavioral analysis. All test sessions were performed between 8:00 am and 1:00 pm.

2.5. Behavioral analysis

For behavioral analysis, the maze was divided into 13 sections. The following behavioral parameters based on the ethograms of marmoset behavior (Stevenson and Poole, 1976; Stevenson and Rylands, 1988; Barros et al., 2002a, 2003, 2004a,b) were scored for each 20 min trial by experienced observers (inter-rater reliability: >95%) blind to the experimental treatment: (1) *Locomotor activity*: the number of maze sections crossed with both forelimbs; (2) *Exploratory activity*: the number of times that the animal spent sniffing and/or licking any part of the apparatus or standing on the hind legs; (3) *Bodycare activities*: number of times the animal spent grooming (slow and precise repetitive movements of the hand through the fur) or scratching (quick repetitive movements of hand or foot through the fur); (4) *Scent marking*: the number of times that the animal rubbed the anogenital region on any substratum; (5) *Aerial scanning*: time and frequency the animals spent scanning the environment from the horizontal plane upwards, persisting >5 s while the animal remained stationary; (6) *Terrestrial scanning*: time and frequency the animals spent scanning the environment below the horizontal plane, persisting >5 s while the animal remained stationary; (7) *Aerial glance*: frequency of rapid upward sweeping movements of the head lasting <2 s while stationary and (8) *Terrestrial glance*: frequency of rapid downward movements of the head lasting <2 s while stationary. For semi-automated behavioral analysis, the program PROSTCOM 3.20 (Conde et al., 2000) was used.

2.6. Statistical analysis

The data were analyzed by means of a two-way analysis of variance (ANOVA) with pretreatment (4) and treatment (2) as factors. In order to differentiate between cocaine-sensitive and -insensitive animals, the locomotor response was used as a criterion. Animals which showed an increase in locomotor activity after the vehicle-cocaine treatment compared to the vehicle-saline treatment were considered to be "cocaine sensitive". All other animals were considered to be "cocaine insensitive". All behavioral parameters were further analyzed with respect to the cocaine sensitivity of the animals. In order to identify differences in the behavioral response to the treatments between cocaine-sensitive and-insensitive animals pre-planned comparisons were calculated using the LSD-test. All statistical results were interpreted as measures of effect with a *P*-value of 0.05 as a criterion.

3. Results

The injection of cocaine led to an increase in the locomotor activity when all animals were considered together (Fig. 2A; two-way ANOVA, treatment: $F_{1,88}=15.12$, $P=0.0002$). Neither spontaneous nor cocaine-induced locomotor activity was affected by pretreatment with SR142801 when all animals were analyzed together (pretreatment and interaction: $P>0.05$). Sensitivity analysis (Fig. 2B), however, revealed that only 5 of

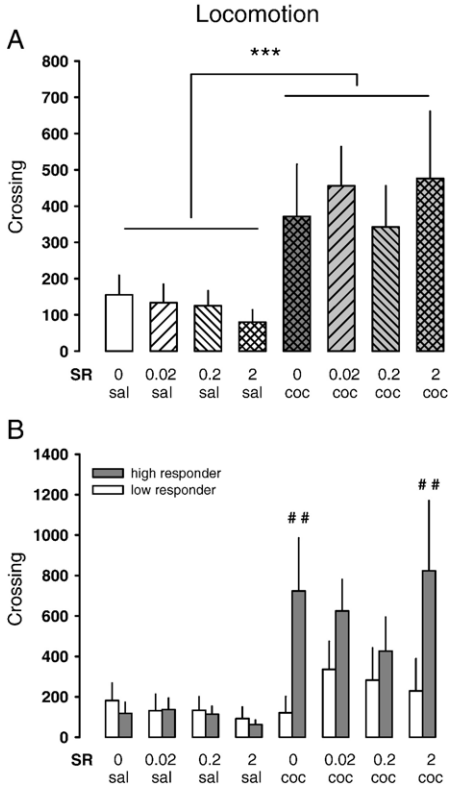

Fig. 2. The effects of cocaine (10 mg/kg, i.p.) on locomotor activity (mean±S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20-min test trial. (A) Effects for all animals tested ($n=12$). (B) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); ***$P<0.001$, two-way ANOVA, factor treatment; $^{\#\#}P<0.01$, high responders vs. low responders).

the 12 animals tested (42%) showed increased locomotor activity after vehicle-cocaine treatment compared to vehicle-saline, and were, thus, considered to be cocaine sensitive (high responders). Seven of the 12 animals tested (58%) showed less activity after vehicle-cocaine compared to vehicle-saline treatment, and were considered to be cocaine insensitive (low responders). There was no effect of the treatment day on which an animal received the vehicle-cocaine treatment regarding its locomotor response, and, thus, the high vs. low responder classification. The cocaine but not the saline effect on locomotor activity differed considerably between the two responder types (high vs. low responders, vehicle-cocaine: $P=0.003$; vehicle-saline: $P>0.05$). While pretreatment with SR142801 did not have an effect when all animals were pooled, sensitivity analysis revealed striking responder type differences. The pretreatment reduced the hyperlocomotor effects of cocaine in the high responder animals with an inverted U-shaped dose–response curve. The high vs. low responder difference in the locomotor response to cocaine was attenuated by pretreatment with 0.02 and 0.2 mg/kg SR142801 ($P>0.05$) but not after pretreatment with 2 mg/kg SR142801 ($P=0.0036$).

The cocaine treatment caused a decrease in exploratory activity when all animals were considered together (Fig. 3A; two-way ANOVA, treatment: $F_{1,88}=3.8$, $P=0.05$). Neither spontaneous nor cocaine-induced decrease in exploratory activity was affected by pretreatment with SR142801 when all animals were analyzed together (pretreatment and interaction: $P>0.05$). Sensitivity analysis (Fig. 3B) did not reveal differences between the high and low responder animals (all treatments: $P>0.05$).

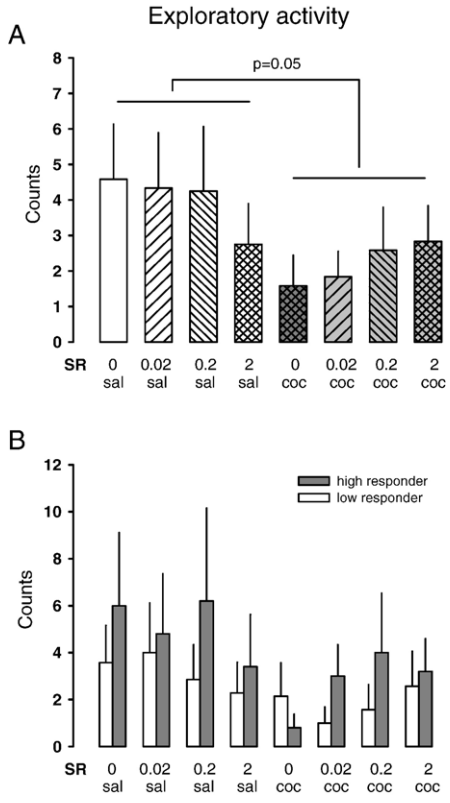

Fig. 3. The effects of cocaine (10 mg/kg, i.p.) on exploratory activity (mean ± S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20-min test trial. (A) Effects for all animals tested ($n=12$). (B) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); $P=0.05$, two-way ANOVA, factor treatment).

Bodycare activity and scent marking behavior were also decreased after cocaine treatment (Fig. 4A and C; two-way ANOVA, treatment, bodycare activity: $F_{1,88}=10.56$, $P=0.0016$; scent marking: $F_{1,88}=4.97$, $P=0.028$). Both behaviors were virtually eliminated by the cocaine treatment. Neither spontaneous nor the cocaine-induced decrease in both behaviors was affected by pretreatment with SR142801 when all animals were analyzed together (pretreatment and interaction: $P>0.05$). Sensitivity analysis (Fig. 4B and D) showed that there was no obvious difference in bodycare activity and scent marking behavior after cocaine between high and low responder animals ($P>0.05$). Neither spontaneous nor the cocaine-induced decline in these behaviors was affected by SR142801 in either responder group ($P>0.05$).

Cocaine neither affected the time nor the frequency of aerial scanning behavior when all animals were considered together (Fig. 5A and C; two-way ANOVA, treatment: $P>0.05$). Neither spontaneous aerial scanning nor the aerial scanning after cocaine was affected by pretreatment with SR142801 when all animals were analyzed together (pretreatment and interaction: $P>0.05$). Sensitivity analysis (Fig. 5B and D), however, showed a dissociating effect of cocaine on the time of aerial scanning between the high and low responder animals (high vs. low responders, vehicle-cocaine: $P=0.0063$, vehicle-saline: $P>0.05$). While cocaine increased the time of aerial scanning in the low responder animals, it decreased aerial scanning time in the high responder animals. This high vs. low responder difference in the response to cocaine was eliminated by pretreatment with 0.02 and 0.2 mg/kg SR142801 ($P>0.05$), but not after pretreatment with 2 mg/kg SR142801 ($P=0.045$). No such effect was observed for the frequency of aerial scanning (high vs. low responders, all treatments: $P>0.05$).

The time (Fig. 6A; two-way ANOVA, treatment, $F_{1,88}=4.98$, $P=0.028$) as well as frequency of terrestrial scanning (Fig. 6C; two-way ANOVA, treatment, $F_{1,88}=4.93$, $P=0.029$) were decreased after cocaine when all animals were considered together. SR142801 pretreatment completely eliminated terrestrial scanning after cocaine, however, statistical analysis yielded neither a pretreatment effect nor a pretreatment × treatment interaction ($P>0.05$). Sensitivity analysis (Fig. 6B and D), on the other hand, showed a dissociating cocaine effect. Cocaine alone increased terrestrial scanning in the high responder animals, while it eliminated the behavior in the low responder animals (high vs. low responders, vehicle-cocaine, time: $P=0.023$; frequency: $P=0.0075$, vehicle-saline, time and frequency: $P>0.05$). The difference between high and low responder animals in their cocaine response was no longer observed after pretreatment with SR142801 (high vs. low responders, all doses: $P>0.05$).

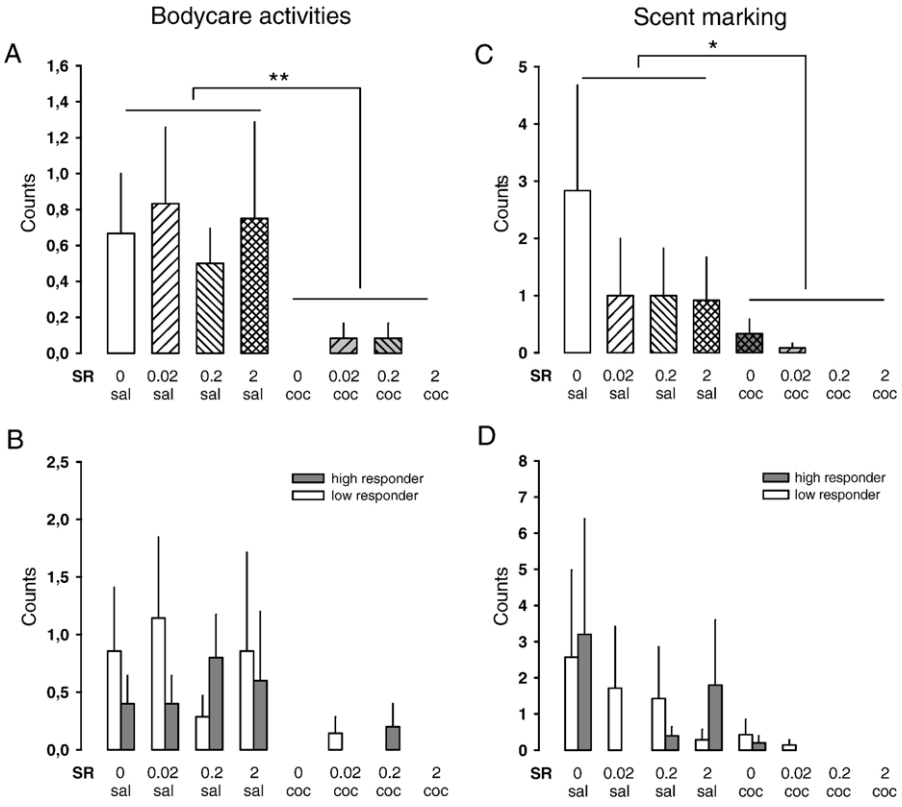

Fig. 4. The effects of cocaine (10 mg/kg, i.p.) on bodycare activities and scent marking behavior (mean ± S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20 min test trial. (A/C) Effects for all animals tested ($n=12$). (B/D) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); *$P<0.05$, **$P<0.01$, two-way ANOVA, factor treatment).

Aerial glance was increased after cocaine treatment when all animals were considered together (Fig. 7A; two-way ANOVA, treatment: $F_{1,88}=4.86$, $P=0.03$). Spontaneous and the cocaine-induced increase in aerial glance was reduced by pretreatment with SR142801 as a tendency when all animals were analyzed together, although statistical analysis did not yield a pretreatment effect or a pretreatment × treatment interaction ($P>0.05$). Sensitivity analysis (Fig. 7B) showed that the increase in aerial glance after cocaine only occurred in the high responder animals but not in the low responder animals (high vs. low responders, vehicle-cocaine: $P=0.021$, vehicle-saline: $P>0.05$). Pretreatment with SR142801 attenuated the high vs. low responder difference by reducing the increase in aerial glance in the high responder animals at doses of 0.2 and 2 mg/kg (high vs. low responders, $P>0.05$), but not at a dose of 0.02 mg/kg (high vs. low responders, $P=0.0089$).

There was no effect of cocaine on terrestrial glance when all animals were considered together (Fig. 7C; two-way ANOVA; treatment: $P>0.05$). Spontaneous terrestrial glance and terrestrial glance after cocaine were not affected by pretreatment with SR142801 (pretreatment and interaction: $P>0.05$). Sensitivity analysis (Fig. 7D) showed a tendency for more terrestrial glance behavior in the high responder animals, although statistical analysis did not yield a high vs. low responder difference at any treatment combination ($P>0.05$).

4. Discussion

The effects of cocaine were investigated on a broad range of marmoset behaviors. Cocaine increased locomotor activity and aerial glance behavior. At the same time exploratory activity, bodycare activities, scent marking and terrestrial scanning behavior were decreased. There was no overall cocaine effect on aerial scanning and terrestrial glance. Interestingly, an increase in locomotor activity after cocaine could be found only in 5 of the 12 animals (42%) tested. Seven of the 12 animals (58%) did not respond with an increased locomotor activity. The analysis of the individual variability indicated a bimodal distribution of effects, very similar to the one found recently in a study investigating the effects of the low potency stimulant, diethylpropion, in marmoset monkeys (Mello et al., 2005). Thereby, the increase in behavioral activity, which is usually considered as an indicator of the stimulant properties of cocaine, was used to subdivide the population of the animals into cocaine sensitive (high responder) and cocaine insensitive (low responder) animals. The subsequent sensitivity analysis revealed that there are two principle types of responses to cocaine in marmoset monkeys. The high responder animals were characterized in their response to cocaine by a profound increase in locomotor activity. But high vs. low responder differences after acute cocaine also occurred in aerial and terrestrial scanning and aerial glance behavior. In the high responder animals, cocaine

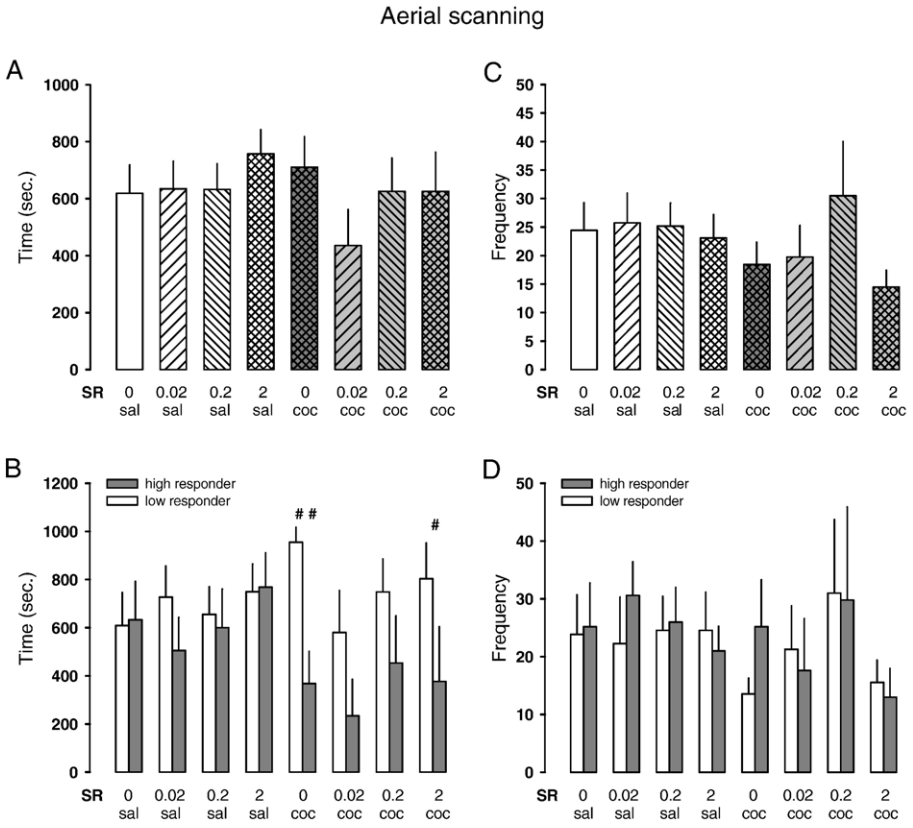

Fig. 5. The effects of cocaine (10 mg/kg, i.p.) on aerial scanning time and frequency (mean ± S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20-min test trial. (A/C) Effects for all animals tested ($n=12$). (B/D) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); $^{\#}P<0.05$, $^{\#\#}P<0.01$, high responders vs. low responders).

increased terrestrial scanning and aerial glance, but decreased aerial scanning. Exploratory activity, bodycare activities, and scent marking were also decreased, but did not differ from the low responder animal's response. The low responder animals did not show hyperlocomotion after cocaine, but instead, responded with an increase in aerial scanning.

Tachykinin NK_3 receptor antagonism with SR142801 alone did not affect any of the behaviors measured in marmosets. The cocaine effects on the marmoset behavior did not appear to be modulated by the tachykinin NK_3 receptor antagonism when all animals were pooled. However, sensitivity analysis revealed that SR142801 had striking effects when responder types were evaluated separately. SR142801 selectively attenuated the cocaine-induced hyperlocomotion and the increase in terrestrial scanning and aerial glance in the high responder animals, while it reduced the increase in aerial scanning in the low responder animals. In all these behaviors tachykinin NK_3 receptor antagonism also attenuated the high vs. low responder differences in the acute behavioral response to cocaine. But also after sensitivity analysis, the tachykinin NK_3 receptor antagonist did not appear to affect all cocaine-induced changes in behavior. The cocaine-induced decreases in exploratory activity, bodycare activities and scent marking, which did not differ between the high and low responder animals, was not affected by SR142801.

This study revealed a complex behavioral response to cocaine in marmoset monkeys. Within this pattern two principal response types could be distinguished, that were clearly segregated from one another, reflecting strong interindividual differences in the acute behavioral response to cocaine in non-human primates. In that, the present study confirms principle responder type differences in marmosets as they were found in a recent study with the low potency psychostimulant, diethylpropion (Mello et al., 2005). In the present study, high responder animals not only showed an increase in locomotor response but also an increase in terrestrial scanning and aerial glance. The increase in terrestrial scanning and aerial glance, together with the tendential decrease in exploratory activity, is associated with an anxiogenic state (Barros et al., 2004a,b), which can be reversed by anxiolytic drugs like diazepam (Barros et al., 2000). At the same time the predominant aerial scanning behavior was decreased in the high responder animals, which may indicate that the anxiogenic component was not dominant in the high responder animals. In callitrichids, visual scanning, which includes the predominant aerial and the less frequent terrestrial scanning, facilitates the detection of objects in the environment and has a high adaptive value (Caine, 1984; Hardie and Buchanan-Smith, 1997). In general, the presentation of a potential threat is associated with an increase in visual scanning (Caine, 1984; Ferrari and Ferrari, 1990; Hardie and Buchanan-Smith, 1997; Caine, 1998; Koenig, 1998). In the low responder

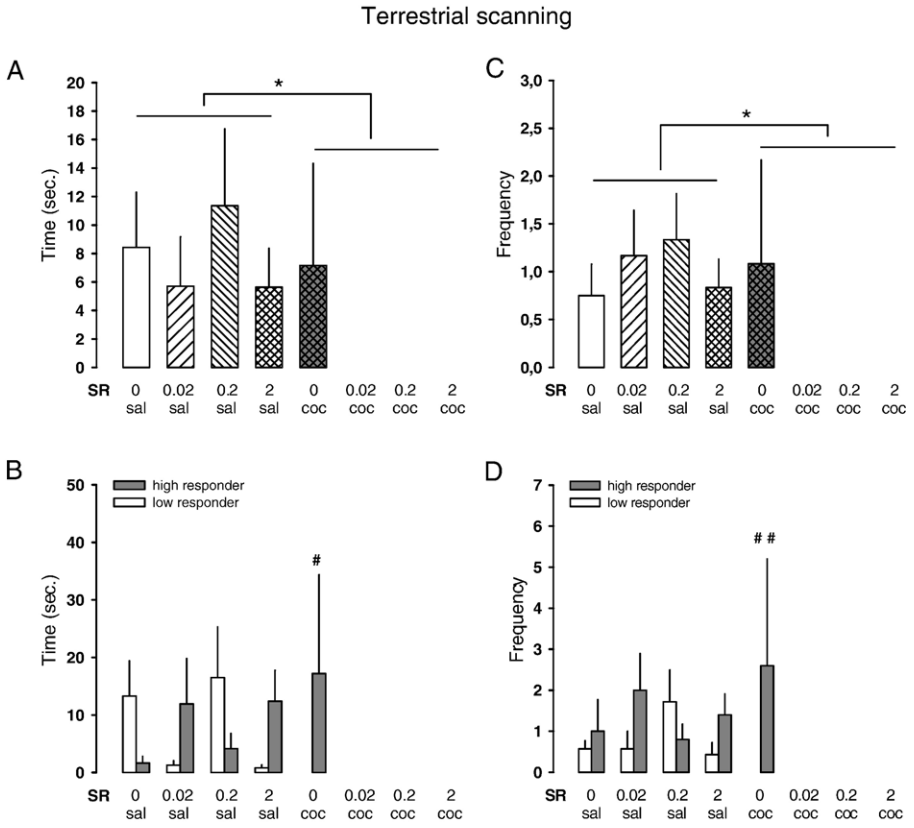

Fig. 6. The effects of cocaine (10 mg/kg, i.p.) on terrestrial scanning time and frequency (mean±S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20-min test trial. (A/C) Effects for all animals tested ($n=12$). (B/D) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); *$P<0.05$, two-way ANOVA, factor treatment; $^{\#}P<0.05$, $^{\#\#}P<0.01$, high responders vs. low responders).

animals the increase in the aerial scanning is the most pronounced behavioral effect of cocaine, which may reflect a predominant anxiogenic response. Both responder types share the almost complete suppression of bodycare activities and scent marking behavior. Interestingly, both responder types match closely to the responder types to the low potency psychostimulant, diethylpropion (Mello et al., 2005). The most important difference in the behavioral response to the two psychostimulants may be the additional increase in the terrestrial scanning after cocaine in the high responder animals. This might reflect a more pronounced anxiogenic component in the high responder animals to cocaine compared to diethylpropion.

The hyperlocomotor effects of cocaine as well as the increase in terrestrial scanning and aerial glance were attenuated in the high responder animals by tachykinin NK_3 receptor antagonism. The suppressory effects of cocaine on bodycare activity and scent marking, however, were not reversed by SR142801. Thus, in the high responder marmoset monkeys the contribution of the tachykinin NK_3 receptor to the acute behavioral effects of cocaine appears to be comparable with that in rats. In rats SR142801 blocked the hyperlocomotor effects of cocaine without affecting the suppression of grooming behavior (Jocham et al., submitted for publication). Since SR142801 alone did not significantly affect locomotor activity in primates and rats, but blocked cocaine-induced locomotor activity, it is suggested that a tonic stimulation of the tachykinin NK_3 receptor is not required for the generation of spontaneous behavior, but rather, that tachykinin NK_3 receptors contribute to an induced increase in locomotor activity. This view is also supported by the findings that the local injection of substance P or its C-terminal analogue, DiMe-C7, into the ventral tegmental area and the substantia nigra is well known to enhance locomotor activity in rats (Kelley et al., 1979; Eison et al., 1982; Barnes et al., 1990). Also the local application of the tachykinin NK_3-receptor agonist senktide, but not of tachykinin NK_1 or NK_2 receptor agonists, into the substantia nigra and ventral tegmental area induced locomotor activity and rearing behavior in rats (Stoessl et al., 1988). The present study also showed that the anxiety-related effects of cocaine can be blocked by tachykinin NK_3 receptor antagonism. In the low responder animals tachykinin NK_3 receptor antagonism reduced the cocaine-induced increase in aerial scanning, and thus, the predominant anxiogenic response. The attenuation of the cocaine-induced anxiety-related behavior by the tachykinin NK_3 receptor antagonist was rather surprising, since the tachykinin NK_3 receptor agonist, senktide (Ribeiro and De Lima, 1998; Ribeiro et al., 1999), substance P (Echeverry et al., 2001), and the substance P N-terminal fragment, SP_{1-7} (Barros et al., 2002b), were found to be anxiolytic in mice, rats, and

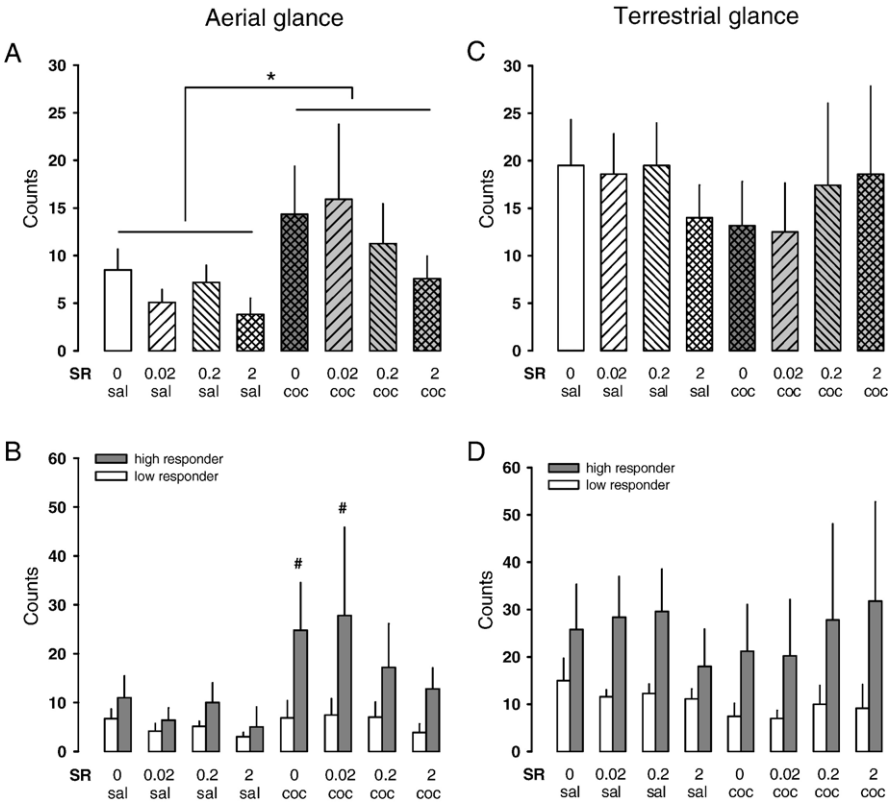

Fig. 7. The effects of cocaine (10 mg/kg, i.p.) on aerial and terrestrial glance (mean ± S.E.M.) and its modulation by the tachykinin NK_3 receptor antagonist, SR142801 (0.02–2.0 mg/kg, i.p.), during a 20-min test trial. (A/C) Effects for all animals tested ($n=12$). (B/D) Sensitivity analysis: group split according to the animals response to cocaine (high responder: increased locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=5$); low responder: no increase in locomotor activity after vehicle-cocaine vs. vehicle-saline ($n=7$); $^{*}P<0.05$, two-way ANOVA, factor treatment; $^{\#}P<0.05$, high responders vs. low responders).

monkeys respectively. Also the local application of substance P, and both C- and N-terminal fragments, SP_{7-11} and SP_{1-7}, into the ventral pallidum of rats had anxiolytic effects (Nikolaus et al., 2000). However, substance P as well as its C-terminal fragment, SP_{7-11}, can also have anxiogenic effects when injected into the dorsal periaqueductal gray of rats (De Araujo et al., 1999; Hasenöhrl et al., 2000). The tachykinin NK_3 receptor antagonist, SR142801, had either an anxiogenic or no effects in mice (Ribeiro and De Lima, 1998; Ribeiro et al., 1999), and no effect on panic symptoms was found in humans (Kronenberg et al., 2005). In this study, no behavior was affected by SR142801 alone in high and low responder animals.

Altogether, the tachykinin NK_3 receptor antagonism attenuated the acute cocaine effects in high and low responder marmoset monkeys, respectively. The most effective doses for antagonizing the behavioral effects of cocaine in monkeys were 0.02 and 0.2 mg/kg SR142801. Blocking the acute cocaine effects in rats required a 10-fold higher dose of SR142801 (Jocham et al., submitted for publication). These findings are in line with the report by Emonds-Alt et al. (1995), which showed a 10–100 fold higher binding of SR142801 in guinea-pigs, gerbils and humans compared to rats. At the highest dose tested in the marmoset monkeys (2.0 mg/kg), no inhibition of the cocaine-induce hyperlocomotion in the high responder animals and of the increase in aerial scanning in the low responder animals was observed, indicating an inverted U-shaped dose–response curve for the effects of SR142801. Such a dose–response curve is described in many neuropeptide studies (Huston et al., 1993; Hasenöhrl et al., 2000), and was also observed in rats blocking the acute hyperlocomotor and the reinforcing effects of cocaine (Jocham et al., submitted for publication). At the highest dose tested, the low affinity of SR142801 to calcium and sodium channels (Emonds-Alt et al., 1995) may have counteracted the tachykinin NK_3 receptor effects. It should be noted that the high vs. low responder subdivision of the animals was made post hoc based on the effects of the vehicle-cocaine treatment administered in the course of the testing. An important drawback, which might also limit the interpretation, is that by the subdivision of the animals group size was reduced, which results in a loss of statistical power when comparing the treatment effects. Results based on the high vs. low responder behavioral profiles have, therefore, an exploratory character and warrant further investigation.

In summary, the present study showed that cocaine has a wide range of different acute effects on behavior in marmoset monkeys. However, the behavioral response is not uniform. Two responder types could be differentiated, which showed a similar response profile as it was previously described for the low potency psychostimulant, diethylpropion (Mello et al., 2005). Tachykinin NK_3 receptor antagonism blocks the acute cocaine effects on behavior in each responder type, respectively. Having no behavioral effects on its own, but blocking

individual cocaine effects, suggests the tachykinin NK_3 receptor antagonist SR142801 as a potential treatment of cocaine-addiction in humans.

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