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Serotonin$_{1A}$-receptor antagonism blocks psychostimulant properties of diethylpropion in marmosets (*Callithrix penicillata*)

Eldon L. Mello Jr.[a], Rafael S. Maior[a], Robert J. Carey[c], Joseph P. Huston[b], Carlos Tomaz[a], Christian P. Müller[b,*]

[a]*Department of Physiological Sciences, Institute of Biology, University of Brasilia, CEP 70910-900 Brasilia, DF, Brazil*
[b]*Institute of Physiological Psychology I and Center for Biological and Medical Research, University of Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany*
[c]*Research and Development (151), VA Medical Center and SUNY Upstate Medical University, 800 Irving Avenue, Syracuse, NY 13210, USA*

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Abstract

Diethylpropion (1-phenyl-2-diethylamine-1-propanone hydrochloride) is a stimulant drug with reinforcing properties that is used to treat obesity in humans. While the anorectic properties of diethylpropion are mediated by a noradrenergic mechanism, stimulant properties depend on its effects on the serotonergic (5-HT) and/or dopaminergic systems. In this study we investigated the role of the 5-HT$_{1A}$-receptor in the acute behavioral effects of diethylpropion in marmosets (*Callithrix penicillata*). Animals were pretreated with the selective 5-HT$_{1A}$-receptor antagonist, *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl) cyclohexane-carboxamide trihydrochloride (WAY 100635; 0.2, 0.4, 0.8 mg/kg, i.p.) or saline (i.p.) and received a treatment with diethylpropion (10 mg/kg, i.p) or saline (i.p.). Diethylpropion induced an increase in locomotor activity in 60% of the monkeys, which were classified as diethylpropion sensitive, but did not affect locomotion in 40% of the monkeys (diethylpropion insensitive). Sensitivity analysis revealed two types of responders to diethylpropion. In the sensitive animals (type A) diethylpropion increased locomotor activity and anxiogenic-like behavior, but decreased bodycare activities. In the insensitive animals (type B) diethylpropion did not affect locomotor and bodycare activity after diethylpropion, but led to a strong increase in anxiogenic-like behavioral responses. Selective 5-HT$_{1A}$-receptor antagonism modulated the acute diethylpropion effects responder type specifically. In the sensitive (type A) monkeys WAY 100635 blocked the diethylpropion-induced increase in locomotor activity, while not affecting anxiogenic-like behavioral responses or the suppression of bodycare activities. In the insensitive monkeys, WAY 100635 had no effect on locomotor activity after diethylpropion, but blocked diethylpropion effects on some anxiogenic-like behavioral responses. In conclusion, these results suggest an essential contribution of the 5-HT$_{1A}$-receptor to the stimulant effects of diethylpropion, which is responder type specific. It also suggests the 5-HT$_{1A}$-receptor to be a source of the interindividual variance in the acute behavioral response to the stimulant diethylpropion in monkeys.

Keywords: Diethylpropion; WAY 100635; Marmoset; Figure-eight maze; Sensitivity

1. Introduction

The phenylethylamine diethylpropion (1 phenyl-2-diethylamine-1-propanone hydrochloride) is a low potency psychostimulant (Johanson et al., 1976; Hoekenga et al., 1978). Like amphetamine and other phenylethylamines diethylpropion typically causes an increase in locomotor activity (Tang and Kirch, 1971; Safta et al., 1976; Reimer et al., 1995; Gevaerd et al., 1999; Da Silva and Cordellini, 2003), induces conditioned place preference in rodents (Reimer et al., 1995; Planeta and DeLucia, 1998), is self-administered by monkeys (Johanson et al., 1976), and substitutes for cocaine in self-administration paradigms in rats (Wood and Emmett-Oglesby, 1988) and monkeys

* Corresponding author. Tel.: +49 211 81 13491; fax: +49 211 81 12024.
E-mail address: muellecr@uni-duesseldorf.de (C.P. Müller).

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(Johanson and Schuster, 1976; Griffiths et al., 1976, 1978). In humans diethylpropion can cause "happiness" (Jonsson et al., 1967) and "euphoria" (Jasinski et al., 1974), but also nervousness, irritability, insomnia and hyperkinesis (Khan et al., 1987), and may at high doses or after prolonged application induce a schizophrenia-like psychosis (Fookes, 1976; Carney, 1988; Brooke et al., 1988). However, its potency is considerably lower than that of amphetamine (Jasinski et al., 1974). Like other amphetamine derivates it has anorectic properties in animals (Tang and Kirch, 1971; Garattini et al., 1978; Foltin, 1989, 2001) and is used to treat obesity in humans (Bray, 2000; Ryan, 2000). Currently, diethylpropion is considered to be one of the safest short-term anti-obesity drugs in patients with mild to moderate hypertension (Weiser et al., 1997).

Amphetamine and other phenylethylamines have profound effects on monoaminergic activity. However, the pharmacological profile depends to a large extent on the major effects of each drug on either the serotonergic, noradrenergic or dopaminergic system. Like amphetamine, diethylpropion has a stronger affinity to the noradrenergic and dopaminergic than to the serotonergic system (Garattini et al., 1978). It has been reported that the anorectic effects of diethylpropion are mediated by its noradrenergic rather than by its dopaminergic or serotonergic effects (Borsini et al., 1979; Samanin and Garattini, 1993). In contrast, diethylpropion induced hyperlocomotion and place preference depend on dopa-minergic and/or serotonergic effects (Gevaerd et al., 1999). The mediation of different behavioral effects of psychostimulants by different monoaminergic systems is supported by the findings of Griffiths et al. (1976) showing that there is no relationship between the potency as an anorectic drug and the self-administration properties. Since anorectic effects of diethylpropion appear to be noradrenalin dependent, other behavioral effects may be inhibited by a non-noradrenergic mechanism without affecting the anorectic properties, thus, providing a useful approach to improve therapeutic utility of diethylpropion. Recently it was shown that pharmacological blockade of the 5-HT_{1A}-receptor with the selective 5-HT_{1A}-receptor antagonist, *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl) cyclohexane-carboxamide trihydrochloride (WAY 100635; Fletcher et al., 1996), can inhibit cocaine-induced hyperlocomotion by a serotonergic mechanism (Carey et al., 2001; Müller et al., 2002a), suggesting a participation of the 5-HT_{1A}-receptor in psychostimulant induced hyperactivity. This experiment was designed to investigate the contribution of the 5-HT_{1A}-receptor to the acute behavioral effects of the low potency psychostimulant, diethylpropion, in non-human primates (*Callithrix penicillata*). Given the high interindividual differences in the diethylpropion effects in monkeys and humans (Sjöberg and Jonsson, 1967; Johanson et al., 1976), WAY 100635 effects were evaluated with respect to the diethylpropion sensitivity of each animal.

2. Materials and methods

2.1. Subjects

Ten adult marmosets (*Callithrix penicillata*, 2 males and 8 females) were used as subjects. Animals weighed 220–410 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 after a pretreatment and the 30 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, Brazil, and followed the 'Principles of Laboratory Animal Care' (NIH publication No. 85-23, revised 1996).

2.2. Drugs

WAY 100635 (*N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl) cyclohexane-carboxamide trihydrochloride; Sigma, USA) was dissolved in 0.9% physiological saline and injected i.p. in the doses of 0.2, 0.4 and 0.8 mg/kg. The dose range was based on previous behavioral experiments investigating the effects of WAY 100635 in non-human primate tests of anxiety (Barros et al., 2003). Diethylpropion (1-phenyl-2-diethylamine-1-propanone hydrochloride; Henrifarma, Brazil) was dissolved in 0.9% physiological saline and injected i.p. in a dose of 10 mg/kg. This dose was shown to induce hyperlocomotion and conditioned place preference in rats (Reimer et al., 1995). The injection volume for WAY 100635, saline and diethylpropion injections was 1 ml/kg.

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.

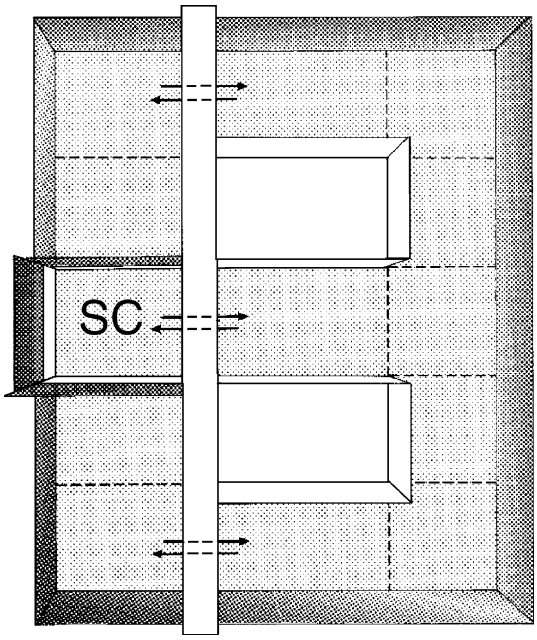

Fig. 1. Top view of the figure-eight continuous maze used for testing (SC indicates the start compartment; for a detailed description: see text).

2.4. Procedure

Before habituation to the test environment took place, the animals were handled and habituated to the transport cage (35×20×23 cm) in four sessions of 5, 10, 15 and 20 min duration, spaced 24 h apart. To avoid confounding effects of exposing the marmosets to a novel environment while measuring their response to the diethylpropion treatment, all subjects were submitted to four 30-min habituation trials to the figure-eight maze, spaced 48 h apart. Previous studies had shown that after four habituation trials activity levels remain constant (Barros et al., 2003). Following the habituation trials, five 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 either an i.p. injection of WAY 100635 (0.2, 0.4 and 0.8 mg/kg) or saline. After the pretreatment the animals were returned to the transport cage for 20 min before they received an i.p. injection of 10 mg/kg diethylpropion or saline. Immediately following the treatment injection the marmoset was released into the maze's back chamber start compartment, thus commencing a 30-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 a.m. and 1:00 p.m.

2.5. Behavioral analysis

For behavioral analysis, the maze was divided into 13 sections. The following behavioral parameters were scored for each 30-min trial by an experienced observer 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; (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 hands 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 the animals spent scanning the environment from the horizontal plane upwards; (6) *Terrestrial scanning*: time the animals spent scanning the environment below the horizontal. Locomotor activity was scored using a semi-automated behavior analysis program (Chromotrack 4.02, San Diego Instruments), whereas the frequency of exploratory activities was measured by focal-all occurrences samplings.

2.6. Statistical analysis

The data were analyzed by means of one-way analysis of variance (ANOVA) for repeated measures on the treatment factor. In order to identify differences versus the saline–saline treatment pre-planned comparisons were calculated using LSD-tests. In order to identify diethylpropion-sensitive animals the locomotor response was used as a criterion. Animals which showed an increase in locomotor activity after the saline–diethylpropion treatment compared to the saline–saline treatment were considered to be "diethylpropion sensitive". All other animals were considered to be "diethylpropion insensitive". All behavioral parameters were further analyzed with respect to the diethylpropion sensitivity of the animals. In order to identify differences in the behavioral response to the treatments between diethylpropion-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 saline–diethylpropion caused an increase in the locomotor activity which, however, did not reach P-levels <0.05 when all animals were analyzed together (Fig. 2A). The pretreatment with WAY 100635 did not substantially modify the diethylpropion effects on locomotion. The sensitivity analysis (Fig. 2B) revealed that 6 of the 10 animals tested showed an increase in the locomotor response to diethylpropion (P<0.05). These animals were considered to be diethylpropion sensitive. The other 4

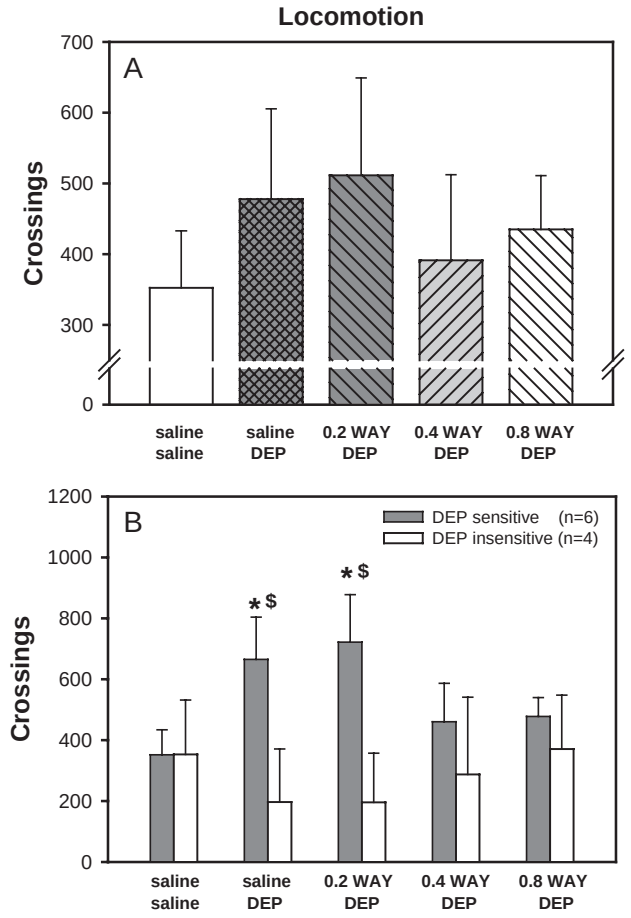

Fig. 2. The effects of diethylpropion (10 mg/kg, i.p.) on locomotor activity (mean±SEM) and its modulation by the 5-HT_{1A}-receptor antagonist, WAY 100635 (0.2–0.8 mg/kg, i.p.), during a 30-min test trial. (A) Effects for all animals tested (n=10). (B) Sensitivity analysis: group splitting according to the animals response to diethylpropion (*sensitive*: increased locomotor activity after saline–diethylpropion vs. saline–saline; *insensitive*: no increase in locomotor activity after saline–diethylpropion vs. saline–saline; *P<0.05 vs. saline–saline; $^{\$}P$<0.01 sensitive vs. insensitive).

animals did not show an increase in locomotor activity as a response to diethylpropion compared to saline–saline (P>0.05). These animals were considered to be diethylpropion insensitive. The WAY 100635 pretreatment did not modify the locomotor activity in the diethylpropion insensitive animals after the diethylpropion treatment. However, it blocked the diethylpropion-induced increase in locomotor activity in the diethylpropion sensitive animals at a dose of 0.4 and 0.8 mg/kg WAY 100635 (P>0.05 vs. saline–saline). The pretreatment with 0.2 mg/kg WAY 100635 did not modify the diethylpropion-induced increase in locomotor activity in the diethylpropion sensitive animals (P<0.05 vs. saline–saline).

The treatments had a profound effect on the exploratory activity ($F_{4,36}$=6.17, P<0.001; Fig. 3A). The injection of diethylpropion decreased exploratory activity (P<0.01) compared to saline–saline treatment. This decrease was not affected by the pretreatment with WAY 100635 (P<0.001, all WAY 100635–diethylpropion groups vs. saline–saline). Sensitivity analysis (Fig. 3B) showed a decreased exploratory activity after the diethylpropion treatment in the diethylpropion sensitive (P<0.01) and as a tendency in the insensitive animals (P<0.052). The WAY 100635 pretreatment did not affect the diethylpropion-induced decrease in exploratory activity in the diethylpropion sensitive group (P<0.01, all WAY 100635–diethylpropion groups vs. saline–saline). In the diethylpropion insensitive group WAY 001635 slightly potentiated the inhibitory effect of diethylpropion (P<0.05, 0.2 mg/kg WAY 100635–diethylpropion; P<0.01, 0.4 and 0.8 mg/kg WAY 100635–diethylpropion vs. saline–saline). However, there was no statistical difference in the effect of WAY 100635 on diethylpropion-induced suppression of exploratory activity between diethylpropion sensitive and insensitive animals (P>0.05).

Bodycare activities comprise grooming and scratching behavior of the animals (Fig. 4A). The treatments did not

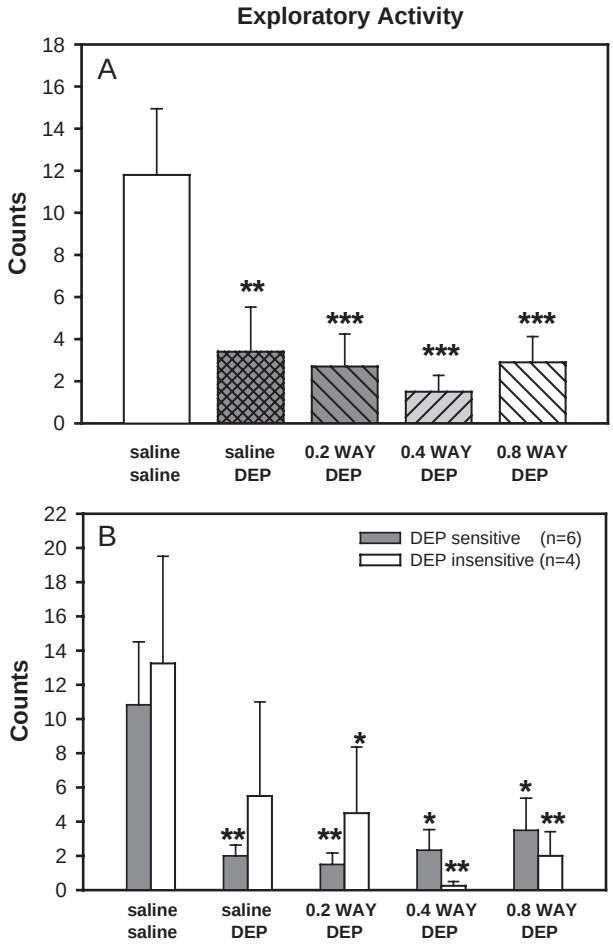

Fig. 3. The effects of diethylpropion (10 mg/kg, i.p.) on exploratory activity (mean ±SEM) and its modulation by the 5-HT_{1A}-receptor antagonist, WAY 100635 (0.2–0.8 mg/kg, i.p.), during a 30-min test trial. (A) Effects for all animals tested (n=10). (B) Sensitivity analysis: group splitting according to the animals response to diethylpropion (*sensitive*: increased locomotor activity after saline–diethylpropion vs. saline–saline; *insensitive*: no increase in locomotor activity after saline–diethylpropion vs. saline–saline; *P<0.05, **P<0.01, ***P<0.001 vs. saline–saline).

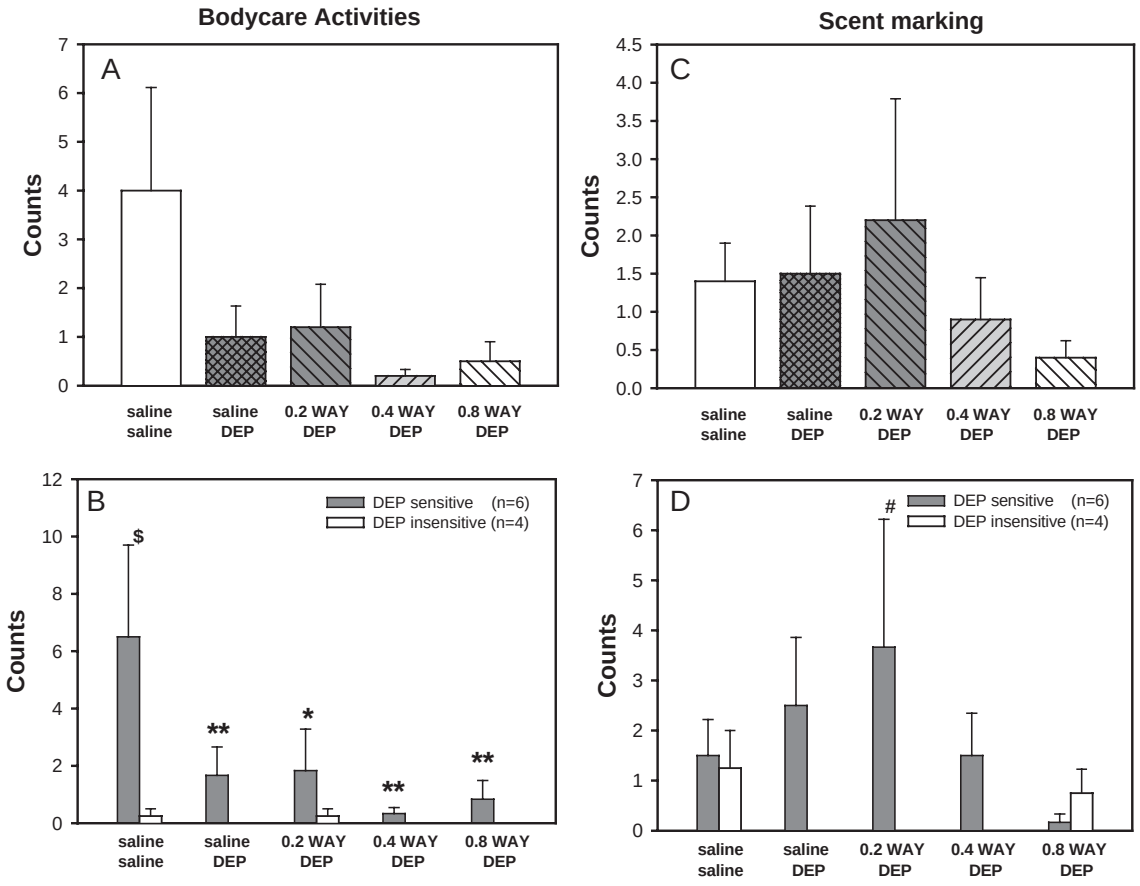

Fig. 4. The effects of diethylpropion (10 mg/kg, i.p.) on bodycare activities (scratching and grooming) and on scent marking (mean ±SEM) and its modulation by the 5-HT_{1A}-receptor antagonist, WAY 100635 (0.2–0.8 mg/kg, i.p.), during a 30 min test trial. (A, C) Effects for all animals tested (n=10). (B, D) Sensitivity analysis: group splitting according to the animals response to diethylpropion (*sensitive*: increased locomotor activity after saline–diethylpropion vs. saline–saline; *insensitive*: no increase in locomotor activity after saline–diethylpropion vs. saline–saline; *P<0.05, **P<0.01 vs. saline–saline; $^{\#}P$<0.05, $^{\$}P$<0.01 sensitive vs. insensitive).

affect this parameter. However, there was a tendency ($F_{4,36}$=2.39, P<0.069) for a decreased response after the diethylpropion treatment which was not affected by the pretreatment with WAY 100635. The sensitivity analysis revealed a strong difference in the bodycare activities between diethylpropion-sensitive and -insensitive animals after the saline–saline treatment (P<0.01). The diethylpropion insensitive animals hardly showed any bodycare activities in the 30 min test trials, which might have masked a possible inhibitory effect of diethylpropion in these animals. In the diethylpropion sensitive animals the diethylpropion treatment attenuated bodycare activities (P<0.01). The pretreatment with WAY 100635 did not modulate this effect (P<0.05, 0.2 mg/kg WAY 100635–diethylpropion vs. saline–saline; P<0.01, 0.4 and 0.8 mg/kg WAY 100635–diethylpropion vs. saline–saline).

The diethylpropion treatment did not affect scent marking behavior (P>0.05; Fig. 4C). Sensitivity analysis showed that scent marking behavior virtually disappeared in the diethylpropion insensitive group after diethylpropion treatments (Fig. 4D). Statistical comparisons showed a difference between diethylpropion sensitive and insensitive animals only after the 0.2 mg/kg WAY 100635–diethylpropion treatment (P<0.05).

The diethylpropion treatment caused a pronounced increase in aerial scanning time ($F_{4,36}$=2.86, P<0.04; saline–diethylpropion vs. saline–saline: P<0.01; Fig. 5A) but not in the frequency of aerial scanning (P>0.05; Fig. 5C). Pretreatment with 0.4 and 0.8 mg/kg WAY 100635 blocked the increase in aerial scanning time (P>0.05 vs. saline–saline). The sensitivity analysis showed profound differences in the levels of aerial scanning time between the diethylpropion sensitive and insensitive animals (Fig. 5B). Interestingly, diethylpropion sensitive animals showed only a small increase after the diethylpropion treatment (P>0.05), while in the insensitive animals diethylpropion strongly increased aerial scanning time (diethylpropion-saline vs. saline–saline: P<0.001). WAY 100635 partially blocked this effect in the diethylpropion insensitive animals dose-dependently with 0.8 mg/kg WAY 100635 as the most effective dose (P>0.05 vs. saline–saline). Sensitive and insensitive animals differed not only in the time of aerial scanning after the diethylpropion treatment (P<0.001) but also after all doses of WAY 100635–diethylpropion

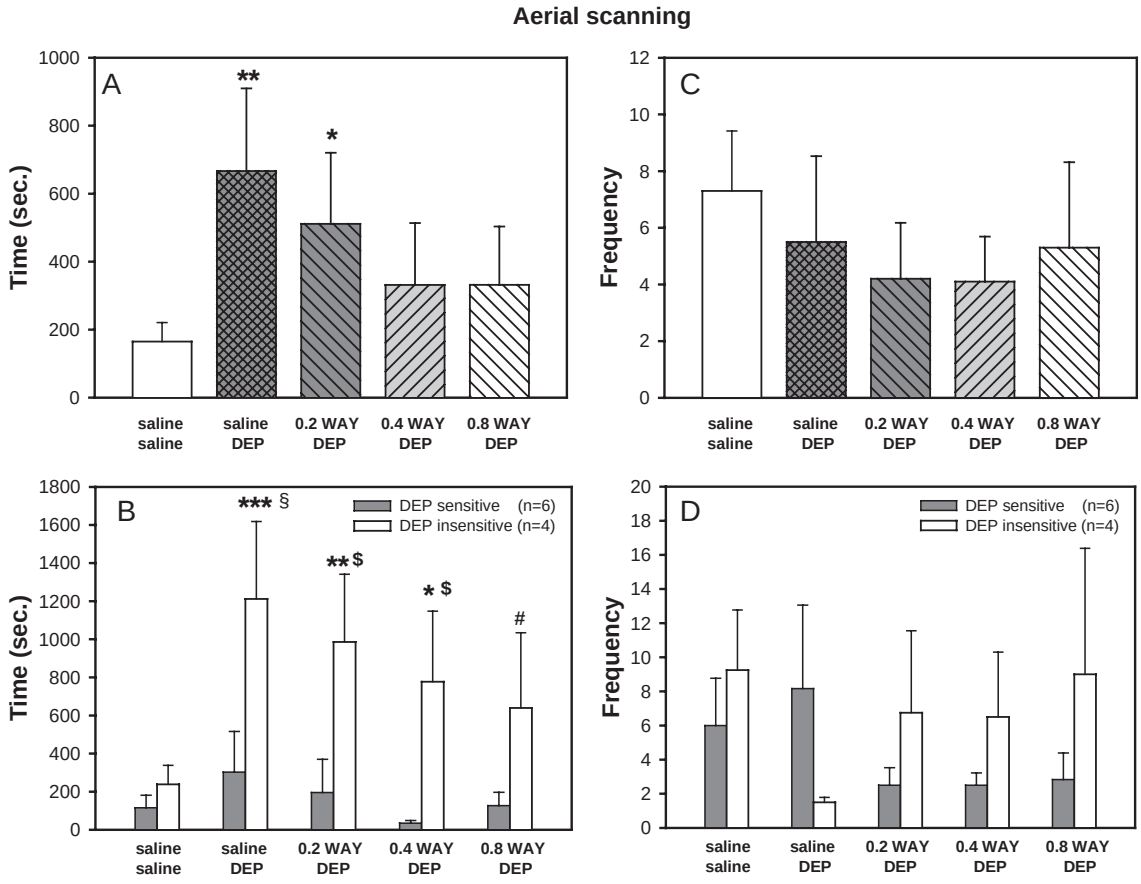

Fig. 5. The effects of diethylpropion (10 mg/kg, i.p.) on aerial scanning (mean±SEM) and its modulation by the 5-HT_{1A}-receptor antagonist, WAY 100635 (0.2–0.8 mg/kg, i.p.), during a 30-min test trial. (A, C) Effects for all animals tested (n=10). (B, D) Sensitivity analysis: group splitting according to the animals response to diethylpropion (*sensitive*: increased locomotor activity after saline–diethylpropion vs. saline–saline; *insensitive*: no increase in locomotor activity after saline–diethylpropion vs. saline–saline; *P<0.05, **P<0.01, ***P<0.001 vs. saline–saline; $^{\#}P$<0.05, $^{\$}P$<0.01, $^{\S}P$<0.001 sensitive vs. insensitive).

(P<0.01, 0.2 and 0.4 mg/kg WAY 100635–diethylpropion, P<0.05, 0.8 mg/kg WAY 100635–diethylpropion). There were no clear effects on the frequency of aerial scanning (Fig. 5D).

In contrast to the increase in aerial scanning time, diethylpropion caused a decrease in terrestrial scanning which reached P-levels <0.05 for the frequency ($F_{4,36}$=3.51, P<0.02; saline–diethylpropion vs. saline–saline: P<0.01; Fig. 6C) but not for the time (Fig. 6A). A dose of 0.4 mg/kg WAY 100635 partially reversed this decrease (P>0.05 vs. saline–saline), while 0.2 and 0.8 mg/kg WAY 100635 did not have any effect (P<0.01 and P<0.05 vs. saline–saline). The sensitivity analysis (Fig. 6D) showed that diethylpropion had the strongest effects in the insensitive animals (diethylpropion-saline vs. saline–saline: P< 0.01). However, in these animals none of these doses of WAY 100635 reversed the inhibitory effect of diethylpropion (P<0.01, 0.2 and 0.4 mg/kg WAY 100635–diethylpropion; P<0.05, 0.8 mg/kg WAY 100635–diethylpropion vs. saline–saline). However, there were no differences between the diethylpropion or WAY 100635 effects between the sensitive and insensitive animals (P>0.05). Sensitivity analysis further revealed a difference between diethylpropion-sensitive and -insensitive animals for the time spent in terrestrial scanning (Fig. 6B) indicating a different effect of 0.4 mg/kg WAY 100635 on the diethylpropion-induced suppression (P<0.05).

4. Discussion

The effects of the low potency psychostimulant diethylpropion were investigated in a broad range of marmoset behaviors. An increase in locomotor activity could be found only in 60% of the animals after diethylpropion. This increase, which is usually considered as an indicator of the stimulant properties of a drug (Hoekenga et al., 1978), was used to subdivide the population of the animals into diethylpropion-sensitive and diethylpropion-insensitive animals. The behavioral profile of diethylpropion also comprised an inhibitory effect on exploratory activity. Diethylpropion furthermore potentiated the dominant aerial scanning, but inhibited the less pronounced terrestrial scanning. There was also an overall tendency to block bodycare activities, while it had no obvious effect on scent marking behavior. Sensitivity

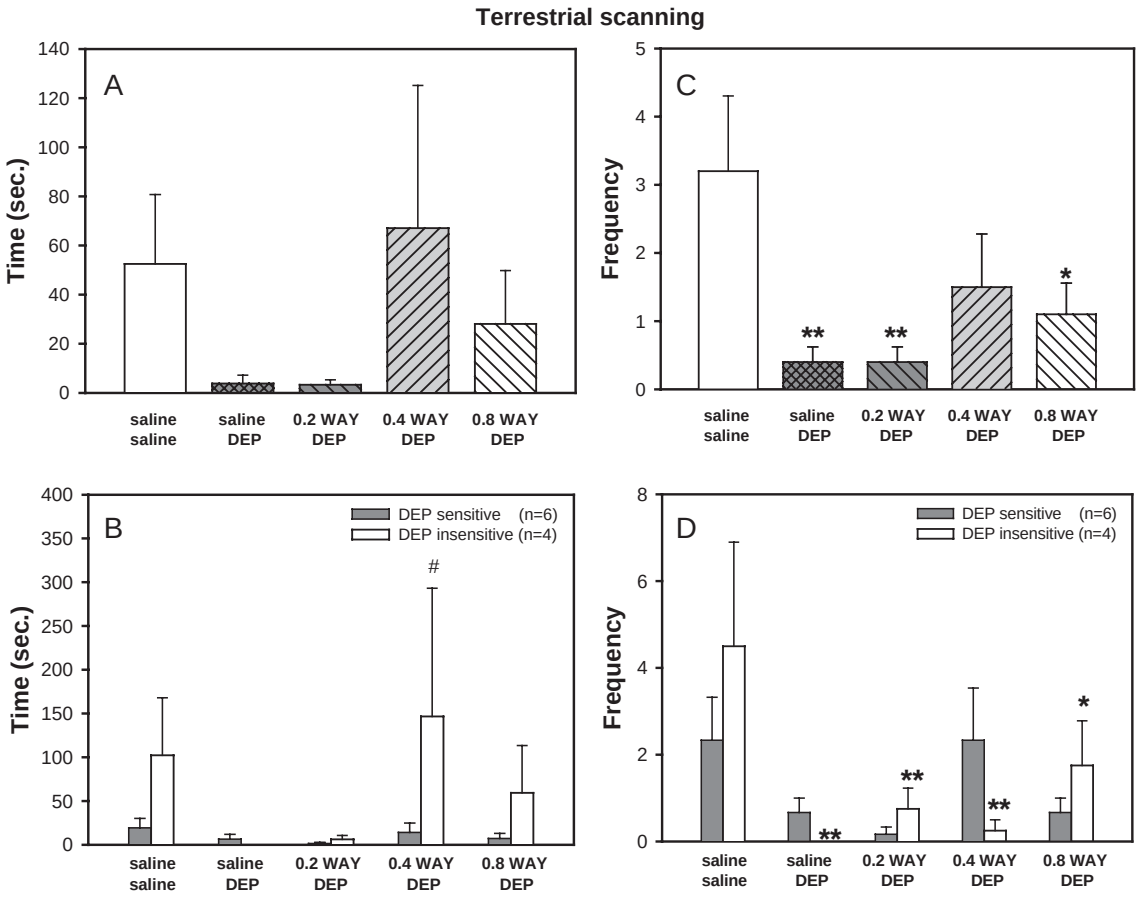

Fig. 6. The effects of diethylpropion (10 mg/kg, i.p.) on terrestrial scanning (mean±SEM) and its modulation by the 5-HT_{1A}-receptor antagonist, WAY 100635 (0.2–0.8 mg/kg, i.p.), during a 30-min test trial. (A, C) Effects for all animals tested (n=10). (B, D) Sensitivity analysis: group splitting according to the animals response to diethylpropion (*sensitive*: increased locomotor activity after saline–diethylpropion vs. saline–saline; *insensitive*: no increase in locomotor activity after saline–diethylpropion vs. saline–saline; *P<0.05, **P<0.01 vs. saline–saline; $^{\#}P$<0.05 sensitive vs. insensitive).

analysis revealed that there are two principle types of responses to diethylpropion in the marmosets. Type A monkeys (sensitive) are characterized in their response to diethylpropion by a profound increase in locomotor activity, a decrease in exploratory activity and a decrease in bodycare activities. Type B monkeys (insensitive) did not show hyperlocomotion and a decrease in bodycare activities, but showed a profound increase in aerial scanning and a decrease in terrestrial scanning following diethylpropion treatment. Exploratory activity was only decreased as a tendency. This study furthermore showed that the 5-HT_{1A}-receptor antagonist, WAY 100635, affects both responder types in different ways. In the sensitive animals (type A) it blocked the diethylpropion-induced hyperlocomotion while not affecting locomotor response in the insensitive (type B) animals. In the insensitive animals WAY 100635 partially reversed the diethylpropion-induced increase in aerial scanning. In contrast, there were no clear effects on the visual scanning response to diethylpropion in the sensitive (type A) animals. These data suggest that the 5-HT_{1A}-receptor does not only play an essential role in the mediation of important behavioral effects of the low potency psychostimulant diethylpropion, but is also the source of some interindividual differences in the response to diethylpropion. Interestingly, WAY 100635 did not have obvious effects on the diethylpropion-induced suppression of the exploratory activity in both types of animals and on the suppression of bodycare activities, which occurred only in the sensitive (type A) animals. Accordingly, the 5-HT_{1A}-receptor does not contribute to the whole spectrum of the acute behavioral effects of diethylpropion.

The observation that diethylpropion did not increase overall locomotor activity was surprising since other groups had shown it (Tang and Kirch, 1971; Safta et al., 1976; Reimer et al., 1995; Gevaerd et al., 1999; Da Silva and Cordellini, 2003). However, highly variant locomotor responses to a stimulant drug in a medium dose range are not unique to diethylpropion but were also reported for other psychostimulants (e.g. Müller et al., 2004). The main reason for these effects are interindividual differences of the animals (e.g. Hooks et al., 1991). The failure to induce hyperlocomotion in all animals tested may be due to the dose choice for diethylpropion, which was in a range that was found by others to have reinforcing properties (Reimer et al., 1995) and to be sufficient to reduce food intake (Garattini et al., 1978). Using the locomotor response as a criterion for

diethylpropion-sensitivity in this study, 60% of the animals increased activity, while 40% did not show an obvious effect. In that, our observation confirms studies in monkeys and humans which showed high interindividual differences in the behavioral effects of diethylpropion (Sjöberg and Jonsson, 1967; Johanson et al., 1976). Further behavioral analysis according to the locomotor response to diethylpropion revealed that these animals, which showed a high locomotor response, also showed a decrease in exploratory activity and a decrease in bodycare activities, but no obvious alterations in the aerial or terrestrial scanning behavior. A decrease in exploratory activity in marmosets is associated with an anxiogenic state (Barros et al., 2004a), which can be reversed by anxiolytic drugs like diazepam (Barros et al., 2000). Thus, the diethylpropion-induced decrease in exploratory activity may be interpreted as an anxiogenic effect. Anxiogenic-like behavioral effects had also been demonstrated for other psychostimulants like cocaine (Yang et al., 1992; Goeders, 1992) and may be considered to be an integral part of the behavioral spectrum of psychostimulants. This counts also for the suppression of bodycare activities, as a decrease in grooming activity was reported in rats after diethylpropion (Da Silva and Cordellini, 2003) and other psychostimulants (e.g. Cooper and Van der Hoek, 1993; Müller et al., 2002b). Interestingly, diethylpropion did not obviously affect aerial or terrestrial scanning behavior in the sensitive (type A) 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). The presentation of a potential threat is associated with an increase in visual scanning (Caine, 1984, 1998; Ferrari and Lopes Ferrari, 1990; Hardie and Buchanan-Smith, 1997; Koenig, 1998). In conclusion, the diethylpropion-sensitive marmosets (type A) response to diethylpropion can be characterized as hyperlocomotor, anxiogenic and bodycare suppressive. In contrast to the sensitive (type A) animals, the insensitive animals (type B) did not show hyperlocomotion after the diethylpropion treatment. In addition, there was only a tendency for an inhibitory effect on exploratory activity. Furthermore, the bodycare activities of these animals had been so low that a suppressive action of diethylpropion may have been masked by a floor effect. These animals, however, showed a strong increase in aerial scanning but a suppression of terrestrial scanning after diethylpropion. The magnitude of this effect also argues against the possibility that the lack of a hyperlocomotor response in these animals is due to a lowered bioavailability of diethylpropion. The effect on exploratory activity and the potent effect on aerial scanning suggest a more pronounced anxiogenic effect of diethylpropion in the type B responders (Barros et al., 2004b). In conclusion, the behavioral response to diethylpropion by the insensitive marmosets (type B) is characterized by a lack of hyperlocomotor effects, a high anxiogenic component and no bodycare suppressive effects.

The pretreatment with WAY 100635 can not only provide information about which role the 5-HT_{1A}-receptor plays in the general population in the mediation of the behavioral effects of diethylpropion, but can also provide clues about the role of the 5-HT_{1A}-receptor as a source of the interindividual variance in the response to the low potency psychostimulant diethylpropion. When all animals were pooled WAY 100635 did not modulate the locomotor, exploratory or bodycare activities after a diethylpropion treatment. It only attenuated the effects on aerial and terrestrial scanning dose-dependently. The lack of effect on the diethylpropion-induced suppression of exploratory activity in this experiment is surprising since it was recently shown that WAY 100635 can reverse a decrease in exploratory activity induced by predatory stress in *Callithrix penicillata* (Barros et al., 2003). Accordingly, it may be speculated that the anxiety states induced by predatory stress and that induced by a psychostimulant like diethylpropion, which both lead to a suppression of exploratory activity, may be different and/or differentially involve a 5-HT_{1A}-receptor contribution.

When WAY 100635 effects were analyzed with regard to the diethylpropion sensitivity of the monkeys, profound effects could be detected. In the sensitive (type A) animals WAY 100635 attenuated the diethylpropion-induced increase in locomotor activity, but had no effect on the suppression of exploratory activity and bodycare activities. These results expand the findings in rats, where WAY 100635 reversed the cocaine-induced hyperlocomotion, but had no effect on the suppression of grooming behavior (Carey et al., 2001; Müller et al., 2002b). The lack of an effect on exploratory and bodycare activities after diethylpropion suggests that the 5-HT_{1A}-receptor is neither involved in the mediation of the anxiogenic-like response or the bodycare suppression of diethylpropion in the sensitive animals. Overall, the findings in the diethylpropion sensitive monkeys support the data in rodents that the 5-HT_{1A}-receptor plays mainly a role in the "positive effects" of psychostimulants but not in their "negative effects" (Müller et al., 2004).

In the insensitive (type B) animals WAY 100635 had no effect on locomotion after diethylpropion, but it attenuated diethylpropion effects on aerial and terrestrial scanning, an anxiety related behavioral response. However, also in the insensitive animals (type B) not all anxiety related behavioral effects of diethylpropion were affected by the WAY 100635 pretreatment. As in the sensitive animals WAY 100635 did not reverse the decrease in exploratory activity. When comparing the effects of WAY 100635 on the behavioral profile of diethylpropion between sensitive (type A) and insensitive (type B) monkeys a double dissociation became obvious: WAY 100635 reversed the hyperlocomotor effects in the sensitive animals not affecting the diethylpropion effects on locomotion in the insensitive animals. In contrast, WAY 100635 reversed an anxiogenic-like diethylpropion effect in the insensitive animals, not affect-

ing this behavior in the sensitive animals. From that observations it is suggested that the 5-HT_{1A}-receptor is one source of the interindividual differences in the acute behavioral response to the low potency psychostimulant diethylpropion in monkeys.

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References

Barros, M., Tomaz, C., 2002. Non-human primate models for investigating fear and anxiety. Neurosci. Biobehav. Rev. 26, 187–201.

Barros, M., Boere, V., Huston, J.P., Tomaz, C., 2000. Measuring fear and anxiety in the marmoset (*Callithrix penicillata*) with a novel predator confrontation model: effects of diazepam. Behav. Brain Res. 108, 205–211.

Barros, M., Mello, E.L., Maior, R.S., Müller, C.P., De Souza-Silva, M.A., Carey, R.J., Huston, J.P., Tomaz, C., 2003. Anxiolytic-like effects of the selective 5-HT1A receptor antagonist WAY 100635 in non-human primates. Eur. J. Pharmacol. 482, 197–203.

Barros, M., De Souza-Silva, M.A., Huston, J.P., Tomaz, C., 2004a. Multibehavioral analysis of fear and anxiety before, during, and after experimentally induced predatory stress in *Callithrix penicillata*. Pharmacol. Biochem. Behav. 78, 357–367.

Barros, M., Alencar, C., Tomaz, C., 2004b. Differences in aerial and terrestrial visual scanning in captive black tufted-ear marmosets (*Callithrix penicillata*) exposed to a novel environment. Folia Primatol. 75, 85–92.

Borsini, F., Bendotti, C., Carli, M., Poggesi, E., Samanin, R., 1979. The roles of brain noradrenaline and dopamine in the anorectic activity of diethylpropion in rats: a comparison with d-amphetamine. Res. Commun. Chem. Pathol. Pharmacol. 26, 3–11.

Bray, G.A., 2000. A concise review on the therapeutics of obesity. Nutrition 16, 953–960.

Brooke, D., Kerwin, R., Lloyd, K., 1988. Diethylpropion hydrochloride-induced psychosis. Br. J. Psychiatry 152, 572–573.

Caine, N.G., 1984. Visual scanning by tamarins: a description of the behavior and tests of two derived hypothesis. Folia Primatol. 43, 59–67.

Caine, N.G., 1998. Cutting costs in response to predatory threat by Geoffroy's marmostes (*Callithrix geoffroyi*). Am. J. Primatol. 46, 187–196.

Carey, R.J., DePalma, G., Damianopoulos, E., 2001. Cocaine and serotonin: a role for the 5-HT(1A) receptor site in the mediation of cocaine stimulant effects. Behav. Brain Res. 126, 127–133.

Carney, M.W., 1988. Diethylpropion and psychosis. Br. J. Psychiatry 152, 146–147.

Cooper, S.J., Van der Hoek, G.A., 1993. Cocaine: a microstructural analysis of its effects on feeding and associated behaviour in the rat. Brain Res. 608, 45–51.

Da Silva, L.B., Cordellini, S., 2003. Effects of diethylpropion treatment and withdrawal on aorta reactivity, edothelial factors and rat behavior. Toxicol. Appl. Pharmacol. 190, 170–176.

Ferrari, S.F., Lopes Ferrari, M.A., 1990. Predator avoidance behavior in the buffy-headed marmoset (*Callithrix flaviceps*). Primates 31, 323–338.

Fletcher, A., Forster, E.A., Bill, D.J., Brown, G., Cliffe, I.A., Hartley, J.E., Jones, D.E., McLenachan, A., Stanhope, K.J., Critchley, D.J., Childs, K.J., Middlefell, V.C., Lanfumey, L., Corradetti, R., Laporte, A.M., Gozlan, H., Hamon, M., Dourish, C.T., 1996. Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT1A receptor antagonist. Behav. Brain Res. 73, 337–353.

Foltin, R.W., 1989. Effects of anorectic drugs on the topography of feeding behavior in baboons. J. Pharmacol. Exp. Ther. 249, 101–109.

Foltin, R.W., 2001. Effects of amphetamine, dexfenfluramine, diazepam, and other pharmacological and dietary manipulations on food "seeking" and "taking" behavior in non-human primates. Psychopharmacology 158, 28–38.

Fookes, B.H., 1976. Schizophrenia-like reaction to diethylpropion. Lancet 2, 1206.

Garattini, S., Borroni, E., Mennini, T., Samanin, R., 1978. Differences and similarities among anorectic agents. In: Garattini, S., Samanin, R. (Eds.), Central Mechanisms of Anorectic Drugs. Raven Press, New York, pp. 127–143.

Gevaerd, M.S., Sultowski, E.T., Takahashi, R.N., 1999. Combined effects of diethylpropion and alcohol on locomotor activity of mice: participation of the dopaminergic and opioid systems. Braz. J. Med. Biol. Res. 32, 1545–1550.

Goeders, N.E., 1992. Potential involvement of anxiety in the neurobiology of cocaine. Ann. N.Y. Acad. Sci. 654, 357–367.

Griffiths, R.R., Winger, G., Brady, J.V., Snell, J.D., 1976. Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. Psychopharmacology 50, 251–258.

Griffiths, R.R., Brady, J.V., Snell, J.D., 1978. Relationship between anorectic and reinforcing properties of appetite suppressant drugs: implications for assessment of abuse liability. Biol. Psychiatry 13, 283–290.

Hardie, S.M., Buchanan-Smith, H.M., 1997. Vigilance in single and mixed-species groups of tamarins (*Saguinus labiatus* and *S. fuscicollis*). Int. J. Primatol. 18, 217–234.

Hoekenga, M.T., Dillon, R.H., Leyland, H.M., 1978. A comprehensive review of diethylpropion hydrochloride. In: Garattini, S., Samanin, R. (Eds.), Central Mechanisms of Anorectic Drugs. Raven Press, New York, pp. 391–404.

Hooks, M.S., Jones, G.H., Smith, A.D., Neill, D.B., Justice, J.B., 1991. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 9, 121–128.

Jasinski, D.R., Nutt, J.G., Griffith, J.D., 1974. Effects of diethylpropion and d-amphetamine after subcutaneous and oral administration. Clin. Pharmacol. Ther. 16, 645–652.

Johanson, C.E., Schuster, C.R., 1976. A comparison of cocaine and dietylpropion under two different schedules of drug presentation. In: Ellinwood, E.H., Kilbey, M.M. (Eds.), Cocaine and Other Stimulants. Plenum, New York, pp. 545–570.

Johanson, C.E., Balster, R.L., Bonese, K., 1976. Self-administration of psychomotor stimulant drugs: the effects of unlimited access. Pharmacol. Biochem. Behav. 4, 45–51.

Jonsson, C.O., Sjöberg, L., Ek, S., Vallbo, S., 1967. Studies in the psychological effects of a new drug (diethylpropion). Time curves for five subjective variables. Scand. J. Psychol. 8, 39–46.

Khan, S.A., Spiegel, D.A., Jobe, P.C., 1987. Psychotomimetic effects of anorectic drugs. Am. Fam. Phys. 36, 107–112.

Koenig, A., 1998. Visual scanning by common marmostes (*Callithrix jacchus*): functional aspects and the special role of adult males. Primates 39, 85–90.

Müller, C.P., Carey, R.J., De Souza Silva, M.A., Jocham, G., Huston, J.P., 2002a. Cocaine increases serotonergic activity in the hippocampus and nucleus accumbens in vivo: 5-HT1A-receptor antagonism blocks behavioral but potentiates serotonergic activation. Synapse 45, 67–77.

Müller, C.P., De Souza Silva, M.A., DePalma, G., Tomaz, C., Carey, R.J., Huston, J.P., 2002b. The selective serotonin1A-receptor antagonist WAY 100635 blocks behavioral stimulating effects of cocaine but not ventral striatal dopamine increase. Behav. Brain Res. 134, 337–346.

Müller, C.P., Thönnessen, H., Jocham, G., Barros, M., Tomaz, C., Carey, R.J., Huston, J.P., 2004. Cocaine-induced "active immobility" and its modulation by the serotonin$_{1A}$-receptor. Behav. Pharmacol. 15, 481–493.

Planeta, C.S., DeLucia, R., 1998. Involvement of dopamine receptors in diethylpropion-induced conditioning place preference. Braz. J. Med. Biol. Res. 31, 561–564.

Reimer, A.R., Martin-Iverson, M.T., Urichuk, L.J., Coutts, R.T., Byrne, A., 1995. Conditioned place preferences, conditioned locomotion, and behavioral sensitization occur in rats treated with diethylpropion. Pharmacol. Biochem. Behav. 51, 89–96.

Ryan, D.H., 2000. Use of sibutramine and other noradrenergic and serotonergic drugs in the management of obesity. Endocrine 13, 193–199.

Safta, L., Cuparencu, B., Sirbu, A., Secareanu, A., 1976. Experimental observations on the effect of amphepramone on the behavior, locomotion, pentretrazol seizures and electroencephalogram. Psychopharmacology 50, 165–169.

Samanin, R., Garattini, S., 1993. Neurochemical mechanism of action of anorectic drugs. Pharmacol. Toxicol. 73, 63–68.

Sjöberg, L., Jonsson, C.O., 1967. Studies in the psychological effects of a new drug (diethylpropion): individual differences. Scand. J. Psychol. 8, 81–87.

Tang, A.H., Kirch, J.D., 1971. Appetite suppression and central nervous system stimulation in the rhesus monkey. Psychopharmacologia 21, 139–146.

Weiser, M., Frishman, W.H., Michaelson, M.D., Abdeen, M.A., 1997. The pharmacologic approach to the treatment of obesity. J. Clin. Pharmacol. 37, 453–473.

Wood, D.M., Emmett-Oglesby, M.W., 1988. Substitution and cross-tolerance profiles of anorectic drugs in rats trained to detect the discriminative stimulus properties of cocaine. Psychopharmacology 95, 364–368.

Yang, X.M., Gorman, A.L., Dunn, A.J., Goeders, N.E., 1992. Anxiogenic effects of acute and chronic cocaine administration: neurochemical and behavioral studies. Pharmacol. Biochem. Behav. 41, 643–650.