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Dexmedetomidine selectively suppresses dominant behaviour in aggressive and sociable mice

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Abstract

Dexmedetomidine is a highly specific α_2-adrenoreceptor agonist, which is now clinically used to induce sedation in patients in the intensive care units. Behavioural effects of dexmedetomidine have been little studied so far. The drug was reported to reduce behaviour such as locomotion or measures of anxiety or aggression in animals. The aim of the present study was to ascertain whether dexmedetomidine inhibits behaviour uniformly or with respect to particular stimuli or situations. Therefore, behavioural effects of dexmedetomidine were studied in the social conflict test in male mice (after three weeks of individual housing), which provides a wide spectrum of behavioural activities in two types of animals (aggressive and sociable mice) as well as in the activity cage. Dexmedetomidine (5–40 μg/kg i.p.) decreased locomotion in the activity cage and this effect was fully antagonized by atipamezole, a selective α_2-adrenereceptor antagonist. However, dexmedetomidine did not reduce locomotion during social conflict. The only significant effects during social conflict were a selective and dose-dependent antiaggressive effect in aggressive mice and a selective reduction of social investigation ('sociability') in sociable mice. Thus, dexmedetomidine appears to inhibit predominantly dominant behaviour evoked by biologically important stimuli. The ability of dexmedetomidine to reduce aggression might be utilized for treatment of aggressive states. Sedation caused by dexmedetomidine can be easily disrupted and thus the drug may have an advantage over benzodiazepines or neuroleptics, which are used in this indication.
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1. Introduction

α_2-adrenoreceptor agonists (e.g. clonidine, xylazine, and medetomidine) are used in animal medicine for more than 40 years for inducing anesthesia and sedation. Administration of these drugs causes light sedation and animals can be easily manipulated (Göltenboth and Klös, 1990; Young et al., 1999). Recently, a very selective α_2-adrenoreceptor agonist dexmedetomidine has received considerable attention in anesthetic practice because of its sedative, hypnotic, anxiolytic and analgesic effects, which can be to some extent compared to the effect of benzodiazepines (Mattila et al., 1991). Dexmedetomidine is now clinically used to induce sedation in patients in the intensive care units (Venn et al., 1999) because it induces sedation and analgesia without significant influence on ventilation (Belleville et al., 1992). Qualitatively, dexmedetomidine induces a sedative response that exhibits properties similar to natural sleep, unlike other anesthetics. Patients receiving dexmedetomidine experience a clinically effective sedation yet are easily still and uniquely arousable, an effect not observed with any other clinically available sedative.

Very little is known about effects of α_2-adrenoreceptor agonists and antagonists, particularly dexmedetomidine, on aggression and anxiety. Clonidine has been found to decrease, increase or to be without any effect on aggression (Sanchez et al., 1993; Skrebuhhova-Malmros et al., 2001; Nikulina and Klimek, 1993; Aley and Kulkarni, 1989) and for example clonidine-induced aggression model has been used in aggression research (Maj et al., 1981). The effect of α_2-adrenoreceptor antagonists (e.g. yohimbine and idazoxan) is mostly anxiogenic (Blanchard et al., 1993) and antiaggresive (Kemble et al., 1991; Haller et al., 1996), but they also enhanced aggression in several studies (Haller et al., 1994; Ferrari and Giuliani, 1993; Gentsch et al.,

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1989). Clonidine was also found to be also both anxiolytic and anxiogenic (Soderpalm and Engel, 1988) and anxiogenic activity of yohimbine was reversed with clonidine (Johnston and File, 1989). Moreover, there are reports that yohimbine, an α_2-adrenoreceptor antagonist, not only increased but also decreased anxiety-like behaviour in the elevated plus-maze test (Baldwin et al., 1989; Cole et al., 1995).

Behavioural studies with novel and more selective α_2-adrenoreceptor agonists are very rare and have been focused on detection of indirect anxiety signs using elevated plus-maze (Salonen et al., 1992), ultrasonic vocalisation, or marble burying behaviour (Millan et al., 2000b) without analyzing their influence on other behaviour occurring concomitantly. In these studies only one behaviour occurring in a particular test is usually measured (e.g. social contact, ultrasonic vocalisation, marble burying, etc.), which leads to conclusion of anxiolytic, antiaggressive, or sedative effect of dexmedetomidine. Published experimental data rather show that the observed behavioural sign is usually attenuated and that is why there are different conclusions about an α_2-adrenoreceptor agonist's effect.

Therefore, the aim of the present study was to ascertain the effects of dexmedetomidine on the whole spectrum of behaviour occurring during the same test (the social conflict) in the same animals after the treatment. Firstly, we evaluated the effect of dexmedetomidine in the activity cage test and we antagonized it by an α_2-adrenoreceptor antagonist atipamezole. Social conflict is ethologically oriented model based on the analysis of offensive, defensive-escape, social, locomotor and other behavioural acts and postures occurring during social conflict in mice. We divided mice according to their social status (aggressive and sociable) after the placebo treatment because it is known that the initial level of aggressiveness can significantly influence the effect of centrally acting drugs (Krsiak et al., 1998). Anxiolytic-like, anxiogenic-like, antiaggressive, aggressogenic, sedative and other behavioural changes can be easily detected and evaluated and this model was used for ascertaining behavioural profile in many drugs (Krsiak, 1975, 1979; Sulcova and Krsiak, 1989).

2. Materials and methods

2.1. Subjects

Male albino random-bred mice derived from ICR (outbred stock from the Institute of Cancer Research) strain (Velaz, Prague, Czech Republic) weighing 18–20 g at the beginning of the experiment (6 weeks old) were used. They were housed singly in self-cleaning cages ($n=49$) or in groups of 10 ($n=183$). The self-cleaning cages used for the individual housing were made of solid metal walls 13 cm high with wire-mesh floors (8×17 cm) which were placed 3 cm above trays with wood shavings. This wire-mesh floor provides that the isolates were not handled throughout the period of single housing. The group-housed mice, which served as an opponent in the social conflict test ($n=49$) and for the activity cage test ($n=134$), were housed in large standard plastic cages (26×42×15 cm) with floors covered with wood shavings. All mice were housed under room lighting (with lights on from 6 a.m. to 6 p.m.) and under temperature ranging from 22 to 24 °C. Food and water were available ad libitum.

Social conflict between group-housed and isolated mouse was observed in transparent cages (20×30×20 cm) with wood shavings on the floor and tops covered with transparent covers with apertures for air. The observations were performed under room lighting from 8 a.m. to 1 p.m.

Experiments were approved by the Expert Committee for Protection of Experimental Animals of the 3rd Faculty of Medicine and were performed in accordance with the Animal Protection Act of the Czech Republic (No. 246/1992 Sb).

2.2. Activity cage

In the first part of the experiment, mice were acutely given dexmedetomidine in four different doses (5, 10, 20 and 40 μg/kg and placebo, $n=10$ for each treatment). In the second part of the experiment, mice were treated with atipamezole in four different doses (0.03, 0.1, 0.3 and 1.0 mg/kg) alone and in combination with 20 μg/kg dexmedetomidine ($n=7$–11 for each treatment). The horizontal and vertical locomotor activities of the mice were registered 30 min later by the locomotor activity apparatus (Ugo Basile 7431) for 4 min. Mice were observed in transparent cages (20×30×20 cm) with 50 ml wood shavings on the floor and tops covered with transparent cover with apertures for air. Interruptions of light beams to the photocells (two pairs of 16 photocells 3 and 6 cm above the floor under transparent cover) during horizontal and vertical movement of the animal were registered. The observations were performed under room lighting from 8 a.m. to 1 p.m.

2.3. Social conflict

Social conflict always involves one singly housed and one group-housed mouse, being placed as pairs in the observational cages. Each isolate was paired with the same group-housed partner throughout the experiment. The isolates were allowed 30 min adaptation in the observational cages before the group-housed partners were introduced; the interaction ended after 4 min. This procedure, which suppresses aggression in group-housed mice and reduces their social behaviour, facilitates active social behaviour and aggression in isolates.

Before the experiment, mice were housed singly or in groups for 3 weeks. Next, singly housed mice (isolates, the test mice) were acutely given drug and social interaction was performed 30 min after the drug administration. Group-housed mice (the stimulus animals) remained untreated. Each mouse was given 3 different doses of dexmedetomidine (5, 10 and 20 μg/kg) and placebo using Latin square design in weekly intervals. Altogether, four social interactions were performed and each mouse ($n=49$) was treated with all doses of dexmedetomidine and placebo.

According to results from activity cage (Fig. 1) and published findings (Millan et al., 2000b), the doses of dexmedetomidine (5–20 μg/kg) and the interval 30 min after the administration appears to be most appropriate for ascertainment of behavioural and receptor changes.

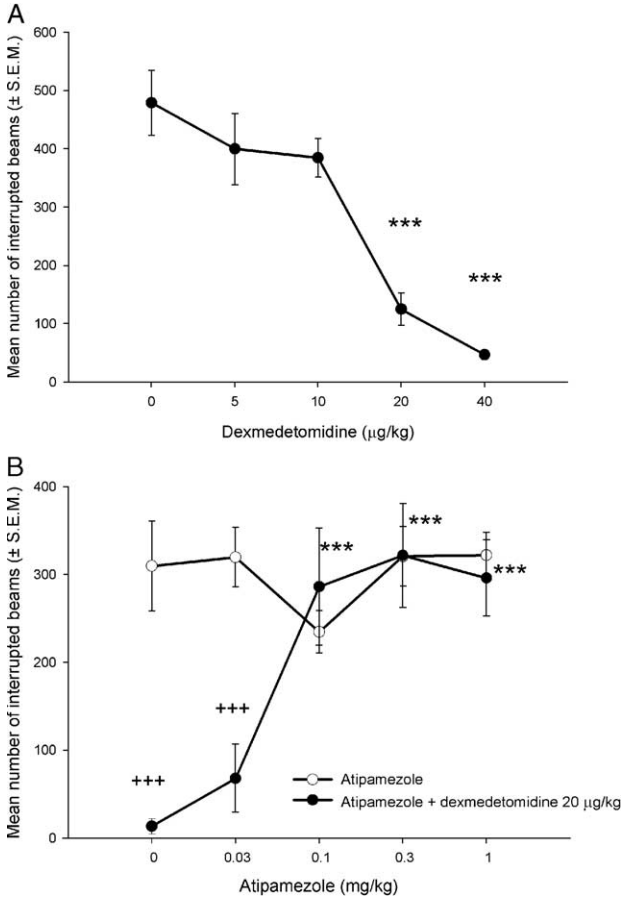

Fig. 1. Effect of dexmedetomidine (A) (saline, 5, 10, 20 and 40 μg/kg i.p., $n=10$ for each group) and dexmedetomidine (20 μg/kg) in combination with atipamezole (B) (0.03, 0.1, 0.3, 1.0 mg/kg i.p., $n=7$–11 for each group) on the horizontal activity (locomotion) of mice. Horizontal activity was measured in the photocell activity cage (lasted 4 min 30 min after the dexmedetomidine administration). ***$P<0.001$ when compared to the saline-treated (control) group of mice (one-way ANOVA with post-hoc Tukey test).

The behaviour of animals during the interaction was recorded on videotape. Next, the tapes were analyzed by an observer with no knowledge of the drug treatment. This was done with a keyboard that was connected to a standard PC and software for behavioural analysis (Noldus Observer).

2.4. Measures

The frequency, total duration and latency to its first occurrence of a number of aggressive, defensive-escape (timid), social and locomotor activities derived from the ethogram of mice (Grant and Mackintosh, 1963) and described in detail previously (Krsiak, 1975; Krsiak et al., 1984) were recorded. In short, the acts and postures evaluated in the present paper were defined as follows:

Sociable activities (social investigation): social sniff—also referred to as naso-nasal and ano-genital contacts, sniffing the partner's head, body, genitals or tail; climb—the mouse places its forepaws on the partner's back, mostly in the shoulder region, and usually sniffs this area at the same time; and follow—following the partner by quiet walking.

Aggressive activities: attack—a fierce lunging at the partner often associated with biting; threat—a sideways or an upright stance with head and forebody movements toward the partner and trying to bite the partner (offensive sideways or upright posture); and tail rattle—rapid vibrations of the tail.

Timid activities: defence—the mouse responds to the partner's social behaviour by raising forepaws, hunching the back (defensive upright posture) or by some rotation of the body bringing the legs closest to the other animal off the ground (defensive sideways posture); escape—a rapid running or jumping away from the partner; and alert posture—a sudden interruption of all movements with eyes and ears being directed toward the partner;

Locomotor activities: walk—any walking across the cage which is not apparently related to the partner; and rear—the mouse stands only on his hind legs and usually sniffs air or walls at the same time.

Duration was not measured for escapes and attacks because of the momentary character of these acts (i.e. measurement of duration was not considered accurate enough and meaningful in these acts).

The inter-observer reliability of the recorded items was satisfactory as determined by several observers independently scoring a videotaped record of behaviour of 70 mice in interactions lasting 4 min each. The correlation ranged from $r=0.83$ to 0.97.

2.5. Drug

Dexmedetomidine (Abbott Laboratiores, Czech Republic) and atipamezole (Orion Corporation, Finland) were diluted in saline and administered intraperitoneally in a volume 0.1 ml/10 g of body weight. After administration, isolated mice were always placed into the observational cage.

2.6. Data analysis

Behavioural elements, their frequency, duration and latency were summed in four behavioural categories (sociable, aggressive, locomotor and timid) for the statistical analysis. Next, we selected mice that exhibited aggressive behaviour (at least one attack during the social encounter, $n=35$ out of 49) and non-aggressive mice ($n=14$ out of 49) after the placebo treatment. Statistical evaluation and interpretation of timid activities is limited due to their rare frequency and we present this data for integrity. The behavioural categories were evaluated by one-way repeated measures ANOVA (analysis of variance) with the factor treatment (saline, 5, 10 and 20 μg/kg of dexmedetomidine). Subsequent analysis was performed using Tukey *t*-test to reveal significant differences between the control and the dexmedetomidine-treated group of mice. If necessary, a Friedman repeated measures analysis of variance on ranks was used. The data from activity cage were evaluated by one-way ANOVA (dexmedetomidine alone) and by two-way ANOVA (combination of atipamezole with dexmedetomidine). All statistical tests used two-tailed criterion, with an alpha level of $P<0.05$.

3. Results

3.1. Locomotor activities

3.1.1. Activity cage

Acute administration of dexmedetomidine in the activity cage (Fig. 1) significantly and dose-dependently decreased horizontal activity ($F(4,49)=20.370$, $P<0.001$). The subsequent analysis using Tukey test revealed significant differences between control and 20 μg/kg of dexmedetomidine group of mice ($t=7.455$, $df=49$, $P<0.001$) and this difference was more pronounced after a dose of 40 μg/kg of dexmedetomidine ($t=10.314$, $df=49$, $P<0.001$). Atipamezole (0.03–1.0 mg/kg) dose-dependently antagonised the sedative effect of dexmedetomidine (20 μg/kg); maximal antagonistic effect was reached at a dose of 0.1 mg/kg. Atipamezole alone had no effect on locomotion in the activity cage (Fig. 1).

3.1.2. Social conflict

In the social conflict test, the dexmedetomidine treatment (5–20 μg/kg) had no effect in aggressive and in sociable mice on the number, duration or latency of the locomotor activities ($F(3,139)=1.584$, $P=0.198$ for the frequency, $F(3,139)=0.792$, $P=0.501$ for the duration, and $F(3,139)=1.456$, $P=0.231$ for the latency in the aggressive mice and $F(3,55)=2.353$, $P=0.087$ for the frequency, $F(3,55)=1.928$, $P=0.141$ for the duration, and $F(3,55)=0.507$, $P=0.680$ for the latency in the sociable mice, Tables 1 and 2).

3.2. Aggressive activities

In aggressive mice, one-way repeated measures ANOVA showed a significant effect of the treatment on the number ($F(3,139)=13.980$, $P<0.001$), duration ($F(3,139)=13.321$, $P<0.001$) and latency ($F(3,139)=19.517$, $P<0.001$) of aggressive acts (attacks, threats, and tail rattles). Aggressive activities were decreased directly to the dexmedetomidine dose; the number ($t=4.357$, $df=139$, $P=0.014$) and duration ($t=4.066$, $df=139$, $P=0.025$) of aggressive activities were decreased after a dose of 10 μg/kg of dexmedetomidine and this decrease was much more pronounced after a dose of 20 μg/kg of dexmedetomidine ($t=8.961$, $df=139$, $P<0.001$ for number, $t=8.786$, $df=139$, $P<0.001$ for duration, and $t=10.159$, $df=139$, $P<0.001$ for latency; Fig. 2, Table 1).

In sociable mice, Friedman RM ANOVA on ranks showed significant effect of treatment on the on the number ($\chi^2=14.962$,

Table 1
Behaviour after the dexmedetomidine (DXM) treatment in the aggressive mice

Treatment (mean± S.E.M.)	Control ($n=35$)	DXM 5 μg/kg ($n=35$)	DXM 10 μg/kg ($n=35$)	DXM 20 μg/kg ($n=35$)
Locomotor acts (rear and walk)				
Frequency	69.40±4.64	64.37±4.78	73.43±5.79	60.40±4.75
Duration (s)	45.51±3.79	46.02±3.39	48.77±3.83	41.27±4.12
Latency (s)	17.39±2.41	25.34±3.01	20.54±3.61	37.87±11.86
Aggressive acts (attack, threat, and tail rattle)				
Duration (s)	41.09±2.62	31.87±3.68	28.47±3.48[a]	13.83±3.65[c]
Latency (s)	48.65±9.94	137.25±32.46	142.73±33.96	428.00±45.93[c]
Sociable acts (social sniff, climb, and follow)				
Frequency	19.49±2.35	24.17±2.80	21.14±2.98	17.77±2.99
Duration (s)	14.95±2.12	24.74±3.85	19.23±3.33	19.08±4.20
Latency (s)	306.54±27.99	306.81±26.24	360.91±22.87	395.16±22.95
Timid acts (defence, escape, and alert)				
Frequency	0.63±0.25	0.77±0.28	0.94±0.26	1.77±0.37
Duration (s)	0.50±0.22	1.07±0.50	1.03±0.30	2.49±0.71
Latency (s)	638.84±25.76	639.33±24.16	601.78±24.82	560.41±21.39

[a]$P<0.05$ and [c]$P<0.001$ when compared to the control group (one-way repeated measures ANOVA with post-hoc Tukey *t*-test).

Table 2
Behaviour after the dexmedetomidine (DXM) treatment in the sociable mice

Treatment (mean± S.E.M.)	Control ($n=14$)	5 μg/kg ($n=14$)	10 μg/kg ($n=14$)	20 μg/kg ($n=14$)
Locomotor acts (rear and walk)				
Frequency	72.07±6.31	76.50±5.91	66.29±5.82	57.21±8.31
Duration (s)	48.66±4.31	47.00±4.82	41.16±2.85	37.74±5.72
Latency (s)	12.28±4.61	17.23±4.73	16.65±3.20	17.68±5.18
Aggressive acts (attack, threat, and tail rattle)				
Frequency	0.57±0.50	36.36±18.86	19.64±16.98	10.57±10.57
Duration (s)	0.15±0.12	9.16±4.26	4.84±3.97	2.99±2.99
Latency (s)	674.64±33.18	442.78±70.96[a]	577.64±65.44	669.97±50.03
Sociable acts (social sniff, climb, and follow)				
Duration (s)	52.39±5.41	37.12±3.35	36.96±6.05	19.77±9.12[b]
Latency (s)	135.83±28.81	241.28±39.06	245.31±42.00	403.72±40.01[c]
Timid acts (defence, escape, and alert)				
Frequency	0.79±0.32	0.71±0.38	1.07±0.51	1.21±0.58
Duration (s)	1.16±0.68	0.93±0.64	1.29±0.58	1.83±0.86
Latency (s)	628.05±29.54	654.91±28.62	612.28±43.92	607.60±39.85

[a]$P<0.05$, [b]$P<0.01$, and [c]$P<0.001$ when compared to the control group (one-way repeated measures ANOVA with post-hoc Tukey *t*-test).

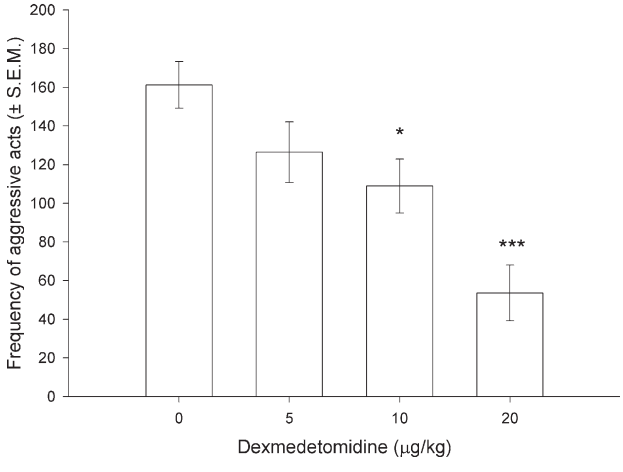

Fig. 2. Effect of dexmedetomidine (saline, 5, 10 and 20 μg/kg) on the number of aggressive acts (attacks, threats, and tail rattles) in the aggressive mice ($n=35$). Social conflict was performed 30 min after the dexmedetomidine administration and lasted for 4 min. Each mouse received all four treatments in randomized order in weekly intervals. *$P<0.05$ and ***$P<0.001$ when compared to the saline-treated (control) group of mice (one-way repeated measure ANOVA with post-hoc Tukey test).

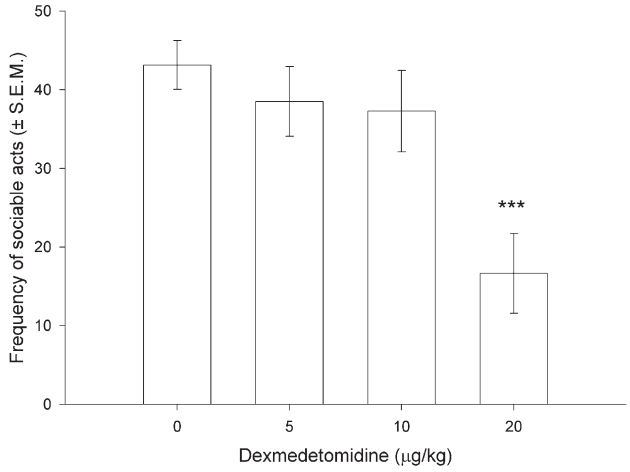

Fig. 3. Effect of dexmedetomidine (saline, 5, 10 and 20 μg/kg) on the number of sociable acts (sniffs, climbs, and follows) in the sociable mice (n=14). Social conflict was performed 30 min after the dexmedetomidine administration and lasted for 4 min. Each mouse received all four treatments in randomized order in weekly intervals. ***P<0.001 when compared to the saline-treated (control) group of mice (one-way repeated measures ANOVA with post-hoc Tukey test).

df=3, P=0.002) and duration (χ^2=14.127, df=3, P=0.003) and one-way repeated measures ANOVA showed a significant effect of the treatment on the latency (F(3,55)=4.748, P<0.006) of aggressive acts. For the number and duration, there was no difference between control and dexmedetomidine-treated mice. For the latency, a dose of 5 μg/kg of dexmedetomidine significantly decreased latency to the first occurrence of aggressive acts (t=4.652, df=55, P=0.011, Table 2).

3.3. Sociable activities

In sociable mice, one-way repeated measures ANOVA showed a significant effect of the treatment on the number (F(3,55)=7.715, P<0.001), duration (F(3,55)=4.196, P=0.011) and latency (F(3,55)=10.681, P<0.001) of sociable acts (sniffs, climbs, and follows). Sociable acts decreased directly to the dexmedetomidine dose; the number (t=6.252, df=55, P<0.001) and duration (t=5.013, df=55, P=0.006) of sociable acts were significantly decreased and latency was increased (t=7.927, df=55, P<0.001) after a dose of 20 μg/kg of dexmedetomidine (Fig. 3, Table 2).

In aggressive mice, dexmedetomidine treatment had no effect on the number, duration or latency of the sociable acts (F(3,139)=0.991, P=0.400 for the frequency, F(3,139)=1.240, P=0.299 for the duration, and F(3,139)=2.104, P=0.104 for the latency, Table 1).

4. Discussion

Dexmedetomidine significantly reduced locomotion in the activity cage. The highest doses caused sedation and decreased number of horizontal locomotor acts and this effect was fully reversed by an α_2-adrenoreceptor antagonist atipamezole. Sedative effect of dexmedetomidine was described in some previous studies, which used different locomotor or open-field tests (Hunter et al., 1997; Lahdesmaki et al., 2003; Buerkle and Yaksh, 1998). Although these findings and our results suggest that dexmedetomidine has a strong sedative effect, we have not observed this effect during the social conflict. Studies observing, e.g., locomotion usually describe just a few behavioural signs and do not analyze the behaviour of the animal as a whole. For example, psychomotor-stimulant drugs can be wrongly interpreted as sedative in these tests, while occurrence of intense stereotypy rather than locomotor activity is present (Sharp et al., 1987). During the social conflict, locomotion was unaffected by the dexmedetomidine treatment both in the aggressive and sociable mice at the dose which caused sedation in the activity cage (20 μg/kg). It seems that external stimuli (e.g. social partner) can disrupt sedative effect of dexmedetomidine and thus we have not observed sedation in this test. It was described that a release of catecholamines can be triggered by external stimuli (e.g. social encounter and handling) and in those animals sedation is usually not observed (Ihalainen and Tanila, 2002; Tanila et al., 1999; Tornatzky and Miczek, 1994; Sgoifo et al., 1996). This effect most probably played a major role during the social conflict in our experiment.

Aggressive mice showed high level of aggressiveness as well as locomotion after the placebo treatment. The dexmedetomidine treatment dose-dependently and significantly (10 and 20 μg/kg) decreased aggressive behaviour compared to the placebo treatment without reducing locomotion. Sociable mice exhibited high level of social investigation and locomotion in control encounters. Dexmedetomidine dose-dependently and significantly reduced social investigation. This decrease, which reached statistical significance at the highest dose (20 μg/kg), was not accompanied with the changes of other activities (aggressive, locomotor, and timid). Similarly, in the aggressive mice, the decrease of aggression was not associated with changes of other activities. It was described that dexmedotomidine dose-dependently reduced time spent in social interaction in rats and the number of attacks in mice (Millan et al., 2000b). Regrettably, other behaviour occurring concomitantly in these experiments was not measured so that it is difficult to assess selectivity of these effects of dexmedetomidine.

The selective anti-aggressive effect of certain drugs has been described very rarely. Nonselective 5-HT_1 (serotonin) receptor agonists (RU24969 and eltoprazine) and recently developed 5-HT_{1A} receptor agonists alnespirone and S-15535 reduced aggression quite specifically and did not decrease social interest or exploration (Olivier et al., 1995; de Boer et al., 1999, 2000). The selective anti-aggressive effect was described for 5-HT2A receptor antagonist ritanserin (Sakaue et al., 2002), 5-HT_{1A} receptor agonist MKC-242 (Sakaue et al., 2001), 5-HT_{1B} receptor agonists anpirtoline and CP-94,253 and for 5-$HT_{1B/D}$ receptor agonists zolmitriptan (de Almeida and Miczek, 2002). In some studies the antiaggressive effect of atypical neuroleptics was not accompanied by the decrease of locomotion (Aguilar et al., 1994; Redolat et al., 1991). The benzodiazepine receptor partial agonist Ro 19-8022 was found to have anxiolytic-like and potent anti-aggressive effects without causing muscle relaxation or ataxia (Podhorna and Krsiak, 2000). The selective decrease of aggression was also

observed after the treatment of nicotinic agonists lobeline (Redolat et al., 2002) and delta9-tetrahydrocannabinol (Miczek, 1978). Very few of these drugs are used in human medicine and thus dexmedetomidine might provide an advantage in the treatment of aggressive states.

One could argue that the decrease of aggression after dexmedetomidine is due to its blood-pressure-lowering effect. Dexmedetomidine belongs to α_2-adrenoreceptor agonist and possesses blood-pressure-lowering effects in humans (Talke et al., 2003), cats (Selmi et al., 2003), or rabbits (Xu et al., 1998). However, in some species, including rodents and dogs, administration of dexmedetomidine increased mean arterial pressure (Bloor et al., 1992; Bol et al., 1997).

Our results suggest that dexmedetomidine preferably inhibits the reaction of the animal to the main external stimulus. In the activity cage where animals were placed into the novel environment, which increased locomotion, exploratory behaviour was attenuated according to the dexmedetomidine dose. In mice, in which the social encounter evoked aggression, dexmedetomidine selectively decreased number of aggressive acts without affecting other behaviour. Finally, in sociable mice with high level of social investigation toward their social partner, dexmedetomidine selectively decreased this behaviour. In previous studies, decrease of locomotion in the open-field test or decrease of the number of total entries to elevated plus-maze arms was observed as well as decreased aggression, sociability or anxiety signs (Salonen et al., 1992; Millan et al., 2000b). The only sign which was increased after dexmedetomidine administration was number of licks in Vogel conflict test (Millan et al., 2000b). However, analgesic and xerostomic properties of dexmedetomidine can be responsible for this effect (Millan et al., 2000a).

Our study shows that the same test in different animals can lead to different results, that dexmedetomidine inhibits behaviour which is stimulated in different situations or tests and that there is no simple way to describe dexmedetomidine action as, e.g., anxiolytic or antiaggressive. This inhibition seems to be not rate dependent (i.e. behaviour with highest frequency is attenuated) because in sociable mice the frequency of locomotor acts after the placebo treatment was higher than the frequency of sociable acts.

In conclusion, the present results suggest that dexmedetomidine appears to inhibit predominantly dominant behaviour evoked by biologically important stimuli. In a novel environment, which stimulates locomotion in laboratory rodents, we observed inhibition of locomotion and sedation. In mice that exhibit sociable behaviour toward their partner, the most prominent effect after dexmedetomidine treatment was inhibition of sociable activities. In aggressive mice, we observed very potent and selective antiaggressive effect. Selective antiaggressive effect was not described very often and those substances are mainly in preclinical phase of development. Dexmedetomidine is already used in human medicine and thus can be used for treatment of aggressive states. Moreover, sedation caused by dexmedetomidine can be easily disrupted and thus it has an advantage over benzodiazepines or neuroleptics, which are used in this indication.

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