

On the improvement of inhibitory response control and visuospatial attention by indirect and direct adrenoceptor agonists

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Received: 10 January 2011 / Accepted: 17 June 2011 / Published online: 19 July 2011
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Abstract

Rationale The clinical efficacy of the monoamine and noradrenaline transporter inhibitors methylphenidate and atomoxetine in attention deficit/hyperactivity disorder implicates noradrenergic neurotransmission in modulating inhibitory response control processes. Nonetheless, it is unclear which adrenoceptor subtypes are involved in these effects.

Objectives The present study aimed at investigating the effects of adrenoceptor agonists on inhibitory response control as assessed in the rodent 5-choice serial reaction time task, a widely used translational model to measure this executive cognitive function.

Results Consistent with the previous reported effects of atomoxetine, the noradrenaline transporter inhibitor desipramine improved inhibitory response control, albeit the effect size was smaller compared to that of atomoxetine. Methylphenidate exerted a bimodal effect on inhibitory response control. Interestingly, the preferential β_2 -adrenoceptor agonist clenbuterol improved inhibitory response control. Moreover, clenbuterol improved visuospatial attention in the task, an effect that was also observed with the preferential β_1 -adrenoceptor agonist dobutamine. By contrast, although the preferential α_1 -adrenoceptor and α_2 -adrenoceptor agonists (phenylephrine and clonidine, respectively) and the

non-selective β -adrenoceptor agonist (isoprenaline) were found to alter inhibitory response control, this was probably secondary to the simultaneous increments in response latencies and omissions observed at effective doses.

Conclusions Taken together, these findings further strengthen the notion of noradrenergic modulation of inhibitory response control and attentional processes and particularly reveal the involvement of β_2 -adrenoceptors therein.

Keywords Adrenoceptors · Attention · Clenbuterol · Impulsive behaviour · Noradrenaline · Rat

Introduction

Disturbances in inhibitory control over behaviour play a central role in the symptomatology of attention deficit/hyperactivity disorder (ADHD; Barkley 1997; Sonuga-Barke 2005). Neuroimaging studies have greatly contributed to our growing understanding of the neural substrates of inhibitory response control processes (Aron and Poldrack 2005) and the observed structural and functional changes in the brains of ADHD patients (Valera et al. 2007). In addition to human preclinical approaches, much of our understanding of the neural substrates of inhibitory response control is derived from rodent lesion and neuropharmacological studies (Eagle et al. 2008; Pattij and Vanderschuren 2008; Winstanley et al. 2006).

Consistent with the therapeutic efficacy of the noradrenaline (NA) transporter inhibitor atomoxetine in ADHD patients (Chamberlain et al. 2007), recent studies have demonstrated that atomoxetine also improves inhibitory response control in several translational rodent models (Bari et al. 2009; Blondeau and Dellu-Hagedorn 2007; Robinson et al. 2008). Thus, these findings implicate noradrenergic neurotransmission in modulating inhibitory

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response control processes, although the precise mechanisms underlying these effects are not fully understood. Early neuronal recording experiments and subsequent studies in laboratory animals have shown that NA neurons of the locus coeruleus (LC) are phasically discharged upon exposure to novel, salient and arousing environmental stimuli (see for example, Aston-Jones and Bloom 1981; Foote et al. 1980; Sara et al. 1994). This phasic activity of the LC NA system might promote processing of these stimuli in upstream projection areas, including cortical areas, and thereby facilitate the preparation of subsequent appropriate behavioural responses. In addition, moderate tonic activity of the LC has been associated with optimal behavioural performance (Aston-Jones et al. 1999). In the rodent brain, frontal cortical areas importantly modulate inhibitory response control processes (Chudasama et al. 2003) and furthermore receive afferent projections from the LC (for review see, Foote and Morrison 1987). In turn, frontal cortical areas might modulate activity of the LC via efferent projections (Jodo et al. 1998; Sara and Herve-Minvielle 1995). Collectively, this has led to the view that the NA system—perhaps acting in concert with the dopaminergic system—plays a key role in optimizing behavioural responses including prefrontal cortical and executive cognitive function (Arnsten 2000; Aston-Jones and Cohen 2005; Sara 2009). Considering the current working hypothesis on noradrenergic functioning, this might also explain the therapeutic efficacy of methylphenidate in ADHD, which has been shown to enhance NA levels at low doses (Berridge et al. 2006; Devilbiss and Berridge 2006).

To date, little is known with regard to the involvement of different adrenoceptor subtypes in inhibitory response control, although previous work in rodents suggested a functional role of α -adrenoceptors (Milstein et al. 2007; Puumala et al. 1997; Ruotsalainen et al. 1997; Sirvio et al. 1994). Generally, these studies suggest α 1-adrenoceptor involvement, as an agonist of this adrenoceptor subtype was found to selectively improve inhibitory response control (Puumala et al. 1997). Moreover, α 2-adrenoceptor agonists also ameliorate inhibitory response control, albeit these beneficial effects were only observed at doses that simultaneously impaired somatomotor performance (Milstein et al. 2007; Ruotsalainen et al. 1997; Sirvio et al. 1994). Thus, these preclinical findings with α -adrenoceptor agonists in part support the clinical beneficial effects of the α 2-adrenoceptor agonists clonidine and guanfacine in ADHD (Arnsten et al. 2007). Interestingly, in both healthy volunteers and rats, the α 2-adrenoceptor antagonist yohimbine has been demonstrated to impair inhibitory response control (Sun et al. 2010; Swann et al. 2005). To our knowledge, β -adrenoceptor involvement in inhibitory response control has not been investigated in detail before. Therefore, further dissecting the contribution of specific adrenoceptors therein could provide novel insights into the mechanism of action of

atomoxetine and methylphenidate. To that end, we investigated the effects of various selective α -adrenoceptor and β -adrenoceptor agonists in addition to those of indirect agonists on inhibitory response control in rats. More specifically, we tested the effects of the monoamine reuptake inhibitor methylphenidate, the noradrenaline reuptake inhibitor desipramine, the α 1-adrenoceptor and α 2-adrenoceptor agonists phenylephrine and clonidine, the non-selective β -adrenoceptor agonist isoprenaline and lastly the β 1-adrenoceptor and β 2-adrenoceptor agonists, dobutamine and clenbuterol. To assess drug effects, rats were trained in the 5-choice serial reaction time task (5CSRTT), which is a widely employed rodent operant cognitive task adopted from the human continuous performance task that measures aspects of visuospatial attention as well as inhibitory response control (see for reviews, Bari et al. 2008; Robbins 2002).

Material and methods

Subjects

In total, 60 male Wistar rats were obtained from Harlan CPB (Horst, The Netherlands). At the start of the experiments, animals were 12 weeks old, weighed approximately 250 g and were housed in pairs in macrolon cages (42.5×26.6×18.5 cm; $l \times w \times h$) under a reversed 12-h light/dark cycle (lights on at 7:00 p.m.) at controlled room temperature (21±2°C) and relative humidity of 60±15%. Animals were maintained at approximately 90% of their free-feeding weight, starting 1 week prior to the beginning of the experiments by restricting the amount of standard rodent food pellets (Harlan Teklad Global Diet, Blackthorn, UK). Water was available ad libitum throughout the entire experiment. All experiments were conducted with the approval of the animal ethical committee of the Vrije Universiteit, Amsterdam, the Netherlands.

Apparatus

Experiments were conducted in identical rat five hole nose poke operant chambers with stainless steel grid floors (MED-NPW-5L, Med Associates Inc., St. Albans, VT, USA) housed in sound-insulating and ventilated cubicles. Set in the curved wall of each box was an array of five holes. Each nose poke unit was equipped with an infrared detector and a yellow light emitting diode stimulus light. Rodent food pellets (45 mg, Formula P, Bio-Serv, Frenchtown, USA) could be delivered at the opposite wall via a dispenser and a white house light could illuminate the chamber. A computer equipped with MED-PC version 1.17 (Med Associates Inc.) controlled experimental sessions and recorded data. The animals were tested once daily from Monday until Friday during the dark phase of the light/dark cycle.

Behavioural procedure

To habituate animals to the operant chambers, rats were exposed to the operant chambers for 20 min with the houselight on and the food cup containing three food pellets for two consecutive sessions. Subsequently, in the next two sessions, pellets (100 per session) were delivered with an average delay of 15 s to allow the animals to associate the sound of pellet delivery with reward. Following this, the rats were trained in the 5CSRTT paradigm. A detailed description of the 5CSRTT behavioural procedure in our laboratory has been provided previously (Van Gaalen et al. 2006a). In short, rats were trained to detect and respond to a brief visual stimulus in one of five nose poke units in order to obtain a food reward. Each session terminated after 100 trials or 30 min, whichever occurred first. Initially, the duration of this stimulus was 32 s and was gradually decreased to 1 s over sessions until animals reached stable baseline performance (accuracy >80% correct choice and <20% errors of omission, for at least five consecutive sessions). Responding during stimulus presentation or within the limited hold (LH) period of 2 s was counted as a correct response. Incorrect, premature responses during the fixed 5-s intertrial interval and errors of omission (no responses or a response after the LH) did not lead to the delivery of a food reward and resulted in a 5-s time out period during which the houselight was extinguished, whereas perseverative responses, i.e. repeated responding during the presentation of the stimulus, were measured but did not have any programmed consequences. Two different measures of inhibitory control were measured, namely (1) the percentage of premature responses before stimulus onset, calculated as $[\text{number of premature responses} / (\text{correct} + \text{incorrect} + \text{omitted trials})] \times 100$ and (2) the percentage of perseverative responses into the stimulus unit after correct choice, a measure of compulsive behaviour, calculated as $[\text{number of perseverative responses} / (\text{correct} + \text{incorrect} + \text{omitted trials})] \times 100$. In addition, the following other behavioural parameters were measured that reflect task performance, namely (3) accurate choice, i.e. percentage correct responses calculated as $[\text{number correct trials} / (\text{correct} + \text{incorrect trials})] \times 100$; (4) latency to make a correct choice, i.e. the mean time between stimulus onset and nose poke in the illuminated unit; (5) omission errors, i.e. the percentage of omitted trials during a session calculated as $[\text{number of omitted trials} / (\text{correct} + \text{incorrect} + \text{omitted trials})] \times 100$ and (6) feeder latency, i.e. the latency to collect a pellet following correct choice.

Drugs

Methylphenidate hydrochloride (Fagron, Nieuwerkerk a/d IJssel, Netherlands), clenbuterol hydrochloride, desipra-

mine hydrochloride, dobutamine hydrochloride, phenylephrine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA), clonidine hydrochloride (Boehringer Ingelheim, Ingelheim am Rhein, Germany) and isoprenaline sulphate (ACF Chemiefarma, Maarssen, the Netherlands) were dissolved in sterile saline. All drugs were injected 30 min before testing, with the exception of methylphenidate, isoprenaline and clenbuterol that were injected 20 min before testing. Desipramine (dose range, 1–10 mg/kg), clenbuterol (dose range, 0.01–0.1 mg/kg), dobutamine (dose range, 1–6 mg/kg) and phenylephrine (dose range, 0.3–3 mg/kg) were injected intraperitoneally, clonidine (dose range, 0.01–0.03 mg/kg) and isoprenaline (dose range, 0.1–1 mg/kg) were injected subcutaneously and methylphenidate (dose range, 1–10 mg/kg) was administered orally via oral gavage. In group 1 ($n=14$), the order of testing drugs was (1) desipramine, (2) clonidine and (3) phenylephrine. In group 2 ($n=14$), isoprenaline was tested; in group 3 ($n=16$), methylphenidate was tested, and in group 4 ($n=16$), dobutamine and clenbuterol were tested. Drugs were freshly prepared before testing and injected in a volume of 1 ml/kg body weight according to a Latin square within-subjects design on Tuesdays and Fridays with baseline training sessions on the other weekdays. Drug doses were based on previous reports employing instrumental behaviour paradigms (Arnsten and Dudley 2005; Munzar and Goldberg 1999; O'Donnell 1990; Van Gaalen et al. 2006b).

Statistical analyses

Data were subjected to repeated measures analysis of variance (ANOVA) with drug dose as within-subjects variable using the Statistical Package for the Social Sciences version 14 (SPSS Inc., Chicago, IL, USA). The homogeneity of variance across groups was determined using Mauchly's tests for equal variances and in case of violation of homogeneity, Huynh–Feldt epsilon (ϵ) adjusted degrees of freedom were applied and the resulting more conservative probability values were depicted and used for subsequent analyses. In case of statistically significant main effects, further post hoc comparisons were conducted using Newman–Keuls multiple comparison tests. The level of probability for statistically significant effects was set at 0.05.

Results

Baseline performance

Drug testing commenced upon stable baseline performance in the 5CSRTT. Repeated measures ANOVA of the five last baseline training sessions revealed that in all groups behavioural performance had stabilized before drug testing in terms of the percentage of accurate choice [group 1, $F(4,52)=1.40$,

$p=0.25$; group 2, $F(4,52)=0.33$, $p=0.85$; group 3, $F(4,60)=0.63$, $\varepsilon=0.43$, $p=0.52$; group 4, $F(4,60)=1.25$, $p=0.30$], the percentage of omission errors [group 1, $F(4,52)=1.37$, $p=0.26$; group 2, $F(4,52)=2.06$, $\varepsilon=0.71$, $p=0.12$; group 3, $F(4,60)=0.65$, $p=0.63$; group 4, $F(4,60)=1.01$, $\varepsilon=0.78$, $p=0.40$] and the percentage of premature responding [group 1, $F(4,52)=1.14$, $p=0.35$; group 2, $F(4,52)=0.30$, $\varepsilon=0.60$, $p=0.75$; group 3, $F(4,60)=1.06$, $\varepsilon=0.59$, $p=0.37$; group 4, $F(4,60)=1.79$, $\varepsilon=0.59$, $p=0.18$]. Furthermore, during testing of all separate drugs, repeated measures ANOVA on the intervening pre-drug baseline training sessions revealed that behavioural performance on accurate choice, percentage omissions and percentage premature responding did not shift and remained stable (all $p>0.05$; data not shown).

Methylphenidate

Methylphenidate had a biphasic effect on the percentage premature responses [Fig. 1a; $F(3,45)=15.72$, $\varepsilon=0.47$, $p<0.001$] and strongly tended to decrease premature responding at the low dose (1 mg/kg; $p=0.055$), whereas it increased this parameter at the highest dose (10 mg/kg; $p=0.002$) compared to vehicle. Accurate choice was decreased by methylphenidate [Fig. 1b; $F(3,45)=5.33$, $p=0.003$], and methylphenidate also speeded correct response latencies [Fig. 1c; $F(3,45)=3.28$, $p=0.029$]. Further comparisons

revealed that only 10 mg/kg methylphenidate impaired visuospatial attention ($p=0.001$) and speeded response latencies ($p=0.035$) compared to the vehicle. The percentage of omissions was not altered by methylphenidate [Fig. 1d; $F(3,45)=0.63$, $p=0.60$] or was the percentage of perseverative responses and latency to collect reward after correct choice [Table 1; $F(3,45)=0.61$, $\varepsilon=0.53$, $p=0.51$ and $F(3,45)=0.40$, $\varepsilon=0.73$, $p=0.69$, respectively].

Desipramine

The selective NA reuptake inhibitor desipramine dose dependently decreased the percentage of premature responses [Fig. 2a; $F(3,39)=8.51$, $p<0.001$] and further analyses revealed that compared to vehicle this was the case for both the 3 and 10 mg/kg dose of desipramine ($p=0.022$ and $p<0.001$, respectively). In addition to the effects of desipramine on premature responding, desipramine increased correct response latencies [Fig. 2c; $F(3,39)=4.46$, $p=0.009$] and the percentage of omissions [Fig. 2d; $F(3,39)=6.85$, $\varepsilon=0.85$, $p=0.002$]. Further analyses revealed that only 10 mg/kg desipramine significantly increased response latencies and omissions compared to the vehicle ($p=0.005$ and $p<0.001$, respectively). Likewise, the latency to collect reward after correct choice was increased by desipramine [Table 1; $F(3,39)=3.37$, $\varepsilon=0.79$, $p=0.04$]. Further analyses

Fig. 1 Methylphenidate exerts a bimodal effect on the percentage premature responses (a), decreases the percentage correct choice (b), shortens correct response latency (c) and does not affect the percentage omissions (d) in the 5CSRTT. All data are expressed as mean±SEM. * $p<0.05$ and ** $p<0.005$ compared to vehicle treatment

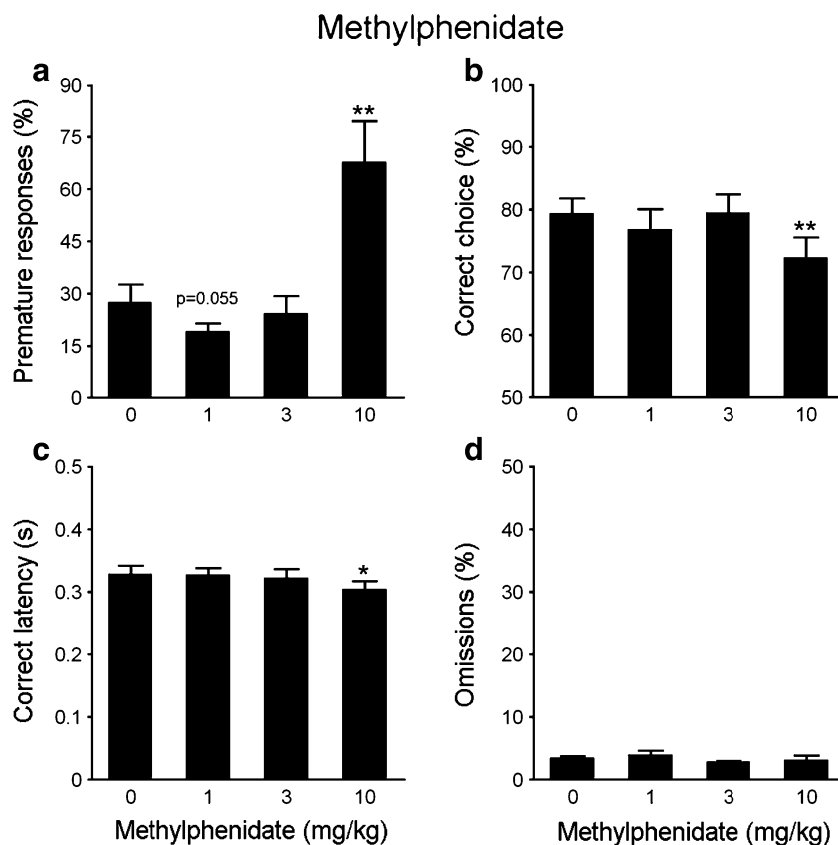


Table 1 Effects of indirect and direct adrenoceptor agonists on the percentage of perseverative responses and latencies to collect food reward after correct choice

Drug	Dose (mg/kg)	Perseverative responses (%)	Feeder latency (s)
Methylphenidate	0	3.81±1.16	0.90±0.04
	1.0	3.69±1.13	0.92±0.05
	3.0	5.69±1.63	0.94±0.06
	10.0	5.12±2.23	0.88±0.06
Desipramine	0	6.64±1.50	0.99±0.07
	1.0	9.00±2.26	1.23±0.15*
	3.0	8.93±1.38	1.06±0.06
	10.0	9.86±1.61	1.25±0.12*
Phenylephrine	0	7.43±1.48	0.98±0.07
	0.3	7.50±1.73	1.08±0.16
	1.0	10.21±2.23	0.91±0.04
	3.0	7.36±1.58	1.15±0.10
Clonidine	0	9.21±2.25	1.09±0.10
	0.01	9.86±2.41	1.36±0.22
	0.03	4.21±0.71*	1.19±0.06
Isoprenaline	0	5.29±2.53	0.98±0.05
	0.1	2.64±0.84	1.10±0.07
	0.3	4.21±1.44	1.07±0.05
	1.0	4.57±2.08	1.19±0.08*
Dobutamine	0	12.54±7.24	1.21±0.13
	1.0	9.23±4.10	1.31±0.12
	3.0	8.08±2.70	1.16±0.11
	6.0	4.77±1.67	1.25±0.13
Clenbuterol	0	7.53±2.14	1.27±0.16
	0.01	7.07±1.75	1.33±0.14
	0.03	8.60±1.65	1.45±0.13
	0.1	6.40±1.39	1.82±0.25

Drug doses are expressed in milligrams per kilogram and all data are expressed as the mean±SEM

* $p < 0.05$ versus vehicle

showed that 1 and 10 mg/kg desipramine increased collection latencies compared to vehicle ($p = 0.049$ and $p = 0.008$, respectively). Accurate choice was not affected by desipramine [Fig. 2b; $F(3,39) = 0.31$, $p = 0.82$] or was the percentage of perseverative nose pokes after correct choice [Table 1; $F(3,39) = 0.85$, $p = 0.48$].

Phenylephrine

The α_1 -adrenoceptor agonist phenylephrine decreased the percentage of premature responses [Fig. 3a; $F(3,39) = 6.97$, $p = 0.001$] and this occurred only at the dose of 3.0 mg/kg compared to the vehicle ($p < 0.001$). Phenylephrine also increased the latency to make a correct choice [Fig. 3c;

$F(3,39) = 10.72$, $\varepsilon = 0.49$, $p = 0.002$] and increased the percentage of omissions [Fig. 3d; $F(3,39) = 4.77$, $\varepsilon = 0.55$, $p = 0.025$]. Further comparisons showed that 3.0 mg/kg phenylephrine significantly slowed response speed and increased omission rate compared to vehicle ($p = 0.007$ and $p = 0.016$, respectively). Moreover, phenylephrine significantly improved accurate choice [Fig. 3b; $F(3,39) = 2.92$, $p = 0.046$]. Further comparisons revealed that the high dose of 3.0 mg/kg phenylephrine tended to improve accurate choice compared to the vehicle, yet this effect did not reach statistical significance ($p = 0.063$). The percentage of perseverative nose pokes and latency to collect reward after correct choice were not altered by phenylephrine [Table 1; $F(3,39) = 1.52$, $p = 0.22$ and $F(3,39) = 2.16$, $\varepsilon = 0.65$, $p = 0.14$, respectively].

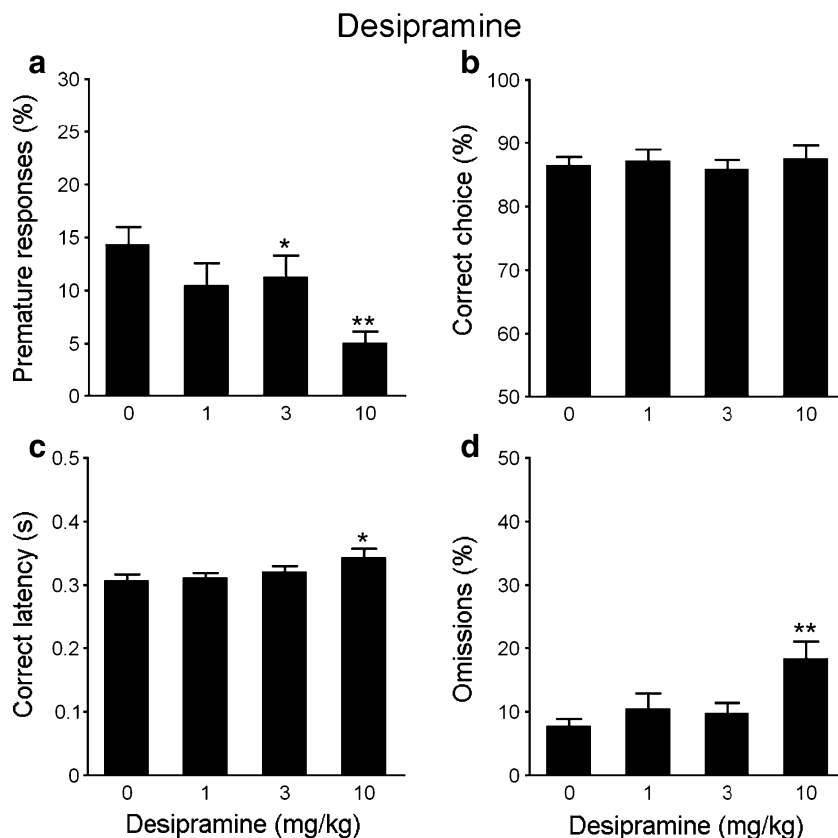
Clonidine

The α_2 -adrenoceptor agonist clonidine reduced the percentage of premature responses [Fig. 3e; $F(2,26) = 8.47$, $p = 0.001$], and further analyses revealed that both doses decreased premature responding compared to vehicle (both $p = 0.008$). In addition, clonidine dose dependently lengthened the latency to make a correct response [Fig. 3g; $F(2,26) = 40.54$, $p < 0.001$] at both doses compared to the vehicle (both $p < 0.001$). Clonidine also dose dependently increased the percentage of omissions [Fig. 3h; $F(2,26) = 42.25$, $p < 0.001$], and both doses increased omission rate compared to vehicle (both $p < 0.001$). The percentage of perseverative responses after correct choice was significantly reduced by clonidine [Table 1; $F(2,26) = 3.68$, $p = 0.039$]. Further analyses showed that only 0.03 mg/kg clonidine reduced the number of perseverative nose pokes after correct choice compared to vehicle treatment ($p = 0.031$). Clonidine did neither affect accurate choice [Fig. 3f; $F(2,26) = 1.29$, $p = 0.29$] nor the latency to collect reward after correct choice [Table 1; $F(2,26) = 1.40$, $\varepsilon = 0.63$, $p = 0.26$].

Isoprenaline

The non-selective β -adrenoceptor agonist isoprenaline reduced the percentage of premature responses [Fig. 4a; $F(3,39) = 3.98$, $p = 0.014$]. Further analyses showed that 0.3 mg/kg isoprenaline reduced premature responding compared to vehicle ($p = 0.024$). Isoprenaline dose dependently lengthened the latency to make a correct response [Fig. 4c; $F(3,39) = 17.11$, $p < 0.001$] and further comparisons revealed that all doses lengthened the latency compared to the vehicle (0.1 and 1.0 mg/kg, both $p < 0.001$ and 0.3 mg/kg, $p = 0.002$). The percentage of omissions was increased by isoprenaline [Fig. 4d; $F(3,39) = 6.80$, $p = 0.001$] at all doses compared to vehicle (0.1 mg/kg, $p = 0.002$; 0.3 mg/kg, $p = 0.003$ and 1.0 mg/kg, $p < 0.001$). Furthermore, isoprenaline also lengthened the latency to collect reward after correct

Fig. 2 The noradrenaline reuptake inhibitor desipramine decreases the percentage premature responses (a), does not affect the percentage correct choice (b), and increases both correct response latency (c) and the percentage omissions (d) in the 5CSRTT. All data are expressed as mean±SEM. * $p<0.05$ and ** $p<0.005$ compared to vehicle treatment



choice [Table 1; $F(3,39)=4.12$, $\varepsilon=0.70$, $p=0.026$], and this was only the case at 1.0 mg/kg compared to the vehicle ($p=0.023$). Accurate choice [Fig. 4b; $F(3,39)=1.04$, $p=0.39$] and the percentage of perseverative responses after correct choice [Table 1; $F(3,39)=0.76$, $p=0.53$] were not affected by isoprenaline.

Dobutamine

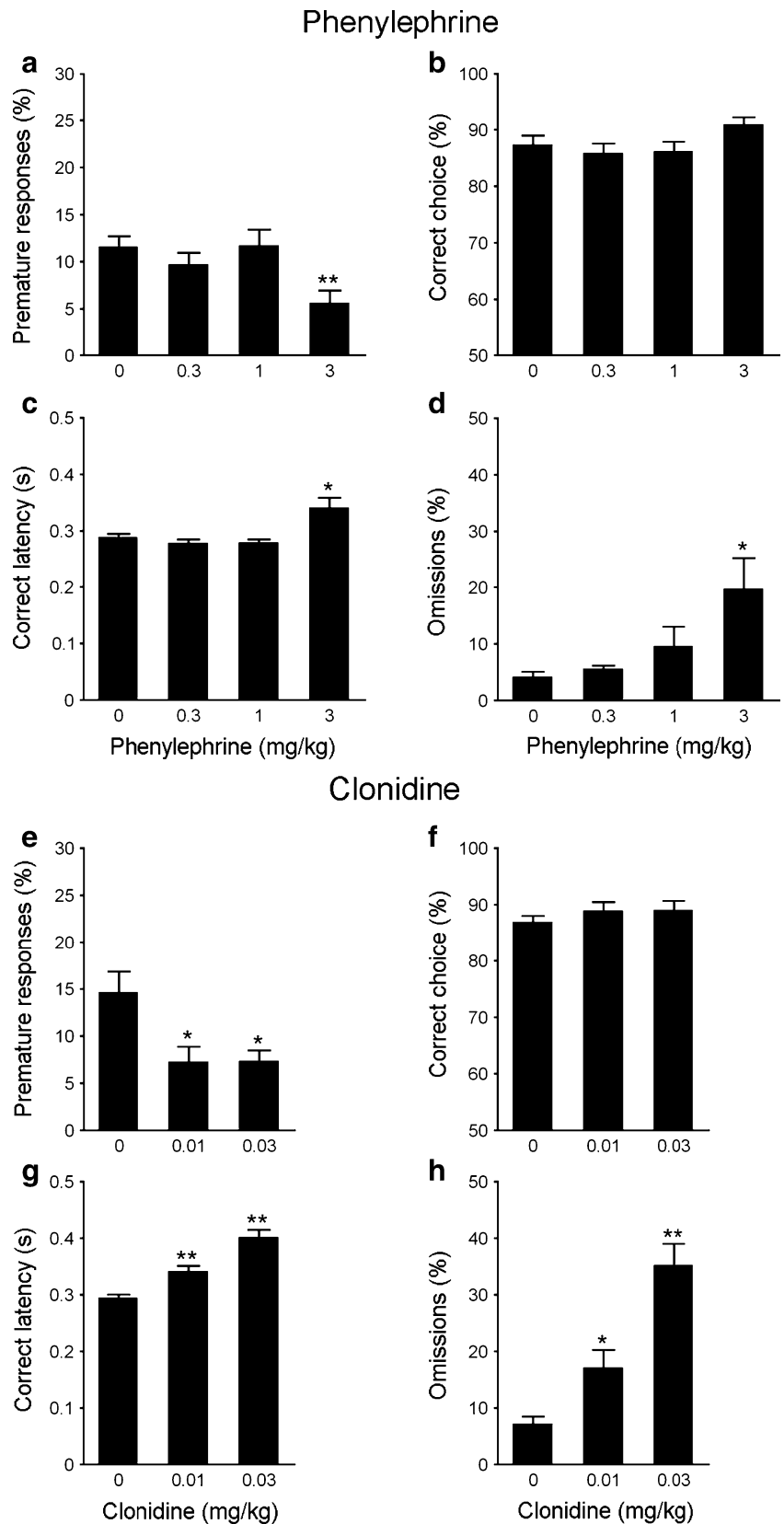
Three animals were excluded from all analyses, as these individuals consistently omitted over 50 trials in all drug dose treatments including vehicle treatment. Challenges with the β_1 -adrenoceptor agonist dobutamine tended to decrease the percentage of premature responses, although the main dose effect did not reach statistical significance [Fig. 5a; $F(3,36)=3.21$, $\varepsilon=0.66$, $p=0.059$]. Dobutamine did increase the percentage of omissions [Fig. 5d; $F(3,36)=4.25$, $p=0.011$] and further comparisons revealed that only 3 mg/kg dobutamine increased the omission rate compared to the vehicle ($p=0.002$). In addition, dobutamine improved accurate choice [Fig. 5b; $F(3,36)=4.14$, $p=0.013$], and further analyses revealed that 6 mg/kg dobutamine improved visuospatial attention compared to the vehicle ($p=0.001$). The latencies to make a correct choice [Fig. 5c; $F(3,36)=2.06$, $p=0.12$] and collect food reward after correct choice [Table 1; $F(3,36)=1.06$, $\varepsilon=0.57$, $p=0.36$]

were not altered by dobutamine or was the percentage of perseverative responses [Table 1; $F(3,36)=1.53$, $\varepsilon=0.47$, $p=0.24$].

Clenbuterol

One animal was excluded from all analyses due to a consistent high number of omissions during vehicle and drug treatments (>50 trials). The administration of the selective β_2 -adrenoceptor agonist clenbuterol reduced the percentage of premature responses [Fig. 5e; $F(3,42)=6.48$, $\varepsilon=0.73$, $p=0.004$], and further comparisons showed that all doses of clenbuterol decreased premature responding compared to vehicle (0.01 mg/kg, $p=0.036$; 0.03 mg/kg, $p=0.008$ and 0.1 mg/kg, $p=0.009$). Likewise, clenbuterol lengthened the latency to make a correct response [Fig. 5g; $F(3,42)=10.31$, $\varepsilon=0.81$, $p<0.001$] at the 0.1 mg/kg dose compared to the vehicle ($p<0.001$). Clenbuterol also increased the percentage of omissions [Fig. 5h; $F(3,42)=19.16$, $\varepsilon=0.38$, $p<0.001$] and this also only occurred at the highest dose of 0.1 mg/kg compared to the vehicle ($p=0.001$). Accurate choice was dose dependently improved by clenbuterol [Fig. 5f; $F(3,42)=6.35$, $p=0.001$], and both 0.03 and 0.1 mg/kg clenbuterol increased the percentage correct choice compared to vehicle ($p=0.002$ and $p=0.005$, respectively). The per-

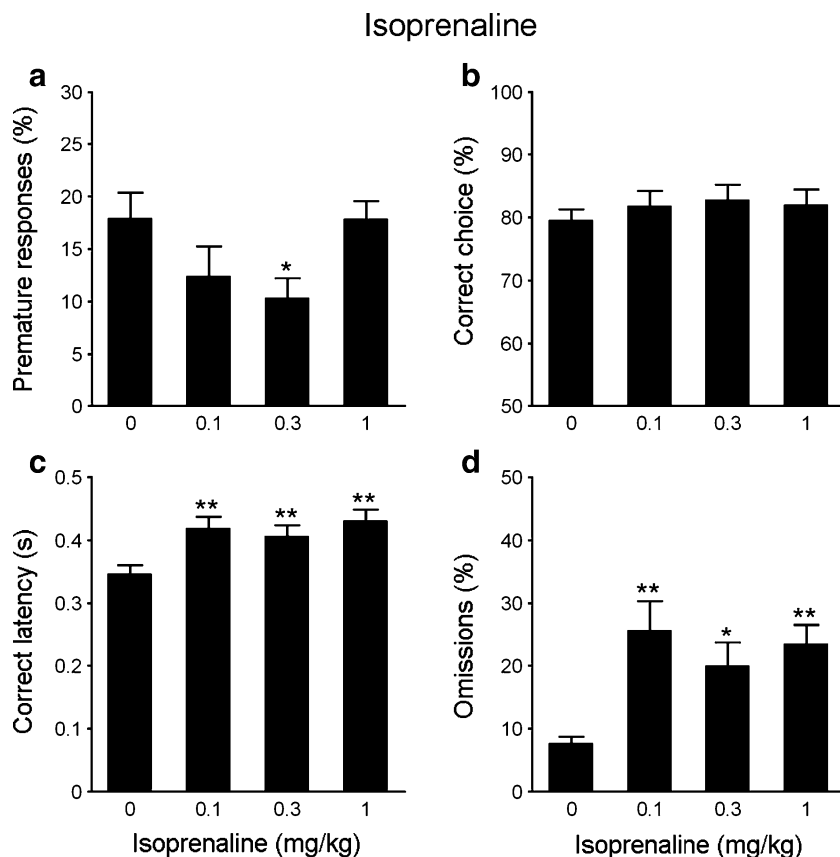
Fig. 3 The preferential α 1-adrenoceptor and α 2-adrenoceptor agonists phenylephrine and clonidine decrease the percentage premature responses (**a, e**), do not affect the percentage correct choice (**b, f**), and increase correct response latency (**c, g**) and the percentage omissions (**d, h**) in the 5CSRTT. All data are expressed as mean \pm SEM. * p <0.05 and ** p <0.005 compared to vehicle treatment



centage of perseverative responses after correct choice and the latency to collect food reward were not affected by

clenbuterol [Table 1; $F(3,42)=0.45, p=0.72$ and $F(3,42)=2.82, \epsilon=0.51, p=0.094$; respectively].

Fig. 4 The non-selective β -adrenoceptor agonist isoprenaline decreases the percentage premature responses (**a**), does not affect the percentage correct choice (**b**), and increases correct response latency (**c**) and percentage of omissions (**d**) in the 5CSRTT. All data are expressed as mean \pm SEM. * p <0.05 and ** p <0.005 compared to vehicle treatment



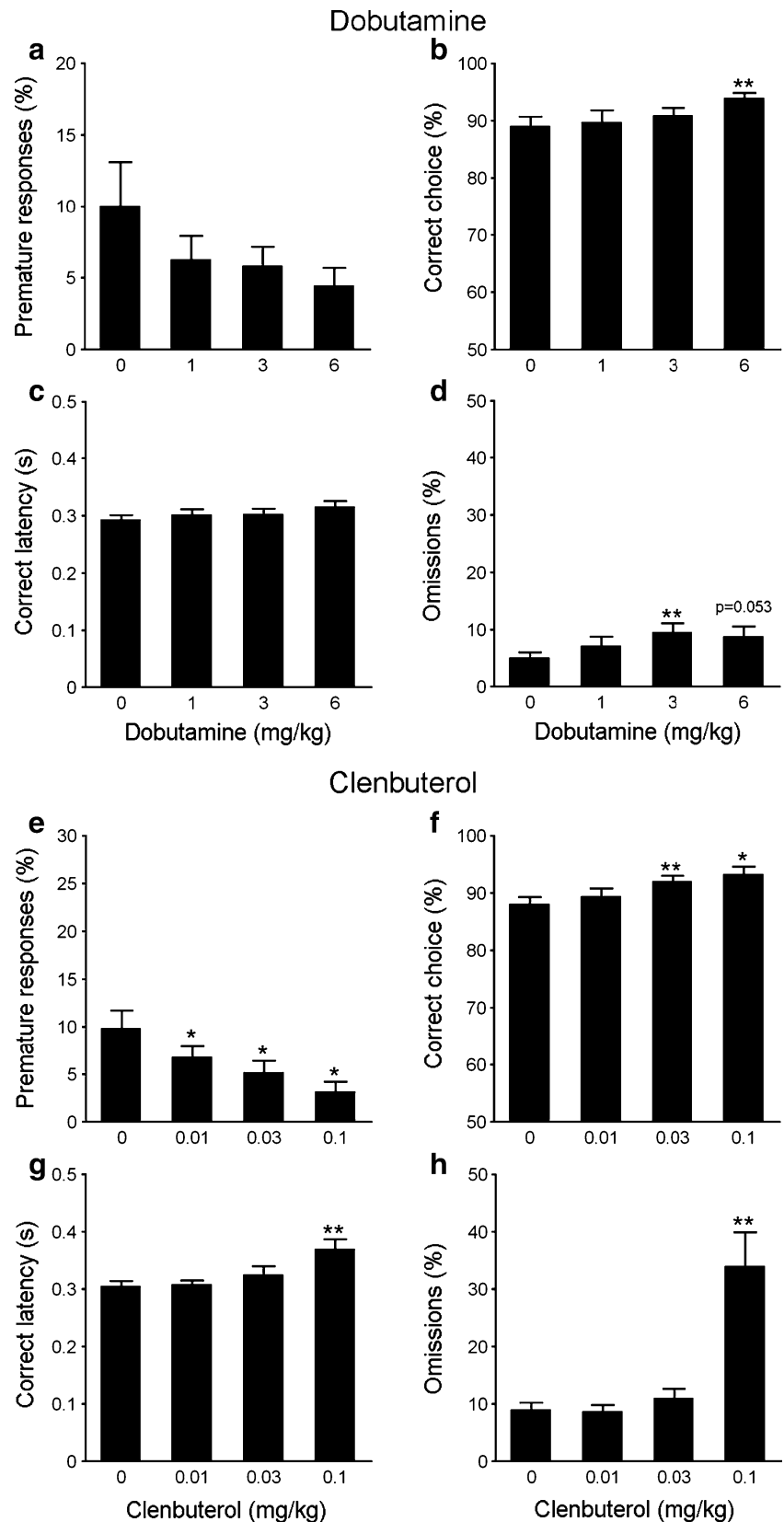
Discussion

The present data are consistent with a functional role of noradrenergic transmission in inhibitory response control processes. In particular, the NA reuptake inhibitor desipramine was found to improve inhibitory response control at a dose that did not affect somatomotor activity. Likewise, methylphenidate seemed to have a similar effect at a low dose, whereas opposite effects were found at higher doses that impaired inhibitory response control by increasing premature responding. Both the selective α 1-adrenoceptor and α 2-adrenoceptor agonists (phenylephrine and clonidine) and the non-selective β -adrenoceptor agonist (isoprenaline) tested in the present study were found to alter inhibitory control, but these effects were only observed at doses that simultaneously increased response latencies and omission rate. By contrast, the selective β 2-adrenoceptor agonist clenbuterol, and to a lesser extent the β 1-agonist dobutamine, had beneficial effects on inhibitory control and visuospatial attention at doses that did not alter other behavioural parameters in the task.

The current findings with methylphenidate confirm earlier data indicating that methylphenidate increases impulsivity in the 5CSRTT (Milstein et al. 2010; Navarra et al. 2008; Puumala et al. 1996; Van den Bergh et al. 2006). Thus, in the present study, oral administration of 10 mg/kg

methylphenidate also robustly increased premature responding. As methylphenidate increases monoamine neurotransmission by inhibiting the activity of monoamine transporter proteins (Rothman and Baumann 2003), it has been well established that methylphenidate enhances both dopaminergic and noradrenergic transmission in corticostriatal brain regions (Gerasimov et al. 2000; Kuczenski and Segal 1997). In support of this, a large body of evidence has demonstrated that elevating dopamine (DA) signalling by means of the psychostimulant amphetamine or the selective DA reuptake inhibitor GBR12909 robustly increases premature responding in the 5CSRTT (Cole and Robbins 1987; Harrison et al. 1997; Pattij et al. 2007; Van Gaalen et al. 2006a), possibly explaining the current observations with 10 mg/kg methylphenidate. By contrast, in the present study, a low oral dose of methylphenidate (1 mg/kg) tended to reduce the number of premature responses ($p=0.055$). Interestingly, comparable low doses of methylphenidate have been shown to preferentially increase the extracellular levels of NA over DA in the prefrontal cortex and simultaneously improve sustained attention and working memory (Berridge et al. 2006). This could explain the beneficial effect of the low dose methylphenidate on inhibitory control in the current study. Indeed, enhancing NA transmission by the NA reuptake inhibitor atomoxetine improves inhibitory response control

Fig. 5 Effects of the β_1 adrenoceptor agonist dobutamine and β_2 -adrenoceptor agonist clenbuterol on the percentage premature responses (**a, e**), percentage correct choice (**b, f**), correct response latency (**c, g**) and the percentage omissions (**d, h**) as measured in the 5CSRRT. Both dobutamine and clenbuterol improve visuospatial attention at doses that do not alter response latency or the percentage of omitted trials. In addition, clenbuterol exerts a beneficial effect on inhibitory response control by reducing the percentage premature responding. All data are expressed as mean \pm SEM. * p <0.05 and ** p <0.005 compared to vehicle treatment



both in humans (Chamberlain et al. 2009) and laboratory animals (Bari et al. 2009; Blondeau and Dellu-Hagedorn

2007; Paterson et al. 2011; Robinson et al. 2008). In keeping with these findings, the selective NA transporter

inhibitor desipramine also reduced the number of premature responses at 3 mg/kg without affecting other behavioural parameters in the 5CSRTT, although the effect size was smaller compared to the findings with atomoxetine in this same paradigm (Blondeau and Deltu-Hagedorn 2007; Paterson et al. 2011; Robinson et al. 2008). Collectively, these data thus confirm the beneficial effects of elevating NA transmission on inhibitory response control in addition to other executive functions such as attentional set-shifting, behavioural flexibility and working memory (Berridge et al. 2006; Lapid et al. 2007; Seu et al. 2009) and this could underlie the therapeutic efficacy of atomoxetine and methylphenidate.

Given the results obtained with methylphenidate and desipramine, subsequent experiments were aimed at further exploring the possible contribution of α -adrenoceptors and β -adrenoceptors to modulate inhibitory response control. In this regard, previous work in rats and monkeys have implicated prefrontal cortical α 2-adrenoceptor involvement in the beneficial effects of methylphenidate and atomoxetine on working memory (Arnsten and Dudley 2005; Gamo et al. 2010). To this aim, we tested the effects of phenylephrine, clonidine and isoprenaline. Whereas all of these compounds seemed effective in reducing premature responding, this only appeared to occur at doses that also strongly affected other behavioural parameters reflecting task performance, hampering a straightforward interpretation of these findings. Most prominently, the doses of these compounds reducing premature responding also increased the errors of omission and lengthened response latencies. These observations indicate that the effects on inhibitory response control may be secondary to general behavioural changes, e.g. somatomotor-suppressive effects or altered motivation. On the other hand, the observation that the highest dose isoprenaline increased the omissions and the response latencies but not premature responding might argue against such an interpretation. Our current findings are supported by previous studies, in which direct adrenoceptor agonists have been reported to lead to general behavioural alterations including lengthening of response latencies and increments in response omissions in instrumental behaviour (for example see, Jentsch et al. 2009; Mair et al. 2005; Marrs et al. 2005). More relevant to our findings, the α 2-adrenoceptor agonists dexmedetomidine and guanfacine were also found to decrease premature responding in the 5CSRTT at doses that simultaneously increased omission rates (Ruotsalainen et al. 1997; Sirvio et al. 1994) or lengthened latencies to collect food reward (Milstein et al. 2007). Thus, consistent with these observations, a similar behavioural profile was obtained with clonidine in the current study. Although we did not test the lower doses of clonidine, previous work employing such lower doses in a different instrumental behaviour task reveals that the therapeutic window of this compound is

narrow and associated with response rate suppressive effects (Dekeyne and Millan 2006).

The beneficial effects of α 2-adrenoceptor agonists such as clonidine and guanfacine on prefrontal cortical cognitive functions in preclinical as well as clinical models are thought to be primarily mediated through postsynaptic α 2-adrenoceptor activation in the prefrontal cortex (Arnsten 2000; Arnsten et al. 2007). By contrast, presynaptic α 2-adrenoceptor activation is well known to decrease NA transmission (for review see, Berridge and Waterhouse 2003). In addition, α 2-adrenoceptor agonists also have strong hypnotic/sedative effects that are presumably mediated in the basal forebrain, locus coeruleus and thalamus (e.g. Berridge and Foote 1996; Buzsaki et al. 1991; Mizobe et al. 1996). Since all compounds were administered peripherally, it is at present difficult to disentangle the effects of clonidine on prefrontal cortical cognitive function from its somatomotor effects as this would require intracranial administration approach. Thus, while clonidine seemed to improve inhibitory response control consistent with earlier data (Milstein et al. 2007; Ruotsalainen et al. 1997; Sirvio et al. 1994) and the clinical therapeutic efficacy of α 2-adrenoceptor agonists (Arnsten et al. 2007), central actions of clonidine on sedation/hypnosis are difficult to rule out. In contrast to the effects of clonidine on inhibitory response control, increasing activity at α 2-adrenoceptors did not improve visuospatial attention contrasting earlier findings (Berridge et al. 2006; Jentsch et al. 2009; Paine et al. 2007; Sagvolden 2006). However, in the current study, animals were tested under standard task conditions with presumably “optimal” levels of attentional performance and noradrenergic tone. In this regard, there are indications that the beneficial effects of an elevated noradrenergic tone might particularly become apparent under conditions of poor performance or lower baseline noradrenergic tone (Jentsch and Anzivino 2004; Jentsch et al. 2009; Milstein et al. 2007).

The effects of phenylephrine are partly in line with previous data demonstrating that the α 1-adrenoceptor agonist St-587 improved both inhibitory response control and visuospatial attention (Puumala et al. 1997). These beneficial effects of St-587 on visuospatial attention and not inhibitory response control could be antagonized by the α 1-adrenoceptor antagonist prazosin. This suggests particular involvement of these receptor subtypes in attention, for instance by their role in increasing vigilance (Sirvio and MacDonald 1999) and is consistent with the view that α 1-adrenoceptor activation enhances the signal-to-noise ratio and tunes processing of sensory information through subcortical and sensory cortical regions (for reviews see, Arnsten 2000; Berridge and Waterhouse 2003). Accordingly, phenylephrine improved accurate choice, albeit separate post hoc comparisons on the high-dose phenylephrine (3.0 mg/kg) failed to reach statistical significance ($p=0.063$). The effects of phenylephrine on

premature responding occurred in concert with effects on response latencies and omission rate and may therefore will be secondary to its effects on somatomotor activity.

In addition to the well-known involvement of β -adrenoceptors in memory consolidation processes (for review see, Sara 2009), until now few studies have examined the role of these receptors in executive cognitive functioning, namely working memory. Inasmuch one can draw conclusions from these initial studies, they suggest an opposing modulatory role of β 1-adrenoceptors and β 2-adrenoceptors in working memory. While a β 1-adrenoceptor agonist deteriorates working memory (Ramos et al. 2005), a β 2-adrenoceptor agonist was found to improve working memory performance (Ramos et al. 2008). Interestingly, recent work showed that the non-selective β -adrenoceptor antagonist propranolol attenuated the detrimental effects of methylphenidate on premature responding in the 5CSRTT (Milstein et al. 2010). This suggests that methylphenidate impairs inhibitory response control partly through β -adrenoceptor activation at a dose elevating both NA and DA transmission. To our knowledge, the present study is the first reporting on the behavioural effects of β -adrenoceptor agonists in the 5CSRTT.

Whereas the non-selective β -adrenoceptor agonist isoprenaline did reduce premature responding at 0.3 mg/kg, this same dose simultaneously increased omission rate and response latencies comparable to the effects of the α -adrenoceptor agonists hampering a straightforward interpretation of these data. Importantly, the present data indicate that clenbuterol, a preferential β 2-adrenoceptor agonist with approximately tenfold higher affinity for β 2-adrenoceptors over β 1-adrenoceptors (Baker 2010), dose dependently decreased premature responding at doses that did not significantly alter the measures of somatomotor activity. Moreover, in contrast to the high-dose clenbuterol, the intermediate 0.03 mg/kg dose improved visuospatial attention by increasing accurate choice without simultaneous deteriorative effects on omissions or response latencies (Fig. 5f). Thus, in extension to beneficial effects on working memory (Ramos et al. 2008), enhancing the tone at β 2-adrenoceptors also improved inhibitory response control. An important point of consideration is that in addition to the beneficial behavioural effects of particularly clenbuterol observed here, β 2-adrenoceptors and also β 1-adrenoceptors are heavily implicated in cardiac function (Brodde and Michel 1999). Indeed, clenbuterol has been shown to exert myotoxic and potent haemodynamic effects in rats starting at doses of 0.1 mg/kg (Burniston et al. 2002; Sillence et al. 1993). Although in the current study, lower doses of clenbuterol were employed (0.01 and 0.03 mg/kg) we cannot entirely rule out that these same doses affected cardiac function.

Similar to clenbuterol, the β 1-adrenoceptor agonist dobutamine increased visuospatial attention. Nonetheless, this effect was only observed at the highest dose of 6.0 mg/kg.

Although dobutamine has an approximately tenfold higher affinity for β 1-adrenoceptors over β 2-adrenoceptors (Williams and Bishop 1981), it is possible that at this dose the beneficial effects of this drug on visuospatial attention are mediated through β 2-adrenoceptor activation (Baker 2010; Makhay and O'Donnell 1999). At the same time, it should be noted that these beneficial effects on attention were not accompanied by significant improvements of inhibitory control. Thus, whereas β 1-adrenoceptor activation was previously found to impair working memory (Ramos et al. 2005), we did not find evidence for similar effects on attention and inhibitory response control. Collectively, the observation that dobutamine and clenbuterol improved visuospatial attention is consonant with the notion that similar to α 1-adrenoceptor activation (see above), enhancing β -adrenoceptor activity tunes information processing presumably via subcortical and sensory cortical mechanisms (Arnsten 2000; Berridge and Waterhouse 2003).

Our understanding of the contribution of different β -adrenoceptors in inhibitory response control is limited as yet. Altogether, the present experiments with β -adrenoceptor agonists further strengthen the notion of β 2-adrenoceptor and to a lesser extent β 1-adrenoceptor improvement of prefrontal executive function and in particular inhibitory response control and visuospatial attention. In this respect, it is of interest to note that intracranial clenbuterol injections into the prefrontal cortex ameliorated working memory performance in rats implicating a functional role for β 2-adrenoceptors in this brain region in prefrontal function (Ramos et al. 2008). The current observations with β -adrenoceptor agonists are somewhat at odds with the single other study in this area reporting that propranolol attenuates the detrimental effects of methylphenidate on inhibitory response control (Milstein et al. 2010). Evidence from that study suggests subcortical β -adrenoceptor modulation of DA in the effects of methylphenidate, since cortical NA depletion did not attenuate the effects methylphenidate. Clearly, future studies including the effects of selective β -adrenoceptor antagonists and employing intracranial approaches are warranted to further unravel this.

In summary, the present data extend previous findings and show that indirect as well as direct adrenoceptor agonists improve inhibitory response control in the 5CSRTT. Although the observed inhibitory effects of most direct α -adrenoceptor and β -adrenoceptor agonists on impulsive action cannot be interpreted unambiguously, our findings with the β 2-adrenoceptor agonist clenbuterol—and to a lesser extent the β 1-adrenoceptor agonist dobutamine—are consistent with a prominent role of noradrenergic neurotransmission in inhibitory response control. This corroborates the notion that the central noradrenergic system is involved in optimizing behavioural responses including executive cognitive functioning (for reviews, see,

e.g. Aston-Jones and Cohen 2005; Sara 2009) and particularly points to a role of β 2-adrenoceptors therein.

Acknowledgements The authors wish to thank Mieke C.W. Janssen for excellent technical assistance.

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