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ORIGINAL INVESTIGATION

α_2- and β-adrenoceptors involvement in nortriptyline modulation of auditory sustained attention and impulsivity

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Abstract
Rationale The catecholamine innervation of the prefrontal cortex controls attentional focus and inhibits inappropriate behavioral responses. The mechanism of action with which norepinephrine (NE) reuptake inhibitors modulate these cognitive functions has not been fully investigated.
Objective We investigated the effect of systemic administration of the NE reuptake blocker nortriptyline (NT) on attention and impulsivity using an auditory sustained attention task. The task was designed to assess impulsive behavior and the maintenance of attentional focus to an auditory stimulus presented at interresponse time durations (IRT) between 5 and 80 s.
Results NT (2.0 but not 3.0 mg/kg) improved sustained attention and decreased the percentage of premature responses without changing their latency. To better understand the adrenergic component of NT action, we tested the effect of noradrenergic receptor antagonists alone or together with NT. The α_2-receptor antagonist yohimbine, the α_1-receptor antagonist prazosin, or the β-receptor antagonist propranolol alone did not significantly affect attentive performance or premature responses. However, the beneficial effects of NT on sustained attention and premature responses were attenuated by pretreatment with either yohimbine or propranolol. On the contrary, prazosin did not affect the NT-mediated improvement in sustained attention.
Conclusions We conclude that sustained attention displays an inverse U-shaped dependence on NT, mediated—at least in part—by α_2- and β-adrenoceptors. We speculate that low doses of NT improve performance by maximizing the phasic release of NE, while higher doses of NT would elevate tonic levels of NE, thus producing suboptimal levels of phasically released NE.

Keywords Norepinephrine · Nortriptyline · Auditory · Sustained attention · Impulsivity · Response latency · Rat · Operant chamber · Alpha-2 adrenoceptors · Beta adrenoceptors

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by impaired behavioral inhibition (Barkley 1997; Brennan and Arnsten 2008), impulsive decision making, impaired working memory with underlying distractibility, and hyperactivity (Arnsten et al. 1996; Sagvolden 2006; Brennan and Arnsten 2008; Heal et al. 2008) along with severe deficits in executive function (Barkley 1997; Lovejoy et al. 1999; Sonuga-Barke 2005). Importantly, patients with ADHD or prefrontal lesions show poor performance in working memory and behavioral inhibition tasks (Arnsten and Li 2005). Adrenergic mechanisms play a critical role in the onset of attention deficit in patients with ADHD (Pliszka et al. 1996; Biederman and Spencer 1999).

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In rodents, dysregulation of the central noradrenergic (NE) system impairs attention performance, by increasing distractibility, motor hyperactivity, and impulsivity (Carli et al. 1983; Biederman and Spencer 1999; del Campo et al. 2011). In most mammalian species studied so far, NE neurons from the locus coeruleus (LC) (Dahlström and Fuxe 1964) project their axons to attention-processing areas like the prefrontal cortex (PFC) (Arnsten and Goldman-Rakic 1984) and are in turn stimulated by glutamatergic projections from the medial PFC itself (Jodo and Aston-Jones 1997). Since optimal adrenergic transmission facilitates cognitive processes like attention, learning, and working memory, whereas NE depletion results in attentive and working memory deficits (Berridge and Waterhouse 2003; Ramos and Arnsten 2007; Milstein et al. 2007; Tait et al. 2007), NE is a likely candidate neurotransmitter for the control and coordination of cognitive processes (Brennan and Arnsten 2008). While it is well accepted that a dysregulation of NE-LC function might underlie not only ADHD, but also other psychiatric conditions such as schizophrenia, drug addiction, and depression (Arnsten et al. 1996; Arnsten 1998), the mechanisms and membrane receptors responsible for NE control of attention and impulsivity are less clear.

The treatment of attention deficit disorders with stimulants like methylphenidate and amphetamine mixtures raises multiple concerns due also to their addictive profile (Wong et al. 2011; Zhu et al. 2011). The utilization of new generation drugs did not substantially enhance the efficacy profile also due to serious side effects common to all monoamine reuptake blockers. Tricyclics have been successfully used in the treatment of depression during the past two decades, while their attention-enhancer properties have largely been overlooked. Many detrimental properties of tricyclics derive from their antiserotoninergic and antimuscarinic profile (Merriam 2000).

Nortriptyline (NT) is an FDA-approved tricyclic antidepressant with high affinity for the NE transporter and a relatively low binding for serotoninergic and muscarinic sites, whose mechanism of action as an attention-enhancer has not been fully investigated. In the present study, we sought to evaluate the effects and adrenergic components of NT administration on the time span of attention and impulsivity (Merriam 2000). We used a modified version of the five-choice serial reaction time test (5-CSRTT, a test for assessing the behavioral symptoms of ADHD), developed by Robbins (2002). Our version uses auditory stimuli instead of the visual ones used in the 5-CSRTT, to quantify sustained attention and impulsivity under variable intertrial conditions. Also, contrary to the 5-CSRTT, longer interresponse time durations were used to quantify the attention time span of the compounds used. We found that a low—but not a high—dose of NT improves sustained attention and decreases premature responses without changing their latency, and that α_2- and β-adrenergic blockers hamper the effect of NT.

Method

Animals Male Sprague–Dawley rats (Charles River, USA), weighing 250–300 g at the beginning of the experiment were used. The animals were housed three per cage and maintained on a 12-h light/dark cycle schedule. Rats were food restricted and kept around 85% of their natural body weight throughout the experiment using standard rat chow. Water was available ad libitum during the entire study. All animals performed at a stable baseline level before they were given drug treatments. All methods and procedures were in accordance with guidelines set by National Institutes of Health for Ethical Treatment of Animals and received the approval of the University Committee on Animal Research at the University of Texas at Dallas (IACUC # 08-01).

Drugs Nortriptyline was obtained from Sigma (St. Louis, MO, USA), and yohimbine, propranolol, and prazosin were obtained from Tocris (Ellisville, MO, USA). All drugs were dissolved in 0.9% NaCl and in a volume of 1 ml/kg bodyweight and administered intraperitoneally (i.p.). All the drugs were administered 30 min prior to testing session. Optimal doses were determined based on previous studies (Dekeyne et al. 2002; Haapalinna et al. 1997; Mishima et al. 2002; Zhang et al. 2009) and a limited number of scout experiments. Each drug trial was the average of five measurements on the same animal, tested no more than once a day, with the number of animals for each experiment specified in "Results." About one third of the animals were used multiple times, for up to three injections (including vehicle), with at least 1-week interval between each injection, with randomized drug and dose administration to eliminate bias. During this interval, rats were continued to be trained to ensure they were performing at a steady baseline level and that proper washout of the drug has occurred.

Apparatus Experiments were conducted in operant conditioning boxes placed in sound-attenuated chambers (ENV-018 V; 63.5×63.5×40.64 cm; Med Associates, Vermont, USA). Each box was equipped with a food pellet receptacle (ENV-203; Med Associates, Vermont, USA) and a pellet dispenser, which delivered 45-mg food pellets. A retractable lever (ENV-112 cm; Med Associates, Vermont, USA) was located on the left of the receptacle positioned 7.62 cm above the grid floor. Water was available through the spout of a water bottle located on the right of the pellet receptacle. A small general purpose loudspeaker was placed behind the lever. The system was controlled using a personal computer

through a MATLAB program connected to the peripherals by a digital controller (USB 1024LS; Measurement Computing, MA, USA).

Habituation Rats were trained to press the lever, with the lever positioned 7.5 cm above the grid floor, for obtaining food pellets (Sessions et al. 1976; Cole and Michaleski 1986). Habituation took place once a day, five times a week (Monday–Friday). Once the rats ate all the food pellets within a session, which lasted for 60 min, training proceeded to the next stage.

Sustained attention training

Preliminary training The rats were trained to respond to each lever presentation only after the delivery of a target sound (0.25 s at 10,000 Hz, 80–83 dB) before the withdrawal of the lever and were rewarded by a food pellet (45 mg). Levers were withdrawn if there was a response before the sound, followed by a time-out period (longer wait time before the generation of next trial) with no food pellet delivery. There was also no food reward if the rat did not press the lever at all. Animals were trained until they achieved an accuracy level between 70% and 80% within a 60-min daily session for at least five sessions. In the next phase, the target sound was fixed at 5-s interval after the lever was drawn out. A window of 3 s (maximum response time, MaxRT) was provided for lever press, after the stimulus was presented. The fixed interval was increased every time the rats performed at a success level between 70% and 80% at each stage. Correspondingly, the MaxRT was reduced gradually to 1 s to reinforce attention.

Test procedure Our test procedure was designed, according to a definition of sustained attention (Bushnell 1998; Mirsky and Duncan 2001), and using an auditory task with slightly longer intervals than that used in the 5-CSRTT, which has been extensively used as an assay in attention studies.

A similar two-choice version of this task has also been extensively used to test the effect of other neurotransmitter systems on attention (Grilly and Gowans 1988; McGaughy and Sarter 1995). In the final phase of the sustained attention protocol, the testing session was divided into 5 blocks of 100 trials for 60 min. Each block consisted of presentation of the target sound (80–83 dB over a ~60–63-dB background) with interresponse time durations (IRT) of 5, 10, 20, 40, and 80 s. Equal number of each of the five IRTs were presented in random sequence during the 100-trial session. The intertrial interval (separation between consecutive trials, ITI) was fixed at 5 s irrespective of when the lever was pressed. The test session ended when either the 60 min or 100 trials had been completed (Fig. 1).

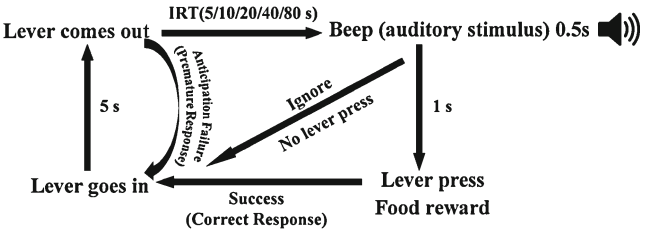

Fig. 1 Schematic representation of sustained attention protocol. Testing session consisted of 5 blocks of 20 trials each for 60 min. Each block consisted of presentation of the target sound after an interresponse time (*IRT*) selected randomly with a flat distribution among 5, 10, 20, 40, and 80 s. Animals had a 1-s time window to lower the lever after the tone. In case of premature or absence of response the lever was withdrawn with no food reward. The intertrial interval (separation between consecutive trials, ITI) was fixed at 5 s irrespective of when the lever was pressed. The test session ended when either the 60 min or 100 trials had been completed

Data analysis Similar to the 5-CSRTT, a response or lever press before the presentation of the target sound (auditory stimulus) was recorded as *anticipation failure* (premature responses). Failure to press the lever at all, in any particular trial, was recorded as *ignore. Successful* trials (correct responses) were lever presses after delivery of the target sound, before withdrawal of the lever, and were rewarded by the delivery of a food pellet.

The percentage of premature, correct, and ignore responses for the total number of trials in every IRT was calculated and averaged for every animal. Analysis of the percentage of premature, correct, and ignore responses was performed separately. We used one-way ANOVA to assess statistical significance of the different treatments at each IRT, followed by Tukey HSD comparison post-hoc test. Student's *t*-test was used to determine statistical significance between different conditions for the sustained attention time span and hold-off time. Repeated measurements were used whenever applicable. A criterion of $p<0.05$ was accepted as indicative of significant difference.

Results

Correct responses

Treatment with i.p. administration of vehicle or with two different doses of NT (2 and 3 mg/kg) revealed significant effects of treatment at all IRTs except 5 and 10 s, with one-way ANOVA analysis. A post-hoc analysis revealed a significant effect ($p<0.05$) of the lower dose of NT (2.0 mg/kg) compared to vehicle on correct responses at all IRTs except 5 and 10 s. However, a higher concentration of NT (3.0 mg/kg) produced no significant changes on the percentage of correct responses at any IRT (Fig. 2a).

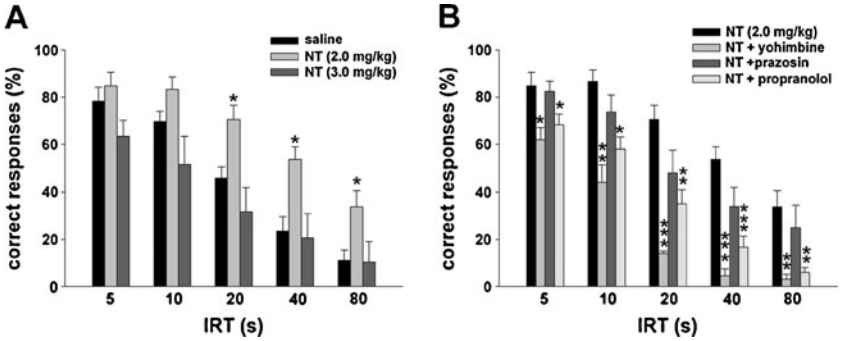

Fig. 2 Effects of NE drugs on correct responses. **a** NT increases the number of correct responses at 2 mg/kg at all IRTs except at 5 and 10 s (n=8), while at 3 mg/kg does not affect performance (n=8). **b** Coadministration of NT with either yohimbine or propranolol produces a significant decrease in the percent of correct responses for all IRTs (n=8, each). Coadministration of NT with prazosin does not produce any significant effects on any IRT (n=8). *p<0.05; **p<0.01; ***p<0.001, significance levels

As a control experiment, as well as to assess a possible role of tonic adrenoceptors activation, we tested the effect of each noradrenergic blocker alone. The administration of the α_2-receptor antagonist yohimbine (2.0 mg/kg), of the α_1-receptor antagonist, prazosin (1.0 mg/kg), or of the β-receptor antagonist propranolol (2.0 mg/kg) failed to produce any significant changes on sustained attention.

In order to assess a possible role of adrenergic receptors in the behavioral properties of NT, we injected noradrenergic blockers together with the attention-enhancing dose of NT (2 mg/kg). Treatment with NT alone or in combination with adrenergic blockers revealed significant effects at all IRTs. A post-hoc analysis indicated that coadministration of NT (2.0 mg/kg) and yohimbine (2.0 mg/kg) significantly reduced the percent of correct responses at all IRTs (p<0.05, n=8, Fig. 2b), while coadministration of prazosin (1.0 mg/kg) with NT did not affect performance and produced no significant changes in correct responses (Fig. 2b). Finally, coinjection of propranolol (2.0 mg/kg) along with NT (2.0 mg/kg) significantly reduced the percent of correct responses at all IRTs (Fig. 2b).

Premature responses

One assessment of impulsive behavior was taken as the percentage of premature responses before presentation of the auditory stimulus (see the "Method" section). In general, as expected, the percent of premature responses increased at longer IRTs. Treatment with vehicle or with the two doses of NT revealed significant effects of treatment at all IRTs except 5 and 10 s, with one-way ANOVA analysis. Complementing the effect on the correct responses, post-hoc analysis showed that 2.0 mg/kg NT resulted in a significant decrease (p<0.05, n=8) in the percent of premature responses for all IRTs except 5 and 10 s (Fig. 3a), while at a higher dose (3.0 mg/kg) NT failed to produce any effects (Fig. 3a).

Administration of yohimbine, prazosin, or propranolol alone did not have any effect on the percent of premature responses for any IRT. On the contrary, treatment with NT alone or in combination with adrenergic blockers revealed significant effects on premature response at all IRTs except in 5 s. Post-hoc analysis showed that coadministration of NT with yohimbine or propranolol increased the percent of premature responses compared

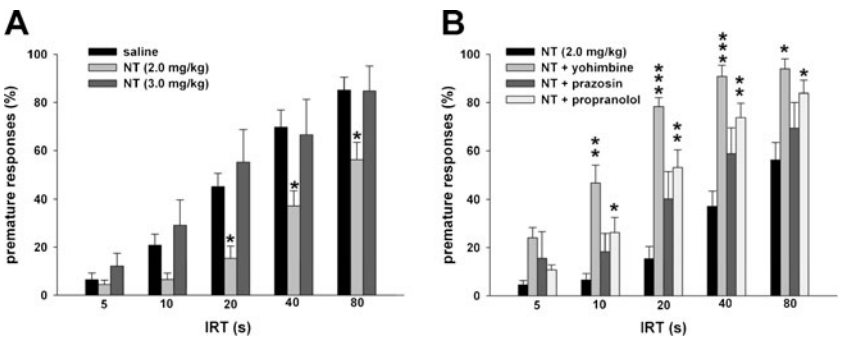

Fig. 3 Effects of NE drugs on impulsivity. **a** NT (2 mg/kg) significantly decreases the number of premature responses at all IRTs except at 5 and 10 s (n=8), indicating a decrease in impulsivity. No change is induced by administration of 3 mg/kg NT (n=8). **b** Coadministration of NT and yohimbine or propranolol increases the percent of premature responses at all IRTs except at 5 s (n=8, each). Coadministration of NT and prazosin does not affect the percent of premature responses on any IRT (n=8). *p<0.05, **p<0.01, and ***p<0.001

with NT alone for all IRTs except in 5 s ($p<0.05$, for yohimbine, $p<0.05$, for propranolol, $n=8$ for each experiment, Fig. 3b), while, simultaneous administration of prazosin and NT produced no significant changes in the percent of premature responses compared with NT alone (Fig. 3b).

An independent assessment of impulsivity was given by the latency of premature responses, for each IRT. Administration of NT 2 or 3 mg/kg failed to affect the premature response latency for all IRTs, as shown in Table 1. Premature response latency was unaffected by all adrenergic antagonists tested, at all IRTs.

Ignore responses

Failure to make a response on any trial was recorded as "ignore" (see the "Method" section). For all trials, the percent of ignore was always less than 5%. Administration of either doses of nortriptyline (2.0 and 3.0 mg/kg) did not produce any significant changes in the percent of ignore responses when compared to vehicle. Similarly, coadministration of nortriptyline with adrenergic blockers did not significantly affect the percent of ignore responses.

Time course of sustained attention and impulsivity

The percentage of correct performance and of premature responses as a function of the IRTs suitably fitted single exponential curves (example in Fig. 4a, b for correct and premature responses respectively for saline and NT 2 mg/kg). We arbitrarily defined as the *sustained attention time span*, the τ of the exponential fit using the following expression:

$$\text{Correct performance} = f(\Delta t; A, \tau_s) = A \cdot \exp[-\Delta t/\tau_s]$$

where, A is the maximum performance, τ_s is a sustained attention time span, and Δt is the independent time variable (IRT=Δt=5, 10, 20, 40, and 80 s)

Similarly, we defined a *hold-off time* with the help of the following expressions:

$$\text{Percentage premature responses} = f(\Delta t; A, \tau_i) = A(1 - \exp[-\Delta t/\tau_i])$$

where, A is a maximum percentage premature responses, τ_i is a hold-off time, and Δt is still the independent time variable (Δt=5, 10, 20, 40, and 80s).

A least square algorithm was used to determine the optimal parameters. Administration of NT (2.0 mg/kg) produced a significant increase in sustained attention span from τ_s=25.15±4.19 s in control to τ_s=60.41±8.41 s (Student's t test, $p<0.01$, $df=7$; $n=8$). Administration of NT (2.0 mg/kg) also prolonged the hold-off time from τ_i= 28.03±3.92 s in control to τ_i=80.57±10.98 s (Student's t test, $p<0.001$, $df=7$; $n=8$ rats). We summarized the corresponding results in Table 2.

Discussion

Our results show for the first time that the NE reuptake blocker NT approximately doubles the span of auditory attention and decreases premature responses, in an α_2- and β-(but not α_1-) adrenoceptors-dependent manner.

Inverse U-shaped dependence of performance on NT

The LC-NE system is known to play an important role in the regulation of cognitive functions including sustained attention, impulse control, and voluntary behavior (Dalley et al. 2004; Arnsten and Li 2005). NT is known to decrease NE reuptake by directly blocking the NE transporter at noradrenergic terminals (Schubert et al. 1970; Frazer 2001). Interestingly, NT improved attention and decreased premature response at a dose of 2.0 mg/kg, yet, failed to produce similar effects at a higher dose of 3.0 mg/kg. This result was unlikely due to the design of the experiment, in which doses and drug administration were randomized, or to the

Table 1 Impulsivity: latency of premature responses

Treatment	5 s	10 s	20 s	40 s	80 s	n
Saline	2.7±0.2	5.5±0.5	10.0±0.8	16.7±1.4	25.0±2.9	8
Nortriptyline (2.0 mg/kg)	2.3±0.2	5.4±0.6	11.2±1.0	19.7±2.7	31.2±4.2	8
Nortriptyline (3.0 mg/kg)	2.3±0.4	4.4±0.8	10.8±1.3	16.0±2.0	20.3±5.3	8
Yohimbine	3.0±0.1	5.2±0.1	7.7±1.1	10.4±1.9	14.7±0.7	5
Prazosin	2.6±0.6	4.5±1.2	10.5±1.9	16.1±4.0	17.3±3.9	5
Propranolol	2.9±0.3	5.4±0.2	8.6±1.0	12.3±1.8	14.8±4.6	5

The latency of premature responses was calculated as the time between lever presentation and lever presses occurred before the delivery of the auditory cue. Averages are calculated for each IRT. None of the drugs used, changed the latency of premature responses at any IRT (unpaired Student's t-test)

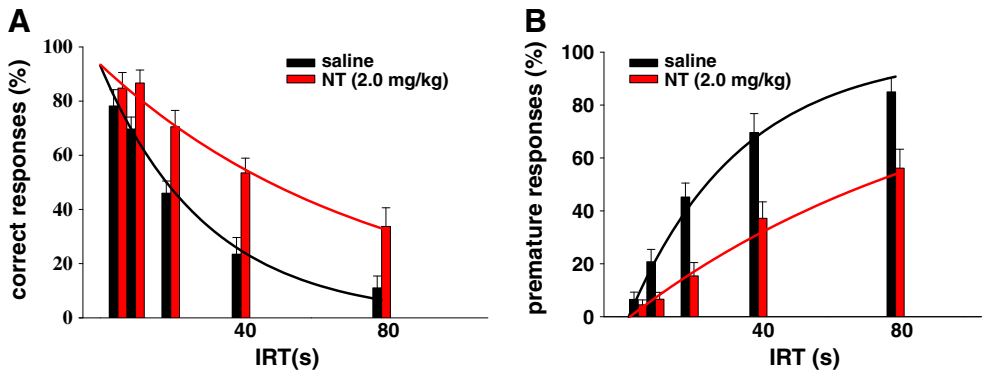

Fig. 4 NT prolongs time constants for sustained attention and impulsivity. **a** The experimental percentage success of the sustained attention task as a function of the IRT fits an exponential decay curve (continuous lines) describing the percentage success rate as (percent correct response)=constant×$e^{-(IRT/\tau)}$. Values of the corresponding time constants (τ) are reported in Table 2. **b** Impulsivity was measured as the time constant from the expression=constant×$(1-e^{-(IRT/\tau)})$. Compare with data in Table 2

activation of a startle response, which is evoked by 10 dB louder stimuli (Floody and Kilgard 2007; Dagnino-Subiabre et al. 2009), while 80–85-dB sounds as used in our experiment evokes a non-startle response (Valsamis and Schmid 2011). The dependence on NT dose is described by a Yerkes-Dodson inverted U-shaped relationship, consistent with a performance correlating with the *phasic* release of NE. In particular, a low dose of NT might optimize the phasic release of NE, at an intermediate level of LC activity, while a higher dose of NT could *increase tonic* but *impair phasic* release of NE (Aston-Jones et al. 1999; Aston-Jones et al. 2007), bringing performance levels to or below baseline. In line with this interpretation, low doses of stimulants like methylphenidate, which blocks the reuptake of NE and other neuromodulators, have been shown to improve cognitive performance in rats by preserving the phasic discharge and producing only a moderate suppression of tonic LC discharge activity (Devilbiss and Berridge 2006).

Table 2 Time span for sustained attention and impulsivity

Treatment	τ_s (s) (sustained attention span)	τ_i (s) (hold-off time)
Saline	25.1±4.2	28.0±3.9
NT (2 mg/kg)	60.4±8.4**	80.6±11.0***
NT (3 mg/kg)	27.3±4.9	37.2±10.5
NT + yohimbine vs. NT	9.3±2.3***	16.5±4.7***
NT + prazosin vs. NT	40.4±12.7	41.7±20.6
NT + propranolol vs. NT	31.4±3.5**	37.3±4.9***

τ_s and τ_i (left and right columns, respectively), defined as in Fig. 4, represent the duration of sustained attention and impulsivity derived from exponential fits with experimental data using a least square algorithm

*p<0.05; **p<0.01; ***p<0.001, significant differences with saline injections; Student's t-test, df=7, n=8

Our results are in agreement with several previous studies indicating that NE reuptake inhibitors including NT, desipramine, reboxetine, or atomoxetine improve performance in attention tasks only at intermediate but not high doses (O'Donnell and Seiden 1983; Dekeyne et al. 2002; Navarra et al. 2008; Gamo et al. 2010). NT has also been proven to be effective in reducing the symptoms in children with ADHD (Prince et al. 2000), associated with some minor side effects (Wilens et al. 1993; Prince et al. 2000).

Involvement of adrenergic receptors

The absence of behavioral effects following the administration of any of the adrenoceptor blockers suggests that in basal conditions NE does not exert a critical role in the task. On the contrary, the behavioral performance at or below baseline after the coadministration of the effective dose of NT together with yohimbine or propranolol indicates that the effects of NT are mediated, at least in part, by either or both α_2 and/or β, but not α_1-adrenoceptors. α_1-Adrenoceptors probably do not play a major role in sustained attention, as indicated by the absence of any effects on performance or impulsivity following the administration of the α_1-adrenergic receptor antagonist prazosin by itself and by its failure to affect the NT-induced attention improvement. Prazosin alone does not affect premature and correct responses in 5-CSRTT, although it reduces a reboxetine-induced increase in accuracy but not the corresponding decrease in impulsivity (Liu et al. 2009). Other studies also showed that prazosin, alone, does not change impulsive behavior in rodents (Koskinen et al. 2003; Bruno and Hess 2006), but, similar to our results, does not affect impulsivity when administered with the NE reuptake blocker methylphenidate (Milstein et al. 2008). This body of literature generally corroborates our results suggesting a modest role of α_1-adrenoceptors in the modulation of attention under normal conditions.

α_2-Receptors

The early discovery that α_2-adrenoceptor agonists or antagonists respectively decrease or increase the release of NE (Taube et al. 1977; Dubocovich 1984) initially suggested their inhibitory function in presynaptic terminals (Dubocovich 1984). Later studies though revealed their widespread cortical distribution in different synaptic sites (Aoki et al. 1998). Activation of postsynaptic α_2-receptors enhances PFC function and, under optimal conditions, mediates attention and working memory in the same brain area (Arnsten and Goldman-Rakic 1985; Franowicz and Arnsten 1998; Ramos and Arnsten 2007).

The yohimbine sensitivity of the NT-induced performance increase, and its failure to affect performance per se, suggests the involvement of postsynaptic α_2-receptors in sustained attention. Our results are consistent with the effects of idazoxan, another α_2-adrenergic receptor antagonist which, when applied alone, does not affect performance, but antagonizes the effects of the NE reuptake blockers desipramine (Zhang et al. 2009) and atomoxetine, (Gamo et al. 2010). Regardless of the cellular interpretation, our data indicate that the mechanisms of action of NT and yohimbine interfere with each other. We cannot exclude complex interactions like an inadequate refilling of synaptic vesicles in adrenergic terminals overwhelmed by simultaneous blockage of the NE reuptaker and of presynaptic α_2-autoreceptors.

β-Receptors

Our data showed that the administration of propranolol alone did not affect performance or impulsivity. A similar result was reported by Bruno and Hess (2006) on an impulsivity assay in an ADHD model (*coloboma* mice), and in a delayed response task propranolol also failed to affect performance (Arnsten and Goldman-Rakic 1985; Li and Mei 1994). On the contrary, the coadministration of propranolol significantly reduced the efficacy of NT on performance, indicating a role for β-adrenoceptors in sustained attention. Our results are consistent with a report of the involvement of β receptors—along with α_2-receptors—on an attention task in the 5-CSRTT (Pattij et al. 2011) and corroborates numerous previous studies supporting a role for β-receptors in cognitive flexibility (Pitman et al. 2002; Vaiva et al. 2003; Alexander et al. 2007; Donovan 2010).

Effect of NT on impulsivity

We evaluated impulsivity with two separate assessments: the percentage of the premature responses and their latencies. Temporal analysis of the percentage of premature responses at different IRTs clearly showed that the optimal dose of NT is also effective in decreasing impulsivity, producing longer values for τ_i. However, the analysis of the latencies for the premature responses—which can be considered an independent assessment of impulsivity—did not show any effect of NT, nor of any of the adrenergic blockers tested, suggesting the possibility that the NT-dependent increase in performance is not necessarily caused by a change in impulsivity. This interpretation is in partial agreement with the observations that adrenergic blockers do not vary motor activity in control animals (Bruno and Hess 2006), while the increase in attention co-occurring with stimulants is not only not associated with a decrease in impulsivity but even with its increase (Navarra et al. 2008).

Conclusions

Our study showed that NT produces an inverted U-shape profile of attentive performance, with an effective dose that significantly improved the span of attention in an auditory attention task. Pharmacological tests further suggested the involvement of both α_2- and β- but not α_1-adrenoceptors in the NT modulation. Our data suggest that NT is a potentially valuable pharmacological tool among NE reuptake inhibitors, particularly in the improvement of attention and inhibitory control in depressed patients with attention impairments.

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