Neuropharmacology 62 (2012) 2178–2183

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

α-Adrenergic receptors in auditory cue detection: α_2 receptor blockade suppresses false alarm responding in the rat

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ARTICLE INFO

Article history:
Received 14 December 2011
Accepted 22 December 2011

Keywords:
Sustained attention
Vigilance
Selective attention
α1
Alertness

ABSTRACT

Numerous studies have suggested a facilitatory role of the noradrenergic system in attention. Cognitive functions relating to attentive states—arousal, motivation, behavioral flexibility, and working memory—are enhanced by norepinephrine release throughout the brain. The present study addresses the role of the adrenergic system on stimulus validity and sustained attention within the auditory system. We examined the effects of adrenoceptor stimulation via systemic injection of α1 and α2-adrenoceptor antagonist and agonist drugs, prazosin (1 mg/kg), phenylephrine (0.1 mg/kg), yohimbine (1 mg/kg), and clonidine (0.0375 mg/kg), respectively. Our results indicate that α1-adrenergic stimulation is ineffective in modulating the biological assessment of auditory signal validity in the non-stressed rat, while α2-adrenoceptor antagonist and agonist drugs were effective in modulating both accuracy and response latencies in the habituated animal. Remarkably, blockade of α2-adrenoceptors significantly improved the animal's ability to correctly reject non-signal events. These findings indicate not only a state dependent noradrenergic component of auditory attentional processing, but a potential therapeutic use for drugs targeting norepinephrine release in neurological disorders ranging from Alzheimer's disease to schizophrenia.

1. Introduction

Activation of the noradrenergic system is known to augment attentional processes, specifically through simultaneous enhancement of sensory inputs and inhibition of background activity (Harley, 1987). Noradrenergic (NA) projections from locus coeruleus (LC) innervate the spinal cord, brain stem, amygdala, cerebellum, hypothalamus, and thalamic relay nuclei, as well as the inferior parietal cortex, temporo-parietal junction, and prefrontal cortex (Levitt et al., 1984). These far-reaching projections prime the brain for activation of target circuits involved in arousal states, learning and memory, vigilance, and attention (Quartermain et al., 1988; Aston-Jones et al., 1991; Woodward et al., 1991; Haapalinna et al., 1997; Paus et al., 1997; Robbins, 1997; Portas et al., 1998; Berridge and Waterhouse, 2003; Lapiz and Morilak, 2006). NA-LC activity has also been shown to play an integral role in target detection (Nieuwenhuis et al., 2005), while also influencing alertness and sustained attention in both human and animal studies (Carli et al., 1983; Coull et al., 1995; Puumala et al., 1997; De Martino et al., 2008; Greene et al., 2009). Recent findings even suggest a cortical NA influence on neuronal networks maintaining task-relevant information through delay-related firing, bridging the gap between cue presentation and subject response, and guiding behavior through working memory (Ramos and Arnsten, 2007).

Integral to both working memory and attention is vigilance, here referring to the arousal state of a subject just prior to and during performance on a specific cognitive task. It has been hypothesized that LC activation corresponds directly to both the degree and scope of vigilance maintained by the subject during cognitive processing. Specifically, that the level of LC activity reflects a complex relationship between both phasic and tonic modes of NA release, the correlation of which enhances or degrades specific attentional features (Lapiz and Morilak, 2006). Phasic modes are generally associated with normal alert-waking states, in which evoked neuronal firing corresponding to salient or target stimulus detection is high and spontaneous firing corresponding to non-essential stimuli is low. Conversely, tonic modes represent a generalized state of alertness for all environmental stimuli and are therefore associated with higher levels of spontaneous firing (Ramos and Arnsten, 2007).

As Aston-Jones and colleagues have proposed, the relationship between phasic and tonic NA-LC activity may be responsible for the type of attentional feature being optimized at a given state of

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doi:10.1016/j.neuropharm.2011.12.024

arousal. When phasic activity is moderate and tonic activity is low, a subject would be primed for "selective attention," the filtering out of target stimuli from the presence of distractors. When tonic levels of NA activity are higher, the phasic activation of NA neurons corresponding to the target stimuli would be masked and selective accuracy would be is reduced. Demonstrating a feature of "scanning attention," this increase in tonic activity yields an increase in vigilance towards background stimuli, allowing for potential acquisition of novel cue relevance (Aston-Jones et al., 1999; Usher et al., 1999).

Given the considerable progress made by earlier studies examining the contribution of norepinephrine release on cognitive processing during tasks explicitly designed to tax various aspects of attention, the focus of the present study is to determine potential beneficial effects of NA-LC modulation on performance of an attentional paradigm previously utilized for its sensitivity to changes in cholinergic activity. Sarter and colleagues have conducted extensive studies investigating the role of acetylcholine in an operant conditioning task aimed at measuring sustained attention within the visual system (Sarter et al., 2005). Of particular interest to the current study is a series of experiments involving bilateral infusions of the immunotoxin 192IgG saporin into the nucleus basalis of Meynert/substantia innominata region of basal forebrain aimed at eliminating cortical cholinergic inputs considered necessary for top-down attentional processing (McGaughy and Sarter, 1998). Lesioned animals consistently showed an impairment in their ability to detect signal events (hit rate) compared to sham animals. However, changes in signal presentation (sequencing, duration, pulsation) failed to elicit decrements in the correct rejection of non-signal events (McGaughy et al., 1996). Those authors suggest a complex rationale for the role of acetylcholine in signal-driven processing beyond the enhancement of cue detection. Specifically, these authors proposed that cortical cholinergic inputs 'mediate the switching of the cortical processing mode from an intracortical to an input-processing mode' thereby correlating increases in cholinergic transmission with enhanced attentional performance on tasks requiring validation of signal input (Sarter et al., 2005).

The aforementioned rationale for cholinergic mediation is a decidedly top-down configuration. By altering the above paradigm to include only the detection of signal or non-signal *auditory* cues, and by testing *noradrenergic* drugs thought to elicit changes in vigilance and arousal, our goal was to evaluate potential bottom-up mediation of valid signal detection and processing.

2. Methods

2.1. Subjects

Male Sprague–Dawley rats weighing 200–250 g at the onset of experimental training were housed in groups of two in a temperature controlled animal facility on a 12 h dark/light cycle, with experimental sessions conducted between 14:00 and 16:00. Throughout the training and testing periods, a strict feeding schedule of 18 g/rat per day was maintained to provide adequate nutrition while still maintaining a proper level of task motivation. Rats were given *ad libitum* access to water throughout the duration of the study. All experimental protocols and animal facilities were in accordance with the guidelines set forth by the Commission on Life Sciences, Institute for Laboratory Animal Research (ILAR) and by the Office of Laboratory Animal Welfare (OLAW). All efforts were made to reduce the number of animals used and to minimize animal suffering. Separate groups of rats were used for testing the $\alpha 1$ and $\alpha 2$ adrenoceptor agonists and antagonists and drug regimen for each group was pseudo randomized to avoid potential carry-over effects. In order to avoid potential confounds related to variable stress levels, all subjects were habituated to the experimental space two weeks prior to the start of the experiment.

2.2. Treatments

Yohimbine hydrochloride (TOCRIS Bioscience, Ellisville, MO, USA), phenylephrine hydrochloride (Sigma–Aldrich, St. Louis, MO, USA) and clonidine hydrochloride (TOCRIS Bioscience, Ellisville, MO, USA) were dissolved in 0.9% NaCl solution, while prazosin hydrochloride (TOCRIS Bioscience, Ellisville, MO, USA) was dissolved in distilled water. All drugs were injected using 1 ml 26G 3/8 syringe and administered 30 min prior to the start of each experimental session. All solutions were administered in a volume of 1 ml/kg via the intraperitoneal route. In the dose–response study, three dosage groups for prazosin (1 mg/kg, 1.25 mg/kg, 1.5 mg/kg), phenylephrine (0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg), yohimbine (0.5 mg/kg, 1 mg/kg, 2 mg/kg) and clonidine (0.025 mg/kg, 0.0375 mg/kg, 0.05 mg/kg) were compared with normal saline injection using one-way analysis of variance (ANOVA) to determine their effect on performance accuracy in both signal and non-signal trials. Fisher's PLSD post hoc tests were then used to determine precisely the dose groups that differed when the treatment effect was significant.

2.3. Apparatus

$8 \times 8 \times 10$ inch wire mesh training cage equipped with retractable levers, multi-stimuli capability, and concealed in a sound attenuating chamber (ENV-022V, 55.9 cm $\times$ 38.1 cm $\times$ 35.6 cm). Loudspeakers inside the chamber provided monotonal auditory cues. All the devices (levers, pellet dispenser, and loudspeakers) were controlled by a PC connected via DAC/ADC converter (Measurement Computing, Norton, MA) through MatLab software which also randomly generated the target for the sequential presentations. The system also automatically recorded success probabilities, submission errors, omissions, and response latencies for all trial conditions.

2.4. Behavioral training

In order to understand the mechanisms relating to the processing of present and non-present stimuli in the auditory system, a sustained auditory attentional task was designed based on a signal/non-signal paradigm previously developed for the visual system (McGaughy and Sarter, 1995). Animals were required to identify the presence of signal events (2 KHz mono-tonal, played 3 s prior to lever presentation, 50 ms duration) and correctly reject non-signal events (no auditory cue given). Following the presentation of the signal, a left lever press was considered a correct response, and scored as a hit. A right lever press on a signal trial was an incorrect response and recorded as a miss. On non-signal trials a right lever press was the correct response, scored as a correct rejection, while a left lever press during non-signal trials was incorrect and scored as a false alarm (Fig. 1). A 45 mg nutrient pellet (Bio Serv, Frenchtown, NJ, USA) was given as reward following a correct response, and incorrect responses were not rewarded. If a lever was not selected within 3 s, the trial was scored as an omission. To further tax the animal's attention, the inter-trial interval was randomized with a range of 5–15 s during each session. In order to avoid any potential side bias, the apparatus was modified during the initial acquisition phase so that only the lever which designated a correct response was presented for each trial, thus ensuring the animal's repositioning between trials. Once the number of omissions equaled less than five percent for each event type, the apparatus was restored to dual lever operation. The final criterion for performance

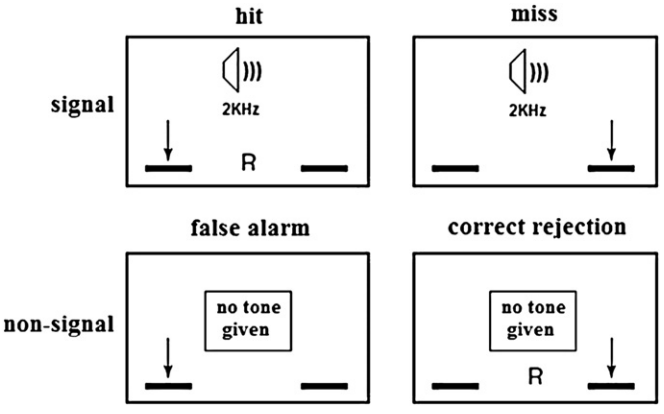

Fig. 1. Illustration of the response rules comprising the sustained attention task. Vertical arrows designate the correct lever press necessary for the specified condition. R indicates the correct response needed to gain reward for each type of trial (*signal or non-signal*). The inter-trial interval was randomized within a range of 5–15 s during each session, with each trial type comprising one half of the total number of trials per session (25). On signal trials, the 2 KHz tone was played 3 s prior to lever presentation and lasted 50 ms. In both trial types the subjects were allowed a maximum response time of 3 s.

was a success probability of 70% or higher during two 30 min sessions with less than five percent omissions achieved in successive training days (>100 trials total).

2.5. Parameters

Although the primary aim of the study was to measure auditory signal validation, our experimental design offered additional attentional parameters of interest. Perseverative conditions and repetitive trial blocks were analyzed for each pharmacological comparison. A repetitive trial block consisted of three or more consecutive trials utilizing the same criterion for reward (at least three signals or non-signals presented in a row). In contrast, a perseverative condition was defined as any trial which immediately followed a repetitive trial block, thus constituting a change in reward criterion. Repetitive and perseverative responses were monitored to observe attentional sustainability in a more generalized fashion, measuring cognitive performance without taxing the animal through rigorous switching between signal detection and non-signal rejection.

2.6. Data analysis

Success probability (SP) was determined from the number of correct responses calculated as a percentage of the total number of responses registered. Anticipatory responses were not viable, as the apparatus's retractable levers insured that no response could occur during the inter-trial interval. Omission errors were registered if no response was made within the maximum allotted response time (MaxRT = 3 s). Correct response latency (RL) was defined as the interval between lever presentation and correct lever selection. All reported values indicate performance score with the standard error of the mean (SP + SEM or RL + SEM). Data were analyzed using two-way repeated measures analysis of variance (ANOVA), with a maximum value of $p = 0.05$ allowed for significant effects.

3. Results

3.1. Dose–response study

Analysis of variance following administration of either prazosin or phenylephrine revealed no significant effect for either treatment group, and Fisher's PLSD post hoc testing confirmed that each dose group did not differ significantly from saline or from each other in modulating performance accuracy in either signal or non-signal trials [Fig. 2a–b]. However, yohimbine produced significant improvement in performance accuracy during non-signal trials [$F(3,20) = 4.21$, $p < 0.02$; Fig. 2c] but had no effect on signal trial performance when compared to saline injection. Post hoc testing of non-signal trial performance showed that the higher dose groups (1 and 2 mg/kg) elicited significantly greater responses than the lowest dose (0.5 mg/kg) and saline [$p < 0.03$ for all comparisons] but did not differ from each other. Conversely, clonidine significantly impaired performance accuracy on signal trials [$F(2,15) = 4.25$, $p < 0.04$; Fig. 2d] but did not affect accuracy during non-signal trials. Post hoc testing of signal trial performance showed that the 0.0375 mg/kg dose of clonidine had a significant effect on performance compared with saline [$p < 0.02$] but did not differ from the smaller dose (0.025 mg/kg). It is important to note that the largest dose of clonidine tested (0.05 mg/kg) resulted in sedative effects (omissions > 50% of total trials). Data collected

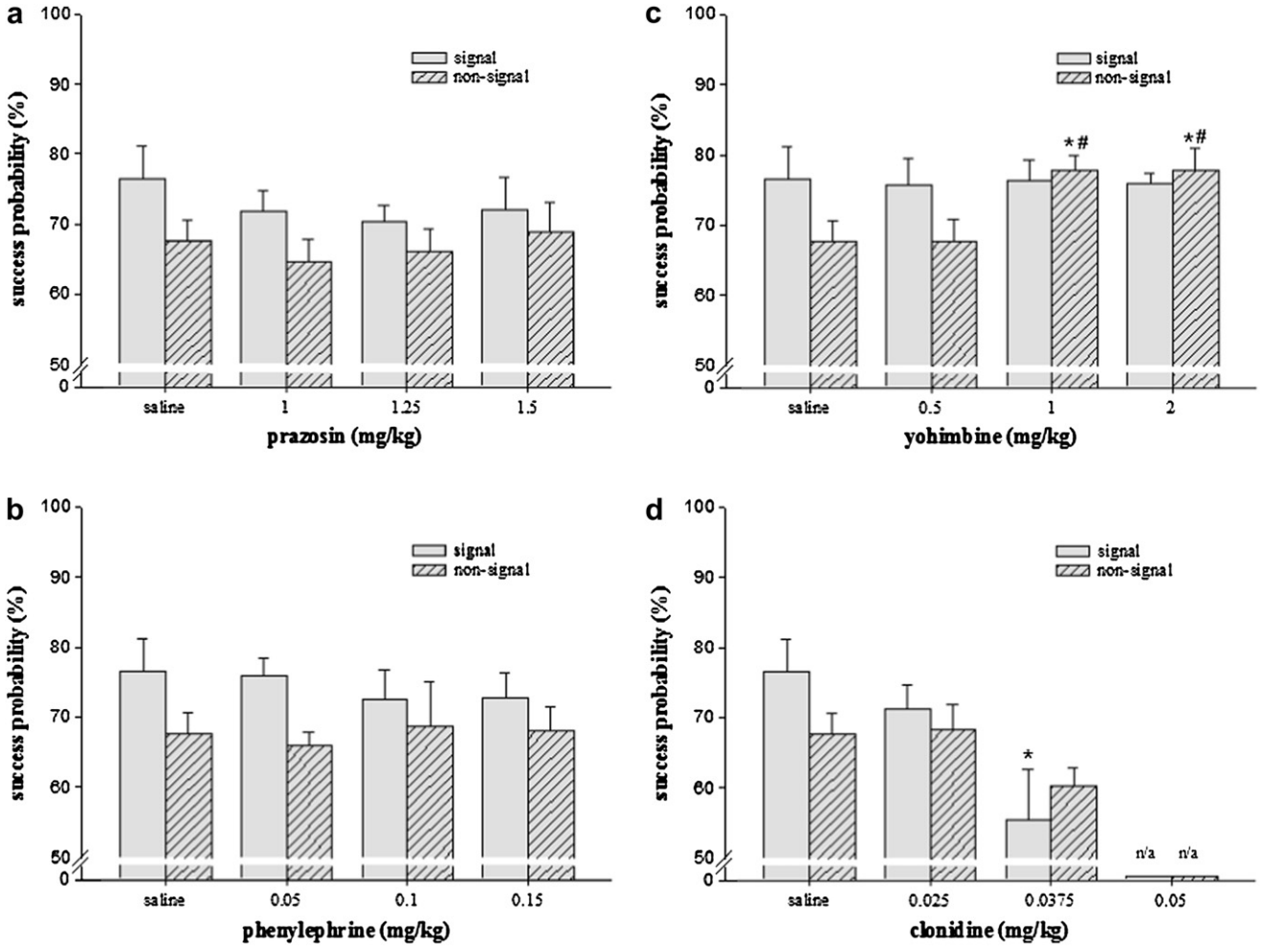

Fig. 2. Signal and non-signal trial performance response to saline and three different doses of each drug; values are mean ± SEM ($n = 6$ in each group); *significantly different from saline ($p < 0.03$); #significantly different from lowest tested dose ($p < 0.03$).

from that group was excluded from the dose–response study (response denoted as n/a in Fig. 2d). Subsequent findings for the effects of α1 and α2 adrenoceptors represent the lowest effective dose for each treatment group.

3.2. Effect of α1 adrenoceptors

Neither signal [78.2 ± 3.6% vs. 80.6 ± 2.3%; Fig. 3a] nor non-signal [66 ± 3.16% vs. 69.9 ± 2.4%; Fig. 3a] accuracies were significantly affected by the administration of the α1-adrenoceptor antagonist prazosin (1.0 mg/kg), though performance was affected similarly in both conditions. However, the α1-adrenoceptor agonist phenylephrine (0.1 mg/kg) impaired performance on hits [72 ± 4.4% vs. 80.6 ± 2.3%; $F(1,11) = 5.26$, $p < 0.05$; Fig. 3a] but did not have an effect on the animals' propensity to make a correct rejection [71.5 ± 3.7% vs. 69.9 ± 2.4%; Fig. 3a]. Both prazosin [614 ± 62 vs. 566 ± 51 ms; Fig. 3b] and phenylephrine [610 ± 62 vs. 566 ± 51 ms; Fig. 3b] showed a trend towards increasing hit response latency, and both prazosin [779 ± 112 vs. 680 ± 82 ms; $F(1,11) = 5.33$, $p < 0.05$; Fig. 3b] and phenylephrine [802 ± 101 vs. 680 ± 82 ms; $F(1,11) = 6.92$, $p < 0.05$; Fig. 3b] significantly increased correct rejection response latency.

Further analysis revealed repetitive trial [74.2 ± 2.7% vs. 72.7 ± 6.5%; Fig. 4a] and perseverative trial [70.5 ± 4.1% vs. 70.7 ± 3.8%; Fig. 4a] performances were not affected by prazosin. Similarly, phenylephrine did not significantly affect accuracy during repetitive [73.8 ± 3.7% vs. 72.7 ± 6.5%; Fig. 4a] or perseverative trials [72.6 ± 4.5% vs. 70.7 ± 3.8%; Fig. 4a]. Only phenylephrine

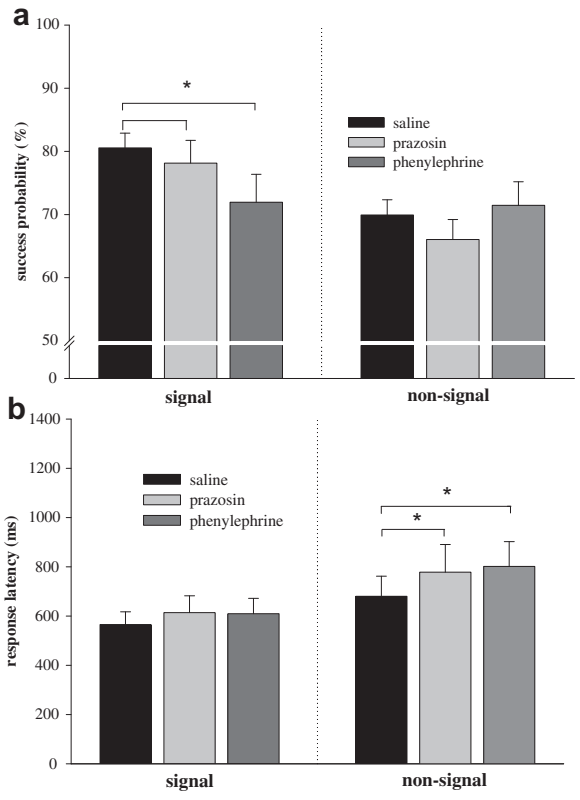

Fig. 3. The effects of systemic injection of phenylephrine 0.1 mg/kg (*dark gray bars*), prazosin 1.0 mg/kg (*gray bars*), and vehicle (*black bars*) on accuracy and correct response latency for signal and non-signal trials. Bars represent mean performance (SEM) of twelve rats in 30-min sessions with a randomized ITI 10 ± 5 s. Conditions where prazosin or phenylephrine produced a significant difference compared to vehicle are marked (*$p < 0.05$; two-way ANOVA).

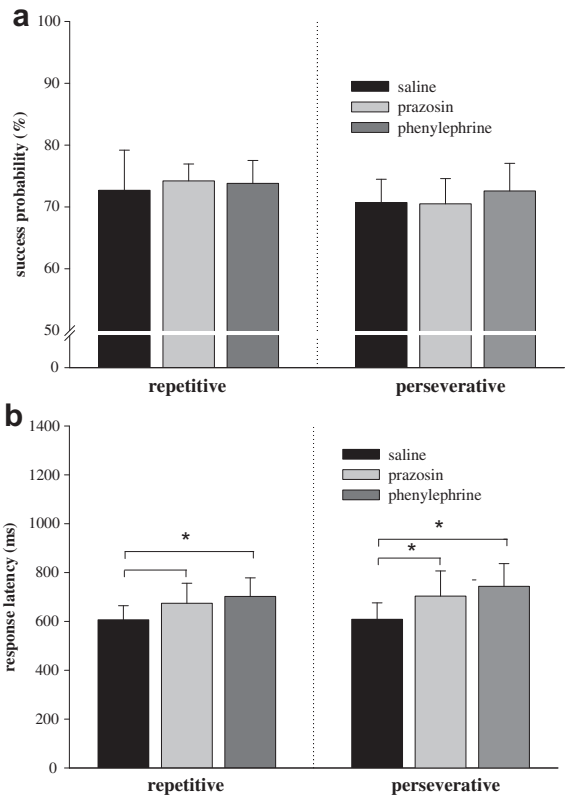

Fig. 4. The effects of systemic injection of phenylephrine 0.1 mg/kg (*dark gray bars*), prazosin 1.0 mg/kg (*gray bars*), and vehicle (*black bars*) on accuracy and correct response latency for repetitive and perseverative trial conditions. Bars represent mean performance (SEM) of twelve rats in 30-min sessions with a randomized ITI 10 ± 5 s. Conditions where prazosin or phenylephrine produced a significant difference compared to vehicle are marked (*$p < 0.05$; two-way ANOVA).

[703 ± 76 vs. 607 ± 58 ms; $F(1,11) = 6.89$, $p < 0.05$; Fig. 4b] significantly increased repetitive trial response latencies. Additionally, prazosin [704 ± 103 vs. 609 ± 67 ms; $F(1,11) = 4.87$, $p < 0.05$; Fig. 4b] and phenylephrine [744 ± 93 vs. 609 ± 67 ms; $F(1,11) = 5.8$, $p < 0.05$; Fig. 4b] significantly increased the response latencies of perseverative trials.

3.3. Effect of α2 adrenoceptors

Yohimbine (1.0 mg/kg), the α2-adrenoceptor antagonist, produced no effect on signal trials [78.8 ± 3.4% vs. 78.3 ± 1.9%; Fig. 5a], while clonidine (0.0375 mg/kg), the α2-adrenoceptor agonist, significantly impaired signal performance [60.3 ± 6.3% vs. 78.3 ± 1.9%; $F(1,12) = 8.82$, $p < 0.05$; Fig. 5a]. Similarly, yohimbine failed to produce a significant effect on the latency to make a correct signal response [469 ± 28 vs. 529 ± 46 ms; Fig. 5b] while clonidine significantly increased hit response latency [930 ± 97 vs. 529 ± 46 ms; $F(1,12) = 33.21$, $p < 0.0001$; Fig. 5b]. Interestingly, yohimbine dramatically improved performance on non-signal trials [79.7 ± 2.9% vs. 68.5 ± 1.9%; $F(1,12) = 25.52$, $p < 0.001$; Fig. 5a] but did not significantly decrease response latency [650 ± 45 vs. 735 ± 60 ms; Fig. 5b]. Conversely, clonidine did not have an effect on non-signal performance [64.2 ± 4.4% vs. 68.5 ± 1.9%; Fig. 5a] but did increase the latency to make a correct rejection [1090 ± 101 vs. 735 ± 60 ms; $F(1,12) = 21.3$, $p < 0.001$; Fig. 5b].

Yohimbine did not significantly improve performance during repetitive trials [79.8 ± 2% vs. 75.1 ± 2.9%; Fig. 6a] or perseverative trials [73.3 ± 3.7% vs. 71.1 ± 5.2%; Fig. 6a]. However, yohimbine

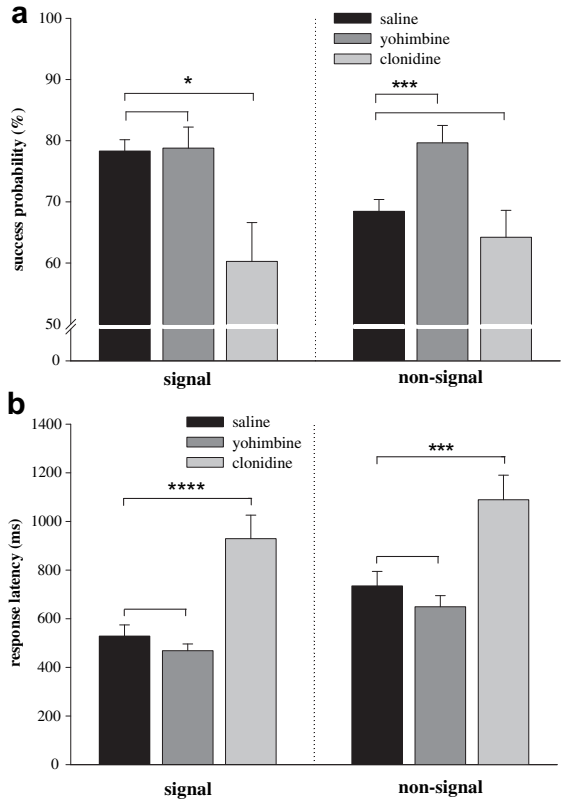

Fig. 5. The effects of systemic injection of clonidine 0.0375 mg/kg (*gray bars*), yohimbine 1.0 mg/kg (*dark gray bars*), and vehicle (*black bars*) on accuracy and correct response latency for signal and non-signal trials. Bars represent mean performance (SEM) of thirteen rats in 30-min sessions with a randomized ITI 10 ± 5 s. Conditions where prazosin or phenylephrine produced a significant difference compared to vehicle are marked ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$; two-way ANOVA).

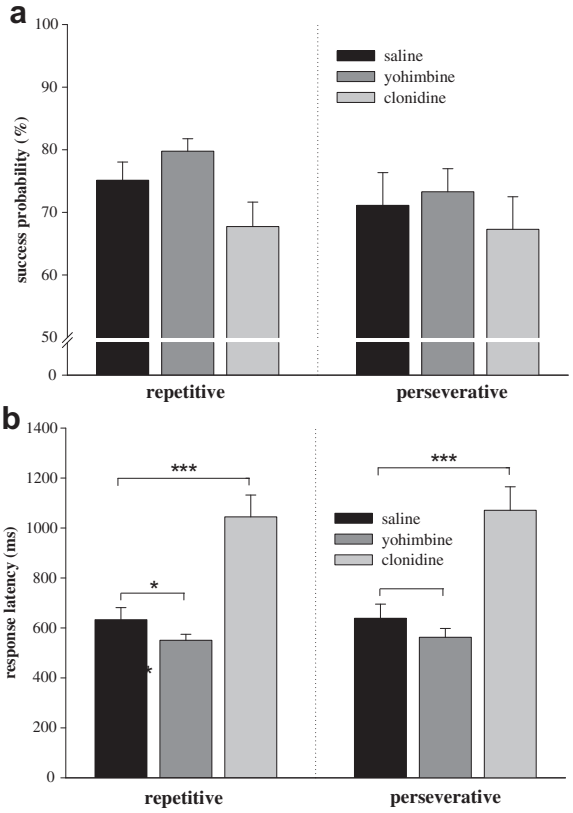

Fig. 6. The effects of systemic injection of clonidine 0.0375 mg/kg (*gray bars*), yohimbine 1.0 mg/kg (*dark gray bars*), and vehicle (*black bars*) on accuracy and correct response latency for repetitive and perseverative trial conditions. Bars represent mean performance (SEM) of thirteen rats in 30-min sessions with a randomized ITI 10 ± 5 s. Conditions where prazosin or phenylephrine produced a significant difference compared to vehicle are marked ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; two-way ANOVA).

significantly decreased the response latency of repetitive trials [550 ± 24 vs. 633 ± 49 ms; $F(1,12) = 5.01$, $p < 0.05$; Fig. 6b] but did not affect the response latency of perseverative trials [562 ± 36 vs. 639 ± 57 ms; Fig. 6b]. Clonidine failed to affect repetitive trial [67.8 ± 3.9% vs. 75.1 ± 2.9%; Fig. 6a] and perseverative trial [67.3 ± 5.2% vs. 71.1 ± 5.2%; Fig. 6a] performance, yet increased the response latency for both repetitive [1045 ± 88 vs. 633 ± 49 ms; $F(1,12) = 29.46$, $p < 0.001$; Fig. 6b] and perseverative trials [1071 ± 94 vs. 639 ± 57 ms; $F(1,12) = 21.62$, $p < 0.001$; Fig. 6b].

4. Discussion

Numerous studies have linked NA-LC deficiency with various psychotic and neurological disorders, ranging from Alzheimer's disease to schizophrenia (Van Kammen and Kelley, 1991; Riekkinen et al., 1999; Yamamoto and Hornykiewicz, 2004). In the present study, we sought to relate invalid stimulus processing with deficits in vigilance associated with those disorders. By modifying a sustained attention protocol previously utilized for the visual system to distinguish signal and non-signal trials (McGaughy and Sarter, 1995), we created an auditory version suitable for dissociating present from non-present tonal cues.

Previous studies have shown that behavioral paradigms designed to test a subject's ability to discriminate present from non-present stimulus cues require activation of neuronal networks encompassing cholinergic projections from basal forebrain to anterior, posterior, and sensory cortices, as well as noradrenergic projections from locus coeruleus to basal forebrain and thalamus (McGaughy et al., 1996; Sarter et al., 2001). In this traditional model for the mechanisms underlying sustained attention, acetylcholine is the critical neurotransmitter involved in the regulation of sensory processing, while norepinephrine release merely induces the arousal state necessary to initiate attentional processing. However, our findings suggest a more specific role for norepinephrine in signal vs. non-signal cue discrimination.

If the traditional view of NA-LC activation as an arousal component were inclusive, the expectation would be that stimulation or blockade of alpha adrenergic receptors alone would enhance or attenuate the processing of sensory inputs by the aforementioned network mediating sustained attentional performance. In effect, the change in 'arousal' would directly influence the subject's ability to maintain a vigilant state and the impact on task performance would co-vary with effects previously elicited by cholinergic modulation alone. Specifically, in studies involving both normal rats and rats with cholinergic deafferentation caused by 192IgG saporin lesioning of nucleus basalis, the primary effect was a decrease in accuracy during signal trials (McGaughy et al., 1996). Surprisingly, in our experiments, treatment with drugs targeting either α1 or α2 adrenoceptors failed to produce similar effects.

In the case of α1 receptor stimulation, application of the agonist phenylephrine significantly impaired performance on signal trial accuracy yet had no effect on non-signal performance. Blockade of α1 adrenoceptors with prazosin did not significantly affect accuracy on either trial type. Interestingly, both phenylephrine and prazosin slowed reaction time when subjects were required to make a correct rejection (non-signal). One possible explanation for the

inconsistency in performance measures following α1 stimulation may lie in the phasic-tonic patterns of NA-LC activity, as proposed by Aston-Jones. Because the current behavioral task required animals to be properly habituated, the minimal stress levels would correspond to a phasic state of norepinephrine release, thus limiting the efficacy of α1 adrenoceptor activation (Aston-Jones et al., 1999; Ramos and Arnsten, 2007).

A clearer picture of attentional modulation emerges when examining the effects of α2 stimulation. Generally, application of yohimbine and clonidine elicited similar absolute values of modulation above and below baseline performance respectively. Clonidine not only impaired signal accuracy, but uniformly increased response latency in all trial conditions. Yet, accuracy during repetitive trial conditions was not significantly decreased when compared to vehicle injection, evidence that clonidine did not merely alter performance by sedative means. Conversely, yohimbine failed to significantly improve perseverative accuracy, yet showed a trend toward improving accuracy during repetitive trial conditions. Yohimbine's effect on response latency is not so easily interpreted. While one would expect to see a symmetrical relationship between clonidine and yohimbine with respect to reaction time, the physical limitations of the animal preclude this symmetry. Because the animal naturally performs at optimum speed during the task, demonstrating a significant improvement in reaction time above baseline is problematic. This "floor effect" essentially allows for modulation in only one direction, an increase in response latency in the presence of clonidine compared to baseline performance.

Perhaps most intriguing are the findings attributed to the non-signal events. Dissociating performance on those task portions requiring the correct rejection of nonexistent auditory cues demonstrates the most relevant information carried by our results. While those drugs primarily activating α1 receptors did little to modulate non-signal processing, those drugs acting primarily on α2 receptors provided the highest level of significance inherent within the study. Clonidine notably increased response latencies during both correct rejection and false alarm responses, illustrating a uniform slowing of the decision making process when signal validity is necessary for reward. Moreover, yohimbine dramatically improved the animal's ability to distinguish non-signal events by increasing the number of correct rejections and decreasing the number of false alarm responses.

These findings constitute two clinically relevant points. α2 antagonists like yohimbine can improve sustained attention when signal validity is the target feature of discrimination. And given its profound effect on non-signal processing in the auditory system, yohimbine has potential therapeutic benefits for patients suffering paracusia-like symptoms associated with various psychological disorders (Ensum and Morrison, 2003; Papageorgiou et al., 2004; Shea et al., 2007).

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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