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Alpha 2A adrenergic receptor agonist, guanfacine, attenuates cocaine-related impairments of inhibitory response control and working memory in animal models

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ABSTRACT

There is considerable evidence that centrally acting α2A adrenergic receptor agonists can attenuate impairments in executive function that result from dysfunction of the prefrontal cortex. Such positive effects resulted in the recent approval by the United States Food and Drug Administration (FDA) of the α2A agonists clonidine and guanfacine for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), but also suggest that they could have beneficial effects in substance abuse disorders and other neuropsychiatric conditions. The purpose of this study was to evaluate guanfacine for its ability to attenuate behavioral alterations associated with acute cocaine exposure in rats trained to perform a task of sustained attention, the five choice serial reaction time task (5C-SRTT) and monkeys trained to perform a task of working/short term memory, the delayed match to sample (DMTS) task. In the rodent 5C-SRTT acute intraperitoneal (i.p.) administration of cocaine (3.5–15.0 mg/kg) did not affect accuracy, but was associated with dose-dependent increases in premature responses and timeout responses. Guanfacine (0.1–1.0 mg/kg i.p.) dose-dependently decreased premature responses and timeout responses associated with cocaine and it attenuated similar deficits in inhibitory response control observed in a variable ITI version of the 5C-SRTT. In the DMTS task in monkeys, acute intramuscular (i.m.) administration of cocaine (4.0 mg/kg) was associated with impairments in accuracy at long delay intervals, an effect that was attenuated by guanfacine (0.4 mg/kg). These animal studies suggest that guanfacine may have therapeutic potential for treating impairments of executive function that are associated with the abuse of cocaine.

1. Introduction

The generic term "executive function" is commonly used to designate the variety of cognitive processes that are important to successful human behaviors and adaptive abilities including attention, working memory, problem solving, task planning, cognitive flexibility (task or rule switching) and the inhibition of inappropriate responses (Luria, 1973; Baddeley and Hitch, 1974; Lezak, 1983; for recent reviews see Jurado and Rosselli, 2007; Ardila, 2008). Deficits in executive function are now thought to contribute to all components of the substance abuse cascade including the vulnerability, initiation and maintenance of addiction-related behaviors, as well as recidivism in patients who have attempted to end their dependence (Everitt et al., 2007; Porrino et al., 2007; Li and Sinha, 2008; Verdejo-García et al., 2008; Goldstein and Volkow, 2011). Accordingly, it has been argued that targeting the impairments of executive function in substance abuse disorders is an important strategy for improving overall treatment efficacy (Sofuoglu, 2010).

There is considerable evidence from both animal models and humans that centrally acting α2A adrenergic receptor agonists (e.g., clonidine, guanfacine) can attenuate alterations in executive function that result from dysfunction of the prefrontal cortex (PFC) including inattention and distractibility, poor impulse control, and impairments of working memory, planning and decision-making, and the regulation of emotion (e.g., impulsive aggression) (see review, Arnsten, 2010). The positive effects of clonidine and guanfacine on inattention, distractibility and impulse control resulted in their recent approval by the United States Food and Drug Administration (FDA) for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The evidence described above might also suggest that α2A adrenergic receptor agonists such as clonidine and guanfacine could have beneficial effects in substance abuse disorders and addiction, although this line of research has not been rigorously pursued to date.

One advantage of α2A adrenergic agonists as a potential therapy for substance-abuse-related disorders is their previous clinical track record. In addition to their recently approved clinical indication for ADHD,

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clonidine and guanfacine have been prescribed for hypertension for decades and they have also been commonly used (off label) to treat the symptoms of a number of other conditions including menopause, sleep disorders, pain disorders, drug and alcohol withdrawal, and some neuropsychiatric conditions (e.g., tic disorders, anxiety disorders, post-traumatic stress disorder, schizophrenia, see review, Crassous et al., 2007). The antihypertensive effects of α2A adrenergic agonists and their ability to decrease heart rate are thought to result from the activation of brainstem α2A adrenergic receptors to suppress sympathetic nerve activity from the vasomotor center to the heart and blood vessels (reviewed, Sorkin and Heel, 1986), while their beneficial effects on behavior are thought to result from the stimulation of post-synaptic α2A receptors on dendritic spines of pyramidal cells in the PFC, effectively increasing the functional connectivity of PFC networks (Wang et al., 2007; Arnsten, 2010).

There is evidence to suggest that guanfacine might offer some advantages over clonidine for the treatment of neuropsychiatric disorders since it has weaker antihypertensive and sedative actions than clonidine, but is more potent in enhancing PFC function (Arnsten et al., 1988), advantages that may be related to its more selective affinity for the α2A subtype (Uhlen et al., 1994) and lower affinity for the imidazoline receptor (Coupry et al., 1989). This argument, especially the superior effects on PFC function, was supported in a clinical study in young healthy volunteers where guanfacine, but not clonidine improved spatial working memory and planning ability (Jakala et al., 1999).

The purpose of the study described here was to evaluate guanfacine for its ability to attenuate behavioral alterations associated with acute cocaine exposure in rats trained to perform a task of sustained attention, the five choice serial reaction time task (5C-SRTT) and monkeys trained to perform a task of working/short term memory, the delayed match to sample (DMTS) task.

2. Material and methods

All procedures employed during this study were reviewed and approved by the Georgia Regents Sciences University Institutional Animal Care and Use Committee and are consistent with AAALAC guidelines. Measures were taken to minimize pain and discomfort in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. Significant efforts were also made to minimize the total number of animals used while maintaining statistically valid group numbers.

2.1. Drugs

Cocaine hydrochloride was generously provided by the National Institute on Drug Abuse. Guanfacine hydrochloride was obtained from Sigma-Aldrich Corporation., St. Louis, MO, USA.

2.2. Rodent studies

2.2.1. Test subjects

Male albino Wistar rats (Harlan Sprague–Dawley, Inc., Indianapolis, IN, USA) approximately 2 months old were housed individually in a temperature controlled room (25 °C), maintained on a 12:12 h normal light-dark cycle (lights on at 7 AM) with free access to water and food during the first week (see subsequent food restriction procedures below).

2.2.2. Behavioral studies

Rats were tested using an automated 5-Choice Serial Reaction Time Task (5C-SRTT) as we have described previously (Terry et al., 2012). Training and testing in the 5C-SRTT were conducted using eight ventilated, sound attenuated operant chambers (Med Associates, St. Albans, VT, USA). Each operant chamber consisted of nine nose pokes/apertures (2.5 cm wide, 4 cm deep), four of which were closed off with metal inserts; thus, every other nose poke was available. The apertures, arranged on a curved panel 2 cm above the floor of the chamber, were equipped with a photocell beam to detect nose pokes. Each aperture was equipped with a lamp (2.8 W) on the rear wall that could be illuminated randomly and for varying durations. Food pellets (45 mg chow pellet, BioServ, Frenchtown, NJ, USA) were delivered automatically to a magazine, located on the opposite wall to the nose pokes, that was also equipped with a light that turned on to indicate that a pellet had been dispensed. The food magazine was equidistant from all nose poke apertures. The house light remained on for the entire session unless an error or omission occurred. The apparatus was controlled using MedPC software (Med Associates, St. Albans, VT, USA).

2.2.2.1. 5C-SRTT training. After arrival test subjects were separated into single housed conditions in preparation for food restriction and handled daily for one week to reduce stress and anxiety in preparation for training. From week 2 until the end of the study animals were food restricted to approximately 85% of their age-dependent, free-feeding weights based upon Harlan Laboratories growth rate curves. At week 3, animals began habituation to the 5C-SRTT apparatus in preparation for training consisting of a non-spatial habituation program. Study subjects were transferred (in their home cages) to the behavioral testing rooms each morning approximately 30 min before testing. 5C-SRTT training began with a stimulus duration (SD) of 10 s, each session being 100 trials or 30 min in duration with inter-trial intervals (ITI) of 5 s. Animals were trained 5 days per week until they reached stable performance levels (defined as 2 consecutive days at >80% accuracy, <20% omissions and completion of all 100 trials) at the 10 s stimulus duration Once criterion was achieved at a given stimulus duration, the animals were moved to the next more challenging stimulus duration (5, 2.5, 2.0, 1.5, 1.25 and 1.0 s). After these training criterion were achieved, rats were tested in a protocol that used a fixed stimulus duration (1.0 s) and inter-trial interval (5.0 s) or a protocol that used the pseudorandom presentation of variable inter-trial intervals (VITI, 1.0, 5.0, and 10.0 s). To assess performance the following parameters were measured: % correct ((# correct / (# correct + # incorrect)) × 100), omissions, premature responses (total # of responses performed after the trial began but before onset of the light stimulus), timeout responses (total # of nose pokes made in any aperture during a timeout period), perseverative responses (total # of nose pokes performed after the correct response had been made but before collecting the reward), trials completed, latency to correct response (time taken from onset of nose poke light stimulus to making the correct nose poke response), latency to incorrect response (time taken from onset of nose poke light stimulus to making the incorrect nose poke response), and latency to reward (i.e., the magazine latency, time taken from making a correct nose poke response to retrieving the reward from the magazine).

2.2.3. Drug administration

Following baseline (vehicle) assessments in the Standard and VITI versions of the 5C-SRTT, test subjects were treated acutely with cocaine and later with a combination of cocaine and the alpha 2 adrenergic agonist guanfacine. Drug testing occurred twice per week (e.g., Tuesday and Thursday or Wednesday and Friday) with 5C-SRTT maintenance training intervening between the drug test sessions; testing occurred only when animals maintained their performance accuracy (>80% accuracy, <20% omissions and completion of all 100 trials). Cocaine was dissolved in vehicle (0.9% saline) and administered by intraperitoneal injection (i.p.) 15 min before 5C-SRTT testing. In the studies in which the combination of guanfacine and cocaine were evaluated, guanfacine (dissolved in vehicle) was administered by i.p. injection 30 min before 5C-SRTT testing followed by cocaine administered by i.p. injection 15 min before 5C-SRTT testing. Drugs and vehicle were administered