Neuropharmacology 60 (2011) 303–311

Contents lists available at ScienceDirect

Neuropharmacology

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

Stimulation of α2-adrenergic receptors in the central nucleus of the amygdala attenuates stress-induced reinstatement of nicotine seeking in rats

Hidetaka Yamada, Adrie W. Bruijnzeel*

Department of Psychiatry, McKnight Brain Institute, University of Florida, 100 S. Newell Dr., Gainesville, FL 32610, USA

ARTICLE INFO

Article history:
Received 9 July 2010
Received in revised form
9 September 2010
Accepted 10 September 2010

Keywords:
Nicotine
Footshocks
Clonidine
Dexmedetomidine
Propranolol
Prazosin

ABSTRACT

Tobacco addiction is a chronic disorder that is characterized by craving for tobacco products, withdrawal upon smoking cessation, and relapse after periods of abstinence. Previous studies demonstrated that systemic administration of α2-adrenergic receptor agonists attenuates stress-induced reinstatement of drug seeking in rats. The aim of the present experiments was to investigate the role of noradrenergic transmission in the central nucleus of amygdala (CeA) in stress-induced reinstatement of nicotine seeking. Rats self-administered nicotine for 14–16 days and then nicotine seeking was extinguished by substituting saline for nicotine. The effect of the intra-CeA infusion of the α2-adrenergic receptor agonists clonidine and dexmedetomidine, the nonselective β1/β2-adrenergic receptor antagonist propranolol, and the α1-adrenergic receptor antagonist prazosin on stress-induced reinstatement of nicotine seeking was investigated. In all the experiments, exposure to footshocks reinstated extinguished nicotine seeking. The administration of clonidine or dexmedetomidine into the CeA attenuated stress-induced reinstatement of nicotine seeking. The administration of propranolol or prazosin into the CeA did not affect stress-induced reinstatement of nicotine seeking. Furthermore, intra-CeA administration of clonidine or dexmedetomidine did not affect operant responding for food pellets. This suggests that the effects of clonidine and dexmedetomidine on stress-induced reinstatement of nicotine seeking were not mediated by motor impairments or sedation. Taken together, these findings indicate that stimulation of α2-adrenergic receptors, but not blockade of α1 or β-adrenergic receptors, in the CeA attenuates stress-induced reinstatement of nicotine seeking. These findings suggest that α2-adrenergic receptor agonists may at least partly attenuate stress-induced reinstatement of nicotine seeking by stimulating α2-adrenergic receptors in the CeA.

1. Introduction

Tobacco addiction is a chronic disorder that is characterized by a loss of control over smoking, affective withdrawal symptoms upon smoking cessation, and relapse after periods of abstinence (American Psychiatric Association, 2000; McLellan et al., 2000; O'Brien, 2003). Nicotine is one of the main components of tobacco smoke that leads to and maintains smoking (Bardo et al., 1999; Crooks and Dwoskin, 1997; Stolerman and Jarvis, 1995). This is supported by studies that show that rodents, dogs, and nonhuman primates readily learn to self-administer nicotine (Corrigall and Coen, 1989; Goldberg et al., 1981; Risner and Goldberg, 1983). Furthermore, nicotine induces conditioned place preference and facilitates intracranial self-stimulation (ICSS) in rats (Harrison et al., 2002; Le Foll and Goldberg, 2005; Pradhan and Bowling, 1971). Conditioned place preference and facilitation of ICSS are indicative of a potentiation of brain reward function (Bardo and Bevins, 2000; Schaefer and Michael, 1992). Nicotine mediates its positive reinforcing effects (e.g., mild euphoria) at least partly via the activation of central nicotinic acetylcholine receptors (nAChRs). Pharmacological blockade of nAChRs or genetic deletion of the β2-subunit of the nAChR decreases nicotine self-administration in rodents (Corrigall et al., 1994; Corrigall and Coen, 1989; Donny et al., 1999; Picciotto et al., 1998; Watkins et al., 1999). Cessation of smoking in humans leads to an acute withdrawal syndrome that is characterized by affective symptoms such as depressed mood, anxiety, and difficulty concentrating (American Psychiatric Association, 2000; Bruijnzeel and Gold, 2005). It has been hypothesized that the acute negative affective aspects of nicotine withdrawal provide a powerful motivational force for the continuation of smoking (Koob et al., 1997; Markou et al., 1998).

Epidemiological studies indicate that exposure to stressors increases the risk for relapse to smoking in humans (Cohen and

* Corresponding author. Department of Psychiatry, McKnight Brain Institute, University of Florida, 100 S. Newell Dr., PO Box 100256, Gainesville, FL 32610, USA. Tel.: +1 352 294 0421; fax: +1 352 392 8217.
E-mail address: awbruijn@ufl.edu (A.W. Bruijnzeel).

0028-3908/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2010.09.013

Lichtenstein, 1990; Doherty et al., 1995; Kassel et al., 2003; McKee et al., 2003; Niaura et al., 2002; Shiffman and Waters, 2004; Swan et al., 1988). Stressors also increase the risk for relapse to other drugs of abuse such as alcohol and opioids (Brown et al., 1995; Kosten et al., 1986). Animal models have been developed to delineate the neuronal mechanisms that underlie stress-induced relapse. In one of these models, rats are allowed to self-administer a drug for a specific amount of time and then drug seeking is extinguished by substituting saline for the drug solution. Exposure to footshocks leads to a resumption of extinguished drug seeking (Shaham et al., 2003). Footshocks have been shown to reinstate extinguished heroin, cocaine, alcohol, and nicotine seeking in rats (Buczek et al., 1999; Erb et al., 2001; Liu and Weiss, 2002; Shaham and Stewart, 1995). In a previous study we reported that exposure to the contextual stimuli associated with prior footshock-stress does not reinstate extinguished nicotine seeking (Zislis et al., 2007). Several studies have reported that footshocks do not reinstate operant responding that was previously maintained by food pellets, sucrose pellets, or sucrose solutions (Ahmed and Koob, 1997; Buczek et al., 1999; Le et al., 1998; Mantsch and Goeders, 1999). This suggests that stressors reinstate nonreinforced responding for addictive substances, but not for natural reinforcers, such as food pellets or sucrose.

Although exposure to stressors plays an important role in relapse to smoking in humans, only a few preclinical studies have investigated the neuronal mechanisms that mediate stress-induced relapse to smoking. Previous studies in our laboratory investigated the role of CRF and noradrenergic transmission in stress-induced reinstatement of nicotine seeking in rats. These studies demonstrated that central administration of the non-specific CRF1/CRF2 receptor antagonist D-Phe CRF(12–41) and the specific CRF1 receptor antagonist R278995/CRA0450, but not the CRF2 receptor antagonist astressin-2B, attenuates stress-induced reinstatement of nicotine seeking (Bruijnzeel et al., 2009; Zislis et al., 2007). Furthermore, it was shown that systemic administration of the α2-adrenergic receptor agonist clonidine attenuates footshock-induced reinstatement of nicotine seeking (Zislis et al., 2007). These studies suggest that CRF and noradrenergic transmission plays an important role in stress-induced reinstatement of nicotine seeking. This pattern of results is in line with the findings of studies that investigated the neurobiological substrates underlying footshock-induced reinstatement of cocaine and alcohol seeking (Erb et al., 2000; Le et al., 2000). The α2-adrenergic receptor agonists clonidine, lofexidine, and guanabenz attenuate stress, but not cue, induced reinstatement of cocaine seeking in rats (Erb et al., 2000). Furthermore, the intracerebroventricular (icv) administration of the non-specific CRF1/CRF2 receptor antagonist D-Phe CRF(12–41) or systemic administration of the specific CRF1 receptor antagonist CP-154,526 attenuates stress-induced reinstatement of alcohol seeking (Le et al., 2000). Recent studies indicate that the activation of α1-adrenergic receptor plays a role in cue and drug-induced reinstatement of drug seeking. The α1-adrenergic receptor antagonist prazosin attenuates nicotine and cue-induced reinstatement of extinguished nicotine seeking in rats (Forget et al., 2010). Furthermore, the norepinephrine transport inhibitor nisoxetine induces the reinstatement of cocaine seeking in squirrel monkeys and this effect is blocked by prazosin (Fuller et al., 1975; Platt et al., 2007). In contrast, prazosin does not prevent forced swim stress-induced reinstatement of cocaine-induced conditioned place preference in mice (Mantsch et al., 2010). These studies suggest that α1-adrenergic receptor antagonists attenuate drug and cue-induced reinstatement of drug seeking but not stress-induced reinstatement of drug seeking.

Experimental evidence suggests that noradrenergic transmission in the central nucleus of the amygdala (CeA) plays a role in stress-induced reinstatement of drug seeking. This is supported by the observation that footshocks induce the release of norepinephrine in the amygdala (Galvez et al., 1996; Iimori et al., 1982). In addition, the administration of a mixture of the β1-adrenergic receptor antagonist betaxolol and the β2-adrenergic receptor antagonist ICI-118,551 into the CeA attenuates footshock-induced reinstatement of cocaine seeking (Leri et al., 2002). The aim of the present experiments was to investigate the role of noradrenergic transmission in the CeA in stress-induced reinstatement of nicotine seeking. The first experiment investigated the effects of clonidine in the CeA and the second experiment investigated the effects of dexmedetomidine in the CeA on stress-induced reinstatement of nicotine seeking. Clonidine (Ki α2: 3.2 nM; Ki α1: 713 nM) and dexmedetomidine (Ki α2: 1.1 nM; Ki α1: 1750 nM) are potent α2-adrenergic receptor agonists and they also bind with a relatively low affinity to α1-adrenergic receptors and imidazoline 1 (I1) and I2 receptors (Smith et al., 2009; Virtanen et al., 1988). Dexmedetomidine is a somewhat more selective α2-adrenergic receptor agonist than clonidine. Dexmedetomidine has a 7 fold greater selectivity for α2 over α1-adrenergic receptors than clonidine (Dexmedetomidine, α2/α1 ratio: 1620; Clonidine, α2/α1 ratio: 220) (Savola and Virtanen, 1991; Virtanen et al., 1988). Both the I1 and I2 receptor have been detected in the central nervous system (Dardonville and Rozas, 2004; Smith et al., 2009). Dexmedetomidine has a lower affinity for the I1 receptor than clonidine (Dexmedetomidine Ki: 637 nM; Clonidine Ki: 55 nM)(Piletz and Sletten, 1993). Both dexmedetomidine and clonidine have a very low affinity for the I2 receptor (Dexmedetomidine Ki: 38,700 nM; Clonidine Ki: 300,000 nM)(Piletz and Sletten, 1993). The third experiment investigated the effects of the nonselective β1/β2-adrenergic receptor antagonist propranolol in the CeA on footshock-induced reinstatement of nicotine seeking. The fourth experiment investigated the effects of the specific α1-adrenergic receptor antagonist prazosin in the CeA on footshock-induced reinstatement of nicotine seeking. These studies may improve the understanding of the role of noradrenergic transmission in the CeA in stress-induced reinstatement of nicotine seeking.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Charles River, Raleigh, NC) weighing 250–300 g at the beginning of the experiments were used. Animals were single-housed in a temperature and humidity-controlled vivarium and maintained on a 12 h reversed light–dark cycle (lights off at 9 AM). All testing occurred during the first 3 h of the dark cycle. Food and water were available ad libitum in the home cages. All subjects were treated in accordance with the National Institutes of Health guidelines regarding the principles of animal care. Animal facilities and experimental protocols were in accordance with the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) and approved by the University of Florida Institutional Animal Care and Use Committee.

2.2. Drugs

Nicotine hydrogen tartrate salt, prazosin hydrochloride, clonidine hydrochloride, propranolol hydrochloride, and pentobarbital sodium salt were purchased from Sigma (Sigma–Aldrich, St. Louis, MO, USA). Dexmedetomidine hydrochloride was purchased from Tocris (Tocris Bioscience, Ellisville, MO, USA). Nicotine and pentobarbital were dissolved in saline (0.9% sodium chloride). Clonidine, dexmedetomidine, prazosin, and propranolol were dissolved in distilled water. Drug doses are expressed as salt with the exception of the nicotine dose which is expressed as free base.

2.3. Surgical procedures

2.3.1. Catherization surgery

Rats were anesthetized with an isoflurane/oxygen vapor mixture (1–3% isoflurane) and prepared with a chronic catheter in the right jugular vein as described previously (Bruijnzeel et al., 2009; Zislis et al., 2007). Catheters consisted of silastic tubing (length 13.5 cm, 0.51 mm inside diameter × 0.94 mm outside diameter, Dow