Drug and Alcohol Dependence 188 (2018) 318–327

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Hypocretin/orexin antagonists decrease cocaine self-administration by female rhesus monkeys

Richard W. Foltin*, Suzette M. Evans

Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive, Unit 120, New York, NY, 10032, USA

ARTICLE INFO

Keywords:
Hypocretin
Orexin
Cocaine
Amphetamine
Self-administration
Non-human primate
Rhesus monkey
Female

ABSTRACT

Background: The hypocretin/orexin system is involved in regulating arousal, and much recent work demonstrates that decreasing hypocretin receptor-1 (HCRTr1) activity using antagonists decreases appetitive behavior, including stimulant drug self-administration and reinstatement.

Methods: The present study determined the effects of hypocretin-1 and HCRTr1 antagonists on responding reinforced by intravenous (i.v.) cocaine self-administration (0.0125 – 0.05 mg/kg/infusion) in 5 female rhesus monkeys. Responding was examined using 3 schedules of reinforcement: 1) a Fixed interval 1 min, Fixed ratio 10 Chain schedule [FI 1-min (FR10:S)], 2) a Progressive Ratio (PR) schedule, and 3) a cocaine vs. candy.

Results: Choice schedule: the HCRTr1 antagonist SB-334867 (8–24 mg/kg, i.m.) decreased cocaine taking under the Chain schedule and PR schedule in all 5 monkeys and in 4 of the 5 monkeys under the Choice schedule. *d*-Amphetamine (0.06 – 0.25 mg/kg, i.m.), tested as a control manipulation, decreased cocaine taking in all 5 monkeys under the Chain schedule. The peptide hypocretin-1 (0.072 mg/kg, i.v.) *increased* cocaine taking in the monkeys with low rates of cocaine taking under the Chain (3/4) and Choice (4/5) schedules. Reinstatement of extinguished cocaine responding following response-independent delivery of a large dose of cocaine (0.3 mg/kg) was attenuated in 3 of the 5 monkeys by the HCRTr1 antagonist SB-334867.

Conclusions: These data expand upon work accomplished in predominantly male rodents suggesting that the hypocretin system modulates the response to appetitive stimuli. A better understanding of this system offers promise as a novel approach in medication development for appetitive disorders.

1. Introduction

The neuropeptides hypocretin-1 and -2 or orexin-1 and orexin-2 (de Lecea et al., 1998; Sakurai et al., 1998) derive from the lateral hypothalamus and project throughout the brain (Koob, 2008). Hypocretins interact with the noradrenergic, cholinergic, serotonergic, and dopaminergic systems as well as with the hypothalamic-pituitary-adrenal (HPA) axis. In concert, these actions have been shown to modulate sleep-wake regulation, energy homeostasis, motivational activation, and stress responsivity (Carter et al., 2009; Giardino and de Lecea, 2014; Sutcliffe and de Lecea, 2002). Given its role in modulating arousal and appetitive behaviors, the hypocretin system offers promise as a novel approach in medication development for appetitive disorders.

Data obtained in laboratory rodents demonstrates a role for hypocretin in the development of sensitization, conditioned-place preference (CPP), self-administration, and reinstatement to cocaine and amphetamine. For example, an HCRTr1 antagonist blocked the development of sensitization to cocaine (Borgland et al., 2006) and amphetamine (Winrow et al., 2010) in rats, and sensitization to amphetamine was associated with increased c-FOS activation in many hypocretin-containing neurons in the rat brain (McPherson et al., 2007). With respect to CPP, Harris et al. (2005) trained a place preference for locations that had been paired with cocaine, morphine, or food in rats and measured c-FOS activation in hypocretin neurons in the lateral hypothalamus. In each case, the acquisition of a CPP was associated with increased c-FOS activation of hypocretin neurons in the lateral hypothalamus, and there was a positive correlation between c-FOS activation and magnitude of the CPP. HCRTr1 antagonism also blocked the development of CPP for an environment paired with cocaine (Gentile et al., 2018).

Few studies have examined the effects of the peptide hypocretin-1 on cocaine self-administration (Boutrel et al., 2005; España et al., 2011). Although there are slight differences across these 2 studies, intracerebroventricular (i.c.v.) infusion of hypocretin-1 did not alter responding that was reinforced under a Fixed Ratio 1 (FR1) schedule of reinforcement in both studies, but infusion of hypocretin-1 into the

* Corresponding author.
E-mail addresses: rwf2@cumc.columbia.edu (R.W. Foltin), se18@cumc.columbia.edu (S.M. Evans).

https://doi.org/10.1016/j.drugalcdep.2018.04.018
Received 1 February 2018; Received in revised form 10 April 2018; Accepted 10 April 2018
Available online 25 May 2018
0376-8716/

ventral tegmental area slightly increased responding for cocaine that was reinforced under a progressive ratio (PR) schedule in both studies.

SB-334867 [SB; (1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-yl-urea hydrochloride); Smart et al., 2001] has been the most commonly used HCRTr1 antagonist in studies assessing the role of hypocretin in cocaine reinforcement. The administration of a HCRTr1 antagonist reduced i.v. cocaine self-administration by rats most commonly only when responding was maintained under more complex or effortful schedules of reinforcement. When cocaine was delivered after every response (FR1), HCRTr1 antagonism had minimal effects on cocaine self-administration (España et al., 2010; Smith et al., 2009; Zhou et al., 2012; but see Hutcheson et al., 2011 for an exception). When cocaine was delivered under a larger FR schedule or a PR schedule of reinforcement, HCRTr1 antagonism consistently decreased cocaine self-administration (Borgland et al., 2009; Brodnik et al., 2015; Gentile et al., 2018; Hollander et al., 2012; España et al., 2010; Levy et al., 2017). Assuming that rats who respond with greater effort under more challenging reinforcement schedules are more motivated for cocaine, and this increased motivation is a model for human cocaine abuse, these findings suggest that the hypocretin system may be involved in the transition from lighter to heavier cocaine use. For example, Schmeichel et al. (2017) examined the effects of HCRTr1 antagonism on responding for cocaine in rats who had short-access (ShA) or long-access (LgA) to cocaine during daily sessions. Under the LgA condition in this model, rats accelerated their cocaine use over days, while rats under the ShA condition did not. It is hypothesized that the increase in cocaine intake under the LgA condition is a model for escalating drug use by humans. When cocaine was delivered under an FR1 schedule, HCRTr1 antagonism decreased cocaine self-administration under the LgA condition without affecting responding under the ShA condition. The lack of effect under the ShA condition parallels the earlier studies using a FR1 schedule. Of note, when cocaine was delivered under a PR schedule, HCRTr1 antagonism decreased cocaine self-administration under both the LgA and ShA conditions; this effect under an effortful schedule parallels the above PR studies. In summary, HCRTr1 antagonism significantly affects cocaine-taking behavior, but the effects in rats appear to be modulated by schedule of access to cocaine both effort-wise and duration-wise.

The hypocretin system also plays a major role in modulating reinstatement of cocaine seeking behavior in rats with a history of self-administering i.v. cocaine. The central administration of hypocretin-1 reinstated cocaine-seeking behavior in rats (Boutrel et al., 2005; Wang et al., 2009). In contrast, administration of an HCRTr1 antagonist attenuated cue-induced reinstatement of responding for cocaine in rats (Bentzley and Aston-Jones, 2015; Mahler et al., 2013; Smith et al., 2009, 2010) but had no effect on cocaine-elicited reinstatement (Mahler et al., 2013). Based on the differential effect of HCRTr1 antagonism on cue-induced vs. cocaine-induced reinstatement, Bentzley and Aston-Jones (2015) have suggested that one way that hypocretin systems affect cocaine taking is by modulating the motivational effects of cues paired with cocaine.

The hypocretin system also affects drug seeking, drug taking, and perhaps transition to heavy use of other drugs in addition to cocaine (e.g., Baimel et al., 2015; Corrigall, 2009; Richards et al., 2008; Smith and Aston-Jones, 2012). There is clearly significant data based on rodent studies supporting an important role for hypocretinergic systems in modulating both the motivation to consume cocaine and the possible transition from controlled to uncontrolled patterns of cocaine use. In contrast, there are no data in human and non-human primates on this topic. The first purpose of this series of studies was to investigate the effects of pretreatment with HCRTr1 antagonists and the peptide hypocretin-1 on i.v. cocaine self-administration by experimentally naïve rhesus monkeys. In addition, the effects of pretreatment with an HCRTr1 antagonist on cocaine-induced reinstatement were examined. Although sex differences have been reported in the hypocretin system in a few studies (e.g., Cason and Aston-Jones, 2013; 2014; Grafe et al., 2017; Zhou et al., 2012), the vast majority of laboratory animal studies have been conducted in males. Therefore, the second purpose of this series of studies was to investigate the effects of these hypocretin manipulations in female monkeys.

2. Methods

2.1. Animals

Five adult female rhesus monkeys (Macaca mulatta) initially weighing between 4.9 and 7.7 kg were fitted with a chronic indwelling catheter in the femoral vein (Access Technologies, Skokie, IL) that terminated in a subcutaneous vascular access port (VAP) (Wojnicki et al., 1994; Cooper et al., 2013). Monkeys were housed in customized, squeeze-capable, rack-mounted, non-human primate cages (Hazleton Systems, Inc., Aberdeen, MD) in the AAALAC-approved animal care facility of The New York State Psychiatric Institute. Each monkey had access to 2 identically-sized chambers (61.5 cm wide x 66.5 cm deep x 88 cm high) connected by a 40 cm × 40 cm opening. Water was freely available from spouts located on the back wall of both chambers. Fluorescent room lights were controlled by an automatic timer and were illuminated from 0700 to 1900. All aspects of animal maintenance and experimental procedures complied with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the New York State Psychiatric Institute Animal Care and Use Committee. In addition to operant responding during sessions, other forms of environmental enrichment included access to a variety of other tactile stimuli (e.g., toys, mirrors, and other objects to manipulate), visual access to the other monkeys, music, and television.

All monkeys were experimentally naïve and were trained in getting in and out of primate restraint chairs for experimental sessions. Based on daily assessment of menstrual cycle status, only 2 of the 5 female monkeys exhibited normal menstrual cycles during the period of data collection; the other 3 cycled intermittently. During the initial study phase, monkeys earned their daily food ration during operant sessions on weekdays and received a ration of approximately 7–9 chow each weekend day (High protein monkey diet #5047, 3.37 Kcal/g; LabDiets®, PMI Feeds, Inc., St. Louis, MO). Food-maintained responding was only assessed during the initial phase of the study. Upon completion of the first tests with an HCRTr1 antagonist, operant sessions for food ceased, and all food was given as chow. Monkeys were not food-restricted, and all gained weight over the course of the study.

2.2. Experimental set-up

For self-administration sessions, monkeys were taken from their home cage and placed into primate chairs for cocaine self-administration sessions that began at 9:00 A.M. A custom-designed right-angle Huber needle infusion set was used to connect the VAP to drug and saline infusion pumps (Multi-Phaser, Model NE-1000, New Era Pump Systems, Inc., Farmingdale, NY). The response panel was mounted on the wall in front of each primate chair. Session lights were evenly spaced around the outside edges of each panel. Each panel had 2 Lindsley levers (Gerbrands, Arlington, MA) with stimulus lights above each lever, one for drug and one for candy (for the choice schedule) mounted at the bottom. A food hopper, a pair of lights over the hopper, and a pellet-dispenser (BRS-LVE model PDC-005, Beltsville, MD) were mounted on the outside of the panel. The catheters had a volume of about 0.4 ml that was always filled with saline. Intravenous cocaine reinforcement (0, 0.0125, 0.0250, 0.050, 0.100, and 0.300 mg/kg/infusion) was accomplished by flushing the 0.4 ml of saline through the catheter and then immediately delivering 0.4 ml of cocaine solution followed by a 0.4 ml saline flush to leave 0.4 ml of saline in the catheter space; thus, each infusion consisted of 0.8 ml of fluid delivered over a 20-sec period. A pair of green lights, located at monkey eye level above the lever, flashed for 20 s (1 s on/1 s off) during the delivery of cocaine.