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Brain temperature effects of intravenous heroin: State dependency, environmental modulation, and the effects of dose

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ABSTRACT

Here we examined how intravenous heroin at a dose that maintains self-administration (0.1 mg/kg) affects brain temperature homeostasis in freely moving rats under conditions that seek to mimic some aspects of human drug use. When administered under standard laboratory conditions (quiet rest at 22 °C ambient temperature), heroin induced moderate temperature increases (1.0–1.5 °C) in the nucleus accumbens (NAc), a critical structure of the brain motivation-reinforcement circuit. By simultaneously recording temperatures in the temporal muscle and skin, we demonstrate that the hyperthermic effects of heroin results primarily from inhibition of heat loss due to strong and prolonged skin vasoconstriction. Heroin-induced brain temperature increases were enhanced during behavioral activation (i.e., social interaction) and in a moderately warm environment (29 °C). By calculating the "net" effects of the drug in these two conditions, we found that this enhancement results from the summation of the hyperthermic effects of heroin with similar effects induced by either social interaction or a warmer environment. When the dose of heroin was increased (to 0.2, 0.4, 0.8, 1.6, 3.2, and 6.4 mg/kg), brain temperature showed a biphasic down-up response. The initial temperature decrease was dose-dependent and resulted from a transient inhibition of intra-brain heat production coupled with increased heat loss via skin surfaces—the effects typically induced by general anesthetics. These initial inhibitory effects induced by large-dose heroin injections could be related to profound CNS depression—the most serious health complications typical of heroin overdose in humans.

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1. Introduction

Brain temperature is an important physiological parameter that depends on metabolic neural activity and affects multiple neural functions (Kiyatkin, 2010). Our previous thermorecording studies (see Kiyatkin, 2013 for review) revealed that psychomotor stimulant drugs, such as methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA), induce dose-dependent increases in brain temperature. By combining brain temperature measurements with recordings from the temporal muscle and skin, we clarified that the brain hyperthermic effects of these drugs result from two physiological mechanisms: increased intra-cerebral heat production due to metabolic brain activation and diminished heat loss due to sustained skin vasoconstriction. We also found that the hyperthermic effects of MDMA and METH are strongly enhanced when these drugs are administered during behavioral activation (i.e., social interaction) and at a moderately warm environment—conditions that often accompany drug use in humans. Under these conditions, METH and MDMA at doses much lower than LD50 induced pathologic hyperthermia, and even lethality in some rats. In the present study we extended this research line to examine how heroin affects brain temperature homeostasis in awake, freely moving rats.

In contrast to psychomotor stimulants, which induce sympathetic activation and locomotor hyperactivity, heroin causes profound sedation, locomotor hypoactivity (freezing) and, at higher doses, a comatose state that may result in lethality (see Simon, 1997; Jaffe et al., 1997). Based on these differences, it could be assumed that intravenous heroin could induce brain hypothermia—a response opposite to that induced by psychostimulants. However, direct data on the effects of heroin on brain temperature are absent and existing data on the effects of heroin on body temperature are limited and controversial (Martin et al., 1977; Geller et al., 1983).

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The primary goal of this study was to examine how intravenous (iv) heroin at a well-studied self-administering dose (0.1 mg/kg) affects brain temperature homeostasis in freely moving rats under conditions that aimed to mimic some aspects of human drug use. While heroin in rats is self-administered within a wide range of doses (0.025–0.2 mg/kg), a 0.1 mg/kg dose appears to be optimal for maintaining consistent behavioral performance with stable inter-injection intervals (Gerber and Wise, 1989). This dose is much lower than the estimated LD50 for iv administration in rats (15–20 mg/kg; Jackson, 1952; Strandberg et al., 2006; Gable, 2004) and heroin at this dose is self-administered by rats during multiple sessions without any significant health complications (Bozarth and Wise, 1985; Kiyatkin et al., 1993; Kiyatkin and Wise, 2002). This dose is also close to typical human doses in terms of drug amount per body weight (5–10 mg/70 kg; Goldstein, 1994; see also www.erowid.org). Temperatures in this study were simultaneously recorded with high temporal resolution from three locations: a brain site, the temporal muscle, and the skin. As a brain recording site, we chose the NAc, a deep brain structure critically involved in sensorimotor integration (Mogenson et al., 1980; Wise, 1989). Simultaneous recording temperatures from temporal muscle and skin allowed us to examine the mechanisms underlying the brain temperature effects of heroin, specifically its effects on intracerebral heat production and heat loss via skin surfaces (Kiyatkin, 2010).

First, we examined the effects of heroin on brain, muscle, and skin temperatures when the drug was used under standard laboratory conditions (quiet rest at 22 °C ambient temperatures). Second, we examined how the temperature effects of heroin are modulated during behavioral activation modeled in rats by social interaction between two animals. Third, we examined how the temperature effects of heroin are modulated at a moderately warm ambient temperature (29.0 ± 0.5 °C, i.e. at the levels corresponding to normothermy [Romanovsky et al., 2002]) that prevents normal heat dissipation to the external environment. Finally, we examined the temperature effects of heroin at doses well above a typical self-administering range–doses that may result in serious health complications (Louria et al., 1967; Compton et al., 2016).

2. Materials and methods

2.1. Subjects, surgery, and thermocouple sensors

We used 25 Long-Evans male rats (Charles River Laboratories, Greensboro, NC) 3–4 months in age and 440 ± 40 g in weight, that were housed individually in a temperature-, humidity-, and light-controlled room (12/12 h light/dark cycle, lights on at 07:00) with free access to food and water. Protocols were performed in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health, Publication 865-23) and were approved by the NIDA-IRP Animal Care and Use Committee.

Each rat underwent the same three-point thermocouple probe implantation procedure described in detail elsewhere (Kiyatkin et al., 2014). Briefly, under general anesthesia (sodium pentobarbital + chloral hydrate), rats were implanted with miniature copper-constantan thermocouple probes (125 μm in diameter) in the NAc shell (AP = 1.2 mm; L = 0.9 mm; DV = 7.2–7.4 mm according to the atlas of Paxinos and Watson, 1998), deep temporal muscle and subcutaneously, along the nasal ridge with the tip approximately 15 mm anterior to the bregma. Using dental cement, we secured the probes to three stainless steel screws threaded into the skull. During the same surgical procedure, rats were implanted with a chronic jugular catheter, which ran subcutaneously to an injection port secured with the head assembly. Rats were allowed a minimum of 4 days of post-operative recovery; jugular catheters were flushed daily with 0.2 ml heparinized saline (10 units/ml) to maintain patency. At the beginning of each experiment, the injection port of the jugular catheter was connected to a plastic catheter extension that allowed for stress- and cue-free delivery of tested substances from outside the chamber, thus minimizing possible detection of the injection procedure by the rat.

While our primary focus was on brain temperature, two other recording locations were used to evaluate basic physiological mechanisms underlying changes in brain temperature. Since the brain and temporal muscle receive arterial blood from the same common carotid artery and thus are equally exposed to blood-delivered heat from the body, the change in NAc-Muscle temperature differentials shows the source of heat production and serves as a measure of drug-induced metabolic brain response (Kiyatkin, 2010). Specifically, increases in NAc-Muscle differentials suggest increased metabolic brain activity, while their decreases suggest metabolic brain inhibition. Skin temperature is determined by the state of peripheral vessels and its decreases suggest vasoconstriction, however it also depends on the temperature of arterial blood inflow. Therefore, Skin-Muscle temperature differentials exclude this latter contribution, providing an accurate measure of changes in skin vascular tone (Kiyatkin, 2010). Specifically, increases in Skin-Muscle differential indicate enhanced heat loss due to vasodilation whereas decreases indicate diminished heat loss due to vasoconstriction.

2.2. Experimental protocol

All recordings took place during the light phase of the rat's cycle in a light- and sound-attenuated chamber under a dim white light. Each morning, we brought the rats from their housing facility, placed them in the chambers, and connected them to the recording instrument (Thermes-16, Physitemp Instruments; Clifton, NJ) via individual sockets attached to a common cord and an electric swivel commutator. We exposed each rat to two habituation sessions (~6 h each) prior to surgeries and one habituation session (6 h) thereafter, which preceded heroin or saline injections. During each recording session, drug or saline injections began at least 2 h after placement in the chamber, thus allowing the rats to habituate to the environment and their temperatures to return to baseline levels. We recorded temperatures continuously and collected the data at 10-s intervals. We maintained room temperature at either 22.5 ± 0.5 °C ("standard laboratory conditions") or 29.0 ± 0.5 °C ("warm environmental conditions"). Additionally, we measured locomotor activity using four photobeams located at the chamber's walls as previously described (Kiyatkin et al., 2014).

In Experiment I (n = 6 rats), we examined the temperature and locomotor effects of heroin delivered iv at a standard self-administering dose (0.1 mg/kg in 0.3 ml saline over 30 s) to quietly resting rats at standard ambient temperature (22 °C). Each rat in this experiment was exposed to three drug sessions, in which rats received three iv heroin injections with an inter-injection interval of at least 120 min that is sufficient for restoring baseline temperatures. In Experiment I we did not employ a saline control. As shown previously (Kiyatkin and Brown, 2004), iv saline injected under cue- and stress-free conditions induces no changes in temperatures.

In Experiment II (n = 5 rats), we examined the temperature and locomotor effects of heroin delivered iv at the same dose (0.1 mg/kg) during social interaction. We placed a novel, drug-naive conspecific male in the experimental rat's chamber 10 min before the experimental rat received a heroin or saline injection. This guest rat was kept in the chamber with the experimental rat for 50 min following the injection. During this time period (a total of 60 min), we allowed the two rats to freely interact with each other.