



Locomotor activity does not predict individual differences in morphine self-administration in rats

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ABSTRACT

Understanding factors contributing to individual differences in opioid addiction vulnerability is essential for developing more effective preventions and treatments. Sensation seeking has been implicated in addiction to several drugs of abuse, yet its relationship with individual differences in opioid addiction vulnerability has not been well established. The primary goal of this study was to evaluate the relationship between locomotor activity in a novel environment, a preclinical model of sensation-seeking, and individual differences in acquisition of i.v. morphine self-administration (SA) in rats. A secondary goal was to evaluate the relationship between activity and elasticity of demand (reinforcing efficacy) for morphine measured using a behavioral economic approach. Following an initial locomotor activity screen, animals were allowed to acquire morphine SA at a unit dose of 0.5 mg/kg/infusion in 4 hour/day sessions (Experiment 1) or 0.2 mg/kg/infusion in 2 hour/day sessions (Experiment 2) until infusion rates were stable. Unit price was subsequently manipulated via progressive reductions in unit dose (Experiment 1) or increases in response requirement per infusion (Experiment 2). Activity levels were not correlated with acquisition of morphine SA in either experiment. Morphine consumption was generally well described by an exponential demand function in both experiments (R^2 values > 0.95 for rats as a group), but activity did not correlate with behavioral economic measures. Locomotor activity in a novel environment did not predict individual differences in acquisition of morphine SA. These data complement findings from some human studies and suggest that the role of sensation seeking in individual differences in opioid addiction vulnerability may be limited.

1. Introduction

Opioid addiction poses a tremendous burden on public health (Center for Behavioral Health Statistics and Quality, 2013; Center for Behavioral Health Statistics and Quality, 2015). Although many people experiment with opioids, only a minority undergo the loss of control over drug use that defines addiction (American Psychiatric Association, 2013; Belin et al., 2016). Understanding the behavioral and neurobiological mechanisms contributing to individual differences in opioid addiction vulnerability is essential for developing more effective preventions and treatments.

Sensation-seeking, or the pursuit of novel and intense experiences and a willingness to take risks in order to attain such experiences (Zuckerman, 1994), has been implicated in vulnerability to addiction to a variety of drugs including stimulants (e.g. cocaine, amphetamine) and alcohol (Bardo et al., 2013; Belin et al., 2016; Hittner and Swickert,

2006; Piazza et al., 1989). However, the relationship between sensation-seeking and opioid addiction vulnerability has not been well established. Some studies have shown a positive relationship between sensation-seeking and opioid use in humans (Franques et al., 2003; Kosten et al., 1994; Vest et al., 2016), while others have shown either no relationship (Conrod et al., 2000; Marino et al., 2013; Nielsen et al., 2012) or a negative relationship (Ahn and Vassileva, 2016). The reasons for these discrepancies across studies are unclear, but may reflect differences in subject characteristics (e.g., age, sex, drug use history, and/or comorbidities), measure(s) of sensation-seeking, or other factors (Marino et al., 2013).

Animal models allow for greater experimental control than human studies, and could be useful for understanding the role of sensation-seeking in opioid addiction vulnerability. Spontaneous locomotor activity in a novel environment is a commonly used preclinical model of sensation-seeking (Blanchard et al., 2009; Pawlak et al., 2008; Piazza

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et al., 1989). Consistent with the relationship between sensation seeking and stimulant use in humans, higher activity reliably predicts greater self-administration (SA) of stimulants (e.g., cocaine, amphetamine), particularly in terms of acquisition (Belin et al., 2008; Belin et al., 2011; Belin and Deroche-Gamonet, 2012; Piazza et al., 1989; Piazza et al., 2000).

Only limited data are available regarding the relationship between spontaneous locomotor activity and individual vulnerability in i.v. opioid SA. In a comparison between several inbred rat strains, those strains with higher activity levels also exhibited greater acquisition of morphine SA under certain conditions (Ambrosio et al., 1995; see Discussion for further details). However, the relationship between locomotor activity and opioid SA in outbred rodents has not been evaluated. This represents an important research gap given that inbred and outbred rats are genetically distinct, and because findings on predictors of addiction vulnerability in inbred and outbred rat strains are not always concordant (Cadoni et al., 2015; Chaouloff et al., 1995; Dilleen et al., 2012; Meyer et al., 2010).

The primary goal of this study was to evaluate locomotor activity as a predictor of individual differences in the acquisition of morphine SA in outbred rats. Because activity did not predict acquisition of morphine SA under the conditions initially studied (0.5 mg/kg/infusion, 4 h/day sessions), we evaluated the generality of this finding to a different model with a lower dose and shorter access period (0.2 mg/kg/infusion, 2 h/day sessions). This approach was used because the relationship between activity and SA of other drugs (e.g. cocaine) can be more apparent when lower unit doses and/or shorter access periods are used (Belin et al., 2016; Kabbaj, 2006; Mantsch et al., 2001).

A secondary goal was to apply a behavioral economics framework to the analysis of individual differences in morphine SA. Behavioral economics involves evaluation of the extent to which consumption of a reinforcer (e.g., drug) is maintained following increases in its unit price, which in drug SA models is operationalized as the cost-benefit ratio of response requirement/unit dose (Bickel et al., 2000; Hursh, 1991; Hursh and Silberberg, 2008). Behavioral economics has been useful for studying individual differences in elasticity of demand (i.e., reinforcing efficacy) of numerous addictive drugs (e.g., cocaine) in both humans and animals (Diergaarde et al., 2008; Grebenstein et al., 2013; Hursh and Silberberg, 2008; LeSage et al., 2016), but has not yet been applied to morphine SA in rodents. Therefore, we evaluated elasticity of demand in animals that acquired morphine SA in both experiments in order to 1) evaluate the precision and generalizability of a behavioral economic framework in the context of morphine SA, and 2) provide a preliminary evaluation of the relationship between locomotor activity and individual differences in behavioral economic measures.

2. Materials and methods

2.1. Animals

Male adult Sprague Dawley rats (Envigo, Indianapolis, IN) weighing 276–300 g at arrival were used. All rats were individually housed in a temperature- and humidity-controlled colony room with unlimited access to water under a reversed 12-h light/dark cycle (lights off at 10:00 h). All behavioral testing occurred during the dark (active) phase. Beginning one week following arrival, food was restricted to 18 g/day to facilitate operant performance, avoid detrimental health effects of long-term ad libitum feeding, and limit catheter migration. Protocols were approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation in accordance with the 2011 National Research Council's Guide for the Care and Use of Laboratory Animals and the 2003 National Research Council Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research.

2.2. Apparatus

2.2.1. Locomotor activity

Locomotor activity was monitored in 43 × 43 cm open field activity chambers (Med Associates, Inc., St. Albans, VT). Each chamber had two 16-beam photocell arrays placed 5 cm and one array 18 cm above the chamber floor to monitor horizontal and vertical activity, respectively. Chambers were placed inside sound-attenuating cubicles equipped with exhaust fans that provided masking noise and ambient lighting. Open-field activity software (Med Associates) was used for operating the apparatus and recording data.

2.2.2. Morphine self-administration

Self-administration (SA) sessions were conducted using 16 standard operant conditioning chambers (model ENV-007, Med Associates, Inc). Each chamber contained two response levers, a white stimulus light located 2 cm above each lever, and a house light that provided ambient illumination. Each chamber was placed inside a sound-attenuating cubicle equipped with an exhaust fan that provided masking noise. An infusion pump (model PHM-100-15, Med Associates) placed outside each cubicle delivered infusions at a rate of 100 µl/kg per second. MED-PC IV software (Med Associates) was used for operating the apparatus and recording data.

2.3. Drugs

Morphine sulfate (NIH National Institute on Drug Abuse Drug Supply Program, Bethesda, MD) was dissolved in sterile saline and heparin (30 units/ml) was added to maintain catheter patency. Morphine doses are expressed as the weight of the salt.

2.4. Surgical procedures

Each rat was implanted with a chronic indwelling catheter into the right jugular vein under isoflurane (1%–3%) anesthesia, using general surgical procedures described in detail elsewhere (Harris et al., 2008; LeSage et al., 2002). The catheter was externalized between the scapulae and attached to a vascular-access harness (VAH95AB, Instech Laboratories, Plymouth Meeting, PA) that allowed connection to a fluid swivel via a tether for morphine administration. Animals were allowed to recover for one week after surgery, during which time they received daily i.v. infusions of heparinized saline, ceftriaxone antibiotic (5.25 mg, first three days only), and s.c. injections of buprenorphine (0.05 mg/kg; first two days only) for analgesia. Infusions of methohexital (0.1 ml, 10 mg/ml, i.v.) were administered to check patency post-session on Fridays throughout all protocols. If a catheter became occluded (indicated by a failure of the animal to exhibit anesthesia within 3–5 s after methohexital infusion), another catheter was implanted into the ipsilateral femoral vein. Failure of this second catheter resulted in removal of the animal from the study.

2.5. Experimental protocols

2.5.1. Experiment 1

Six days after arrival, rats (N = 16) were monitored for locomotor activity in a novel open field for 2 h. At least 24 h later, rats were catheterized as described above. After a 7–10-day recovery period, rats were allowed to acquire i.v. morphine SA during daily 4 h sessions conducted Mon–Fri. During each session, responding on the left (“active”) response lever resulted in an i.v. infusion of morphine sulfate at a unit dose (0.5 mg/kg/infusion) that maintains robust SA and that has previously been used to evaluate other determinants (e.g., pain sensitivity) of individual differences in morphine SA (Park et al., 2017; Nishida et al., 2016). Each infusion was accompanied by offset of the house light and the onset of a white cue light above the active response lever. Following a 5-second timeout period, the cue light above the

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