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Rearing environment differentially modulates cocaine self-administration after opioid pretreatment: A behavioral economic analysis

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ABSTRACT

Background: Research has shown that previous experiences during development, especially if stressful, can alter an organism's response to opioids later in life. Given the previous literature on opioid modulation of cocaine self-administration, the current study raised rats in either an enriched condition (EC) or isolated condition (IC) and employed behavioral economics to study the effects of naltrexone and morphine on cocaine self-administration.

Methods: EC and IC rats were trained to lever press for cocaine using a within-session demand procedure. This procedure measured cocaine consumption under changing cocaine price by decreasing the dose of cocaine earned throughout a session. Rats were able to self-administer cocaine on a FR1; every 10 min the cocaine dose was systematically decreased (0.75–0.003 mg/kg/infusion cocaine). After reaching stability on this procedure, rats were randomly pretreated with 0, 0.3, 1, or 3 mg/kg naltrexone once every 3 days, followed by random pretreatments of 0, 0.3, 1, or 3 mg/kg morphine once every 3 days. Economic demand functions were fit to each rat's cocaine consumption from each pretreatment, and appropriate mathematical parameters were extracted and analyzed.

Results: Naltrexone decreased the essential value of cocaine in IC rats only. However, morphine decreased the essential value of cocaine and the consumption of cocaine at zero price in both EC and IC rats.

Conclusion: These results indicate that environmental experiences during development should be considered when determining the efficacy of opioid drugs, especially for the treatment of substance abuse.

1. Introduction

Multiple lines of evidence suggest that endogenous opioids affect reward processing, but the exact mechanism of their modulatory effect is debated (Koob and Le Moal, 1997; Laurent et al., 2015; Peciña and Berridge, 2005). Exposure to a reinforcer causes release of endogenous opioids in nucleus accumbens (Olive et al., 2001; Roth-Deri et al., 2003). This reinforcer-induced opioid release is important for reward; administration of mu receptor antagonists, such as naltrexone, have been shown to decrease the rewarding properties of some drugs of abuse, including alcohol (O'Malley et al., 2015Ripley et al., 2015; Williams and Woods, 1998) and cocaine (Giuliano et al., 2013; Kiyatkin and Brown, 2003; Ramsey et al., 1999). In contrast, mu receptor agonists, such as morphine, are reinforcing by themselves (Devine and Wise, 1994) and have been shown to enhance consumption of natural rewards (Zhang and Kelley, 2002).

However, some general discrepancies on the effectiveness of naltrexone and morphine in the human literature exist, which may be attributed to individual differences in components of the endogenous opioid system. In humans, genetic factors have been implicated in patients' response to opioids. Individuals possessing the less common mu receptor polymorphism (A118G) may be more responsive to high dose naltrexone for the treatment of alcohol dependence (Anton et al., 2008), and these individuals require higher average morphine doses for pain management after surgery (Hwang et al., 2014). Mouse models of this polymorphism yield similar results; mice homozygous for the less common allele are more sensitive to naltrexone's efficacy in reducing brain stimulation reward (Bilbao et al., 2015) and demonstrate reduced sensitivity to morphine's antinociceptive properties (Mague et al., 2009).

Individual differences in an organism's response to opioids might extend beyond genetics; evidence suggests that experience

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can affect an individual's response to opioids. Episodes of chronic pain (Corder et al., 2013) and social defeat (Chaijale et al., 2013) result in long-lasting changes to opioid efficacy and endogenous opioid signaling in rodents. These studies suggest that stressful states might alter opioid efficacy in nociceptive processing. Since opioids also regulate reward, it is possible that stressful states, such as isolation rearing (Bowers et al., 2008; Djordjevic et al., 2012), might affect drug reinforcement through alteration of endogenous opioid signaling. Given that opioid antagonists are sometimes prescribed for the treatment of alcohol use disorder (O'Malley et al., 2015Oslin et al., 2015) and opioid abuse (Goonoo et al., 2014), understanding how life experience alters opioid efficacy is crucial to improving patient outcomes.

Many studies examining the role of opioids in reward have measured their modulation of alcohol and food intake. While other studies have examined the effects of opioid ligands on cocaine self-administration, these have yielded mixed results. The majority of studies in rodents and monkeys suggest that both opioid agonists (Gerak et al., 2009; Lynch et al., 1998; Negus and Mello, 2002) and antagonists (Corrigall and Coen, 1991; Mello et al., 1990; Ramsey and van Ree, 1991) decrease cocaine self-administration. However, one study found no effect (Ettenberg et al., 1982) and other studies found dose-dependent potentiation of cocaine self-administration (Carroll et al., 1986; Corrigall et al., 1999) after administration of these compounds systemically (Carroll et al., 1986) or into the ventral tegmental area (VTA; Corrigall et al., 1999).

There are several important methodological discrepancies in this literature. The biggest differences among these studies include cocaine dose and schedule of reinforcement. Naltrexone has been effective in decreasing medium- to low-dose cocaine self-administration, but not higher-dose cocaine self-administration (Corrigall and Coen, 1991). Additionally, opioid antagonists are not consistently effective on single schedules of reinforcement in rodents (Ettenberg et al., 1982; Giuliano et al., 2013; Ward et al., 2003), but have been successful at attenuating cocaine self-administration using second-order schedules (Giuliano et al., 2013) and decreasing breakpoints using progressive ratio (Ward et al., 2003; Wee et al., 2009). The literature on opioid agonists also differs by cocaine dose, with the mu selective agonist DAMGO increasing cocaine responding at low cocaine doses, but decreasing it at high cocaine doses (Corrigall et al., 1999), suggesting that opioids affect cocaine self-administration, but only under specific schedules of reinforcement and at certain cocaine doses.

Since the ability of opioids to modulate cocaine self-administration appears to depend, at least in part, on the cocaine unit dose tested, this suggests that opioids are affecting sensitivity to changes in cocaine-associated reinforcement cost; when framed in behavioral economic terms, these previous studies measured drug consumption at various prices of cocaine. Conceptually, price of cocaine is the response effort an animal exerts to obtain an infusion of cocaine, expressed as response requirement per unit dose. Thus, in the case of a fixed ratio 5 (FR5) for a 1 mg/kg/infusion cocaine unit dose, unit price would be described as 5/1. Clearly, higher fixed ratio requirements raise unit price. Additionally, because unit price is a ratio, lower cocaine doses can also produce equivalent changes in the price per unit. An animal would have to obtain more infusions of a low unit dose to earn a specific amount of drug (e.g., 10 infusions of a 0.1 mg/kg/infusion dose to earn 1 mg/kg) compared to fewer infusions of a high unit dose to receive the same amount of drug (e.g., 1 infusion of a 1 mg/kg/infusion dose), making the lower unit dose higher in price. Thus, the experimenter can manipulate unit price by keeping dose constant and raising the ratio requirement (increasing values in the numerator), or by keeping the ratio requirement constant and decreasing the unit dose available (decreasing values in the denominator). When these two things are combined, unit prices are increased in a multiplicative fashion.

Behavioral economics and analysis of demand borrow from economic theory in which consumption of some goods is often inversely related to price. Unlike the standard self-administration dose-effect curve analysis, an economic approach can help to separate hedonic set-point (how much of a good an animal would consume if it were free) and essential value (how willing an animal is to work for a reinforcer as it gets more costly to obtain; Oleson et al., 2011). When applied to animal operant behavior, this paradigm can help address some of the methodological inconsistencies present in previous studies of this kind (i.e., schedule of reinforcement and cocaine dose). This approach has been proposed to help identify potential treatments for drug abuse (Hursh and Winger, 1995), and has recently been employed to this end in rodent self-administration studies (Bentzley et al., 2014; Porter-Stransky et al., 2015).

To assess the effect of early life experiences on the ability of opioids to modulate the essential value of cocaine, the current study measured cocaine self-administration in two different groups of rats; one group was raised in an enriched condition (EC) during adolescence and the other group was raised in an isolated condition (IC). Each group was then pretreated in young adulthood with various doses of naltrexone or morphine before cocaine self-administration sessions. Self-administration sessions utilized a within-session threshold procedure that assessed drug intake at various cocaine doses within a single session (Oleson et al., 2011). By standardizing cocaine consumption across doses and converting cocaine dose to unit price, such that higher cocaine doses are easier to obtain and are lower in price, an economic demand function was fit to rats' cocaine intake (Hursh and Silberberg, 2008). Both hedonic set-point (Q_0) and essential value (α) after pretreatment with opioid ligands were compared between EC and IC rats.

2. Materials and methods

2.1. Subjects and housing

Male Sprague-Dawley rats arrived to the colony on PND 21. Upon arrival, they were randomly separated into one of two housing conditions: either EC (enriched condition, n = 5) or IC (isolated condition, n = 8). EC rats were housed 5–12 per cage in large, stainless steel cages (122 × 61 × 45.5 cm) with ample bedding. Fourteen objects were placed throughout the cage and were rearranged daily and completely replaced every other day. IC rats were housed singly in small stainless steel cages (17 × 24 × 20 cm) with wire mesh bottoms and no objects. Rats remained in their respective conditions for the entire study. Rats were kept in a temperature and humidity controlled colony room on a 12 h light:dark cycle (lights on at 7:00 a.m.). All animal procedures were approved by the University of Kentucky's Institutional Animal Care and Use Committee and conformed to NIH standards.

2.2. Surgical procedures

Between PND 55 and 60, all rats received jugular catheter implantation surgery. Briefly, rats were anesthetized with a ketamine (Butler Schein, Dublin OH)/xylazine (Akorn, Inc., Decatur IL)/acepromazine (Boehringer Ingelheim, St. Joseph MO) cocktail (75/7.5/0.75 mg/kg; 0.15 ml/100 g body weight; i.p.). A jugular catheter was implanted into the right jugular vein, threaded under the skin, and exited the body through an incision on the scalp. The catheter port was attached to the skull using four jeweler's screws and dental acrylic. Rats were allowed to recover for one week before starting self-administration.

2.3. Cocaine self-administration training

All operant procedures occurred in standard 2-lever operant conditioning chambers (28 × 24 × 21 cm; ENV-008CT; MED Associates, St. Albans VT) equipped with syringe pumps for drug delivery (PHM-100; MED Associates). Ten days before surgery, all rats were trained to lever press for food pellets (45 mg Dustless Precision Pellets, Bio-Serv, Frenchtown NJ) on a FR1 schedule for 60 min as described previously (Hofford et al., 2015). Rats received 15 g of food at the end of their session for the first five days of training, but were returned to free feed for the remainder of the experiment. One week after surgery, rats were returned to the operant boxes and connected to the syringe pump via silastic leashes. Rats began cocaine self-administration training where they received 0.75 mg/kg/infusion cocaine (i.v.,