

HEADER: THE EFFECTS OF COMPETING REINFORCEMENT ON MORPHINE SEEKING BEHAVIOR USING A RAT MODEL

The Effects of Competing Reinforcement on Morphine Seeking Behavior Using a Rat Model

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INTRODUCTION

Heroin and other opiates are known for lack of treatment seeking behaviors as well as relapse. Around 23 percent of users will develop an addiction to heroin or other opiates (<http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf>). Rates of relapse are quite ambiguous, but with no treatment, around 50-65 percent of all addicts will go back to using opiates (Krupitsky et al. 2011). A majority of opiate users who suffer from mental health problems, failing health, criminal histories, and unemployment (Banda, Karcher & Poljak, 2012) appear to have a higher rate of abuse and addiction with opiates. Since heroin is a schedule one drug, I will be using morphine, a schedule two drug, as a substitute.

I am utilizing a behavioral economic approach, combining both behavioral psychology and economics. Combining two fields is useful as it brings into two different approaches to try and fix the issues surrounding addiction (French, 2001). Behavioral economics focuses on researching the elasticity of demand of reinforcers and their competing value against other potential reinforcers. Curves show the overall strength of the reinforcing value and the consumption level based on pricing (Hursh & Silberberg, 2008). Behavioral economics also studies how goods (drugs and reinforcers) act together: as complements, substitutes, or independently of one another.

Through this approach, researchers have discovered that demand for drugs is high in the short term (Bickel et al. 2011). It is expected that after a ten-day withdrawal period, demand for morphine should fall. [applied behavioral economics]

A study on opioid withdrawal and choice conducted on rhesus monkeys furthered studies already observing effects on opioid-maintained responding during withdrawal (Wade-Galuska, Galuska, & Winger, 2011). The study looked at mild morphine withdrawal effects on choice of

cocaine or remifentanyl, a μ -opioid agonist. Mild withdrawal was defined as 3 and 20.5 hours and once more between 4 to 5 weeks. After 3 hours withdrawal, monkeys chose the drug they had a higher preference for pre-morphine, but the choice drug became more elastic. After 20.5 hours, monkeys preferred remifentanyl and their demand for the drug became more inelastic. Monkeys preferred the opioid agonist over the cocaine during withdrawal symptoms and the demand for both remifentanyl and cocaine became more inelastic the longer the withdrawal. This assumes that the drugs may have already been in high demand pre-morphine.

A key region of the brain involved in drug addiction and reward is the nucleus accumbens (NAc). Kobrin et. al (2015) studied the effects of NAc dendritic spine length and density in mice that underwent morphine Conditioned Place Preference (CPP) training. Stimulant drugs of abuse have been shown to increase NAc dendritic spine lengths, while ethanol and withdrawal are shown to decrease spine lengths. Morphine CPP mice had an increase in dendrite density and spine length compared to control mice. This means that drug reward may be increased in these mice and even have an increase in long-term potentiation of drug reward in that specific environment. Drug seeking and using behaviors may be increased when placed in a specific or similar environment.

Mental health problems, failing health, criminal histories, and unemployment can all lead to additional stressors on an individual. Bali, Randhawa, and Jaggi (2015) did a meta-analysis of the effects of stressors on opiate use. Some of the stressors they examined was anxiety, PTSD, and fear. Dynorphin/k-opioid receptor systems have been shown to perpetuate drug seeking behaviors, and this system is also commonly associated with stress. In one study, the experimenters discovered that repeated forced swim tests activated this system, and also reinstated extinguished cocaine seeking behaviors (Smith, et al. 2012). Multiple other studies

examined in Bali et al. (2015) show that stress inhibits CPP but enables drug seeking behaviors in rats and mice. The toy in my experiment should act as a stress reliever as it is something new and exciting for the rat. This was expected to help lower morphine seeking behavior.

I will be studying the effects of toys as a competing reinforcer on morphine seeking behavior. My question is: will the presence of a toy have an impact on chamber choice and thus morphing seeking behavior? I believe that the control group will have a higher average time in the morphine chamber because morphine acts as both a positive reinforcer and a negative reinforcer by eliminating withdrawal symptoms (Wade-Galuska, Galuska, & Winger, 2011). The treatment group should have a higher average time in the saline chamber. The toy should act as a substitution good for the morphine. Average time of chamber choice will represent drug or non-drug seeking behavior and may signify relapse rates.

METHODS

Variables

There are two independent variables: drugs and a toy. Morphine was a 5 mg/kg in a 1 ml/kg saline solution (Cordery et al. 2014). The reason for a higher solution was for fast and optimal conditioning within the conditioned place preference chamber (CPP). Naloxone was a 3 mg/kg in a 1 ml/kg saline solution. Toys are novel to the rats and will be switched every trial to ensure novelty. The dependent variable is the behavior the rats exhibit once entering the CPP through chamber choice.

Subject Population

Eight male Sprague-Dawley rats were used. Food and water were available continuously. Rats were living in standard housing with a light cycle of 8am-11pm. Rats were group-housed four per cage. Rats were experimentally naïve prior to the experiment.

Apparatus

Rats were placed in a CPP chamber. There were three chambers measuring 20x33x41 cm with swinging doors allowing the rats to pass through the chambers. Two of the three chambers were used during conditioning. Saline was injected in the preferred chamber and the morphine was injected in the non-preferred chamber which was established during baseline trials. The first chamber was solid black, and the third chamber was a black and white checkered pattern. The center chamber is plain white and used only during testing to allow chamber choice.

Procedure

Before conditioning occurs, rats were tested in the CPP to get a baseline of which chamber each individual rat prefers. Rats were measured as entering a chamber when ~60% of the body was in a chamber. Morphine conditioning took place in the non-preferred chamber to validate rats went to a chamber because they prefer the morphine not the chamber. All rats were initially injected IP with 5 mg/kg of morphine or saline during conditioning and placed in the appropriate chamber. Rats were placed in chambers approximately 27 minutes after injections ensuring rats were in the chamber during peak morphine levels which occur at approximately 30 minutes (Cerletti et al. 1980). Saline injections were kept on the same time to keep a constant. Conditioning occurred for approximately two weeks. By the end of conditioning, rats were tested to ensure addiction was acquired which was measured through choice of chamber. After addiction had been acquired, all rats underwent 3mg/kg Naloxone treatments (Cordery et al. 2014) for ten days post morphine injections to ensure that the rats were sober (Haggkvist et al. 2011). Naloxone also simulates rehabilitation facilities where patients are given drugs to detoxify. During testing, rats were separated into two groups of four. The experimental condition received a toy to play with in the saline chamber, and the control group did not. Toys were small

cat toys such as balls with bells and stuffed rats and were changed every trial to ensure novelty. All rats were placed in the center chamber and allowed to roam freely throughout the chamber. Testing occurred for four trials and each trial lasted for five minutes.

Data Analysis

Preference score equals total time spent in each chamber (secs)/how many visits to each chamber (Moddab, Highland, & Brown, 2015; Cole et al. 2012) thus providing an average time spent in each chamber. T-tests were run on average times spent in the morphine chamber as that is the chamber of interest. Statistical analysis was conducted on GraphPad Software.

RESULTS

The control group received one probe, and the experimental group received three probes to ensure addiction and conditioning were acquired.

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