A METHOD FOR ORAL OXYCODONE SELF-ADMINISTRATION IN TOUCHSCREEN OPERANT CHAMBERS FOR MICE

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Abstract

Opioid Use Disorder (OUD) is a significant public health crisis and there is critical need for new therapeutics. Prescription opioids are often abused and are most often taken orally. Preclinical self-administration (SA) assays are commonly used to model OUD. However, most of these assays employ an intravenous route of drug delivery. To have a more translatable model for human prescription opioid abuse, there is need for integration of oral route of delivery. Our goal was to develop and implement an oral opioid SA assay for mice, for Bussey-Saksida touchscreen chambers. We sought to determine whether we could train mice to orally self-administer oxycodone (OXY), and whether mice would maintain this SA at a target concentration. We also wished to examine sex differences in behavior. We utilized C57BL/6J mice and food restricted them to 85-90% of free-feeding weight, to increase task motivation. During the first, postprandial phase of the study, mice were fed and underwent water restriction during a pre-experiment session (to increase thirst). Mice were then placed in the touchscreen chambers to self-administer water. Once they learned water self-administration, they progressed to self-administer increasing concentrations of OXY (0.05, 0.10, 0.30, 0.50, and 1.00 mg/ml). They then underwent a non-postprandial testing phase. During experiment pre-sessions, they now were not fed, nor water restricted. They were then tested in the touchscreen chambers to see whether they would maintain OXY SA at the highest concentration (1.00 mg/ml). We found that both male and female mice acquired OXY SA during the postprandial, training phase. As concentration increased, number of OXY rewards decreased but amount of OXY consumed (mg/kg) increased. At the two low concentrations (0.05, 0.10 mg/ml), males earned more OXY rewards than females. However, when taking into account mice weight, males and females consumed equivalent amounts of OXY (mg/kg). During our non-postprandial testing phase, both
males and females maintained SA behavior. Our results indicate that we can train mice to acquire and maintain oral OXY SA through this novel touchscreen assay. We also show no baseline sex differences. This assay can be utilized to further investigate factors that contribute to risk for OUD.

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1. Introduction

Opioid Use Disorder (OUD) is a significant public health concern. The number of overdoses and deaths associated with opioid use and abuse have quadrupled since 1999. These overdoses and deaths have continued to consistently rise, having reached epidemic levels [1]. Commonly abused opioids which have driven these overdoses and deaths include heroin and fentanyl, but also prescription opioids such as oxycodone (OXY) [2].

Prescription opioids are used in the clinical setting, being administered and prescribed to patients for pain relief. However, all opioids including prescription opioids have rewarding effects (e.g., euphoria), which fuels their high abuse liability [3]. Due to these rewarding effects, studies have shown that 21 to 29% of patients being prescribed opioids, such as in the case of chronic pain, end up misusing them [4]. Further, studies have shown that a subset of patients (4-6%) abusing prescription opioids end up transitioning to abuse of heroin, a much more potent opioid which its use of is much more likely to result in overdose and death [5]. This transition from prescription to illicit opioids such as heroin has even greater risks. The purity of these illicit opioids is often unknown, and they are often contaminated with even more potent drugs. For example, heroin is often mixed with fentanyl, a more potent opioid, and this “contamination” has been a recent driver of even more overdose and death trends associated with opioids [6-8].

There has been growing awareness of the critical nature and urgency to intervene in the growing prescription opioid abuse problem. Such awareness has led to emphasis on developing new interventions to help prevent and treat OUD. It is known that there is not just one contributing factor that results in OUD, but usually a combination of several – i.e., genetic, psychosocial, and neurobiological factors, which strongly increase the likelihood of an individual developing OUD [9].
Despite the identification of multiple risk factors for OUD, it is still unclear how these risk factors interact to lead to opioid misuse and OUD. There is evidence that opioids “hijack” the circuitry in the brain that processes natural rewards such as food and social interaction [10]. This “hijacking” fuels further opioid intake and ultimately results in dependence and, even when an individual is able to abstain from opioid consumption for some time, relapse cycles [9]. There are available options for treating OUD (e.g. methadone, buprenorphine, etc.), but they are not always effective, with many patients continuing to experience relapse following treatment [11]. Better understanding of the relevant brain circuitry and the adaptations produced by opioid use would shed light on potential novel targets for therapeutics to prevent and treat OUD.

To better understand the neurobiology underlying OUD and prescription opioid abuse, as well as factors which increase risk or resiliency, there is a need for good preclinical models of opioid abuse. To this end, operant drug self-administration (SA) assays have been developed and are commonly used, often with rodents [12]. In these operant assays, animals are trained to press a lever within an experimental chamber, after which they receive a drug such as heroin. Once they have learned the association between the action (lever-pressing) and the consequence (receiving drug), the reinforcing and rewarding effects of the drug motivate the animal to continue lever-pressing to receive more drug.

These SA assays have high utility, as they allow for preclinical modeling of human substance use disorders like OUD, modeling key components such as escalation of drug-seeking, compulsive drug consumption, and continued use despite adverse consequences and even after periods of abstinence [12]. By modeling key components of substance use disorders, these SA assays are thus routinely used to examine the effects of different experimental manipulations on
drug-seeking in animals and provide a translational platform for identifying interventions that may improve SUD outcomes in clinical settings.

To date, most SA assays require intravenous delivery of drugs following lever-pressing. This is a limitation when trying to model prescription opioid abuse, as prescription opioids are most often taken orally [13]. Thus, implementation of oral drug delivery within SA assays would better model human prescription opioid abuse. Despite this, only a few oral opioid SA assays have been developed [14-16].

The goal of our study was thus to design and implement an oral opioid SA assay for Bussey-Saksida touchscreen chambers. We chose to employ the touchscreen chambers due to their high translational utility. We also chose OXY as our oral opioid for the assay, as it is one of the most commonly prescribed and abused prescription opioids [2].

To develop our assay, we adapted a protocol from Phillips et al. [15]. Our primary study objective was to determine whether via our assay, we could train mice to acquire oral OXY SA, and within the operant touchscreen environment. We further wished to examine whether, after oral SA training, mice would be able to maintain oral OXY SA at our target concentration. Our secondary goal was to examine baseline sex differences in oral OXY SA behavior between male and female mice. A very limited number of studies that developed oral OXY SA assays have demonstrated sex differences in rodents. In particular, female rodents were shown to self-administer greater amounts of oral OXY than males [15, 16]. We sought to determine whether we would replicate these sex differences within our touchscreen assay.

Our hypotheses were that male and female mice would both be able to acquire oral OXY SA during a training phase and that they would maintain SA at a target dose/concentration. We
also expected sex differences in a similar manner that prior literature has shown, with female mice self-administering more oral OXY than males.

Overall, our study will allow us to validate a novel, touchscreen oral OXY SA assay for mice, and to establish baseline sex differences. Validation of this assay will allow for its further use in preclinical research which seeks to model OUD characterized by oral consumption. This model will serve as a valuable addition to the OUD model toolbox, complementing the more traditional, intravenous models.

2. Materials and methods

2.1 Mice

Eight male and four female C57BL/6J mice were purchased from The Jackson Laboratory (Bar Harbor, ME, USA) at 9 weeks of age. When mice first arrived at the animal facility, they were given 72 hours to acclimate to the facility within their home cages. Mice were housed four mice per cage, with males and females being housed separately. They were housed within disposable polycarbonate caging (Innovive, San Diego, CA, USA), and were given \textit{ad libitum} access to water and chow (Tekland Irradiated Global 16\% Protein Rodent Diet; #2916, Envigo, Indianapolis, IN, USA). Mice were maintained on a 12/12 light/dark cycle (lights on at 06:00 h).

After acclimation, mice were ear-punched for identification purposes. The mice then underwent two days of experimenter handling, with mice being weighed daily for the remainder of the study. After the initial two days of handling, they began food restriction. Instead of having \textit{ad libitum} access to their food, mice were now fed a daily, restricted allotment of food each afternoon. Mice were feed restricted such that they maintained 85-90\% of free-feeding weight
through the end of the study. All experiments and procedures were approved by the Johns Hopkins Animal Care and Use Committee and followed the Guide for the Care and Use of Laboratory Animals.

2.2 Behavioral Assay

2.2.1 Touchscreen apparatus & general overview of task:

After mice achieved 85-90% of free-feeding weight under food restriction, they began behavioral experiments (oral OXY SA) within Bussey-Saksida touchscreen chambers. Our oral OXY SA task was modeled off of an operant chamber protocol utilized by Phillips et al. 2020.

Our task schedules (FR1 and FR2) for oral OXY SA were programmed via Animal Behavior Environment Test System (ABET II; Lafayette Instrument, Lafayette, IN, USA) software for our touchscreens. Our Bussey-Saksida touchscreen chambers (Model 80614E, Lafayette Instrument, Lafayette, IN, USA) are shown in Figure 1. We programmed a white square to illuminate within the center of the screen of the touchscreen, against a black background, when the task commences. The initial habituation/“initial operant touch” session for training our mice was on an FR1 schedule, in which mice only needed to press the white square once, in order to receive a liquid reward (water, 20 ul per reward). All remaining schedules of oral OXY SA training and testing were programmed via an FR2 schedule, in which mice needed to touch the square twice, consecutively, in order to receive a liquid reward (20 ul, water or OXY; more details will be described). The type of liquid reward (water or OXY) depended on the specific stage of the experiment. Within the task, after each liquid reward is dispensed, the white square is removed from the screen and an intertrial interval (ITI) of several seconds begins; during this ITI, screen touches to the blank screen are recorded, but result in no
consequences. After the ITI, the next trial begins, in which the mice are able to continue touching the screen to receive another liquid reward. There is no limit to the number of liquid rewards a mouse can receive during each experimental session, although each session is restricted to 90 minutes.

Figure 1. Bussey-Saksida touchscreen chambers utilized for our oral OXY SA assay. Bussey-Saksida touchscreen chamber is shown. Components include (1) the touchscreen; (2) the operant chamber; (3) the tower which dispenses liquid rewards into an attached reward trough (within the chamber); (4) jars placed outside the chamber, which contain the liquid rewards to be dispensed into the chamber’s reward trough, via tubing; (5) removeable tray for mice waste; (6) sound-attenuating boxes which the touchscreen chambers are housed within; and (7) house lights within the boxes.

2.2.2 Oral OXY SA task description:
Figure 2. Timeline for our oral OXY SA assay protocol, for Bussey-Saksida touchscreen chambers. Timeline depicts the progression of this study, indicating that the mice begin with the postprandial stage (blue text). Mice begin with water SA on an FR1 schedule, which takes 1+ days, depending on how quickly mice meet criterion. They then SA water on an FR2 schedule for 3 days. They then progress to oral OXY SA at increasing concentrations for 3 days each. Timeline then indicates the mice transitioning to the final, non-postprandial testing phase (red text).

During this phase, mice orally self-administer OXY at the highest, target concentration of 1.00 mg/ml for 7 days.

Postprandial vs. non-postprandial phases:

Figure 2 depicts our experiment timeline. After mice began food restriction and achieve 85-90% free feeding weight as discussed, they begin this experimental protocol. The protocol overall consists of all the mice undergoing a daily 90 min experimental session in the touchscreen chambers, preceded by a 1-hour pre-session. The experiment consists of two phases – a postprandial phase (pre-feeding) and a non-postprandial (no pre-feeding) phase. These two phases determine what exact conditions the mice undergo during their 1-hour pre-session.

The experiment protocol begins with the post-prandial phase, which lasts for 19+ days (depending on how long it takes mice to meet criterion in the initial FR1 water training session; Figure 2). During this phase, the mice are given their daily food allotment during their 1-hour pre-session. During this pre-session, the mice remain in their home cage, which sits atop a
laboratory bench in our touchscreen chamber experiment room. The lights are always dimmed in the experiment room. During this one hour, water bottles are also removed from the home cage. The purpose of this phase is to induce thirst, to motivate mice to learn the oral self-administration task for liquid rewards. After the one hour has completed, food remaining is divided equally and placed into the touchscreen chambers that are assigned to each of those mice. Mice are then placed in the touchscreen chambers for the 90 min oral OXY SA experimental session. After the experiment session, mice are placed back into their home cage along with any remaining, uneaten food.

During the non-postprandial phase, which follows immediately after the 19+ days of the postprandial phase, the conditions are almost the exact same. However, now, during the 1-hour pre-session, mice have access to water without any food. The rationale for these changes, is that by now, the mice will have presumably learned to self-administer oral OXY, and now we can test whether they will maintain SA behavior, independent of needing to induce thirst/increase this task motivation. They are again placed in the touchscreen chambers for 90 min sessions, following their pre-session. After their experiment session, they are placed back into their home cages, and are now provided with their daily food allotment. Experiment sessions (postprandial and non-postprandial) are conducted daily, at the same time in the afternoon each day (13:00-17:00 h).

Task timeline and progression

Day 1 of the experimental protocol begins with FR1 water self-administration training (Figure 2). As mentioned, the protocol begins in postprandial conditions, during which mice receive food, but no access to water, during their 1-hour pre-session. Following the pre-session,
mice are placed in the touchscreen chambers. The SA session begins, and a white square in the center of the screen illuminates. An FR1 water SA schedule is utilized during this first session, which serves to teach mice the basics of the task: that pressing the white square results in a 20 uL liquid reward being dispensed. Mice undergo this initial water training for a minimum one day, and until they reach criteria, which is to achieve 10 active (white square) touches in a single 90 min session. Mice will continue daily sessions of this water training until they meet this criterion needed to progress onto the next stage.

Once mice reach criterion on the FR1 water SA training, they then progress to water SA on an FR2 schedule (Figure 2). During this session, the task is similar to the prior stage. Now, however, the mice need to touch the active button two successive times, to receive their water reward. Mice undergo FR2 water SA for 3 days. Mice remain on an FR2 schedule for the remainder of the study. Once they complete these 3 days of water SA, they progress to SA schedules of increasing concentrations of oxycodone HCl solutions (Sigma-Aldrich). Conditions are the same as water SA, except now, oxycodone has been introduced to their dispensed liquid rewards, at the following concentrations: 0.05, 0.10, 0.30, 0.50, and 1.00 mg/ml. Mice self-administer each concentration for 3 days each (Figure 2), with no criteria to progress to the next higher concentration.

After 3 days of SA at the highest 1.00 mg/ml concentration, mice then transition to the non-postprandial phase, which lasts for 7 days. As mentioned, the mice are now given free access to their water bottles during their pre-session and are not fed until after their touchscreen session for the day. During this non-postprandial phase, the mice undergo SA sessions at the highest, target OXY concentration (1.00 mg/ml) for 7 days (Figure 2). This is the “testing phase,” in which we will test whether mice maintain oral OXY SA behavior, in the absence of
pre-feeding/water restriction. In this final testing phase, we will be able to examine and compare oral OXY SA performance between groups (males versus females), by examining differences in number of liquid rewards earned, and estimated consumption of OXY in mg/kg.

2.2.3 Variables and analyses:

Number of correct screen touches and rewards earned during each experimental session were recorded automatically in the touchscreen chambers. Our other target variable of interest was estimated consumption of OXY (mg/kg) at each concentration. Estimated consumption of OXY (mg/kg) was calculated as follows:

\[
\frac{((Rewards \text{ earned}) \times \text{oxycodone amount (mg) in one 20 uL reward at that concentration}))}{\text{(mouse weight (kg) on day of that experimental session)}}
\]

For statistical analyses, we utilized GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). For the postprandial phase data, we used two-way ANOVA tests to examine the effect of OXY concentration and sex on number of rewards earned, as well as OXY consumption (mg/kg). For our non-postprandial data, we utilized unpaired t-tests to examine sex differences between males and females on rewards earned, as well as consumption of OXY (mg/kg).

3. Results

3.1 Male and female C57BL/6 mice acquire water and oral oxycodone self-administration during training, under postprandial conditions
Figure 3 shows the results of our oral oxycodone SA training during the initial, postprandial phase. When undergoing water SA (0.00 mg/ml concentration), male and female mice both learned to touch the white square for water rewards. Then, when OXY solution was introduced (0.05, 0.10, 0.30, 0.50, and 1.00 mg/ml concentrations), mice continued to self-administer and consume rewards. As concentration of OXY solution increased, the total rewards earned within each SA session (total fluid of rewards consumed) decreased, in a dose-dependent fashion. At the two lowest concentrations (0.05 and 0.10 mg/ml), male mice earned significantly more rewards than female mice (p=0.001 and p=0.016, respectively).

![Rewards Earned-PP](image)

**Figure 3. Rewards earned by male and female mice during the postprandial, training phase.** Figure depicts number of rewards that male (red) and female (blue) mice orally self-administer during 90 min oral SA sessions. Data for each concentration is averaged across the 3 sessions conducted at each concentration. * p < 0.05. PP = postprandial

**3.2 Male and female mice dose-dependently consume increasing amounts of oxycodone (mg/kg) as OXY concentration increases, under postprandial conditions**

Despite the total consumption of fluid decreasing as OXY concentration increased (Figure 3), the amount of OXY consumed (mg/kg) increased across males and females (Figure
4). Despite the sex differences noted in Figure 3, when we accounted for the weight of the mice, the total amount of OXY consumed (mg/kg) was no different between males and females. Males and females both showed a consistent increase in earned mg/kg, as concentration increased, in a dose-dependent manner.

Figure 4. Estimated consumption of OXY (mg/kg) earned by male and female mice at each concentration of OXY, during the postprandial training phase. Figure depicts the amount of earned OXY (mg/kg) that male (red) and female (blue) mice orally SA at each concentration. Data for each concentration are averaged across the 3 sessions that are conducted at each concentration. * p < 0.05. PP = postprandial

3.3 Male and female mice maintain oral OXY SA under non-postprandial conditions

During the non-postprandial, testing phase, both male and female mice successfully maintained oral OXY SA at the highest, 1.00 mg/ml concentration (now in the absence of pre-feeding and water restriction) (Figure 5). A similar pattern as that seen during the postprandial phase, was seen during the non-postprandial phase. In particular, there was a trend toward males earning slightly more rewards than females (not significant; p=0.09). However, similarly as seen in the postprandial phase, when weights of the mice were taken into account, this trend
disappears (Figure 6). Here, we see that males and females consumed equivalent amounts of OXY, when data is calculated and depicted as consumption of oxycodone in mg/kg.

Figure 5. Rewards earned by male and female mice during the non-postprandial, testing phase. Data depicts number of OXY liquid rewards that male (red) and female (blue) mice orally self-administer, at the highest, 1.00 mg/ml target concentration. Data are averaged across the 7 days that the mice self-administer at this concentration. NPP = non-postprandial

Figure 6. Estimated consumption of OXY (mg/kg) orally self-administered during the non-postprandial, testing phase. Data depicts the amount of earned OXY that male (red) and female (blue) mice orally self-administer during the non-postprandial phase of the study. OXY during this phase is self-administered at the highest, target concentration of 1.00 mg/ml, for 7 days. Data are averaged across the 7 sessions conducted during this phase. NPP = non-postprandial

4. Discussion
Our experiment shows that both male and female mice are able to acquire and maintain oral OXY SA through our behavioral assay designed for touchscreen chambers.

4.1 Oral OXY SA training and maintenance:

Our data indicated that when concentration of OXY was increased during our postprandial, training phase (Figure 3), rewards earned decreased in a dose-dependent manner. This is a typical response curve seen in operant opioid SA assays. This decrease in rewards earned occurs due to lesser volumes of OXY being needed to be consumed, as concentration rises, to achieve the same or increased subjective effects. Accordingly, we saw that as OXY concentration increased, the amount of OXY consumed (in mg/kg) increased, in a dose-dependent manner (Figure 4). This increase could also indication escalation in mice intake of OXY, due to its reinforcing effects. During the non-postprandial phase, we saw that both male and female mice were able to maintain oral OXY SA at the highest concentration, despite the postprandial conditions (pre-feeding and water restriction to induce thirst) being removed, indicating that the mice had successfully learned the task and found OXY reinforcing. We thus found that, via our experimental protocol, mice were able to learn to acquire oral OXY SA and maintain this behavior.

4.2 Sex differences:

Initially we saw sex differences in the number of rewards earned for males, at the two lowest concentrations, with males showing greater number earned than females (Figure 3). However, when we accounted for weight of the mice and calculated estimated consumption of OXY (in mg/kg), we saw that males and females consumed equivalent amounts of OXY (Figure
4). Thus, the initial sex difference we saw in rewards earned can be explained by the differences in weights between male and female mice. Males have higher baseline weights than female mice, thus requiring greater amounts of OXY solution in order to consume similar amounts of OXY (in mg/kg) as females.

A similar pattern was seen during the non-postprandial, testing phase, in which we saw a trend toward male mice earning more OXY rewards than females, although the relationship was not significant (Figure 6). Again, when we took into account the differences in weights between male and female mice, and calculated consumption of OXY in mg/kg, we saw that male and female mice consumed equivalent amounts of OXY.

We thus determined that, within our developed oral OXY SA assay for touchscreen chambers, there are no sex differences in performance. Interestingly, prior research has shown sex differences in the direction of female mice self-administering larger amounts of OXY than males, within oral OXY SA tasks [15, 16]. Despite these sex differences being seen, which we were unable to replicate, it should be noted that the number of these studies is very limited. Further, these prior studies utilized an oral OXY SA task developed for standard operant chambers, unlike our touchscreen chambers. Further, one of these studies utilized rats instead of mice, possibly also contributing to differences in findings, among other possible differences in experimental conditions [16].

**4.3 Conclusion & future directions:**

Our findings indicate that male and female mice can successfully acquire and maintain oral OXY SA within our paradigm developed for Bussey-Saksida touchscreen chambers. We
also established that there are no baseline sex differences in the amounts of OXY that males vs. female mice self-administer in this task.

Our study establishes the utility of our oral OXY SA assay, which can be further used and applied to research seeking to better understand the basic science underlying prescription opioid abuse and OUD. In particular, this assay can be used to test the effects of different experimental manipulations on oral SA behavior. This research will shed better light on the different factors that result in increased risk or resiliency toward OUD as well as help to screen potential new therapeutics.

An example of such a study is reflected by our group’s interest in the effects of adolescent social isolation on risk for neuropsychiatric illnesses and substance use disorders in later adulthood [17]. In future studies, we plan to apply this isolation model to examine how this adverse childhood experience may result in increased risk for OUD in adulthood, and the neurobiological underpinnings of this relationship. Utilization of our oral OXY SA touchscreen assay will allow us to determine the effect of SI on oxycodone-seeking and -taking (compared to mice that were group-housed), and to examine potential neurobiological correlates of this altered behavior as a function of their experience during adolescence.

These findings will allow for greater understanding of how these experiences during adolescence exacerbate risk for OUD and prescription opioid abuse in later life, as well as further research in which we can interrogate the neural circuitries that are altered during development due to these adverse experiences. Greater understanding of this neurobiology will allow for experimental manipulation of these circuitries, and experiments examining the effects of these manipulations on oral OXY SA behavior within our touchscreen task. Ultimately, this research will aid target identification for novel therapeutics for OUD and prescription opioid abuse, with
our model serving as an effective model for prescription opioid abuse compared to traditional intravenous models.
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