# Opiate Drug Seeking and Addiction: The Influence of Sucrose Consumption on the Acquisition and Expression of Morphine Conditioned Place Preferences (CPP)

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## Introduction

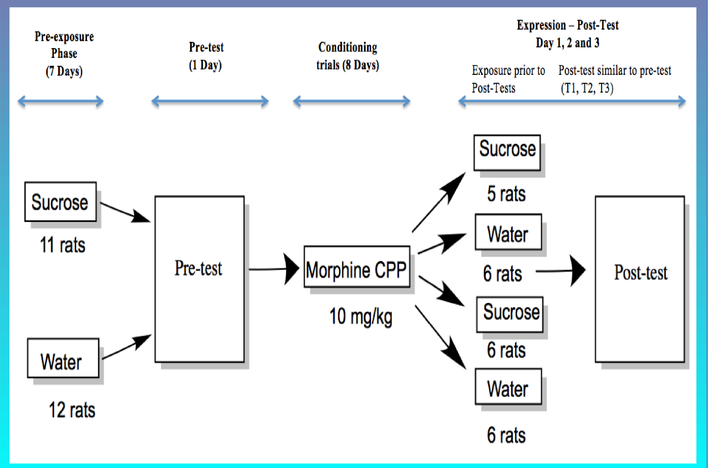
Everyday more than 130 people die from opioid (e.g., heroin, fentanyl) overdose in the U.S. making opioid addiction a national crisis that threatens public welfare (CDC, 2019). These drugs are classified as endogenous opiate receptor agonists and morphine is one such example (Pathan & Williams, 2012). Importantly, opiate receptor agonists also indirectly elevate dopamine release, a critical neurotransmitter in drug reward (McKim & Hancock, 2013). One paradigm for studying rewarding properties of drugs, like opiates, is conditioned place preference (Prus, et al., 2009). Here, a drug (unconditional stimulus, US) is paired with a distinct location and, after several pairings, animals undergo a preference test in the drug free state. Conditioned place preference (CPP) is observed when animals seek out the drug-paired location (conditional stimulus, CS+).

Previous research suggests that sucrose may influence morphine-induced CPP. Hernandez and Hoebel (1988) found that sucrose may have rewarding properties and agonize endogenous opioid receptors and, more indirectly, dopamine systems. Additional research by Lett (1989) found that sucrose enhances opiate seeking behavior as measured by morphine-induced CPP (i.e., sensitization). However, Zhai, et al. (2008) found that sucrose attenuates morphine seeking behavior and weakens morphine-induced CPP (i.e., habituation).

The aim of the present experiment follows:

1. To evaluate the impact of sucrose administered prior to place conditioning on expression of morphine-induced CPP.
2. To evaluate the effects of sucrose administered immediately prior to post-test on expression of morphine induced-CPP.
3. To evaluate the unique effects of sucrose and morphine on locomotor activity during conditioning trials.

## Experimental Design




## Method

- ***Subjects*** – 24 male, Sprague-Dawley rats were obtained from Envigo (60 days of age; young adult at start of experiment).

***Pre-exposure Phase*** *(Sucrose (**S**) vs. Water (**W**)) (Adapted from Zhai., et al., 2008)*

- Animals were individually placed in Plexiglas cages during the pre-exposure phase. Fluid was administered in graduated cylinders with rubber stoppers and straight sipper tubes.
- Animals were weighed and assigned to terminal conditions in a counter balanced manner by body weight.
- Home cage bottles were removed 24 hours prior to the first pre-exposure day.
- Separate groups received either S solution (15%w/v) or W for an hour each day for 7 days.
- After each drinking session, rats were returned to the home cage for 30 minutes of water consumption.

***Place Conditioning Phase (Biased Place Conditioning)***

- *Apparatus* – Place conditioning chambers (4) consisted of two sides, Black/Grid vs. White/Hole, separated by either an open or closed partition (see Figure 1). Data were recorded using digital cameras and a DVR.

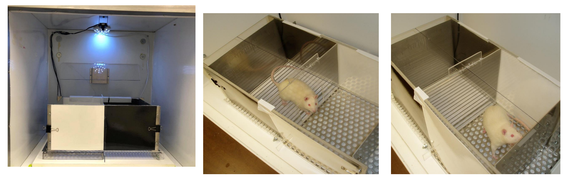


*Figure 1*: Sample images of the place conditioning apparatus.

- *Pre-test (Open Partition)* – All subjects were placed in the apparatus for 900 secs and allowed to move freely between either side. The non-preferred side was determined for each animal ( <450 sec).

- *Training (Closed Partition)* – Rats received morphine (10 mg/kg, IP) on the initially non-preferred side (drug-paired side, CS+) and sterile saline solution (1 ml/kg, IP) on the initially preferred side (non-drug paired side, CS-). Animals were restricted to the appropriate side for each daily 900 sec trial. Animals received either morphine (CS+) or saline (CS-) on alternating days across 8 trials.

- *Post-test (Open Partition)* – Each post-test (T1, T2, T3) was identical to pre-test. However, S pre-exposed animals received either 15 mls of S (15%w/v) or 15 mls of W immediately prior to each post-test. Similarly, W pre-exposed animals received either S or W.

## Results

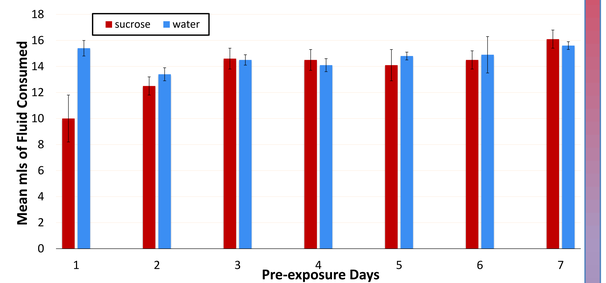



*Figure 2:* Mean amount of S and W consumed across 7 pre-exposure days.

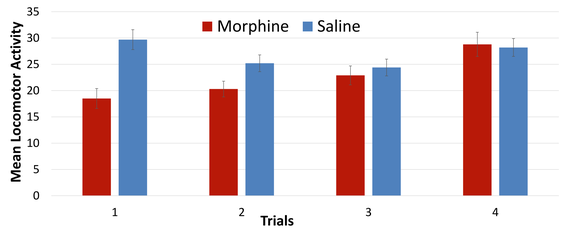



*Figure 3:* Mean locomotor activity for morphine and saline conditions across trials.

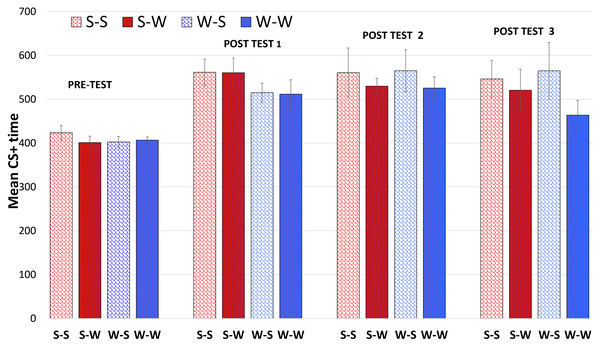



*Figure 4:* Mean seconds spent on non-preferred side (CS+) from pre-test to post-test for pre-exposure (S vs. W) and exposure prior to post-test (S vs. W) conditions.

- ***Pre-exposure Phase (Fluid Consumed; See Figure 2)***
- 2 (Pre-exposure: S vs. W) X 7 (Days) Mixed Factorial ANOVA revealed the following:
- Trend for the S group to consume less fluid than the W group ($F(1,21)=4.03$, $p=.058$), increase in fluid consumption across 7 days ($F(6, 126)=3.27$, $p=.005$), and an interaction driven by the S group consuming less than the W group on day 1 ($F(6,126)=2.97$, $p=.009$; Newman-Keuls test, $p<.05$ ).

- ***Place Conditioning Training Phase (Activity; See Figure 3)***
- 2 (Pre-exposure: S vs. W) X 2 (Morphine vs. Saline) X 4 (Trials) Mixed Factorial ANOVA revealed the following:
- S and W groups display similar activity ($F(1,21)=.52$, $p=.478$), morphine suppresses activity as compared to saline ($F(1,21)=9.80$, $p=.005$), activity increases across training days ($F(3,63)=3.74$, $p=.015$), and an interaction showing morphine, as compared to saline, suppresses activity on trials 1 and 2 ($F(3,63)=7.03$, $p<.0001$; Newman-Keuls $p$'s$<.05$).

- ***Pre-Test versus Post-Test 1,2,3 (Time on Non-preferred Side, CS+; See Figure 4)***
- 2 (Pre-exposure: S vs. W) x 2 (Exposure Prior to Post-tests: S vs. W) x 4 (Pre-test vs. Post-tests 1,2,3) Mixed Factorial ANOVA revealed the following:
- Pre-exposure to S or W did not affect time on the non-preferred side ($F(1,19)=.73$, $p=.404$), exposure to S or W prior to tests did not alter time on the non-preferred side ($F(1,19)=1.57$, $p=.225$), but post-test time on the non-preferred side (T1,T2,T3) significantly increases as compared to pre-test time on the non-preferred side ($F(3,57) = 16.21$, $p <.0001$).
- No interactions were statistically significant.

## Conclusions

- During pre-exposure, the S group initially consumed less sucrose and displayed neophobic tendencies. However, sucrose consumption increased across days and both S and W groups reached similar consumption levels by the end of the pre-exposure phase.
- Morphine suppressed locomotor activity during initial place conditioning trials, but motor-suppressing effects were not observed on subsequent trials. The latter outcome may reflect habituation (tolerance) to morphine's activity suppressing effects.
- Robust morphine-induced CPP was found in a biased place conditioning paradigm, and the rewarding properties were evident given the marked increase in time spent on the non-preferred side from pre- to post-tests.
- Unlike Lett (1989) and Zhai, et al. (2008), pre-exposure to S vs. W did not influence expression of morphine-induced CPP and may be due to methodological differences between the experiments.
- Although S exposure prior to post-tests did not influence CPP, the present work was the first attempt to discover sufficient conditions to detect sucrose's influence, prior to post-test, on morphine CPP expression.
- There is a suggestion that pre-exposure to S may enhance CPP only on post-test 1 (i.e., sensitization). However, there is an indication that on subsequent post-tests, exposure to S prior to post-test may maintain CPP. Finally, the group receiving W during pre-exposure and exposure prior to post-test may show signs of morphine CPP extinction. Future research with larger sample sizes may yield sufficient statistical power to detect these phenomena.