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Background/Introduction

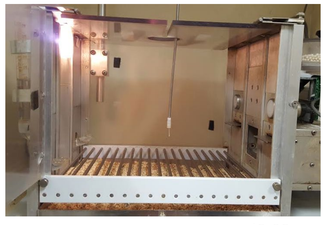
According to the National Institutes on Health, although underage drinking and binge drinking have declined in the past decade, alcohol (EtOH) is still the most commonly abused substance in the United States (NCAAD, 2015) and worldwide (Falk et al., 2016). In addition, approximately 80% of people with an EtOH use disorder also use tobacco, which equates to more than 46 million co-abusers of EtOH and nicotine in the United States (Miller & Gold, 2008). Furthermore, the co-use of EtOH and nicotine increases the difficulty of cessation of either substance (McKee & Weinberg, 2013). However, there is currently no single medication to treat the co-abuse of EtOH and nicotine, despite the two substances having similar mechanisms of action.

The objective of the present study was to determine the effectiveness of the opioid antagonist naltrexone at reducing the consumption of EtOH and nicotine in female alcohol-preferring (P) rats. P rats have been selectively bred to have a genetic predisposition for alcohol abuse, which allows them to be used as an animal model of alcoholism. P rats readily self-administer i.v nicotine (Le et al., 2016), have EtOH consumption during adolescence that is similar to that seen in adulthood, and operantly respond for EtOH until they are impaired/intoxicated (Bell et al., 2006). Thus, P rats are a useful model for studying naltrexone's effects on EtOH and nicotine co-use.

Naltrexone has been FDA approved for alcohol use disorder based on its ability to treat alcohol dependence. Animal studies have shown that naltrexone decreases nicotine self-administration in rats (Ismayilova & Shoaib, 2010; Guy et al., 2014). In addition, naltrexone reduces EtOH self-administration in rats (Williams & Broadbridge, 2009) and also reduces EtOH self-administration in rats given alternating access to either EtOH or nicotine (Le et al., 2014). These findings indicate that naltrexone has the potential to reduce the co-use of EtOH and nicotine.

Modified Operant Chamber

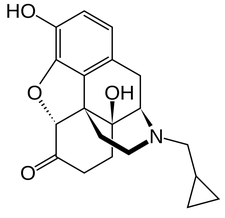
EtOH and water bottles located on left wall of chamber.



Active and inactive levers for nicotine self-administration located on right wall of chamber.

- Allowed rats concurrent access to i.v. nicotine (0.03 mg/kg/infusion) and oral EtOH and water (0 vs 15% EtOH).
- Pressing the active lever provided rats with nicotine through a headmount/catheter connected to the jugular vein.

Naltrexone



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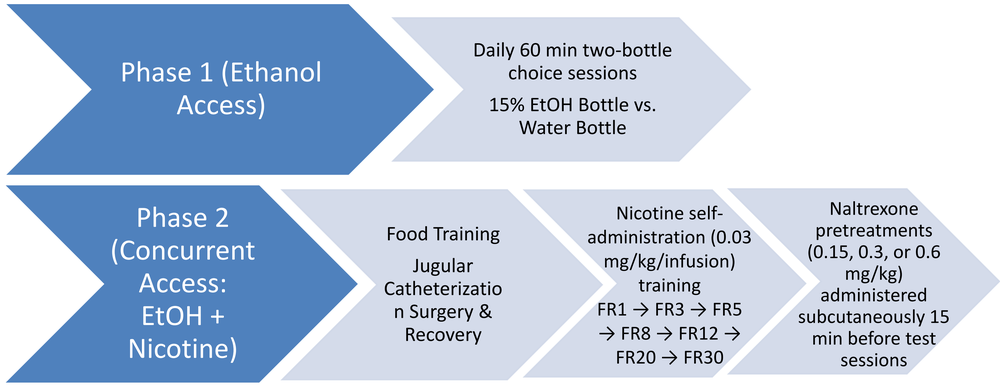
Method

- Twelve adult female P rats
- EtOH acclimation (3 days): water was removed from the home cage and rats were given a bottle of 20% EtOH.
- Phase 1 & 2. Half the rats received naltrexone treatments during Phase 1, and half received treatments during Phase 2.



Results

Figure 1: Effect of naltrexone pretreatment on EtOH consumption in Phase 1 (EtOH-alone model).

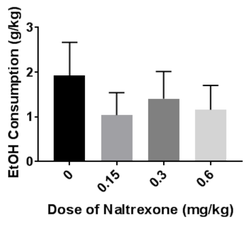


Figure 2: Effect of naltrexone pretreatment on water consumption in Phase 1.

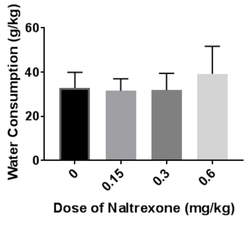


Figure 3: Effect of naltrexone pretreatment on EtOH consumption in Phase 2 (concurrent access).

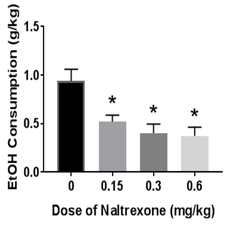


Figure 4: Effect of naltrexone pretreatment on water consumption in Phase 2.

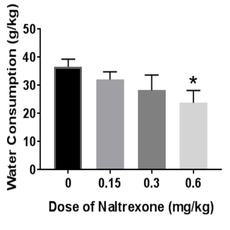


Figure 5: Effect of naltrexone pretreatment on active lever presses for nicotine in Phase 2.

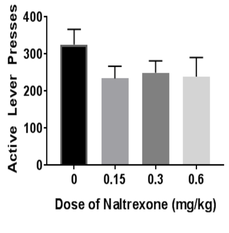
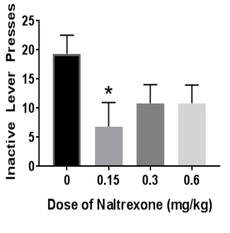


Figure 6: Effect of naltrexone pretreatment on inactive lever presses for nicotine in Phase 2.



Results

In Phase 1 (EtOH alone), naltrexone did not have any significant effect on EtOH consumption or on water consumption (Figure 1 and 2). However, in Phase 2, naltrexone significantly reduced EtOH consumption at all three naltrexone doses tested (0.15, 0.3, and 0.6 mg/kg), $F(3, 18) = 1.57$, $p < 0.05$ when compared to the vehicle control (Figure 3). In addition, naltrexone significantly reduced water consumption in Phase 2 but only at the highest dose tested (0.6 mg/kg), $F(3, 18) = 5.65$, $p < 0.05$ (Figure 4). Also in Phase 2, naltrexone did not have any significant effect on active lever presses for nicotine (Figure 5). However, it did significantly reduce inactive lever presses for nicotine at the lowest dose tested (0.15 mg/kg), $F(3, 18) = 3.38$, $p < 0.05$ when compared to the vehicle control (Figure 6).

Discussion

In the EtOH-alone phase, naltrexone did not have any significant effect on EtOH or water consumption. However, in the co-use phase, naltrexone dose-dependently reduced EtOH consumption; water consumption was also reduced, but only at the highest dose (0.6 mg/kg). Also, in the co-use phase, naltrexone significantly reduced inactive lever presses for nicotine at the lowest dose (0.15 mg/kg), but it had no effect on active lever presses for nicotine. Thus, naltrexone is more effective in treating EtOH use when tested in combination with nicotine rather than when tested alone.

The present study used concurrent access to EtOH and nicotine, which has been used in very few previous studies. It also measured choice for water (natural reward) and inactive lever presses (non-reinforced behavior) to determine if naltrexone had any effect on those behaviors. Because the highest dose of naltrexone (0.6 mg/kg) reduced water drinking, we did not increase the test dose beyond that point. Further research must be conducted to find medications to treat the co-use of EtOH and nicotine.

Future studies may involve counterbalancing the order in which EtOH alone and EtOH+nicotine co-use phases are administered. In addition, a higher FR schedule of nicotine could be used (the highest ratio in the present study was FR30). A higher or lower dose of nicotine could also be used, or multiple doses could be used, in order to determine if naltrexone would have significant effects on active lever presses. Finally, male P rats could be used as the test subjects in order to account for possible sex differences.

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