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"Development of Opioid Withdrawal as a Discriminative Stimulus in Rats"

Background: According to NIDA, there were over 105,000 drug-related overdose deaths in the United States during 2023 (2024). These tragic data show the need for reducing opioid abuse and dependence and for understanding the effects of withdrawal from opioids on the body. Whether it is precipitated or spontaneously initiated, withdrawal is accompanied by a range of adverse effects (e.g., diarrhea, gastrointestinal upset, muscle cramping, and chills) produced by a disruption in the body's neurochemical balance (Kosten, 2002). Symptoms of withdrawal are the primary reason opioid-dependent individuals continue administering opioids. Understanding a subject's ability to discriminate between a withdrawal and non-withdrawal state could provide new insights into both the objective and subjective effects of opioid withdrawal.

Methods: To establish an operant procedure for discriminating between the presence and absence of withdrawal in Long-Evans rats, we trained a cohort of ten rats (7 male and 3 female) to lever press under a fixed-ratio 20 (FR-20) schedule for food reinforcers. Physical dependence on the opioid morphine was then established by administering each rat, 10, 20, 30, and 40 mg/kg twice daily over four days. Dependence was maintained by administering 40 mg/kg once daily. The discrimination of withdrawal was initiated during behavioral sessions in which either saline or 1 mg/kg of naltrexone (NTX) was administered interperitoneally (i.p.).The injection determined which of two levers would provide food reinforcement under the FR-20 schedule (e.g., saline injection was the discriminative stimulus (DS) for responding on the right lever; a NTX injection was the DS for responding on the left lever). Training is still in progress; saline and NTX injections will continue until the subjects meet two training criteria for 9 out of 10 consecutive days: (1) less than 20 responses on the incorrect lever prior to the first reinforcement, and (2) at least 95% responding on the correct lever for the entire session. Following discrimination training, dose-effect curves for NTX will be established using a cumulative-dosing procedure. Dependence will always be maintained between NTX administrations by continuing to re-administer morphine daily.

Results: As shown previously, the chronic regimen reliably induced physical dependence. This was evident from the injections of NTX, which produced signs of withdrawal such as diarrhea. The dose of NTX had to be decreased from 1 to 0.032 mg/kg to avoid the marked rate-decreasing effects that occurred after 1 mg/kg. Whether 0.032 mg/kg will be the final training dose for NTX has yet to be determined; however, subjects are reliably responding for food reinforcement during the behavioral sessions irrespective of the injection and subjects are learning to consistently discriminate between a withdrawal state and a non-withdrawal state.

Conclusion: These findings show that opioid withdrawal leads to observable behavioral changes that can serve as discriminative stimuli. Therefore, this research creates a model for testing new therapies for withdrawal. The ability to detect and treat withdrawal symptoms may have positive effects on the cycle of addiction, sobriety, and relapse in humans. Future work will test NAD (nicotinamide adenine dinucleotide) as a treatment for withdrawal. This would ideally lead to better strategies for managing dependence and improving recovery outcomes.

Reference

Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: implications for treatment. *Science & practice perspectives*, *1*(1), 13–20. https://doi.org/10.1151/spp021113

NIDA. 2024, August 21. Drug Overdose Deaths: Facts and Figures . Retrieved from https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates on 2025, July 9