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"Nicotinamide Adenine Dinucleotide (NAD) Attenuates the Rate-Decreasing Effects of Oxycodone Withdrawal in Rats"

Background: Over 16 million people worldwide and over 2.1 million United States citizens are affected by Opioid Use Disorder (OUD) due to the over-prescription and underestimation of the addictiveness of opioids in the 1990s (Dydyk et al., 2024). When a person misuses or abuses opioids, the amount of nicotinamide adenine dinucleotide (NAD) naturally found in the body is depleted. NAD replacement stimulates cell regeneration to increase energy and neurological health without an abuse liability (McCrakin, 2022). Therefore, we implemented two protocols for inducing dependence in rats to test whether intravenously administering the small molecule NAD+ could effectively attenuate withdrawal and help transition individuals to abstinence.

Methods: Two cohorts of rats were first trained to lever press under a fixed-ratio 30 (FR 30) schedule for food reinforcers. After training one cohort of seven Long-Evans rats (4 male and 3 female), each rat received 3.2 mg/kg once daily, 3.2 mg/kg twice daily, and 10-18 mg/kg twice daily of oxycodone for a minimum of three weeks at each regimen. A second cohort of eight Long-Evans rats (4 male and 4 female) each received 10, 20, 30, and 40 mg/kg twice daily over four days and were then maintained on 40 mg/kg once daily. When responding stabilized after the initiation of these two protocols, spontaneous withdrawal was assessed by the cessation of chronic treatment for at least 24 hours, whereas precipitated withdrawal was determined by administering 0.32-3.2 mg/kg of naltrexone interperitoneally (i.p.) in increasing cumulative doses; both were assessed by disruptions in overall response rate (responses/second) and the duration of pre-ratio pausing (PRP) (seconds). After withdrawal was demonstrated consistently (indicating dependence), surgery was performed to implant a venous catheter and port. Twenty-four hours following catheterization, the chronic oxycodone regimen was restarted and responding was restabilized under the operant schedule. The capacity of NAD to attenuate withdrawal was then tested by permanently discontinuing the chronic oxycodone administration, and subjects were infused intravenously (i.v.) with either saline or 180 mg/kg of NAD+ each night for 10 hours for 10 consecutive days. Subjects responded under the operant task every afternoon during the 10 days to assess the disruptions in behavior.

Results: The chronic regimen used for the first cohort of rats reliably induced physical dependence, as the behavioral rate of responding decreased during both spontaneous and precipitated withdrawal. PRP was also increased. Subjects given 10 days of i.v. NAD+ for 10 hours recovered their pre-chronic non-dependent baseline of responding after 2 days of oxycodone cessation, while the saline group recovered their pre-chronic baseline after 4 days. PRP was restored more quickly in the NAD+ group than the saline group. Data is currently being collected with the second cohort.

Conclusion: In our previous rodent model of opioid-dependence, i.v. NAD+ infusions reduced the duration and magnitude of the rate-decreasing effects that occur during withdrawal from oxycodone. These results indicate that NAD+ may have promising potential as a treatment for dependence. The current experiments also tested a more efficient method of developing opioid dependence in rats, where subjects achieve dependence within a week. Going forward, this protocol should allow for a more rapid examination of the effects of NAD+ on withdrawal while decreasing the resources and time needed to achieve these valuable results.

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