Nicotinamide Adenine Dinucleotide (NAD) Attenuates the Rate-Decreasing Effects of Oxycodone Withdrawal in Rats with No Apparent Abuse Liability

Sarah Melton,1 Tamara Morris,1 Ashley Henderson,1 Aslan Abdurrahman,2 Will Smith,3 Ashton Friend,3 Richard Mestayer,4 and Peter J. Winsauer5

1Louisiana State Univ Hlth Sci Ctr; 2James J. Peter’s VA Medical Center; 3Louisiana State University Health Science Center; 4Springfield Wellness Center; and 5Louisiana State Univ Health Science Ctr

Abstract ID 56040 Poster Board 2

Background: Two current treatments for opioid use disorder (OUD) are the chronic administration of buprenorphine (partial opioid receptor agonist) or methadone (full opioid receptor agonist), as both of these agonists can alleviate withdrawal symptoms. However, neither of these drugs transition individuals with OUD to abstinence, and they both have an abuse liability. We examined whether the intravenous administration of the small molecule NAD+ could effectively attenuate withdrawal and transition individuals to abstinence (Experiment 1) while also having no abuse liability (Experiment 2).

Methods: In Experiment 1, prior to establishing oxycodone dependence, seven Long-Evans rats (4 male and 3 female) were trained to lever press under a fixed-ratio 30 schedule for food reinforcers. When responding stabilized, subjects were administered an increasing chronic regimen of oxycodone (i.e., 3.2 mg/kg of oxycodone once daily, 3.2 mg/kg twice daily, and 10-18 mg/kg twice daily) until both spontaneous and precipitated withdrawal were reflected by disruptions in overall response rate (responses/second) and pre-ratio pausing (seconds). Precipitated withdrawal was demonstrated by administering increasing cumulative doses of naltrexone i.p. (0.32-3.2 mg/kg). After disruption of behavioral responding (withdrawal) was demonstrated consistently, indicating dependence, surgery was performed to implant a catheter and port. Twenty-four hours following catheterization, the chronic oxycodone regimen was restarted for the recovery period from surgery and for reestablishing responding under the operant schedule. When responding stabilized, the chronic regimen of oxycodone was permanently discontinued, and subjects were infused i.v. with either saline or 180 mg/kg of NAD+ each night for 10 hours per day for 10 consecutive days. Subjects responded under the operant task every afternoon during the 10 days to assess the disruptions in behavior. In Experiment 2, four male Sprague-Dawley rats were trained to respond under a fixed-ratio 10 schedule of oxycodone reinforcement after catheterization. During these sessions, overall response rate and pre-ratio pausing (PRP) were recorded. After self administration was established for an oxycodone training dose of 0.032 mg/kg/infusion, saline or NAD+ (1.57 or 3.2 mg/kg/infusion) was substituted for oxycodone until one of three criteria were met.

Results: In Experiment 1, precipitated and spontaneous withdrawal from oxycodone decreased response rate and increased PRP. When oxycodone was permanently discontinued, subjects given 10 days of i.v. NAD+ recovered their pre-chronic baseline of responding after 2 days of oxycodone cessation, while the saline group recovered their pre-chronic baseline after 4 days. PRP was also restored more quickly in the NAD+ group than the saline group. In Experiment 2, the mean number of oxycodone infusions was 23.6 ± 7.6, whereas the number of infusions was markedly reduced when saline (6.7) or NAD+ (6.2 ± 3.7 and 1.6 ± 0.89) was substituted for oxycodone.

Conclusion: In our rodent model of opioid-dependence, i.v. NAD+ infusions reduced the duration and magnitude of the rate-decreasing effects of oxycodone, which were a direct reflection of withdrawal. Of the NAD+ infusion doses tested, neither dose substituted for oxycodone and produced levels of responding closer to those for saline. These results reveal that NAD+ may have promising potential as a treatment for dependence.