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

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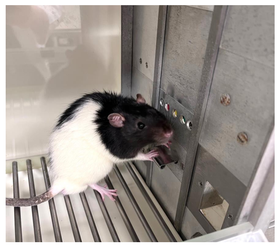
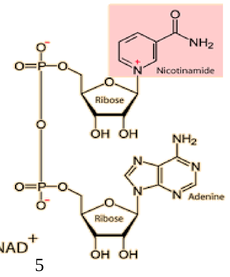
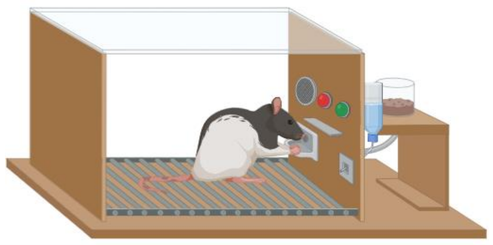
Introduction

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 [3]. 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 [7]. 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



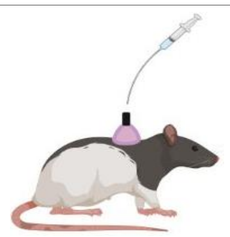
Two cohorts of rats were first trained to lever press under a fixed-ratio 30 (FR 30) schedule for food reinforcers.

Cohort 1 (4 male and 3 female): 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.

Cohort 2 (4 male and 4 female): 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, spontaneous withdrawal was assessed by the cessation of chronic treatment for at least 24 hours; 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).

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.

Results

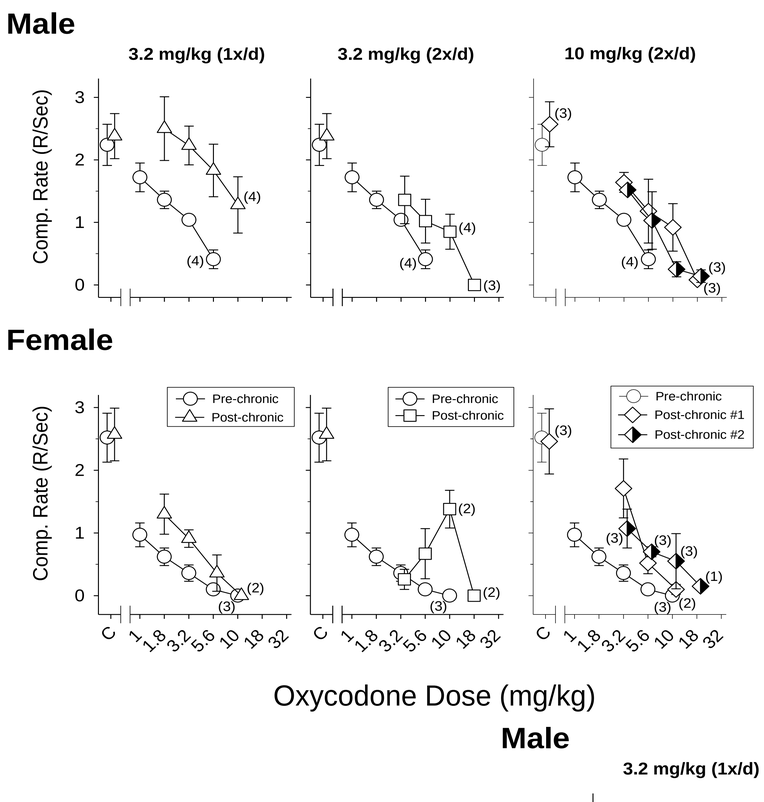


Figure 1: Effects of increasing cumulative doses of oxycodone in male (upper, n=5) and female (lower, n=4) rats during three different chronic regimens of oxycodone. In each panel, the data above C indicate the response rate obtained after saline administration, whereas the data in the dose-effects curves indicate the effect obtained after each cumulative dose. The pre-chronic curve is also repeated in every panel. Numbers in parentheses indicate the number of subjects representing that dose when it differed from the total number of subjects. This was generally due to individual differences in potency of the rate-eliminating effects across subjects.

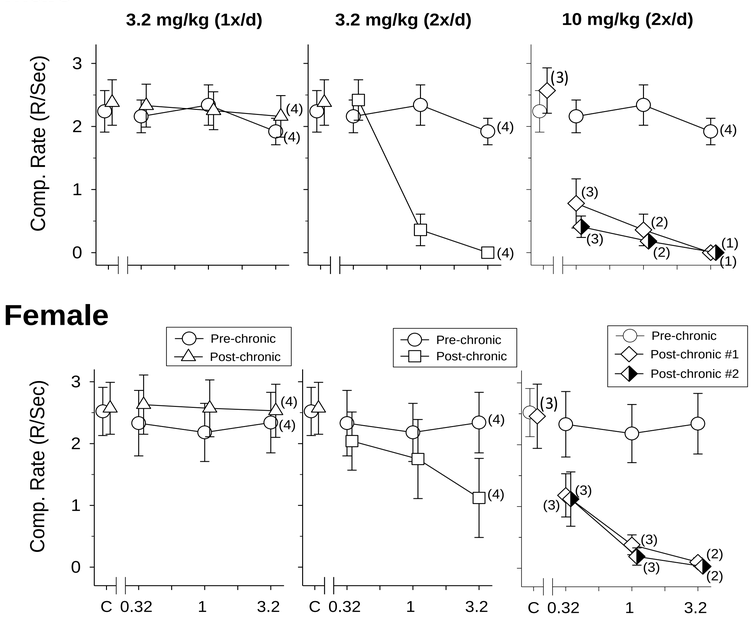


Figure 2: Effects of increasing cumulative doses of naltrexone in male (upper, n=5) and female (lower, n=4) rats during three different chronic regimens of oxycodone. In each panel, the data above C indicate the response rate obtained after saline administration, whereas the data in the dose-effects curves indicate the effect obtained after each cumulative dose. The pre-chronic curve is also repeated in every panel.

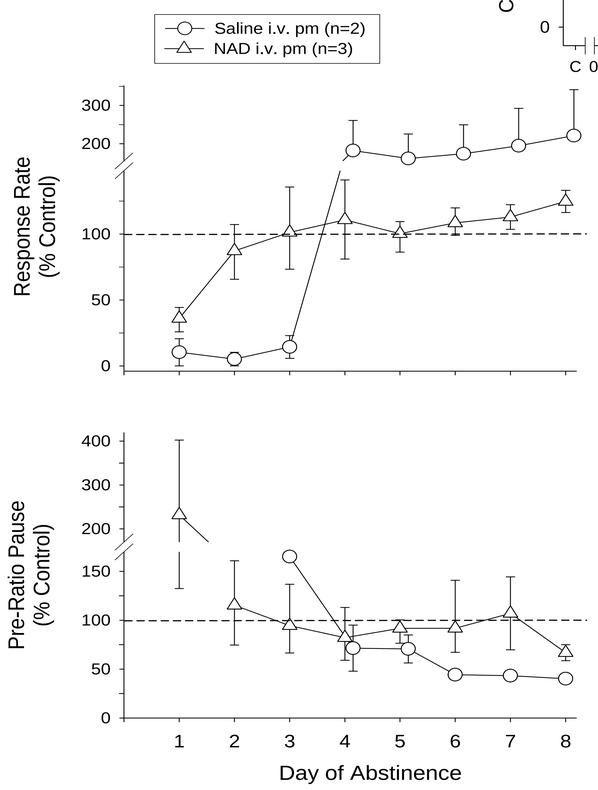


Figure 3: Effects of either i.v. saline or NAD (180 mg/kg) administration on the overall response rate and pre-ratio pause duration in male and female rats that were opioid-dependent on day 1 of 8 days of abstinence. Data are plotted as the mean percent of each subject's baseline values during the chronic oxycodone regimen. Data for pre-ratio pausing was not plotted when response rates were below 0.083 responses per second (i.e., Day 1 and 2 after i.v. saline administration.

Results (cont'd)

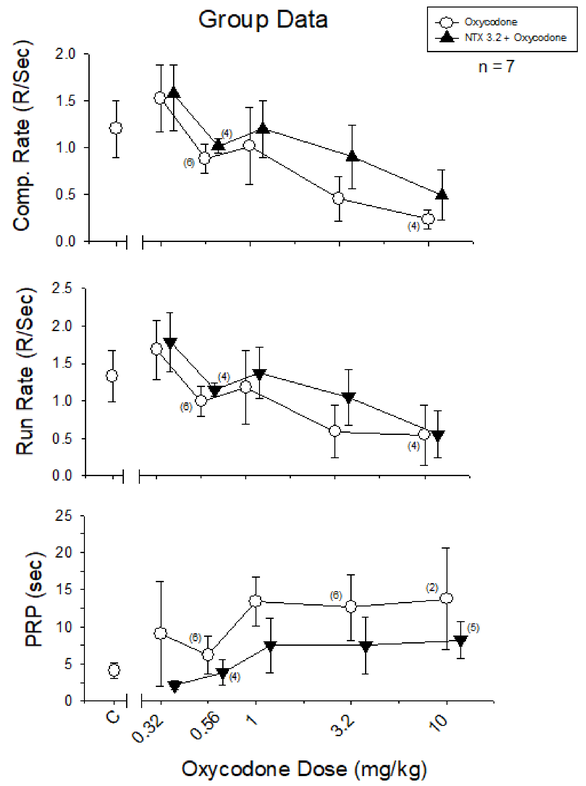


Figure 4: Effects of increasing cumulative doses of oxycodone in 7 rats (4 male, 4 female) with and without the presence of naltrexone 3.2 mg/kg in a non-dependent model. In each panel, the data above C indicate the response rate obtained after saline administration, whereas the data in the dose-effects curves indicate the effect obtained after each cumulative dose. Numbers in parentheses indicate the number of subjects representing that dose when it differed from the total number of subjects. This was generally due to individual differences in potency of the rate-eliminating effects across subjects.

Conclusion and Future Directions

1. We established opioid dependence using chronic injections and confirmed dependence by showing precipitated withdrawal with naltrexone.
2. 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.
3. 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, reducing the time of withdrawal's behavior-decreasing effects by half.
4. These results reveal that i.v. administration of NAD+ may have promising potential as a treatment for dependence.
5. **The new oxycodone dependence 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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