



# Roles of the NAc in Response to Acute Drug Withdrawal



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## Anxiety and dopamine

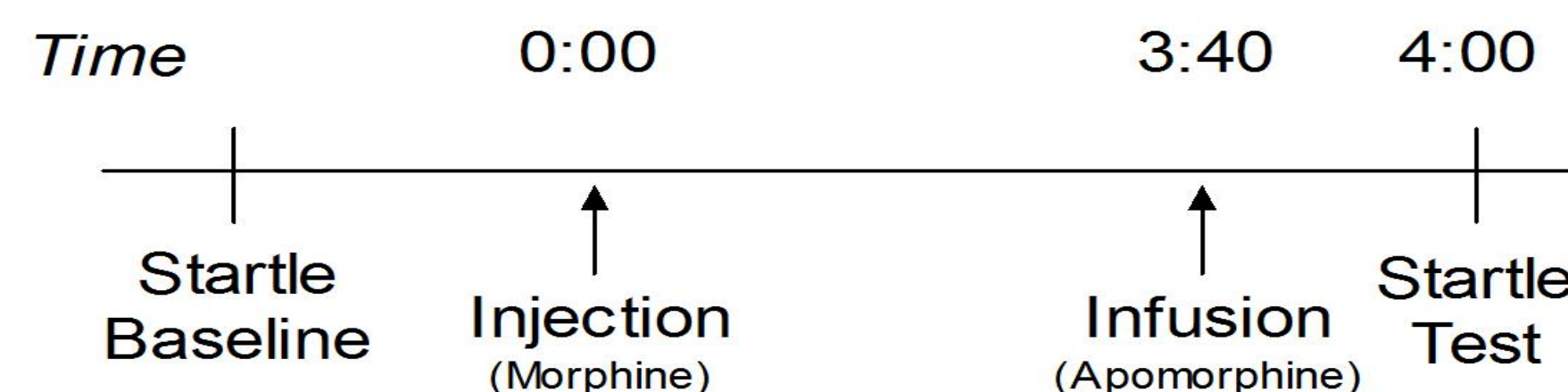
- Those experiencing withdrawal from drugs of abuse display symptoms of dysphoria such as anxiety. Anxiety during withdrawal from an acute opiate exposure also causes potentiation of the acoustic startle reflex (“withdrawal-potentiated startle”(WPS)).<sup>1,3,4</sup>
- The Gewirtz lab’s research has suggested that anxiety during acute withdrawal from opioids is mediated by levels of dopamine in the brain due to experiments with a general dopamine receptor agonist, apomorphine. Opiates disinhibit dopaminergic neurons in the VTA which project to the extended amygdala, including the nucleus accumbens (NAc).<sup>2</sup>
- Withdrawal is hypothesized to be caused by the drop in dopamine levels in the brain. Apomorphine replaces dopamine at dopamine receptors and prevents withdrawal symptoms as measured by acoustic startle.
- While we know dopamine is important in this phenomena, we do not know which brain structures play a role in producing anxiety symptoms during withdrawal.
- Our goal is to discover which brain structures play a role in producing WPS. We will test this by administering apomorphine directly to the NAc, after subcutaneous injection of morphine. We expect that, if the NAc is critical for expressing anxiety during withdrawal, then WPS will be blocked.

## Methods and agonists used

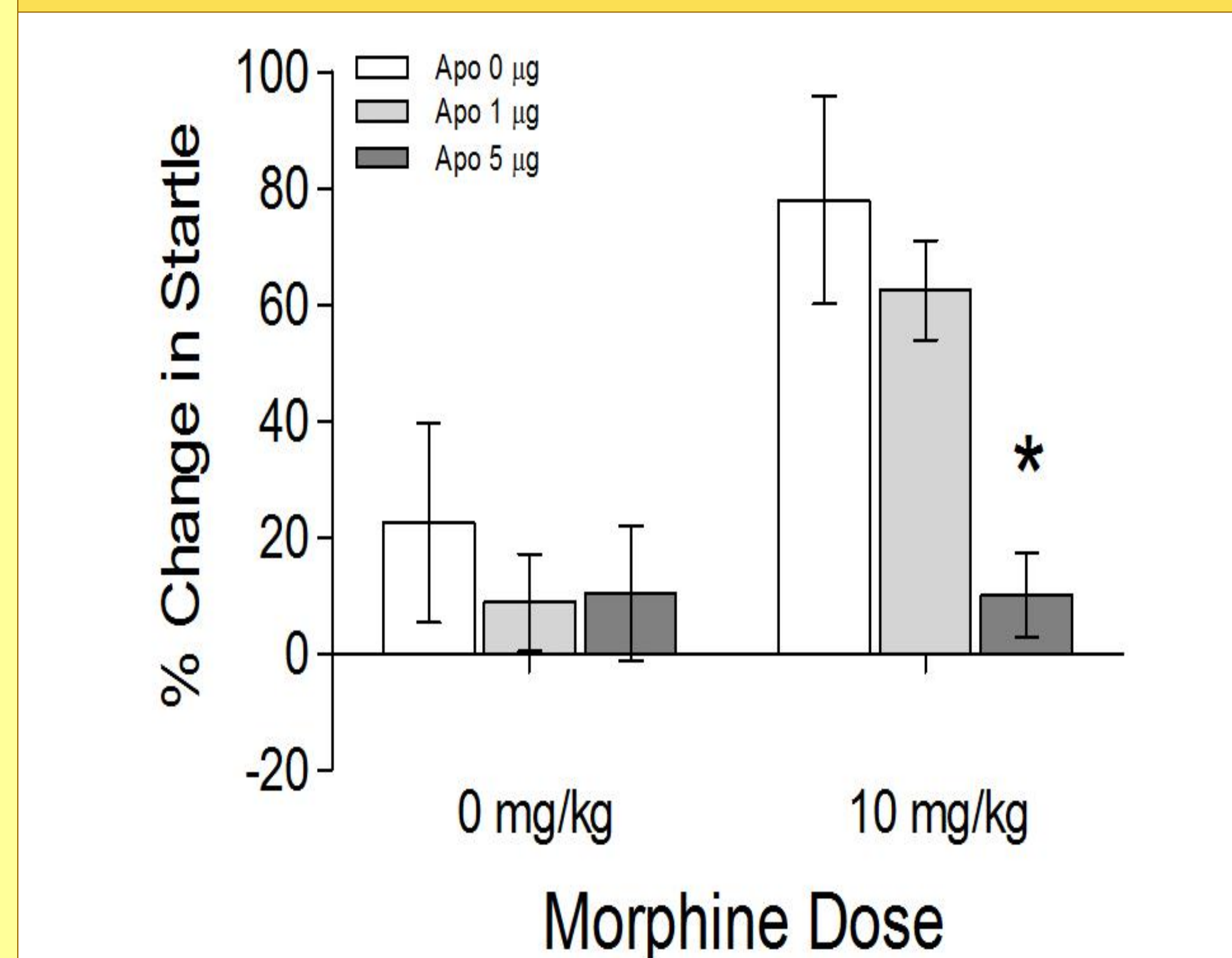
- Animals:** Male Sprague-Dawley rats from Harlan.
- Measure of anxiety during morphine withdrawal:** Withdrawal-potentiated startle apparatus.
- Acoustic Startle test:** -25 minute test
  - Activity measured: 5 minutes, reading collected every 10 s
  - Startle measured: 20 minutes, 95 and 105dB noise bursts
- Acute exposure schedule:** - 2 days handling (weighing, marking tails)
  - 2 days habituation to startle stimulus
  - 2 days of testing
- Test day:** Subjects pretested then either morphine or saline were injected subcutaneously at 0 hours. After 3:40 hours apomorphine or saline were infused. At 4:00 hours subjects were startle tested again.

## Timeline and results

Injection is a subcutaneous injection of morphine or saline  
 Infusion is a local infusion of apomorphine or saline to the NAc  
**Fig. 1 Timeline of test day**



**Fig. 2 Apomorphine infused into the NAc attenuates WPS**



Infusion of 5ug/kg apomorphine directly into the Nac was able to significantly attenuate WPS without reducing the startle reflex.

## NAc is necessary for withdrawal

- Infusion of apomorphine into the NAc attenuated WPS by reactivating dopaminergic neurons in that structure.
- The results suggest the NAc is a key player in producing negative affective symptoms of morphine withdrawal.
- Supports idea that reduced activity in VTA to NAc projecting neurons contribute to negative emotional withdrawal behaviors.
- Previous experiments using the same methods but in the BNST displayed no attenuation in WPS but this does not remove them completely from playing a role in production of anxiety during withdrawal.
- The NAc projects medium spiny neurons to the BNST and this may lead to activation of other extended amygdala structures.<sup>5</sup>
- Further research is necessary to explore how exactly the link between the VTA and extended amygdala produces anxiety and other negative affective symptoms of withdrawal.

## Acknowledgements

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