Roles of the BNST in Response to Acute Drug Withdrawal

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1. 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").[1,3,4]

•The Gewirtz lab's research has suggested that anxiety during acute withdrawal from opoids is mediated by levels of dopamine in the brain due to experiments with a general dopamine receptor agonist, apomorphine. Opiates disinhibit dopamenergic neurons in the VTA which project to the BNST and CeA. [2]

•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 withdrawal-potentiated startle. We will test this by administering apomorphine directly to the BNST, Bed Nucleus of the Stria Terminalis, after subcutaneous injection of morphine with the expectation that, if the BNST is critical for producing withdrawal potentiated startle, then withdrawal potentiated startle will be blocked .*

2. Methods and agonists used

•**Animals**: Male Sprague-Dawley rats from Charles-River laboratories.

•**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 an apomorphine or saline were injected. At 4:00 hours subjects were startle tested again.

3. Timeline and results

Injection is a subcutaneous injection of morphine or saline

Infusion is a local infusion of apomorphine or saline to the BNST

Figure 1 Timeline of test day

Fig. 2 Apomorphine infused into BNST does not attenuate withdrawal induced startle

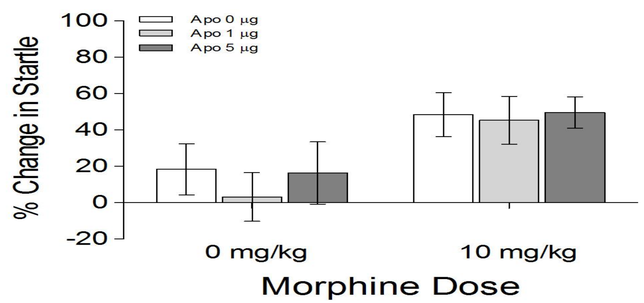
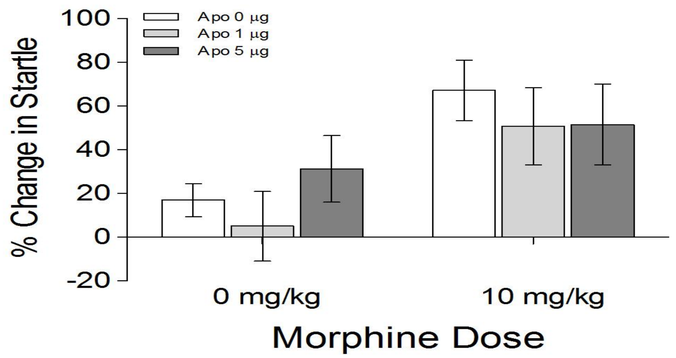


Fig. 3 Apomorphine infused into CeA does not attenuate withdrawal induced startle



4. BNST and CeA are not responsible

• Infusion of apomorphine into the BNST did not attenuate withdrawal potentiated startle despite reactivating dopamenergic neurons in that structure.

• This is contrary to results of an experiment where apomorphine was injected subcutaneously and startle was attenuated.

• With the results suggesting the BNST was not a key player in producing withdrawal symptoms we tested the CeA, the central nucleus of the amygdale.

•The results of this experiment suggested that the CeA is also not responsible for the negative affect produced during withdrawal.

•Though neither of the areas we tested in this experiment were found to be significantly involved in withdrawal symptoms we plan to continue this same test in the future with the shell of the Nucleus Accumbens. This is another area to which dopamenergic neurons from the VTA project.

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