Effect of Deep Brain Stimulation on Nucleus Accumbens Dopamine in a Preclinical Model of Antidepressant Treatment-Resistance

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Introduction
Deep brain stimulation (DBS) is being investigated as a therapy for treatment-resistant depression (TRD)6,7. DBS targets, such as the subcallosal cingulate gyrus (SCG) and nucleus accumbens (NAc) regulate mesoaccumbens dopamine1,4,8. Mesoaccumbens dopamine neurotransmission is dysregulated in depression9 and implicated in prominent symptoms (i.e. anhedonia)10. Alterations in dopamine neurotransmission are also implicated in mania11.

Methods
We monitored the effects of DBS of the IF or NAc on transient dopamine release in the NAc of urethane-anesthetized male rats using WINCS2. Chronic high (130 Hz) or low (10 Hz) frequency DBS was applied in the IL or NAc (90 min, 100 µm and 90 µm). Transient ventral tegmental area (VTA) stimulation-evoked dopamine efflux was monitored in the NAc core. Antidepressant-resistance was induced with 14 days of ACTH (1-24) treatment (100µg/day) and validated with assessment of imipramine (10mg/kg) antidepressant efficacy in the forced swim test1 obstacles.

Figure 1. Experimental design: IL or NAC DBS-mediated changes in transient VTA stimulation-evoked NAC dopamine

Objectives
We aimed to determine how DBS of neurosurgical targets for TRD, the subcallosal cingulate (SCG) and nucleus accumbens (NAc), regulate mesoaccumbens dopamine neurotransmission and the NAC, regulate transient mesoaccumbens dopamine release in control and antidepressant-resistant animals.

Results
Figure 2. High frequency NAC and IL DBS differentially attenuate transient VTA-evoked NAC dopamine efflux

90 minutes of high frequency stimulation (HFS) (130 Hz, 100 µA and 90 µsec) of the NAc and IL significantly attenuated transient VTA stimulation-evoked (23 pulses, 60 Hz, 125 µA) dopamine efflux in the NAc by 45% and 34%, respectively. No significant change was observed with low frequency stimulation (LFS) of either target (10 Hz, 100 µA and 90 µsec).

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Figure 3. A state of tricyclic antidepressant treatment-resistance is induced with chronic ACTH treatment.

Figure 4. In ACTH-treated rats, transient VTA-evoked NAC dopamine efflux was significantly potentiated by HFS of IL

In ACTH-treated rats, 90 minutes of high frequency stimulation (130 Hz, 100 µA and 90 µsec; n=3) significantly potentiated transient VTA stimulation-evoked (23 pulses, 60 Hz, 125 µA) dopamine efflux in the NAc. This effect was opposite to that observed with healthy rats (n=3).

Figure 5. Long-term depression of transient NAC dopamine efflux was observed in control, but not ACTH-treated rats.

Figure 6. Long-term depression is regulated by dopamine and glucocortioid receptors

Dopaminergic mechanisms mediate blockade of HFS-induced LTD, while glucocortioid mechanisms mediate reversal of effect of HFS on transient dopamine

Conclusions
HFS of NAC induces greater magnitude of attenuation in NAC dopamine than IL HFS. Long-term depression of NAC dopamine is induced by HFS of both targets. HFS-mediated long-term depression is blocked in ACTH-treated rats. Blockade of plasticity and reversal of direction of change of transient NAC dopamine efflux in ACTH-treated rats may be mediated by dopaminergic and glucocorticoid mechanisms.

References
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