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### 1118. Nucleus Accumbens Deep Brain Stimulation in an Animal Model of Antidepressant Resistance: Dopamine Dysregulation and Antidepressant-induced Mania

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**Background:** Dysregulated hypothalamic-pituitary-adrenal axis activity and dopamine neurotransmission are implicated in mood dysregulation, antidepressant efficacy and antidepressant-induced mania.

**Methods:** Adrenocorticotropic hormone (ACTH) (100µg/d) was administered for 21 days in rat and antidepressant efficacy of imipramine (10mg/kg) was assessed in the Open Field Test (OFT) and Forced

Swim Test (FST) on day 15. Imipramine-resistant animals then received 7 days of bilateral nucleus accumbens (NAc) deep brain stimulation (DBS; 130 Hz, 200µA, 90µSec) followed by OFT and FST. In addition, the effects of NAc DBS on ventral tegmental area (VTA) stimulation-evoked NAc dopamine release were monitored in ACTH-treated and control rats using fast scan cyclic voltammetry.

**Results:** ACTH pre-treatment blocked imipramine-mediated reductions of immobility in the FST (n=10; p<0.05). NAc DBS effectively reduced immobility in ACTH-treated animals (n=8; p< 0.05). No significant reduction in immobility was observed in sham groups/animals (n=8; p<0.05). Interestingly, a proportion (33%; n=5) of the ACTH-treated animals (DBS & Sham) displayed increased locomotor activity in the open field test, and exaggerated escape behaviors in the FST. Correspondingly, DBS of the NAc significantly potentiated VTA-evoked transient NAc dopamine efflux in antidepressant-resistant animals.

**Conclusions:** This study demonstrated NAc DBS is an effective antidepressant treatment in animals non-responsive to imipramine. Observations of hyperactivity, augmented antidepressant response behaviors and potentiated phasic dopamine efflux suggest disruption of mesoaccumbens signaling in ACTH-treated animals contributing to the development of a mania-like behavior in a subset of vulnerable individuals. Further studies are needed to understand mechanisms mediating this effect.

**Keywords:** Nucleus Accumbens, Deep brain stimulation, Dopamine, Mania, Antidepressant resistance

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