BDNF knockdown in the VTA blocks social stress-induced deficits in social behavior and nucleus accumbens ΔFosB expression

Emelia B. Hakes[1], Garret A. Munoz[1], Caroline E. Bass[2], Ella M. Nikulina[1], Ronald P. Hammer, Jr.[1,3]

[1] Basic Medical Sciences, University of Arizona College of Medicine, Phoenix, AZ; [2] Pharmacology & Toxicology, SUNY Buffalo, Buffalo, NY; [3] Pharmacology and Psychiatry, University of Arizona College of Medicine, Tucson, AZ

BACKGROUND

- Social defeat stress is a salient stressor that translates readily from animal studies to humans.
- Repeated exposure to social defeat stress induces brain-derived neurotrophic factor (BDNF) in the ventral tegmental area (VTA) and the highly stable transcription factor ΔFosB in the nucleus accumbens (NAc) of rats, as well as changes in social approach behavior.[1,2]
- Also induced by chronic drug exposure, ΔFosB has been proposed as a long-term mediator of synaptic plasticity in the reward circuitry.[3]
- It is unknown whether VTA BDNF is required for the effects of social stress.
- **We hypothesized that VTA BDNF knockdown would attenuate the effect of social stress on weight gain, and reverse its effects on social approach behavior and ΔFosB expression in the NAc.**

METHODS

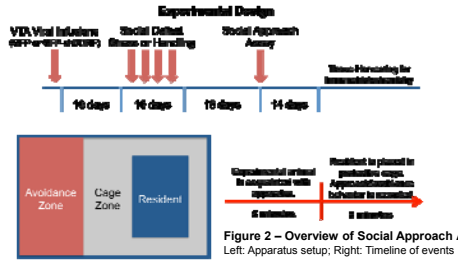


Figure 2 – Overview of Social Approach Assay
Left: Apparatus setup; Right: Timeline of events

Figure 1 – Overview of Social Defeat
Left: Rat in protective cage; Right: Attacks by the resident persisted until the animal reliably engaged in subordinate behavior; Bottom: Timeline of events. *Images/figures courtesy of C.E. Johnston*

- 32 male Sprague Dawley rats underwent stereotaxic surgery to receive bilateral intra-VTA (AP -5.2, ML ±2.15, DV -8.7 from bregma; tilt = 10°) infusions of 0.5 µl of either adeno-associated virus inducing green fluorescent protein (AAV-GFP) or GFP and short hairpin RNA directed against BDNF (shRNA-BDNF). Following recovery, rats were subjected to control handling or intermittent social defeat stress every third day for 10 days.
- Social defeat stress consisted of a brief confrontation between an aggressive male Long Evans rat ("residents") and an experimental intruder rat. (Figure 1) Weight was measured prior to the first handle or defeat and then again following the last.
- Social interaction with a previously encountered resident rat was assessed in a social approach assay 18 days later. Time spent in the avoidance and cage zones were recorded. (Figure 2)
- Rats were perfused with 4% paraformaldehyde 4 weeks after the final social defeat episode.
- Immunohistochemical analysis for ΔFosB was performed by incubating coronal sections with ΔFosB (1:1000 dilution, Santa Cruz, SC-48) rabbit antisera for 48 hours at 4°C.
- Sections were processed using avidin-biotin-peroxidase (Vectastain ABC Elite kit, Vector Laboratories) and then developed with diaminobenzidine as the peroxidase substrate.

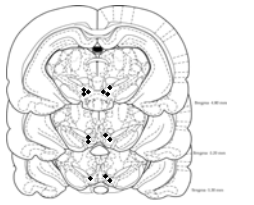
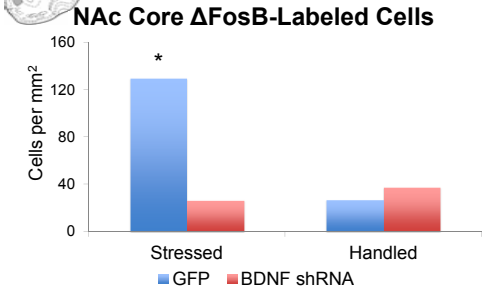
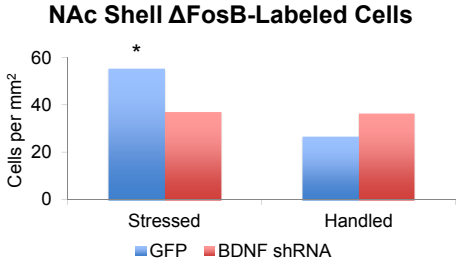


Figure 3 – Validation of Viral Infusion Location
Above: Black diamonds represent GFP expression post-surgery validating the placement of AAV into the VTA.

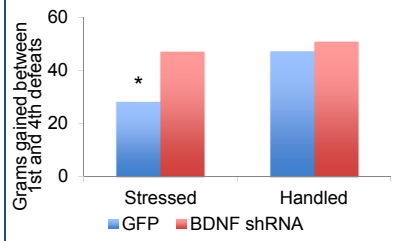
RESULTS

ΔFosB Expression in the NAc

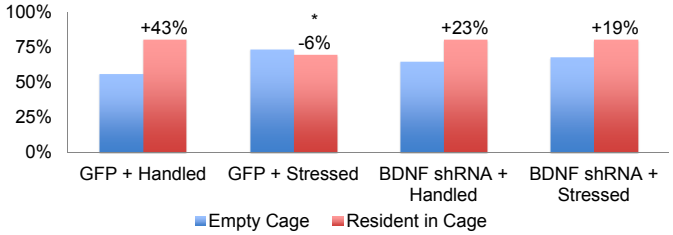




Weight Regulation



Social Behavior



VTA BDNF knockdown:

- blocked stress-induced ΔFosB expression in both the NAc core and shell.
- attenuated effects of stress on weight gain and social behavior.

CONCLUSIONS

- This study implicates VTA BDNF signaling in the effects of stress on social behavior. VTA BDNF appears to be required for the long-lasting effects of social stress on ΔFosB expression in the NAc.
- Activation of BDNF signaling in mesolimbic circuits may underlie the persistent deficits of social behavior induced by stress exposure in some individuals.

References:

1. Nikulina EM, Lacagnina MJ, Fanous S, Wang J, Hammer RP, Intermittent social defeat stress enhances mesocorticolimbic ΔFosB/BDNF co-expression and persistently activates corticotegmental neurons: Implication for vulnerability to psychostimulants. *Neuroscience*. 2012;212:38-48.
2. Fanous S, Terwilliger EF, Hammer RP, Nikulina EM. Viral depletion of VTA BDNF in rats modulates social behavior, consequences of intermittent social defeat stress, and long-term weight regulation. *Neurosci Lett*. 2011;502(3):192-196.
3. Nestler EJ. Transcriptional mechanisms of addiction: Role of ΔFosB. *Philos Trans R Soc Lond B Biol Sci*. 2008;363(1507):3245-3255.

Supported by USPHS Award DA026451 to EMN, and AANS Summer Research Fellowship to EBH.