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

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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

- 32 male Sprague Dawley rats underwent stereotaxic surgery to receive bilateral intra-VTA (AP: ±2.0, ML: ±1.0, DV: ±7.5) 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.

RESULTS

- Social defeat stress consisted of a brief confrontation between an aggressive male Long Evans rat (“resident”) 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 10 days later. Time spent in the avoidance and cage zones were recorded. (Figure 2)
- Rates 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.

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: