ROLE OF NT3/TRKC IN THE REGULATION OF FEAR

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Background: Maladaptive fear is a cardinal feature of many anxiety disorders, often manifested as excessive/inappropriate learned fear and resistance to extinction. The efficacy of behavioral therapies depends on interindividual variation in fear extinction, for which the neurobiological basis is unknown. Fear learning and extinction rely on synaptic plasticity events occurring at a fear network comprising the amygdala, hippocampus, and medial prefrontal cortex. Neurotrophins, known regulators of synaptic plasticity, present as obvious candidates for the regulation of fear processes.

Aims: To investigate the role of neurotrophin 3 (NT3)/Tropomyosin receptor kinase C (TrkC) in the fear network in the regulation of learned fear and extinction.

Methods: Mice trained in contextual fear conditioning and extinction paradigm were used to (i) isolate amygdala synaptoneurosomes (n=8 per group) and perform immunofluorescence assays to study synaptic receptors; (ii) perform *ex-vivo* electrophysiological recordings and pharmacological treatments to study amygdalar synaptic plasticity (n=3-6 per group); (iii) measure TrkC activation in the brain fear network by western blots (n=7-14 per group). Stereotaxic surgeries and local infusions of NT3 in the amygdala (n=6 per group) were performed in combination with behavioral experiments.

Results: We established a model to study interindividual differences in fear extinction. Fear conditioned mice were categorized as extinction (EXT)-success or EXT-failure, according to their inherent ability to extinguish fear. Statistical analysis revealed significant differences when the two groups were compared: EXT-success mice showed attenuated LTP, robust LTD and higher levels of synaptic GluN2B, while EXT-failure mice showed strong LTP, no LTD and higher levels of synaptic GluN2A. Moreover, an inactivation of TrkC overall in the fear network was observed during consolidation and reconsolidation, while an increased TrkC activation was observed at extinction consolidation in the amygdalae of EXT-success, as compared to EXT-failure mice. Scavenging endogenous NT3 with TrkC-Fc in EXT-success slices strengthened LA LTP. In EXT-failure mice, NT3 perfusion attenuated LA LTP, in a GluN2B-dependent manner, and NT3 infusion in the LA was sufficient to rescue extinction deficits.

Conclusions: Our data support a key role for the NT3-TrkC system in interindividual differences in fear extinction in mice, through modulation of amygdalar NMDAR composition and synaptic plasticity.

Keywords: Neurotrophins, Anxiety, Fear extinction, NMDA receptors, Synaptic plasticity

Publications:

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