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Modeling exposure therapy in rats: fear extinction-induced infralimbic protein synthesis underlies reversal of chronic stress-induced cognitive inflexibility

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Abstract:
Stress-related psychiatric disorders, like depression or post-traumatic stress disorder, are prevalent yet poorly treated. These disorders share cognitive flexibility deficits associated with medial prefrontal cortex (mPFC) dysfunction. Psychotherapies invoking cognitive flexibility can be efficacious even in pharmacotherapy-resistant patients, although, as with pharmacotherapies, response to psychotherapy can be incomplete, some patients do not respond, and relapse remains an issue. Thus, understanding the neurobiological mechanisms underlying its efficacy could inform more rapid, efficacious, or long-lasting behavioral therapies, or could inform the development of adjunct treatment strategies designed to improve its effect. Pre-clinically, we have shown that chronic unpredictable stress (CUS) causes deficits in mPFC-mediated cognitive flexibility on the attentional set-shifting test (AST). We have shown that fear extinction learning, which engages mPFC cognitive flexibility and conceptually resembles exposure therapy for PTSD in humans, can model exposure therapy in rats by improving set-shifting performance in the AST that has been compromised by chronic stress (SfN Abstract 468.07, 2014). This study tested whether extinction-induced mPFC protein translation was necessary for the reversal of stress-compromised set-shifting by extinction therapy. After 2 weeks of CUS or control treatment, rats received microinjections of the protein synthesis inhibitor anisomycin or saline vehicle in the ventral mPFC (i.e., the infralimbic region, IL) followed by fear extinction training or control treatment. They were tested on AST 24h later. Anisomycin delivered to IL cortex blocked the rescue of mPFC-mediated cognitive flexibility by extinction in stressed rats. By contrast, control injections of anisomycin into the PrL subregion of mPFC dorsal to the IL did not attenuate the beneficial effects of extinction. Ongoing studies are examining changes in plasticity-related proteins in IL tissue of rats following fear extinction. These results suggest that fear extinction-induced protein translation underlies the therapeutic effect of fear extinction. Such processes may be important to the beneficial effects on cognition that have been compromised by chronic stress, and may suggest targets for the development of adjunct pharmacological tools to enhance the efficacy of behavioral therapy.
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