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Gene regulation in dopamine circuitry and stress-related behaviors
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Traumatic experiences and social stress may contribute to the onset of psychiatric disorders. These situations trigger stress responses including the orchestrated release of hormones, including glucocorticoids (GCs) and prolactin (PRL). This mechanism is beneficial when normally working, but disproportionate or excessively long-lived stress responses can precipitate the development of pathological anxiety, depression, inability to socially perform or addiction. GCs activate directly the glucocorticoid receptor (GR) and PRL binding to its receptor activates STAT5 two widespread transcription factors. To address their respective roles in stress-related behaviors, we generated mice with either GR or STAT5 genes ablation targeted to specific brain cell populations, focusing on the dopamine circuitry.

We reported that GR gene ablation in dopamine neurons had neither effects on studied behaviors nor on VTA dopamine neurons activity. These results were surprising given the reported effects of stress and GCs on dopamine neurons. However, GR gene ablation in post-synaptic dopaminoceptive neurons markedly decreased the activity of pre-synaptic dopamine neurons of the VTA, demonstrating that GC action on dopamine neurons firing is indirect. This mutation deeply affected behavioral responses to cocaine and abolished enduring social aversion induced by repeated social defeats, shifting all defeated animals toward resiliency. Induced social aversion requires enduring activation of dopamine neurons firing, abolished by GR gene inactivation. Induced anxiety and fear memories remained unaffected. Acute inhibition of the activity of DA-releasing neurons fully restored social interaction in socially defeated wild-type mice.

Our data suggest a GR-dependent neuronal dichotomy for the regulation of emotional and social behaviors, and clearly implicate GR as a link between stress resiliency and dopaminergic tone.

Upon stress, the release of PRL is concomitant to that of GCs. Comparison of mice carrying brain-targeted GR and STAT5 gene mutations suggest that these two hormones have opposing effects on a large panel of stress-related behaviors but act on distinct structures in the mesocorticolimbic dopamine pathway.

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