

PSYCHIATRIC DISORDERS

CRF flicks a motivational switch

Stress has a bad reputation — chronic stress often precedes major depression — but acute, short-lasting stress can have positive, motivating effects. A new study shows that corticotropin-releasing factor (CRF), a neuropeptide secreted in response to stress, normally facilitates dopamine release in the nucleus accumbens (NAc) and promotes a positive affective state, but induces a negative state after chronic stress.

CRF administered into the NAc has been shown to facilitate motivated behaviours that involve dopamine transmission. Lemos *et al.* therefore investigated CRF–dopamine interactions in the NAc in mice. They first showed that immunoreactivity for CRF and its two receptors CRFR1 and CRFR2 in cell bodies and fibre terminals in the NAc partially overlapped with immunoreactivity for tyrosine hydroxylase, indicating the potential for CRF to modulate dopamine release. Fast-scan cyclic voltammetry experiments in brain slices revealed that CRF application increased dopamine release in the NAc — an effect that required both CRFR1 and CRFR2.

To assess the behavioural relevance of CRF-triggered dopamine release, the authors performed a place preference test. Here, mice received an intra-NAc infusion of physiological concentrations of CRF in one of two chambers and a vehicle infusion in the other chamber on 2 consecutive days. On the third day, the mice showed a preference for the chamber associated with the CRF infusion. This CRF-associated place preference depended on dopamine release because the infusions had no effect in mice in which dopamine neurons were destroyed using the neurotoxin 6-hydroxydopamine. These findings suggest that CRF-induced dopamine release promotes a positive affective (rewarding) state.

Because lack of motivation is one of the main symptoms of depression, the authors next assessed whether CRF–dopamine interactions are affected by chronic stress. They exposed mice to 2 days of repeated forced swim stress. In NAc slices from these mice, CRF application no longer facilitated dopamine release. Moreover, in a place preference test, chronically stressed mice spent more time in the vehicle-associated chamber than in the CRF-associated chamber, indicating that CRF in the NAc now induced a negative, aversive affective state. Both effects persisted for at least 90 days after stress exposure.

Thus, chronic stress seems to cause a switch in the actions of CRF in the NAc, from promoting dopamine release and inducing an appetitive state to inducing an aversive state. Glucocorticoids released in response to chronic stress may mediate this switch, as repeated swim stress did not affect the capacity of CRF to induce dopamine release in the NAc of mice pretreated with a glucocorticoid receptor antagonist.

These findings point to a CRF–dopamine-based mechanism by which chronic stress induces a negative motivational state. Future studies may clarify the role of glucocorticoids in this process.

Leonie Welberg

ORIGINAL RESEARCH PAPER Lemos, J. C. *et al.* Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature* 19 Sep 2012 (doi:10.1038/nature11436)