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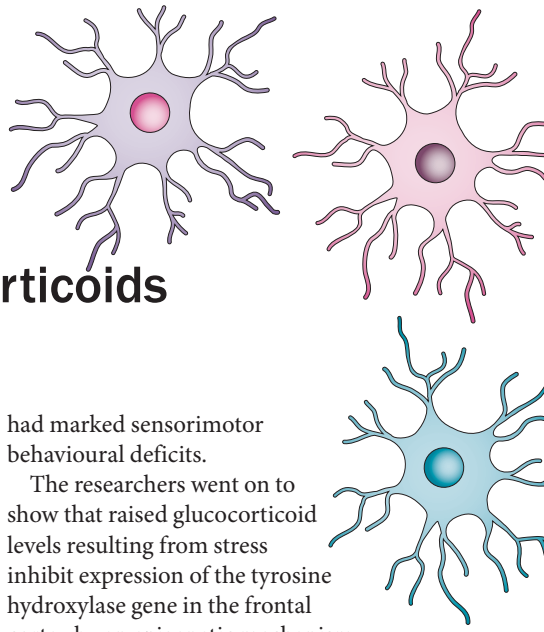


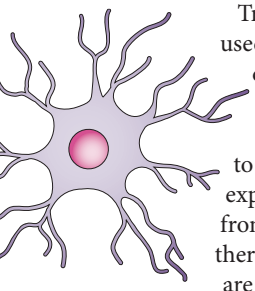
BASIC RESEARCH

From stress to social behaviour—glucocorticoids and dopaminergic circuits pave the way

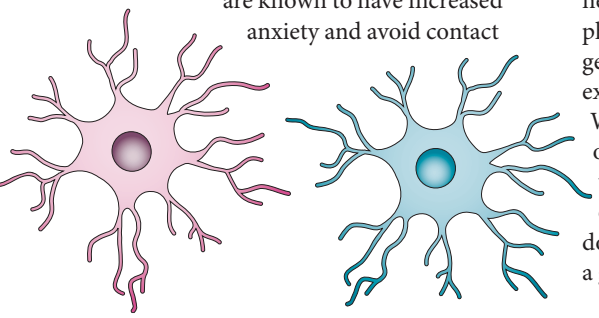
Two new studies published in *Science* clarify the molecular mechanisms linking stress and social behaviour. The results of both studies elucidate the way in which stress-related increases in glucocorticoid levels act on dopaminergic circuits in the brain of mice and how these mechanisms influence behaviour.

Stress can induce powerful biochemical and behavioural changes in animals. Stress responses can be protective against danger, but excessive stress can also have adverse and often long-lasting effects on an animal's health. In humans, high levels of stress have been associated with many psychiatric disorders.

The activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to stress leads to release of glucocorticoids from the adrenal glands. Glucocorticoids bind to the glucocorticoid receptor, which is expressed in virtually all of the body, explaining the wide range of effects of these hormones on development, metabolism, immunity and behaviour. "However," says François Tronche, senior researcher of the first study, "the relevant cellular targets of glucocorticoids remain largely unknown."



Tronche and colleagues used a mouse model of social defeat to investigate the neurochemical response to glucocorticoids and its link to social aversion. Mice that experience repeated aggression from dominant mice and are, therefore, socially defeated, are known to have increased anxiety and avoid contact with other individuals of their species. Tronche and colleagues observed that this type of social stress is associated with a marked increase in circulating levels of glucocorticoids. When the gene encoding the glucocorticoid receptor was selectively inactivated in dopaminoceptive neurons of the nucleus accumbens, which project to the ventral tegmental area where they regulate the activity of dopamine-releasing neurons, social avoidance in response to aggression was abolished.



"The fact that the absence of the glucocorticoid receptor in dopaminoceptive neurons blocks the appearance of social aversion but not the appearance of anxiety suggests the existence of a discrete specification of neuronal circuits underlying behavioural outcomes of social stress," comments Tronche.

"These data show a quite remarkable specificity of glucocorticoids in promoting social aversion behaviours, but not other anxiety behaviours, in response to repeated aggression," concurs Stafford Lightman (University of Bristol, UK), who was not involved in the two studies, "and open a potential therapeutic approach for overcoming pathologies related to exposure to trauma."

In the second study, also in mice, Niwa *et al.* investigated the consequences of social isolation in adolescence—which mimics separation from parents in humans—on adult behaviour. Animals aged 5–8 weeks were isolated for 3 weeks, then restored to the society of other mice. "We found interacting synergistic neurochemical and behavioural phenotypes only when we combined genetic and environmental stressors," explains study researcher Akira Sawa. Whereas no changes in behaviour were observed in socially isolated wild-type mice compared with nonisolated controls, transgenic animals with a dominant-negative mutation in *DISC1*, a gene associated with schizophrenia, had marked sensorimotor behavioural deficits.

The researchers went on to show that raised glucocorticoid levels resulting from stress inhibit expression of the tyrosine hydroxylase gene in the frontal cortex by an epigenetic mechanism. As a consequence, dopamine expression decreases in a specific population of dopamine-releasing neurons (those that originate from the ventral tegmental area and project to the frontal cortex) and behavioural change is triggered. Use of a glucocorticoid antagonist blocks these neurochemical and behavioural changes.

"This lovely study clearly shows the importance of interactions between genetic susceptibility and stress and how these interactions can be mediated by a highly specific epigenetic marking of specific neuronal populations," says Lightman. "Furthermore, it emphasizes the key part played by glucocorticoids in altering cognitive function, especially in genetically susceptible individuals."

Niwa *et al.* plan to continue to research the epigenetic mechanisms whereby glucocorticoids regulate gene expression, and how different populations of dopaminergic neurons are affected by glucocorticoids. "We also plan to investigate if these animals can be used as a model of untreatable depression and if antagonism of the glucocorticoid receptor could be an approach to treat patients with depression," says study researcher Toshitaka Nabeshima.

Joana Osório

Original articles Barik, J. *et al.* Chronic stress triggers social aversion via glucocorticoid receptor in dopaminoceptive neurons. *Science* **339**, 332–335 (2013) | Niwa, M. *et al.* Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science* **339**, 335–339 (2013)