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Spread of genes implicated in post-traumatic stress disorder

Identification of possible genetic markers supports trauma treatment with steroid hormone.

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Researchers exposed rats to soiled cat litter to study their response to stress.

Most people gradually recover from trauma, but a small fraction of individuals develop post-traumatic stress disorder (PTSD) — prompting scientists to look for the biological underpinnings of this extreme response to traumatic situations such as warfare, car accidents and natural disasters.

Research published on 11 August in *Proceedings of the National Academy of Sciences* identifies up to 334 genes that may be involved in vulnerability to post-traumatic stress in rats[1].

Most animal studies of stress use intense stimuli such as electric shocks, designed to produce large, group differences between exposed and unexposed animals. But Nikolaos Daskalakis and his colleagues tried a subtler approach to elicit a wide range of individual responses in rats that had all experienced the same trauma — more closely mimicking the variability of human responses to disturbing events.

"We wanted to capture the differences between a susceptible individual and one that is not susceptible to the same experience," says Daskalakis, a neuroendocrinologist at the Icahn School of Medicine at Mount Sinai in New York.

The researchers exposed around 100 rats to soiled cat litter — which evokes a feared predator — and tested the animals one week later for lingering effects of the trauma. About one-quarter of the exposed animals were classified as 'extreme' responders, showing high levels of anxiety and startling easily on hearing loud noises. Another quarter of the animals were 'minimal' responders, and exhibited anxiety levels similar to those of non-exposed rats.

To probe the mechanisms that control trauma susceptibility, the researchers used DNA microarray technology to screen 22,000 genes in samples from the blood, and the amygdala and hippocampus — brain areas that are involved in fear and memory. In males and females, and across the different tissues, anywhere from 86 to 334 genes showed changes in expression levels that appeared to relate to extreme or minimal responsiveness.

Most genes seemed to be involved in conferring either vulnerability or resilience, but not both. Daskalakis says that the results suggest that at a genomic level, the balance of two different stress-response systems might control individual susceptibility to PTSD.

Testing treatments

On the basis of their analysis, the researchers predicted that expression of the genes associated with trauma vulnerability and resilience is regulated by 73 transcription factors, about one-quarter of which are involved in glucocorticoid receptor signalling. Misregulation of glucocorticoid receptor signalling has long been suspected in PTSD, and some studies have suggested that abnormally low levels of receptor activity is to blame[2].

"It gives us insight into a genetic marker for PTSD susceptibility and potential treatments targeting activation of the glucocorticoid receptor as a part of therapy," says David Diamond, a behavioural neuroscientist at the University of South Florida in Tampa. Finding better indicators for trauma susceptibility could help researchers to develop and monitor treatments, he says.

Daskalakis's group further tested this hypothesis by injecting rats with corticosterone — a naturally occurring glucocorticoid hormone that is released following stress — one hour after trauma exposure. Seven days later, rats that had received the treatment showed reduced after-effects of the trauma, compared to untreated animals.

The team has also been studying treatment of emergency patients in hospitals who have experienced traumatic events, by testing whether PTSD can be prevented by a single, high dose of cortisol — the primary glucocorticoid hormone in humans — given a few hours after trauma.

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References

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