Turning off stress

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Weizmann Institute scientists reveal the actions of a family of proteins that "turn off" the stress response. Their findings could be relevant to PTSD, anorexia, anxiety disorders and depression.

Post-traumatic stress disorder can affect soldiers after combat or ordinary people who have undergone harrowing experiences. Of course, feelings of anxiety are normal and even desirable – they are part of what helps us survive in a world of real threats. But no less crucial is the return to normal – the slowing of the heartbeat and relaxation of tension – after the threat has passed. People who have a hard time "turning off" their stress response are candidates for post-traumatic stress syndrome, as well as anorexia, anxiety disorders and depression.

How does the body recover from responding to shock or acute stress? This question is at the heart of research conducted by Dr. Alon Chen of the Institute's Neurobiology Department. The response to stress begins in the brain, and Chen concentrates on a family of proteins that play a prominent role in regulating this mechanism. One protein in the family – CRF – is known to initiate a chain of events that occurs when we cope with pressure, and scientists have hypothesized that other members of the family are involved in shutting down that chain. In research that appeared in the *Proceedings of the National Academy of Sciences* (PNAS), Chen and his team have now, for the first time, provided sound evidence that three family members known as urocortin 1, 2 and 3 – are responsible for turning off the stress response.

The research group, including Adi Neufeld Cohen, Dr. Michael Tsoory,

Dmitriy Getselter, and Shosh Gil, created genetically engineered mice that don't produce the three urocortin proteins. Before they were exposed to stress, these mice acted just like the control mice, showing no unusual anxiety. When the scientists stressed the mice, both groups reacted in the same way, showing clear signs of distress. Differences between the groups only appeared when they were checked 24 hours after the stressful episode: While the control mice had returned to their normal behavior, appearing to have recovered completely from the shock, the engineered mice were still showing the same levels of anxiety the scientists had observed immediately following their exposure to the stress.

Clearly, the urocortin proteins are crucial for returning to normal, but how, exactly, do they do this? To identify the mechanism for the proteins' activity, Chen and his team tested both groups of mice for expression levels of a number of genes known to be involved in the stress response. They found that gene expression levels remained constant during and after stress in the engineered mice, whereas patterns of gene expression in the control mice had changed quite a bit 24 hours after the fact. In other words, without the urocortin system, the "return to normal" program couldn't be activated.

Chen: "Our findings imply that the urocortin system plays a central role in regulating stress responses, and this may have implications for such diseases as anxiety disorders, depression and anorexia. The genetically engineered mice we created could be effective research models for these diseases."

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