A unique on-off switch for hormone production

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Weizmann scientists have revealed a new kind of on-off switch in the brain for regulating the production of a main biochemical signal from the brain that stimulates cortisol release in the body.

After we sense a threat, our brain center responsible for responding goes into gear, setting off a chain of biochemical reactions leading to the release of cortisol from the adrenal glands.

Dr. Gil Levkowitz and his team in the Molecular Cell Biology Department have now revealed a new kind of ON-OFF switch in the brain for regulating the production of a main biochemical signal from the brain that stimulates cortisol release in the body. This finding, which was recently published in Neuron, may be relevant to research into a number of stress-related neurological disorders.

This signal is corticotropin releasing hormone (CRH). CRH is manufactured and stored in special neurons in the hypothalamus. Within this small brain region the danger is sensed, the information processed and the orders to go into stress-response mode are sent out. As soon as the CRH-containing neurons have depleted their supply of the hormone, they are already receiving the directive to produce more.

The research – on zebrafish – was performed in Levkowitz's lab and spearheaded by Dr. Liat Amir- Zilberstein together with Drs. Janna Blechman, Adriana Reuveny and Natalia Borodovsky, and Maayan Tahor. The team found that a protein called Otp is involved in several

stages of CRH production. As well as directly activating the genes encoding CRH, it also regulates the production of two different receptors on the neurons' surface for receiving and relaying CRH production signals – in effect, ON and OFF switches.

The team found that both receptors are encoded in a single gene. To get two receptors for the price of one, Otp regulates a gene-editing process known as alternative splicing, in which some of the elements in the sequence encoded in a gene can be "cut and pasted" to make slightly different "sentences." In this case, it generates two variants of a receptor called PAC1: The short version produces the ON receptor; the long version, containing an extra sequence, encodes the OFF receptor. The researchers found that as the threat passed and the supply of CRH was replenished, the ratio between the two types of PAC1 receptor on the neurons' surface gradually changed from more ON to mostly OFF. In collaboration with Drs Laure Bally-Cuif and William Norton of the Institute of Neurobiology Alfred Fessard at the Centre National de la Recherche Scientifique (CNRS) in France, the researchers showed that blocking the production of the long receptor variant causes an anxiety like behavior in zebrafish.

Together with Drs. Alon Chen and Yehezkel Sztainberg of the Neurobiology Department, Levkowitz's team found the same alternatively-spliced switch in mice. This conservation of the mechanism through the evolution of fish and mice implies that a similar means of turning CRH production on and off exists in the human brain.

Faulty switching mechanisms may play a role in a number of stress-related disorders. The action of the PAC1 receptor has recently been implicated in post-traumatic stress disorder, as well as in schizophrenia and depression. Malfunctions in alternative splicing have also been associated with epilepsy, mental retardation, bipolar disorder and autism.

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