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Neurobiology

Where mind meets body: a master brain circuit for stress responses

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We discovered in rats the long-sought brain circuit mechanism of "mind–body connection". This mechanism is critical for driving a variety of autonomic and behavioral responses when mammals undergo psychological stress. This new knowledge will be an essential basis for the future development of novel strategies for treating stress-related disorders.

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When feeling stressed or nervous, you notice the pounding heart, pale face, and dry mouth—fundamental autonomic responses to psychological stress. Stress responses are conserved in many mammalian species and thought to be beneficial for wild animals, such as when they encounter their enemies. For their survival from the life-threatening situation, it would be helpful to boost their physical performance by eliciting stress responses, such as increasing body temperature (warming up) and supplying more blood (oxygen and fuels) to the brain and muscles. Even in humans, an appropriate amount of stress may lead to better performance in their social activities. However, excessive stress can cause stress-related disorders associated with aberrant stress responses, such as psychogenic fever, panic disorder, and post-traumatic stress disorder.

In the brain, psychological stress and emotions are processed in neural circuits in the cerebral cortex and limbic system. The stress signals from the emotion circuits are believed to elicit stress responses by affecting the circuits in the hypothalamus and brainstem that control body conditions. However, the circuit mechanism of the “mind–body connection” remained unknown.

We first sought for neural pathways in the rat brain that provide stress signals to the autonomic control center in a hypothalamic area called the dorsomedial hypothalamus. We discovered a group of neurons in the cerebral cortex with the aid of a neural tracer to visualize neural connections to this hypothalamic area and a cellular marker of neuronal activation. This group of neurons became active in response to the animals' exposure to psychological stress, and then transmitted the stress-driven signals to excite

neurons in the dorsomedial hypothalamus. These stress-activated neurons were distributed in an unexplored, very deep area of the medial prefrontal cortex.

We then used optogenetic techniques to examine the role of the identified neural pathway from the medial prefrontal cortex's deep area to the dorsomedial hypothalamus in stress responses. We could selectively stimulate or inhibit this neural pathway with neuronal fibers' illumination through optical fibers inserted into the brain. Stimulation of this pathway elicited autonomic (sympathetic) responses mimicking stress responses: increases in metabolic heat production in brown adipose tissue, heart rate, and blood pressure. On the other hand, inhibition of this pathway mostly abolished the increases in body temperature, heart rate, and blood pressure that were induced by exposure of the animals to social defeat stress, an animal model of psychosocial stress from conflict with a dominant conspecific. Furthermore, rats in which this neural pathway was selectively lesioned with a genetic technique didn't show heat production in brown adipose tissue and hyperthermia in response to social defeat stress. Nonetheless, they did exhibit intact ability to control body temperature and blood pressure under normal conditions.

We then questioned whether this pathway is also involved in stress-related behavior. Normal rats exhibit active social interaction behaviors with other rats, but once attacked and defeated by dominant rats (stressors), they no longer approach them. Interestingly, the neural pathway's optogenetic inhibition suppressed this avoidance behavior from stressors and restored active interaction with them. Besides, when the rats that had been defeated reencountered the stressors, they exhibited a reduction of skin blood flow in the tail. This phenomenon represents a sympathetic stress response similar to the pale face in humans. However, optogenetic inhibition of the neural pathway also abolished this response.

These results show that the identified neural pathway mediates master stress signaling from the prefrontal cerebral cortex to the hypothalamus that drives a variety of sympathetic and behavioral stress responses, but does not contribute to basal controls of vital homeostatic functions. Because we found that the medial prefrontal cortex's deep area receives stress inputs from multiple regions of the cerebral cortex and limbic system, this deep prefrontal cortical area likely integrates signals from the emotion circuits and provides the integrated master signals to the hypothalamus to drive the body’s responses.

This is the first discovery of the mind–body circuit connection in the brain to the best of our knowledge. The identified neural pathway seems to be a promising target for treating the aberrant sympathetic and behavioral stress responses. For example, it can be used for developing medication for stress-related disorders with few side effects because this pathway does not contribute to basal homeostasis. Besides, we succeeded in generating “stress response-free” rats by ablating this pathway. This animal model would be useful to investigate the impacts of chronic psychological stress on functions and aging of various organs. This discovery provides a new avenue for studying the physiological aspects of stress and emotions.