Endocrine cells in the brain influence the optimization of behavior

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A person exposed to stress can usually rapidly adapt the own behavior to the specific situation. Biochemical messenger substances in the brain or so-called neurotransmitters play a central role in this rapid transformation process. We know that hormones also have a stress-regulating function, but that their effects are more slowly apparent. However, recent findings reported by the team under Professor Soojin Ryu, leading researcher at the German Resilience Center of Johannes Gutenberg University Mainz (JGU) in Germany, indicate that this may

not actually be the case. Using a combination of genetic and optical techniques, the research team has been able to demonstrate that corticotrophs, the cell populations that stimulate the adrenal cortex and produce the stress hormones of the hypothalamic-pituitary-adrenal axis, can rapidly influence avoidance behavior immediately after the onset of a stress situation. This insight may contribute to the development of effective treatments that can facilitate the management of acute stress-induced reactions or might even be able to alleviate acute stress-related conditions. The findings have recently been published in the eminent journal *Nature Communications*.

The human body is controlled by two well-orchestrated systems, i.e., the hormonal system and the nervous system. The hypothalamus located in the middle of the basis of the brain has a key role here providing the link between the body and the other regions of the brain as well as directly and indirectly controlling a series of essential physiological vegetative functions. In addition, it is the most important control organ of the human endocrine system (hormonal system), because it regulates when and how much of a hormone is produced. Both the hypothalamus and its production of hormone are also subject to the influences of emotional stress. The pituitary gland or hypophysis is connected to the hypothalamus and together they form a single functional unit called the hypothalamic-pituitary-adrenal (HPA) axis.

Hormones secreted by the hypothalamus include the so-called releasing hormones, such as the corticotropin-releasing hormone (CRH). This stimulates the production of the adrenocorticotropic hormone (ACTCH) in the pituitary gland. ACTH is a hormone secreted by the anterior lobe of the pituitary and it regulates the production of other hormones, such as the stress hormone cortisol (hydrocortisone).

It can be basically assumed that the neurotransmitters of the central nervous system rapidly determine whether fight or flight behavior is to

develop in a given situation. To date, medical science has conjectured that the stress-regulating effects of the hormones of the hypothalamic-pituitary-adrenal (HPA) axis come into play far more slowly. Stress researchers found it very problematic to establish the concrete role of the HPA axis in the rapid adaptation of behavior in a stress situation in more detail in standard animal models. This is because the location of the hypothalamus and pituitary gland in mammals makes them difficult to access. To overcome these obstacles, Professor Soojin Ryu's work group at the German Resilience Center at Johannes Gutenberg University Mainz decided to create an innovative optogenetic research technique. They managed to develop a genetically modified zebrafish larva in which they were able to manipulate the activity of the hypothalamic-pituitary-adrenal axis using light and thus observe the resultant changes to the reactions of the modified cells.

Two original concepts have been brought together in the new technique of Professor Soojin Ryu's group: On the one hand, it employs optogenetic methods, i.e., a combination of optical and genetic techniques. This makes it possible to precisely control, in a targeted and extremely rapid manner, the functional reactions of genetically modified cells. The process first involves the modification of light-sensitive proteins using genetic techniques. These are then introduced into specific target cells or tissues. The functioning of these proteins can then be regulated using light and the reaction of the modified cells can be controlled. In addition, Ryu's approach also pioneers the use of a new animal model in stress research, here the zebrafish. The advantage of the zebrafish, especially the transparent larvae of these small tropical fish of the group of teleosts, is that their development in the embryonic phase is similar to that in humans. They also mature very rapidly and are thus ideal for the purposes of genetic research. Moreover, the transparency of the larvae makes it easy to observe the tissue sections of their bodies.

The researchers at the German Resilience Center in Mainz introduced a

synthetic enzyme into their animal model that elevates the levels of the intracellular messenger substance cyclic adenosine monophosphate (cAMP) only in the corticotropic cells of the HPA axis. Their elevation is important for the release of hormones in the corticotropic cells of the anterior pituitary. The levels of the resulting so-called transgenetic animal stress hormones can be increased by means of exposure to light. This means the researchers can thus observe the accompanying changes to behavior.

The newly published research results of Professor Soojin Ryu and her team at the German Resilience Center show that the corticotropic cells in the pituitary become directly active on the onset of a stress situation that is perceived as distressing. These then influence both locomotion and avoidance behavior as well as the sensitivity to the stimulus. The researchers interpret this as evidence that the corticotropic cells in the pituitary play a significant role in the rapid adaptation of behavior to local environments perceived as antagonistic.

More information: Rodrigo J. De Marco et al. Optogenetically enhanced pituitary corticotroph cell activity post-stress onset causes rapid organizing effects on behaviour, *Nature Communications* (2016). DOI: 10.1038/ncomms12620

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