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How chronic stress can lead to anxiety

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A fascinating study shows that chronic stress causes alterations in certain immune cells, which triggers the release of a molecule that reaches the brain and promotes the development of anxiety behaviors.

Basically, stress is a physiological adaptation to danger: when we face a threat, the brain orders the release of hormones like adrenaline in the blood to increase the respiratory rate, the cardiac pulsations, the contribution of oxygen to the tissues, as well as the level of arousal and cerebral attention, changes which, collectively, make it possible to quickly combat or flee the danger. This is called the flight or fight reaction, absolutely essential for survival.

The physiological changes that accompany stress can, however, become harmful when the stress perceived by the brain becomes chronic, that is, occurs over long periods.

A very large number of studies have clearly shown that prolonged psychological stress disrupts several physiological systems, particularly in terms of immunity: people exposed to chronic stress have a higher degree of inflammation, have an increased risk to develop viral respiratory infections and respond less well to different vaccines (1).

A LINK BETWEEN IMMUNITY AND BRAIN

Another well-documented effect of chronic stress or certain traumatic events is the development of certain mental pathologies such as post-traumatic stress disorder (PTSD), anxiety and depression.

The research of recent years suggests that a link between stress and the brain also involves the immune system: it has been shown that stress stimulates the inflammatory response and the release of cytokines and that these molecules are involved in flight behavior when faced to a danger.

In our distant ancestors, who lived in an extremely precarious environment, this flight response stimulated by the inflammatory response played a crucial role in avoiding the many dangers that threatened them. In our much safer era, however, these avoidance behaviors become pathological and can promote the development of disorders such as anxiety and depression.

In this sense, it is interesting to note that the administration to patients with depression of an antibody neutralizing the inflammatory molecule TNF alpha causes a significant improvement in depressive symptoms. There is therefore clearly a link between the immune response caused by stress and the appearance of mental disorders.

CRACKED MITOCHONDRIA

A very interesting study suggests that this link between immunity and mental disorders generated by chronic stress could involve the mitochondria, the energy centers of our cells (2). Since chronic stress disrupts immunity, the researchers subjected animals to a stressful environment (small electrical shocks repeated at intervals) and examined the function of $CD4^+$ lymphocytes, a key component of the immune response. They observed drastic changes in the morphology of the mitochondria within these cells, including the appearance of cracks in their structures, which were correlated with the appearance of anxious behavior by animals. This anxiety seems to be associated with the changes seen in $CD4^+$ lymphocytes, since mutants lacking these cells showed no signs of anxiety disorders following exposure to the same environment.

Further analysis revealed that the breaks in the mitochondria were accompanied by an increase in xanthine levels in the blood of anxious animals, a molecule derived from the metabolism of certain DNA constituents (purines). The injection of xanthine has proven to be sufficient to generate anxiety behaviors on its own, without requiring external stress, confirming the central role of this molecule in the phenomenon of anxiety. The data collected by the researchers indicates that xanthine released by the lymphocytes migrates to the brain where it acts at the level of the amygdala to trigger anxiety behaviors.

We often tend to consider the brain as a separate organ, with the consequence that mental disorders are generally considered as diseases unrelated to the rest of the body. The results of this study clearly show that this is not the case, and that metabolic disturbances that occur outside the brain, in this case in the immune system, can play a key role in triggering anxiety disorders. This therefore suggests that the treatment of certain mental disorders would not only involve the use of pharmacological substances which act at the level of the brain, but also by more global approaches which target the whole body.

Managing stress well is obviously not easy, but more and more options are available. The first is physical activity, which has a well-documented anxiolytic role, but other activities like yoga, tai chi, and meditation can be very positive.

(1) Glaser R et JK Kiecolt-Glaser. Stress-induced immune dysfunction : implications for health. Nat. Rev. Immunol. 2005; 5: 243-251.

(2) Fan KQ et coll. Stress-induced metabolic disorder in peripheral CD4+ T cells leads to anxiety-like behavior. Cell 2019; 179: 864-879.

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