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Chronic Pain: Early-life stress leaves lasting traces in the brain

Researchers from the Heidelberg Faculty of Medicine of Heidelberg University and the Central Institute of Mental Health (ZI) in Mannheim have identified a neural mechanism in female mice through which early-life stress may increase vulnerability to chronic pain and anxiety disorders. The findings have been published in the journal Science.

Early-life stress, such as neglect or other adverse experiences, has long been recognized as a risk factor for both mental and physical illness. However, why its effects often emerge only many years later, and why women appear to be more strongly affected than men, remains poorly understood. Researchers from the Heidelberg Medical Faculty of Heidelberg University and the Central Institute of Mental Health (ZI) Mannheim investigated, in an experimental mouse study, the brain mechanisms that may underlie the link between early stress and later chronic pain. Their findings show that early-life stress can create a hidden vulnerability to chronic pain in female mice that becomes apparent only after a subsequent nerve injury. The results have now been published in *Science*.

Childhood Adversity May Increase the Risk of Chronic Pain and Anxiety

The research team led by Dr. Sebastian Wieland from the Institute of Anatomy and Cell Biology at Heidelberg University and the Department of General Internal Medicine, Psychosomatics and Psychotherapy at Heidelberg University Hospital (UKHD) investigated how early social stress, modeled by isolation after weaning, influences the response to a later nerve injury.

The results revealed that female mice exposed to early-life stress developed significantly greater and more persistent hypersensitivity to mild mechanical stimuli after nerve injury, as well as more pronounced anxiety-related avoidance behavior compared with animals that had not experienced early stress. This stress-induced amplification was not observed in male mice. Early-life stress alone also did not produce the observed combination of behavioral changes.

A Hidden Pain Amplifier in the Brain

The team also identified a potential biological mechanism. They discovered a lasting alteration in the neural connections between the paraventricular thalamus and the central amygdala, two brain regions involved in processing stress, threat, and pain.

In female mice, early-life stress changed the function of this brain circuit in a way that caused it to transmit certain neural signals more strongly following a later nerve injury. No such alteration was observed in male animals. In addition, the circuit showed increased activity even in anticipation of a potential threat, promoting anxiety-related avoidance behavior.

By selectively inhibiting this neural network, the researchers were able to reduce both the additional pain hypersensitivity and the heightened avoidance behavior without affecting the acute pain response caused by the injury itself. This finding suggests that the identified circuit contributes specifically to the stress-related, long-term amplification of pain sensitivity and avoidance behavior.

“Our study shows that early-life stress can leave lasting traces in the brains of female mice by persistently altering a threat-processing network. These changes do not immediately result in chronic symptoms. Instead, they create a hidden vulnerability that only becomes apparent after a later injury and may selectively increase susceptibility to chronic pain. The findings help us better understand how experiences during early stages of life can influence the risk of chronic diseases in adulthood,” explains study leader Dr. Sebastian Wieland.

A Neurobiological Explanation for a Clinical Observation

The findings were obtained in an animal model and cannot be directly transferred to humans. Nevertheless, they are of particular importance from a psychosomatic perspective because they provide a neurobiological explanation for the long-

standing clinical observation that early psychosocial adversity can influence later vulnerability to chronic pain.

“This study strikingly illustrates how closely psychological experiences and physical processes can be linked at the biological level. The findings therefore underscore the importance of a biopsychosocial understanding of chronic pain disorders,” says Professor Hans-Christoph Friederich, Medical Director of the Department of General Internal Medicine, Psychosomatics and Psychotherapy at Heidelberg University Hospital.

The study is the result of a long-standing collaboration between the Department of General Internal Medicine, Psychosomatics and Psychotherapy at Heidelberg University Hospital, the Division of Functional Neuroanatomy at Heidelberg University's Institute of Anatomy and Cell Biology, and the Department of Psychopharmacology at the Central Institute of Mental Health Mannheim within the framework of Collaborative Research Center (SFB) 1158. The experimental work was conducted primarily in the Division of Functional Neuroanatomy in close cooperation with the ZI Mannheim.

“The combination of psychosomatic medicine and experimental neuroscience enables us to investigate clinical observations on the long-term consequences of psychosocial adversity at the level of neural circuits. This interdisciplinary collaboration helps us better understand the biological foundations of the interaction between psychosocial experiences, pain processing, and behavior,” explains Professor Thomas Kuner, Head of the Division of Functional Neuroanatomy.

Dr. Wieland's research group will now investigate the spatial and molecular signature of the pain vulnerability induced by early-life stress. In the long term, this work may contribute to the identification of new biomarkers and the development of more targeted, sex-specific therapies for chronic pain. Whether comparable mechanisms also play a role in humans will need to be examined in future studies.

Publication

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Further information

Sebastian Wieland, M.D.
Heidelberg Medical School, University of Heidelberg
Senior Physician at the Psychosomatic Evening Clinic,
Department of General Internal Medicine, Psychosomatics, and Psychotherapy, Heidelberg University Hospital
Group Leader in the Division of Functional Neuroanatomy,
Institute of Anatomy and Cell Biology, University of Heidelberg
Email: sebastian.wieland(at)med.uni-heidelberg.de

- Heidelberg University Hospital