The secrets behind stress-induced illness

December 22 2010

Researchers use the labyrinth test to gauge the anxiety of a mouse. Credit: Max Planck Institute of Psychiatry

(PhysOrg.com) -- Both humans and animals have different reactions to stress. Ongoing exposure to stress causes some individuals to show symptoms of disease, while others are resilient and do not become ill. For a long time, the reasons behind these different reactions have been unclear. Now, scientists working with mice at the Max Planck Institute of Psychiatry have identified the molecular composition of the AMPA receptor, a common binding site in the central nervous system, as a possible cause of the differences. The neurotransmitter glutamate, which is responsible for the mediation of nerve impulses, binds to this receptor. In future, this discovery may help to predict individual risk for stress-related diseases.

Everyone reacts differently to stress: While ongoing strain or even a one-off, highly stressful situation, for example a traumatic experience, may give rise to a psychiatric illness such as depression or post-traumatic stress disorder in some individuals, others remain healthy. In all this, resilience to stress is largely determined by an individual's biological make-up. However, the molecular mechanisms involved have been largely unknown to date.

Working with mice, a research group headed by Matthias Schmidt at Munich's Max Planck Institute of Psychiatry has discovered that stress resilience is influenced by the composition of the AMPA receptor in the brain. The receptor is composed of four subunits, GluR1 to GluR4, and acts as a binding partner for the neurotransmitter glutamate. As an ion channel, it mediates the transmission of electric impulses between nerve cells and thus can influence perception, feelings, reactions and behavior. The composition of the AMPA receptor is determined by both genetic and epigenetic (or environmental) factors.

The specific composition of the receptor in terms of subunits GluR1 and GluR2 is important for its ability to allow calcium ions to flow into the cell, triggering an electrical impulse and altering neuronal communication in the brain. The researchers have shown that stress-vulnerable mice have a low proportion of GluR1 and a high proportion of GluR2. Stress-resilient mice, in contrast, have only a low proportion of GluR2.

In this study, the scientists subjected young mice to social stress for several weeks by exposing the small groups to new members every three to four days, so that the hierarchical structures of each group had to be fought out afresh on each occasion. This leads to a measurable hormonal stress reaction which subsides in stress-resilient animals when the cause of stress is removed. In stress-vulnerable animals, however, the stress hormones remain elevated, as in the case of patients with depression.

It is interesting to note that behavioural studies reveal that the composition of the AMPA-receptor, and therefore stress resilience, correlates with measurable changes to short-term memory. Consequently, even in the absence of stress, a GluR2-rich AMPA receptor leads to altered neuronal activity and poor memory in mice. If it were possible to use this correlation as a biomarker in humans to determine the composition of the AMPA receptor, it could help to predict individual risk for stress-related diseases. Further studies are planned to investigate whether specific enhancement of the AMPA receptor function would lend itself to future therapeutic interventions.

More information: Mathias V. Schmidt, et al. Individual stress Vulnerability Is Predicted by Short-Term Memory and AMPA Receptor Subunit Ratio in the Hippocampus, *Journal of Neuroscience*, Advance online publication, December 15, 2010