How social rank can trigger vulnerability to stress

July 13 2017

Credit: martha sexton/public domain

Stress is a major risk factor for a range of psychopathologies. However, stress does not affect everyone equally: in the face of sustained

adversity, some people develop depression symptoms while others adapt and remain resilient. Identifying risk factors and biomarkers for vulnerability to developing stress-induced depression in order to identify individual susceptibility before stress exposure has been a major challenge. EPFL scientists have now shown that social organization can affect differential vulnerability to chronic stress and underscored brain energy metabolism as a predictive biomarker for social status and susceptibility to stress-induced depression. The work is published in *Current Biology*.

The work was carried out by the lab of Carmen Sandi at EPFL, which has long history of research on stress. Previous studies have repeatedly shown that following exposure to defeat experiences, some mice show signs of depression such as avoiding social contact, while other mice behave as unstressed, retaining normal social interests. But most of this work identified vulnerability in the mice based on symptoms developed after stress exposure, not before.

The EPFL researchers were intrigued by the fact that differential vulnerability to stress is observed in mice known as C57BL/6J, which are genetically identical. The mice in the study had also been exposed to the same housing and living conditions to exclude the influence genetic factors or issues related to early life trauma.

Since mice typically live in groups of four per cage, the scientists reasoned that the hierarchical order established within the homecage might be related to the vulnerability to stress. By giving mice from the same homecage competitive challenges, the researchers could identify the dominant and the subordinate animals in each group. Then, following chronic stress exposure, they found that dominant animals are the ones that display a susceptibility to stress by showing strong social avoidance. On the other hand, subordinate mice behaved like the non-stressed ones, showing resilience.

Subsequently, the scientists collaborated with the lab of Rolf Gruetter at EPFL to apply an in vivo neuroimaging technique known as proton nuclear magnetic resonance (1H-NMR) spectroscopy that measures metabolite levels in the brain. They focused on two brain regions: the nucleus accumbens, which is involved in motivation and reward, and the medial prefrontal cortex, which is involved in planning.

The neuroimaging showed that the metabolic profile of the nucleus accumbens relates to social status and vulnerability to stress. More precisely, non-stressed, subordinate individuals showed lower levels of metabolites related to energy metabolism (glutamate, phosphocreatine, total creatine, N-acetylaspartate, and taurine) in the nucleus accumbens than dominant mice. But after exposure to chronic stress, the metabolite levels of energy-related metabolites were increased in subordinate, but not in dominant mice.

The study is the first to non-invasively identify risk factors and biomarkers that predict social status and stress-induced depression-like behavior. On an experimental level, the findings can now help make progress on investigating of mechanisms related to vulnerability and resilience to stress, as it will help stratifying individuals in longitudinal studies. On a clinical level, the study shows that energy metabolism in the nucleus accumbens can be a potential biomarker for stress vulnerability. And the study also has multiple implications on a societal level, given the ubiquitous nature of hierarchies in our society.

"Our findings reinforce the view that losing status is more pertinent to depression than social subordination," says Carmen Sandi. "In the future, it will be important to study whether social status can also predict depression or anxiety when individuals are chronically exposed to stressors of a non-social nature". Her group will now capitalize on these findings to investigate the value of interventions that target energy metabolism in the brain, in order to help vulnerable individuals to cope

with stress.

More information: Larrieu T., Cherix A., Duque A., Rodrigues J., Lei H., Gruetter R. and Sandi C. Hierarchical status predicts behavioral vulnerability and nucleus accumbens metabolic profile following chronic social defeat stress. *Current Biology* 13 July 2017. DOI: 10.1016/j.cub.2017.06.027

Provided by Ecole Polytechnique Federale de Lausanne