Neuroscientists discover new player in how brain deals with stress

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Neuroscientists investigating the 'brain code' claim to have made a significant step forwards in understanding how the brain deals with stress- and mitigates its impact.

Examining what they term 'thin' and 'mushroom-like' parts of nerve cells in the brain, which are responsible for learning and remembering, they discovered that it is possible to alter what is remembered – thereby mitigating the stress of painful memories.

A team from the University of Leicester has identified a particular protein that the brain produces in response to stress. Tests on mice revealed that those without this protein were less 'outgoing' and preferred to 'hide in the dark'.

The findings, published in *Proceedings of the National Academy of Sciences* (*PNAS*), are potentially important for understanding stress-related psychiatric diseases in humans. The work was supported by a Marie Curie Excellence Grant from the European Commission.

Dr Robert Pawlak, lecturer in Neuroscience at the University of Leicester, said the breakthrough study had determined that production of the protein by the brain may help to protect individuals from "too much anxiety" and help organisms to cope with various adverse life events.

Dr Pawlak, from the University Department of Cell Physiology and Pharmacology, said: "Every day stress "reshapes" the brain – nerve cells

change their morphology, the number of connections with other cells and the way they communicate with other neurons. In most cases these responses are adaptive and beneficial – they help the brain to cope with stress and shape adequate behavioural reaction. However, upon severe stress things can get out of control, the brain "buffering" capacity is exhausted and the nerve cells in the hippocampus – an area of the brain responsible for learning and memory - start to withdraw their processes, don't effectively communicate with other cells and show signs of disease.

"One strategy that brain cells particularly like to use to cope with stress is changing the shape of tiny processes they normally employ to exchange information with other neurons, called dendritic spines. Spines can be as small as 1/1000 of a millimeter and have various shapes. Long spines (called "thin" spines) are like children - very mobile and inquisitive, constantly change shape and "conversation" partners – they help us learn new things. Once spines learn, they change into mature "couch potatoes" – they are mushroom-shaped, have stable connections, do not change partners and do not like to move".

"Mushroom spines help us remember things we once learned - but it is not always good. Some very stressful events would better be forgotten quickly or they may result in anxiety disorders. There is a constant battle of forces in our brain to help maintain the right balance of thin and mushroom spines – or how much to remember and what better to forget.

"We have identified a protein that the brain produces in response to stress in order to reduce the number of mushroom spines and therefore reduce future anxiety associated with stressful events. This protein, lipocalin-2, is normally not produced, but its fabrication dramatically increases in response to stress in the hippocampus. When we added lipocalin-2 to neurons in culture the way it occurs on stress, neurons started losing their "memory spines" – the mature, mushroom-shaped

ones.

"We therefore asked – what if we remove lipocalin-2 from the brain and subject mice to stress? Would that affect the way they react? To this end we used mice in which the lipocalin-2 gene was disrupted and found that, on stress, they were more anxious than normal mice. For example, they were less "outgoing" and preferred hiding in dark, enclosed spaces instead of exploring the neighborhood normally. We found that in these mice mushroom spines were more readily formed in the brain after stress and therefore they had stronger memories of the stressful event.

"Thus, the brain produces lipocalin-2 in order to protect us from "too much anxiety" and help us cope with various adverse life events.

"Identification of lipocalin-2 as a new player the brain uses to help us cope with stress is an important step forward. We are getting closer to deciphering molecular mechanisms of stress that, if not functioning properly, may lead to stress-related psychiatric diseases".

"Stress-related psychological and mental disturbances are extremely common and affect more than 30% of the population. We are keen to investigate whether the mechanisms discovered by us apply to humans and could help inform clinical strategies to deal with anxiety disorders and depression".

More information: Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation, by Mariusz Mucha, Anna E. Skrzypiec et al., *PNAS* (2011).

Provided by University of Leicester