Neuroscientists discover new 'chemical pathway' in the brain for stress

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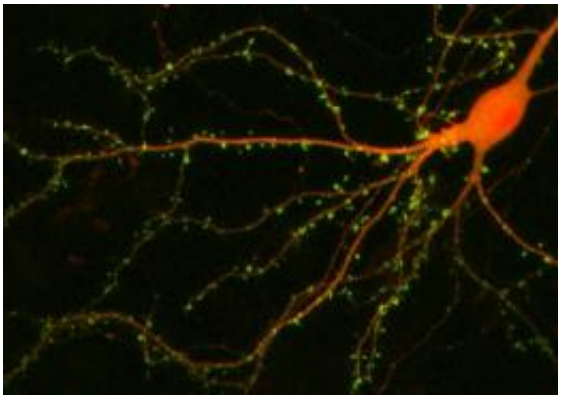


Nerve cells (red) reach out and communicate with each other at junctions called synapses (green) that release chemicals to promote anxiety. Credit: University of Leicester

A team of neuroscientists at the University of Leicester, UK, in collaboration with researchers from Poland and Japan, has announced a breakthrough in the understanding of the 'brain chemistry' that triggers our response to highly stressful and traumatic events.

The discovery of a critical and previously unknown pathway in the brain that is linked to our response to stress is announced today in the journal *Nature*. The advance offers new hope for targeted treatment, or even prevention, of stress-related psychiatric disorders.

About 20% of the population experience some form of anxiety disorder

at least once in their lives. The cumulative lifetime prevalence of all stress-related disorders is difficult to estimate but is probably higher than 30%.

Dr Robert Pawlak, from the University of Leicester who led the UK team, said: "Stress-related disorders affect a large percentage of the population and generate an enormous personal, social and economic impact. It was previously known that certain individuals are more susceptible to detrimental effects of stress than others. Although the majority of us experience traumatic events, only some develop stress-associated psychiatric disorders such as depression, anxiety or posttraumatic stress disorder. The reasons for this were not clear."

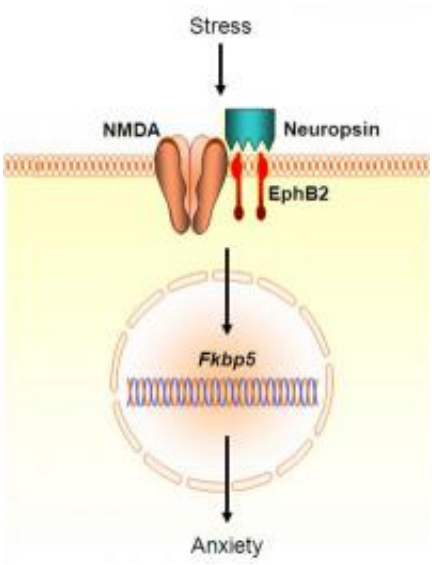
Dr Pawlak added that a lack of correspondence between the commonness of exposure to psychological trauma and the development of pathological anxiety prompted the researchers to look for factors that may make some individuals more vulnerable to stress than others.

"We asked: What is the molecular basis of anxiety in response to noxious stimuli? How are stress-related environmental signals translated into proper behavioural responses? To investigate these problems we used a combination of genetic, molecular, electrophysiological and behavioural approaches. This resulted in the discovery of a critical, previously unknown pathway mediating anxiety in response to stress."

The study found that the emotional centre of the brain – the amygdala – reacts to stress by increasing production of a protein called neuropsin. This triggers a series of chemical events which in turn cause the amygdala to increase its activity. As a consequence, a gene is turned on that determines the stress response at a cellular level.

"We then examined behavioural consequences of the above series of cellular events caused by stress in the amygdala," said Dr Pawlak.

"Studies in mice revealed that upon feeling stressed, they stayed away from zones in a maze where they felt unsafe. These were open and illuminated spaces they avoid when they are anxious."



Newly discovered neurochemical cascade promoting stress-induced anxiety. Neuropsin interacts with cell membrane proteins NMDA and EphB2 to induce expression of the Fkbp5 gene. Credit: University of Leicester

"However when the proteins produced by the amygdala were blocked – either pharmacologically or by gene therapy – the mice did not exhibit the same traits. The behavioural consequences of stress were no longer present. We conclude that the activity of neuropsin and its partners may determine vulnerability to stress."

Neuropsin was previously discovered by Professor Sadao Shiosaka, a co-author of the paper. This research, for which the bioinformatics modelling was done by Professor Ryszard Przewlocki and his team, has for the first time characterized its mechanism of action in controlling

anxiety in the amygdala.

The study took four years to complete, during which scientists from the Department of Cell Physiology and Pharmacology collaborated with colleagues from the Medical Research Council Toxicology Unit at the University of Leicester, the Department of Molecular Neuropharmacology, Polish Academy of Sciences in Krakow, Poland and Nara Institute of Science and Technology in Japan. The work was supported by the European Union, the Medical Research Council and Medisearch – the Leicestershire Medical Research Foundation. The first author, Benjamin Attwood, sponsored by Medisearch, took 3 years off from his medical studies curriculum to complete the necessary experiments. He commented: "It has been a thoroughly absorbing project to uncover how our experiences can change the way we behave. Hopefully this will lead to help for people that have to live with the damaging consequences of traumatic experiences."

Dr Pawlak added: "We are tremendously excited about these findings. We know that all members of the neuropsin pathway are present in the human brain. They may play a similar role in humans and further research will be necessary to examine the potential of intervention therapies for controlling stress-induced behaviours."

"Although research is now needed to translate our findings to the clinical situation, our discovery opens new possibilities for prevention and treatment of stress-related psychiatric disorders such as depression and posttraumatic stress disorder."

More information: Neuropsin cleaves EphB2 in the amygdala to control anxiety, DOI: 10.1038/nature09938