Control of fear in the brain decoded

September 6 2011

A) A schematic cross-section of a mouse brain showing the distribution of CRHR1 gene activity and the associated neurotransmitter specificity. B) A glutamatergic neuron of the hippocampus. Credit: MPI of Psychiatry

When healthy people are faced with threatening situations, they react with a suitable behavioural response and do not descend into a state of either panic or indifference, as is the case, for example, with patients who suffer from anxiety. With the help of genetic studies on mice, scientists from the Max Planck Institute of Psychiatry have discovered two opposing neuronal regulatory circuits for the generation and elimination of fear. Both are controlled by the stress-inducing messenger substance corticotropin-releasing hormone (CRH) and its type 1 receptor (CRHR1). The availability of these factors in neurons that release glutamate in brain areas of the limbic system activates a neuronal network which causes anxiety behaviour. Conversely, in dopamine-releasing neurons in the mid-brain, these factors give rise to behaviour that reduces fear. Because disorders of the stress factors may be observed in many patients with affective illnesses, the scientists suspect

that the pathological alteration of the CRHR1-dependent regulatory circuits may be at the root of such emotional maladies.

An organism's response to stress is one of the key strategies essential to its survival in dealing with environmental factors. A balanced emotional reaction is of particular importance here and is subject to a highly complex molecular regulation system. Corticotropin-releasing hormone (CRH), which is released in the brain and places the organism in a state of alert, is a central molecular factor of the stress response. In addition to its effect as a hormonal messenger substance, it also controls the activity of neurons through binding to its receptors.

Many patients with anxiety disorders and depression display an altered hormonal stress response and have increased volumes of CRH in the brain. To investigate the underlying pathological processes, the research team working with Jan Deussing at the Max Planck Institute of Psychiatry carried out studies on the mouse model system. This enabled them to selectively deactivate an important factor, for example the CRH type 1 receptor, in certain cells, and thus establish the locations where the receptor is normally active and identify its function.

Using immunohistochemical methods and a series of transgenic mouse lines, the researchers succeeded in mapping the gene activity of the type 1 CRH receptor in the mouse brain in detail for the first time. Interestingly, a specific activity pattern emerged in different neuron groups which release different neuronal messenger substances. In regions of the forebrain (cortex, hippocampus, thalamus, septum), CRHR1 is detectable in glutamatergic and GABAergic neurons. As the limbic system, these regions are linked and, as the current study shows, trigger fear-inducing behaviour in glutamatergic neurons.

In regions of the midbrain (substantia nigra, ventral tegmental area), CRHR1 arises in dopamine-releasing neurons. The functional

examination of the mice gave rise to the fairly sensational discovery that the stress hormone CRH actually reduces fear through its receptors in this part of the brain. These neurons demonstrably trigger the direct release of dopamine in regions of the forebrain and hence cause behaviour that overcomes fear.

The opposing effects of the fear-generating and fear-eliminating effect of the CRH/CRHR1 was demonstrated for the first time by this study and prompted the re-evaluation of the use of CRH-receptor antagonists as anxiolytic and antidepressant drugs. The authors speculate that the over-activity of the CRH system in patients with mood disorders is not general but probably limited to certain regulatory circuits in the brain, thus causing imbalanced emotional behaviour. "The use of CRH-receptor 1 antagonists could be particularly useful in patients in who one of these systems is out of sync," says research group leader Jan Deussing.

More information: Glutamatergic and Dopaminergic Neurons Mediate Anxiogenic and Anxiolytic Effects of CRHR1, by Damian Refojo et al., *Science Express*, online September 1, 2011. DOI: 10.1126/science.1202107

Provided by Max-Planck-Gesellschaft