What is this thing called “pain”? – functional consequences of synaptic plasticity in the nociception-emotion link in the amygdala

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Abstract

We, most of us, know what pain is like. Pain is an “unpleasant sensory and emotional experience” and therefore always “subjective” (International Association of Study of Pain). The biological function of the pain is clear: It lets the individuals avoid inconvenient and aversive situations in one’s body in the present and in the future to increase the possibility of survival. It is thus reasonable that the pain is strongly linked with (negative) emotion in a Darwinian sense. The central question is how this function is realized in the nervous system. Functional brain imaging in human and rodents in these 15 years identified multiple brain regions and connections activated by nociception, which are collectively called “Pain matrix”. This includes, in addition to the thalamus and somatosensory cortex, the anterior cingulate, medial prefrontal, insular cortice, nucleus accumbens, and the amygdala. Of these, the central amygdala is of particular interest in exploring the biological significance of the pain because it is strategically well situated to receive and regulate nociception-related signals independently of thalamocortical pathways. For example, the majority of projection neurons in the lamina I of the dorsal horn or the spinal trigeminal nucleus project to the lateral parabrachial nucleus (LPB) from which direct monosynaptic projections target the central amygdala (CeA). We have shown that optogenetic stimulation of the LPB-CeA projection is sufficient to establish threat/fear learning and its monosynaptic excitatory transmission undergoes robust synaptic potentiation in the CeA in persistent pain models. In addition, manganese-enhanced MRI revealed a sustained activity in the CeA of this model. Finally, chemogenetic suppression of CeA neurons results in attenuated wide-spread mechanical allodynia in this model. It is thus likely that the CeA plays a pivotal role in linking nociception and emotion, which in turn modulates the nociceptive sensitivity in the long-lasting pain, which would shape the expression of pain itself.