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The amygdala: different pains, different mechanisms

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An important but not well-understood issue in pain research is the possibly different mechanisms of acute and chronic types of pain. Increasing evidence suggests that chronic pain is not simply the prolonged presence of acute pain (Banks and Watkins 2006). The article by Ikeda et al. (2006) provides intriguing novel information about pain mechanisms in the amygdala in an animal model of chronic neuropathic pain (spinal nerve ligation model). These appear to be distinct from plastic changes in the amygdala observed at the more acute stage of arthritic pain (Neugebauer 2006).

The significance of the study by Ikeda et al. (2006) is twofold. The authors demonstrate synaptic plasticity and increased neuronal excitability in the amygdala in neuropathic pain using an identical approach to that described in the arthritis pain model (Bird et al., 2005; Neugebauer et al., 2003). The reproducibility of the previous findings clearly establishes the role of the amygdala in different types of pain. Even more importantly, though, the authors show that mechanisms of chronic neuropathic pain involve an N-methyl-D-aspartate (NMDA) receptor-independent form of plasticity in the amygdala, whereas increased NMDA receptor function is critical for plasticity associated with acute arthritic pain (Bird et al., 2005; Li and Neugebauer 2004).

Long known for its important role in emotional learning and behavior and affective disorders, the amygdala is particularly prone to neuroplastic changes (Maren 2005; Phelps and Ledoux 2005). Pain carries a negative affective valence and is intimately related to depression and anxiety disorders (Gallagher and Verma 2004). Accumulating evidence suggests that the amygdala is an important neural substrate of the reciprocal relationship between pain and negative affect (Neugebauer 2006). The amygdala comprises several anatomically and functionally distinct nuclei. The central nucleus of the amygdala (CeA) provides the output for major amygdala functions and modulates pain behavior through projections to descending pain control centers in the brainstem (Heinricher and McGaraughty 1999; Neugebauer 2006). The CeA receives purely nociceptive inputs from the dorsal horn via the parabrachial area (PB) and affect-related information from the circuitry of the lateral-basolateral amygdala (LA-BLA) (Neugebauer 2006). These anatomically and functionally distinct lines of input at the PB-CeA and BLA-CeA synapses can be analyzed separately in brain slice preparations as shown in previous studies (Neugebauer et al., 2003) and confirmed by Ikeda et al. (2006).

Despite the knowledge of nociceptive inputs to the amygdala, their functional significance in pain states was not known until a few years ago when synaptic plasticity and central sensitization in the CeA was demonstrated in a model of arthritic pain (Neugebauer et al., 2003; Neugebauer and Li 2003). It remained unknown, however, if the changes that occurred

within a few hours after arthritis induction would remain in chronic pain states or become extinct due to adaptive mechanisms. The study by Ikeda et al. (2006) is the first to show that neuroplastic changes in the amygdala persist in chronic neuropathic pain. In brain slices taken from animals one week after spinal nerve ligation, synaptic transmission at the PBCeA and BLA-CeA synapses was enhanced compared to controls, indicating synaptic plasticity independent of peripheral or central sensitization outside the amygdala. Interestingly, synaptic transmission at the PB-CeA synapse was enhanced only contralateral to the site of peripheral nerve injury (in the right amygdala) whereas the bilateral increase of BLA-CeA transmission was not side-specific. This would be consistent with a general affect-related role of BLA inputs to the CeA compared to a more input-dependent function of the nociceptive PB-CeA synapse. The role of different amygdala nuclei and synapses in different types and components of pain needs to be addressed in future studies. The same is true for cellular pain mechanisms in other brain areas such as thalamic nuclei and cortical areas, which are still understudied.

Enhanced transmission at the PB-CeA synapse correlated significantly with increased pain behavior (allodynia) of neuropathic rats. These data provide further evidence for a positive correlation between amygdala activity and pain behavior that was also observed in previous studies in the arthritis pain model (Neugebauer 2006). The significance of this correlation is that it represents a paradigm change from the traditional view of the amygdala linked to endogenous pain control as a mechanism of environmentally induced analgesia, whereas the study by Ikeda et al. (2006) supports a pain-producing or pain-enhancing role. One might speculate that the amygdala assumes a pain facilitatory function, when pain is the primary concern and deserves the attention of the organism in conditions that activate or disturb the pain system (inflammatory or neuropathic pain states). However, in life-threatening situations (actual or perceived), when survival demands “fight or flight”-like decisions, the amygdala acts to suppress attention to pain as a less important but possibly distracting factor to guarantee survival.

The second important novelty of the study by Ikeda et al. (2006) is that amygdala plasticity in chronic neuropathic pain, unlike in acute arthritis, is NMDA receptor-independent. A non-NMDA receptor antagonist (CNQX) essentially abolished evoked responses at the PB-CeA synapse; conversely, an NMDA receptor antagonist (AP5) had no significant effect on synaptic transmission. These results argue against the contribution of (enhanced) NMDA receptor function to synaptic plasticity in the chronic neuropathic pain model. In contrast, synaptic plasticity and increased neuronal excitability of CeA neurons measured several hours after arthritis induction require enhanced NMDA receptor function (Bird et al., 2005; Li and Neugebauer 2004). This mechanism involves the protein kinase A (PKA) dependent phosphorylation of NMDA receptors.

The possibly differential contribution of NMDA receptors to acute and chronic pain is reminiscent of the distinct mechanisms of early and late phases of long-term potentiation (LTP), another form of neuroplasticity at central synapses. NMDA receptors are required for the induction of certain forms of LTP, whereas the late phase of LTP depends on protein synthesis. The mechanisms that account for this switch remain to be determined. The implications of the finding by Ikeda et al. (2006) for the role of NMDA receptor antagonists in pain management are not clear at this point. It would be premature to speculate that NMDA receptors are less useful as drug targets in chronic and/or neuropathic pain. First, it is not clear if the findings apply to chronic versus acute or to neuropathic versus inflammatory pain conditions. Second, the present study focused only on the amygdala and the situation may be different in other parts of the pain neuromatrix.

In summary, the study by Ikeda et al. (2006) shows that neuroplastic changes in the amygdala persist in chronic neuropathic pain but involve different mechanisms than acute arthritic pain.

The findings have broad implications for research into pain mechanisms beyond the amygdala. The present study emphasizes the need to determine and distinguish the mechanisms that account for different types of pain, because different drug targets may be useful in acute and chronic pain and in pain of different origins.

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