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Editorial comment

Is finding the common biological link(s) between pain and affect an infinity quest?

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Clinical studies have demonstrated comorbidity between pain and depression or anxiety [1,2]. The prevalence of depression in patients with chronic pain reaches 5–100%, the prevalence of anxiety disorder reaches 11–60%, and the prevalence of pain in patients with depression disorder reaches 15–100% depending on the study and type of pain [3,4]. These comorbidities affect negatively the life of the patients. It is still not clear whether there is a causal relationship in the development of comorbidity between chronic pain and anxiety/depression or whether chronic pain and anxiety/depression have distinctly different mechanisms that coexist independent of each other. This question is not only of considerable academic interest but also of potential clinical importance when developing therapeutic interventions for the comorbid chronic pain and affective disorder.

Experimental animal studies have shown that chronic neuropathic pain is associated with structural and functional changes in brain areas that are important for processing of emotions, such as the amygdala [5–8]. Since brain areas important for emotions have reciprocal connections with pain-relay nuclei and play a role in regulation of pain [9], it might be speculated that the functional and structural changes in these areas provide a common mechanism for maintenance of pain and affect changes, such as depression or anxiety. In line with this proposal, some [5,10–12], but not all [13,14], studies with experimental animal models of chronic neuropathic pain have demonstrated co-occurrence of anxiety or depression, which, however, has varied depending on many factors. Among them are the age of the animals, the duration of the pathophysiological condition, and the type of affect studied [12]. Moreover, since genetic factors are known to influence both the development of chronic pain [15] and affective states [16], it is likely that genetic factors also play an important role in their comorbidity.

Among potential common molecular and neurochemical links between pain and anxiety is corticotropin-releasing factor (CRF) and its CRF_1 receptor in the central nucleus of the amygdala, as indicated by attenuation of anxiety-like behavior and hypersensitivity following amygdaloid administration of a CRF_1 receptor antagonist in arthritic animals [17]. In line with this, a sustained pain stimulus induced CRF expression in the central nucleus of the amygdala and also in the adjacent bed nucleus of the stria terminalis [18] that is another structure considered important for anxiety [19] and aversive pain response [20]. While acute activation of the amygdaloid CRF_1 receptor has an anxiogenic and pronociceptive effect [17], a recent study indicates that the role of CRF in affect control is complex and varies with the brain nucleus and the duration of the pathophysiological condition. This is indicated by the finding that prolonged CRF over-expression in the central amygdala attenuated stress-induced anxiety-like behavior while prolonged CRF over-expression in the bed nucleus of the stria terminalis increased depressive-like behavior, without influencing anxiety levels [21]. In addition to the amygdaloid CRF, there are several other potential common biological mechanisms, including non-neuronal cells as well as neurons that might be involved in the comorbidity of pain and affective state [22]. Experimental human studies on the interaction of affect and pain have shown that the direction in the change of pain varies with the valence of the co-existent affect [23]. This finding suggests that no single mechanism is likely to explain the co-existence of pain with various affects. Moreover, even the same molecule known to be involved in regulation of pain and affect, CRF, in the same affect-controlling brain site, central nucleus of the amygdala, had an opposite effect on sensory-discriminative versus emotional-like pain behavior [8]. Based on earlier findings, it seems obvious that due to the complexity of the system regulating pain and affective state, previous literature alone may not allow conclusive statements that explain mechanisms of comorbidity between pain and affective state. Therefore, it is of importance to perform further experiments investigating potential causality of the comorbidity between pain and affect.

In this issue, Baastrup et al. [24] present their experimental animal study addressing the specific question whether anxiety-like behavior and at-level mechanical hypersensitivity following experimental spinal cord contusion are causally related. They show that pregabalin, a dual-acting analgesic and anxiolytic compound reduced both hypersensitivity and anxiety-like behavior, while the classic analgesic drug morphine only reduced hypersensitivity. This result suggests that hypersensitivity and anxiety-like behavior have separate underlying mechanisms. The result supports the coexistent model in which anxiety and chronic pain, as revealed by hypersensitivity, coexist in the injured animal but do not affect each other. An anxiolytic drug midazolam, however, failed to influence

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either anxiety-like behavior or hypersensitivity [24]. While the failure to attenuate anxiety-like behavior with an anxiolytic drug may complicate the interpretation of results, this failure may also be explained by too low a dose of midazolam, as suggested by the authors. Although it is a plausible assumption that hypersensitivity provides an index of ongoing pain in experimental animal studies, as in the study of Baastrup et al. [24], one should be cautious when interpretations on ongoing pain in comorbidity studies are based on the assessment of reflex responses. Namely, while hypersensitivity induced by peripheral injury in experimental animals is probably the most commonly used index of ongoing pain, there are studies that challenge the concept that the injury-induced hypersensitivity invariably indicates occurrence of ongoing pain [14].

The findings by Baastrup et al. [24] provide a valuable extension to the literature by demonstrating that hypersensitivity and anxiety-like behavior following a spinal cord injury have at least partly different underlying mechanisms as suggested by dissociative antihypersensitivity and anxiolytic effects induced by pregabalin and morphine. While their results support the hypothesis that pain and anxiety may co-exist independent of each other in animals with a spinal cord injury, it remains to be studied whether the results can be generalized to comorbidity of pain with other types of affects, such as depression, and to other models of chronic pain. Better understanding of mechanisms underlying comorbidity of pain with various affects is likely to help in developing more selective therapies for patients with chronic pain and an accompanying affective disorder.

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