PAIN® 143 (2009) 163–164

PAIN®

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Editorial

Chronic stress and pain – A plea for a concerted research program

Chronic functional pain syndromes have commonly been associated with ongoing exposure to stress or with post-traumatic stress disorder (PTSD). Considering the inherent tremendous burden for the affected patients, their families and for society, it is critical that we better understand the cause and effect relationships between chronic stress and pain.

In this context, one recently advocated approach would be to target altered hormonal pathways [1]. The literature is now replete with studies indicating that pain syndromes such as fibromyalgia [5], chronic pelvic pain [6], certain types of low-back pain [4] and rheumatic arthritis [10] may be associated with a dysfunctional reactivity of the hypothalamic–pituitary–adrenal (HPA) axis. The blunted adrenocortical reactivity (relative hypocortisolism) observed in these studies may be related to chronic exposure to stress or to PTSD (for review see [9]). One hypothesis is that this may lead to a disinhibition of the secretion of proinflammatory mediators by immunocompetent and glial cells, resulting in an ongoing sensitization of nociceptive neurons and hence in an enhanced pain sensitivity [3]. Taken together, these findings seem to point towards the adequacy of a psychoneuroimmunological approach focusing on the contribution of stress-related dysfunctional communication among the nervous, immune and endocrine systems in pathophysiological nociceptive processing.

A cautious approach, however, is essential. We should not fall to the temptation to assume that all hypotheses made and data collected are generalizable. In this context, Kraus and colleagues [7] have published a very interesting study in the present issue of Pain. The investigators used psychophysical methods to characterize pain sensitivity in PTSD, a disease commonly associated with chronic pain, current pain and pain-related disability. The main and somewhat intriguing finding was a reduced pain sensitivity (significantly increased heat and cold pain thresholds) in both combat veterans suffering from PTSD and combat controls as compared to healthy controls. With longer lasting heat stimuli, the authors could also discriminate between veterans with and veterans without PTSD, the former having significantly lower pain reports. This paper is very important since the authors are among the first to provide evidence that stress-related diseases may under certain conditions be associated with a depressed pain sensitivity rather than with an enhanced pain sensitivity. These data raise several key issues, but some of these have been only partly addressed by the investigators. In the following I discuss some points that may deserve particular attention and that may constitute useful guidelines for future research on interactions between stress and pain:

(1) In human studies an empirical characterization of pain sensitivity (quantitative sensory testing) should be included as systematically as possible. These protocols should include threshold measurements and the computation of stimulus response functions. This is important as slopes may have shifted under certain conditions, without any concomitant alterations in thresholds. Experimental measures of pain plasticity (development of hyperalgesia and allodynia) should also be included whenever possible. In clinical studies, these measurements should be performed in addition to the documentation of clinical pain.
(2) Gender and age may have an impact and should be considered systematically. There may, for example, be age- and sex-related differences in neural, endocrine and immune functions that are relevant for the particular research topic.
(3) Time may be an important factor. In this respect, the issue of causal relationships should be addressed. Does ongoing stress really foster pain or does pain maintain or enhance stress reactions? Are a minimum period and intensity of stress required for the alteration of pain sensitivity? In addition, biochemical parameters may change over time (e.g. secretion of stress hormones and regulation of receptors). Longitudinal studies should help to answer these questions.
(4) Studies should be integrative or collaborative, allowing for the parallel recording of psychological (personality, coping strategies, etc.), neuropsychological (e.g. involvement of altered functioning of the limbic system) and biochemical (e.g. stress hormones, gonadal hormones and proinflammatory cytokines) data.
(5) The effects of potential mediators should be characterized in detail. Glucocorticoids may, for example, inhibit pain processing via several pathways. However, glucocorticoids may also enhance nociception. It has for instance been shown for neuropathic pain that activated central glucocorticoid receptors may induce an upregulation of NMDA receptors [8]. Effects may again depend on time and also on concentrations (see inversed U-shaped functions).
(6) The identification of mechanisms that operate at the cellular and molecular levels requires studies in animal models. These investigations should be complementary to the human studies. Adequate stress models constitute a prerequisite and should mimic the respective situations in humans as closely as possible (see e.g. persistent versus intermittent stress, [2]). Again, integrative studies incorporating behavioral, neurophysiological, endocrinological and immunological measurements should be performed.

doi:10.1016/j.pain.2009.03.012

To conclude, I am of course aware that the above suggestions cannot all be followed in every study or in each laboratory. Considering the significance of the problem, however, both at the individual level and at the societal level, joint and coordinated efforts should be taken to understand the complex relationships between stress and pain so as to develop adequate diagnosis and treatment strategies. Why not initiate a concerted research program?

Conflict of interest

The author has no conflicts of interest regarding this editorial.

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