Mechanisms of cognitive impairment in chronic pain patients can now be studied preclinically by inducing cognitive deficits with an experimental animal model of chronic neuropathic pain

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1. Chronic pain impairs cognitive abilities in patients by unknown mechanisms

There is accumulating clinical evidence indicating that chronic pain may impair various aspects of cognition, such as attention, working memory, decision-making and executive function (for a review see e.g. [1]). The mechanisms underlying the chronic pain-associated cognitive impairment are still poorly known. Human studies allow unequivocal assessments of cognition and pain, but mechanistic studies can be performed only to a limited extent in humans. In contrast, experimental animal studies allow controlled invasive studies assessing molecular and cellular level mechanisms, while the weakness of animal studies is that cognition and pain need to be indirectly evaluated by assessing motor behavior in various cognition-demanding tasks.

2. Cognitive deficits can be induced by chronic pain in animals

Interestingly, recent studies in experimental animals indicate that cognitive deficits may be induced also in animal models of chronic pain (for reviews see [1,2]). Thereby, experimental animal models of chronic pain promise to extend possibilities to study mechanisms contributing to the pain-associated changes in cognition. Of course, for several reasons one needs to be cautious when interpreting results on animal behavior in terms of cognition. For example, one needs to exclude direct effects on the motor system before considering that a change in behavior reflects a change in cognition.

3. In chronic pain, sleep disorders, anxiety and depression also cause cognitive deficits

Moreover, both in human and experimental animal studies a number of confounding factors may significantly influence the results when assessing pain-induced changes in cognition. Among them are e.g. chronic pain-induced sleep disturbances or mood disorders (such as anxiety or depression) that may themselves influence cognitive functions [3–5]. Therefore, it is challenging to determine whether e.g. chronic pain per se causes a cognitive deficit, such as memory impairment, or whether the pain-associated memory change is due to a change e.g. in motivation caused by the effect of pain on mood. The reciprocal interactions between pain and functions regulating cognitive performance provide a further complication, since e.g. attention that is an important factor in the control of cognitive task performance is itself influenced by pain and, conversely, attention controls pain perception [6].

4. Mechanisms of cognitive deficits from chronic pain can now be studied—In rats

In this issue of the Scandinavian Journal of Pain, Moriarty and co-workers [7] report about their study on chronic neuropathic pain-associated cognitive changes and their mechanisms in experimental animals. They used a well-established model of chronic neuropathic pain induced by unilateral ligation of two spinal nerves. Mid-aged rats were used since previous results suggested that the most pronounced cognitive impairment induced by experimental neuropathy in the rat is observed in mid-aged animals [8]. As expected, spinal nerve ligation (SNL) produced tactile and cool allodynia-like hypersensitivity but also the responses to heat were facilitated. The facilitation of pain-related behavior lasted at least to the 65th postoperative day, which was the end point of the study. Cognitive testing in SNL animals with verified pain hypersensitivity was performed from the 19th to the 60th post-operative day and the results compared with those of sham-operated control animals. In general, the authors found impairment of cognitive performance of SNL animals and the effect was selectively influencing only some aspects of cognition. In an object recognition test, the SNL rats had a deficit of recognition memory as indicated by the finding that sham controls explored longer novel than familiar objects that were exposed to them in the test arena, while no such difference in exploration activity was observed in SNL animals. When assessing aversive memory using the air puff-induced passive avoidance test, the authors found no difference in the performance...
between the SNL and sham groups. In a test of spatial memory, the Morris Water Maze, neither learning- or memory-related performance was impaired in the SNL rats. However, when assessing cognitive flexibility by reversal training in the Morris Water Maze, the performance of SNL animals was reduced when they attempted to find the reversed target location in the maze.

5. Is synaptophysin in the hippocampus involved in pain-associated cognitive deficits?

By determining the expression of synaptophysin, a presynaptic protein that has been associated with changes in cognitive performance, the authors attempted to find a neurobiological correlate for their behavioral findings. However, in the hippocampal CA1 region and the medial prefrontal cortex, two brain areas involved in cognition, the expression of synaptophysin in excitatory or inhibitory neurons was not changed in SNL animals that had deficits in behavioral tests of recognition memory and cognitive flexibility. Thus, a mechanism or brain region other than the decreased expression of synaptophysin in the hippocampal CA1 region may be critical for the SNL-associated cognitive deficits. In contrast to the findings by Moriarty et al. in the SNL model of neuropathy [7], spared nerve injury model of neuropathy has produced a working memory deficit in the Eight Arm Radial Maze test that was associated with a decreased expression of synaptophysin in the hippocampal CA1 region [9]. This finding suggests that the experimental conditions (such as pain model, cognition test, etc.) may be among parameters determining the chronic pain-associated cognitive deficit and its underlying mechanism.

6. More preclinical studies on mechanisms of pain-associated cognitive deficits are to be expected

The thorough investigation by Moriarty et al. in this issue [7] adds to the series of studies by the same authors and many others (for reviews see [1,2]) showing that in spite of obvious limitations in the interpretation of animal behavior in terms of cognition, experimental animal models provide a promising platform for performing mechanistic studies on chronic pain-associated changes in cognition.

Conflict of interest statement

None declared.

References


