【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project：　Elucidation of abnormal functioning of neuronal circuits underlying neuropathic pain and its application for drug discovery

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Research Project Number：19H05658　Researcher Number：40373394
Keyword：Neuropathic allodynia, primary afferent Aβ fiber, optogenetics, spinal dorsal horn neuronal circuit

【Purpose and Background of the Research】

Damage to the nervous system causes neuropathic pain, a highly debilitating chronic pain condition that is frequently resistant to morphine. A cardinal symptom of neuropathic pain is mechanical allodynia, pain that is produced by innocuous mechanical stimulus, such as light touch. A major question is where and how touch information is pathologically converted to pain in the context of nerve damage.

We have previously discovered an essential role of glial cells in the spinal cord in the pathogenesis of neuropathic pain (Nature 2003) and indicated a strong ability of glial cells to alter the function of neuronal cells in the nervous system (Nat Rev Neurosci 2018). In this proposed research program, by using our developed research skills and scientific knowledge in the field of pain and glia combined with a new approach for investigating neuropathic allodynia and a technique for visualization and functional operation of neuronal subsets, we will identify neuronal circuits that are required for neuropathic allodynia. Furthermore, we will determine a cause of functional abnormality of the circuits after nerve injury by focusing on the role of glial cells and top-down signaling from the brain to the spinal dorsal horn. In addition, we will explore drugs that act on neurons and glia implicated in neuropathic allodynia by performing a screening of small-molecule chemical libraries (mainly clinically approved drugs).

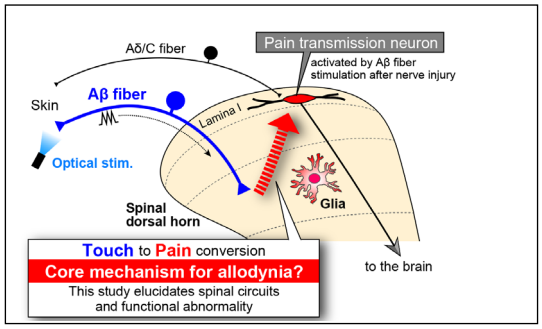

Figure 1　Proposal

【Research Methods】

In our proposed research program, experiments will be performed by using a new approach for investigating morphine-resistant neuropathic allodynia by optogenetics that enable a selective stimulation of touch-sensing primary afferent Aβ fibers and a technique for functional operation of neuronal subsets combined with histology, electrophysiology and imaging. First, we will examine the role of neuronal subsets in the spinal dorsal horn in Aβ fiber-derived neuropathic allodynia. Furthermore, the role of these subsets in Aβ fiber-derived information signal to lamina I SDH neurons after nerve injury will be analyzed. Abnormal functioning of identified neuronal subsets will be examined by focusing on the role of glia. Because recent studies have shown that top-down signaling from the brain directly affects pain processing in the spinal dorsal horn, we will examine the role of identified subsets of dorsal horn neurons as receiving cells of top-down signaling from the brain. Lastly, we will explore drugs that act on neurons and glia implicated in neuropathic allodynia by screening clinically approved drugs.

【Expected Research Achievements and Scientific Significance】

These findings from our proposed research program will identify neuronal circuits that are required for neuropathic allodynia and determine the role of glia and top-down signaling from the brain, which in turn advances our knowledge of 'how touch-sensing Aβ fiber signals are pathologically converted to pain in the context of nerve damage'. Our findings will not only advance in understanding of the mechanisms that underlie neuropathic pain but also provide new targets for treating this chronic pain.

【Publications Relevant to the Project】

・Tsuda M: New approach for investigating neuropathic allodynia by optogenetics. Pain 160 (Suppl 1): S53-S58 (2019)
・Inoue K, Tsuda M: Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci 19: 138-152 (2018)

【Term of Project】

FY2019-2023

【Budget Allocation】

153,700 Thousand Yen

【Homepage Address and Other Contact Information】

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