AL02 **LPA signaling-mediated feed-forward pain memory system and opioid-insensitivity in chronic pain**

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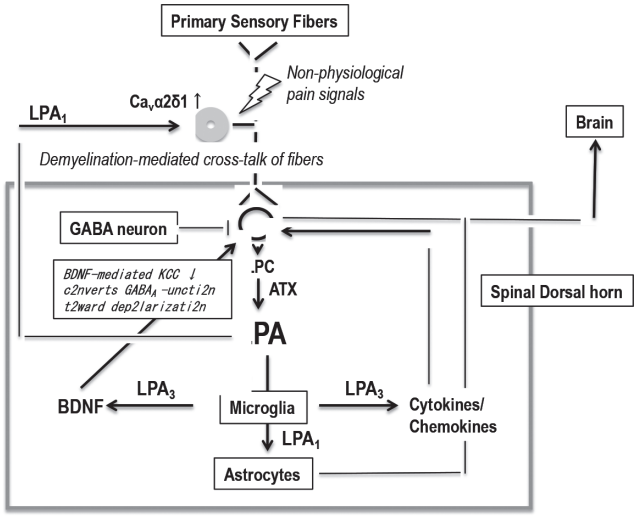
As chronic pain is now treated with several new medicines, it is no longer called intractable. However, the large-scale investigation tells us that medicinal treatment is not yet satisfactory. One of reasons may be related to the case that hidden mechanisms emerge during long-medicinal treatments. To solve this possibility, we should approach to find the crucial and definitive mechanisms and develop medicines to kill these mechanisms. My colleagues and I have tried to find the definitive mechanisms of various types of chronic pain through pathophysiological and pharmacological studies. One of successful studies is the discovery that lysophosphatidic acid (LPA) receptor signaling is involved in the development and maintenance of various types of chronic pain. The first study demonstrates that LPA1 receptor signaling initiates the partial sciatic nerve ligation (pSNL)-induced neuropathic pain and its underlying mechanisms. The loss-of-function and gain-of-function studies revealed that LPA1 plays roles in dorsal root demyelination, a mechanism for allodynia, and in DRG $Ca_V\alpha 2\delta 1$ upregulation, a mechanism for hyperalgesia. Following studies demonstrate that LPA production in the spinal dorsal horn is regulated in a feed-forward system. Intense and non-physiological pain transmission due to nerve damages causes an excess activation of c/i PLA2, which elevates intracellular LPC levels, leading to a leakage to extracellular space. Extracellular ATX converts LPC to LPA, and thus produced LPA then produces microglial cytokines, which in turn activates neuronal PLA2. Some aliquots of LPA will go back to dorsal root and demyelinate the fibers. LPA may also produce BDNF, which downregulates KCC2 and converts the functional switch of $GABA_A$ receptor functions from hyperpolarization to depolarization. Further studies demonstrated that LPA production occurs at the late phase (2-3 weeks), and established chronic pain completely disappears by repeated treatments with LPA1 antagonist. Similar findings of LPA production and complete blockade of established pain by LPA1 receptor antagonist are observed in different neuropathic pain models including paclitaxel-induced, diabetic, and cerebral stroke-induced neuropathic pain. Very recently, there are reports that peripheral and central levels of LPA increase as the pain severity goes in neuropathic pain patients. All these observations may suggest that the inhibitors of LPA1 receptor signaling are promising drug targets.



Similar LPA-involvements were also observed in mouse models for intermittent cold (ICS) or psychological stress (IPS, empathy)-induced fibromyalgia, which are totally insensitive to morphine. Detailed analyses reveal that LPA1-mediated chronic pain mechanisms and loss of opioid analgesia are independent each other in these fibromyalgia models, suggesting that opioid-insensitivity would be a novel therapeutic target.