Dual FAAH and MAGL inhibition might play a key role in visceral pain

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Pain is a complex phenomenon that is accompanied with disturbing and emotional feelings. Chronic pain is the most commonly presented clinical complaint in USA and affects >100 million people, which results in big economic burden (1). Chronic pain can be considered in four categories: neuropathic, inflammatory, musculoskeletal, and visceral/mechanical.

Evaluating and managing any patient with chronic abdominal pain are challenging. Drugs such as nonsteroidal anti-inflammatory drugs, opioids, anti-depressants, and anticonvulsants are clinically used in the treatment of pain (2). Cannabis has been traditionally used to treat gastrointestinal diseases, including abdominal pain, for centuries, and its mechanism has been understood within the past two decades after identification of the endocannabinoid system (ECS) and cannabinoid receptors (CB1 and CB2) (3).

Woodhams et al. (4) aimed to describe the role of the ECS in the sensory, emotional, and cognitive aspects of pain. In this article, the authors tried to explain the importance of ECS in modulating pain and the role of fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) enzymes in ECS. They clearly described the beneficial effects of cannabinoid modulators in analgesia. These modulators are effective as selective FAAH inhibition, selective MAGL inhibition, and combined inhibition of FAAH and MAGL enzymes. By these modulations, ECs, anandamide, and 2-arachidonylglycerol increase in systemic circulation, and this effect has been shown to relieve pain in animal models.

The authors also aimed to explain the mechanisms of stress-induced analgesia and ECS in visceral pain. Visceral pain is one of the most common types of pain, and ECS modulation has been shown to be effective in pain in stress-induced animal pain models. However, it is known that visceromotor response (VMR) to balloon distension of the colon is a robust behavioral model of visceral nociception in rodents. In addition to their article, we found that selective FAAH inhibition and dual FAAH/MAGL inhibition produced profound analgesic effect; however, selective MAGL inhibition was not effective in colorectal distension-induced visceral pain model (5). Therefore, we think that dual FAAH/MAGL inhibition and selective FAAH inhibition might be preferred for determining the effect of pain management in further studies.

The analgesic effects of dual FAAH and MAGL inhibitors have been shown in different models of nociception (6,7). Furthermore, dual inhibition produces greater cannabimimetic effects than full inhibition of FAAH and MAGL alone (5,7). Thus, we think that dual FAAH/MAGL inhibition rather than selective inhibition might be preferred in pain models.

In conclusion, ECS plays important role in the pain control system, and we think that modulation of dual FAAH/MAGL receptors can play a key role in pain control mechanism.

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