Therapeutic potential of the endocannabinoid system to treat chronic pain in inflammatory disease

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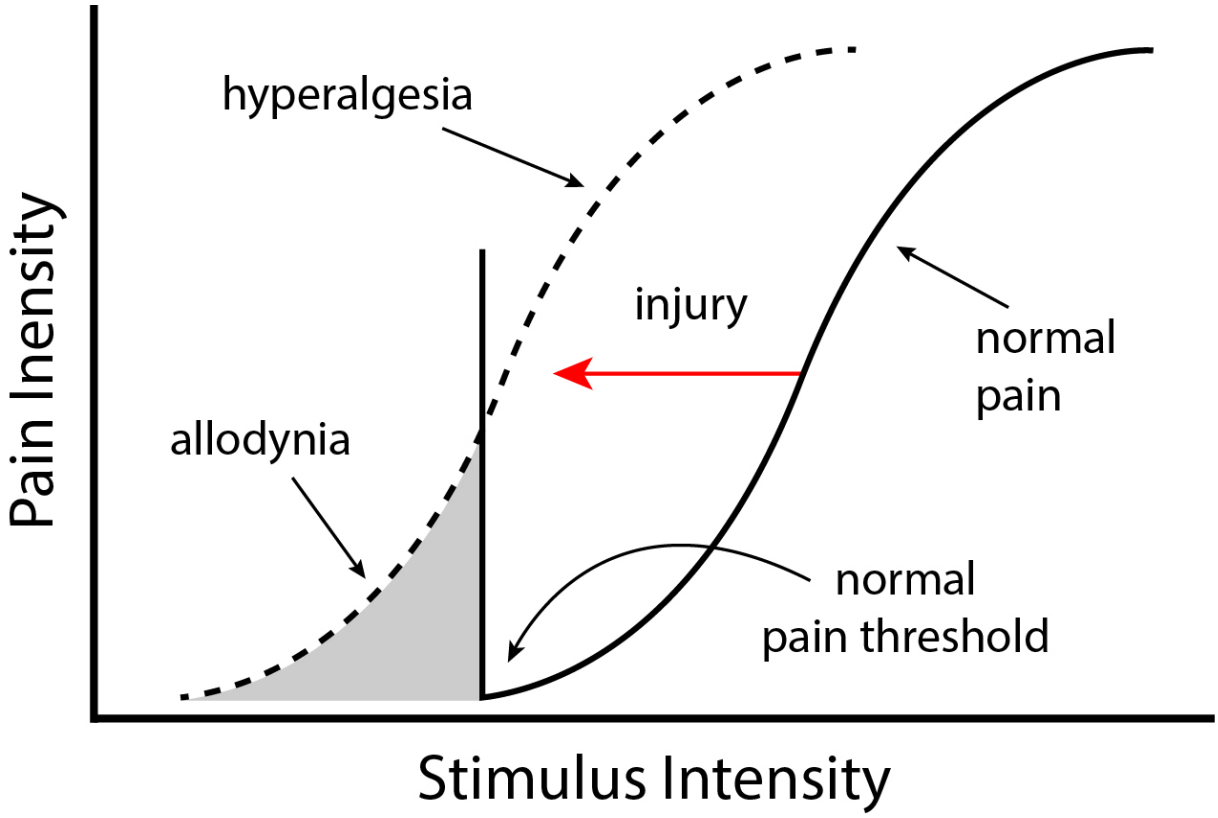

Figure 1: Abnormal pain response in IBD and Endometriosis.

Pharma researchers Julie Blaising and Philip Smith from F. Hoffmann-La Roche Ltd. discuss the endocannabinoid system as a pathway to treat inflammatory diseases such as Inflammatory Bowel Disease (IBD) and endometriosis

The endocannabinoid system (ECS) is a complex system that comprises the cannabinoid receptors 1 and 2 (CB1 and CB2, respectively), endocannabinoid (EC) ligands, and enzymes involved in the synthesis and degradation of endocannabinoids. [1] It is broadly expressed in the body and modulates physiology and immunity. [2, 3]

Nociceptor sensitization is a common principle that drives chronic pain

Concept of allodynia: Pain due to a stimulus that does not usually provoke pain.

Concept of hypersensitivity/ hyperalgesia: Conditions that lead to the perception of unusually severe pain in situations that normally cause only moderate pain.

- Nociceptor sensitization typically develops as a consequence of inflammation or tissue damage.

- Sensitized nociceptors have increased signaling in response to noxious stimulation.
- Due to nociceptor sensitization, patients experience pain at lower thresholds.
- In many patients, symptoms persist long after resolution of inflammation and/or tissue healing.

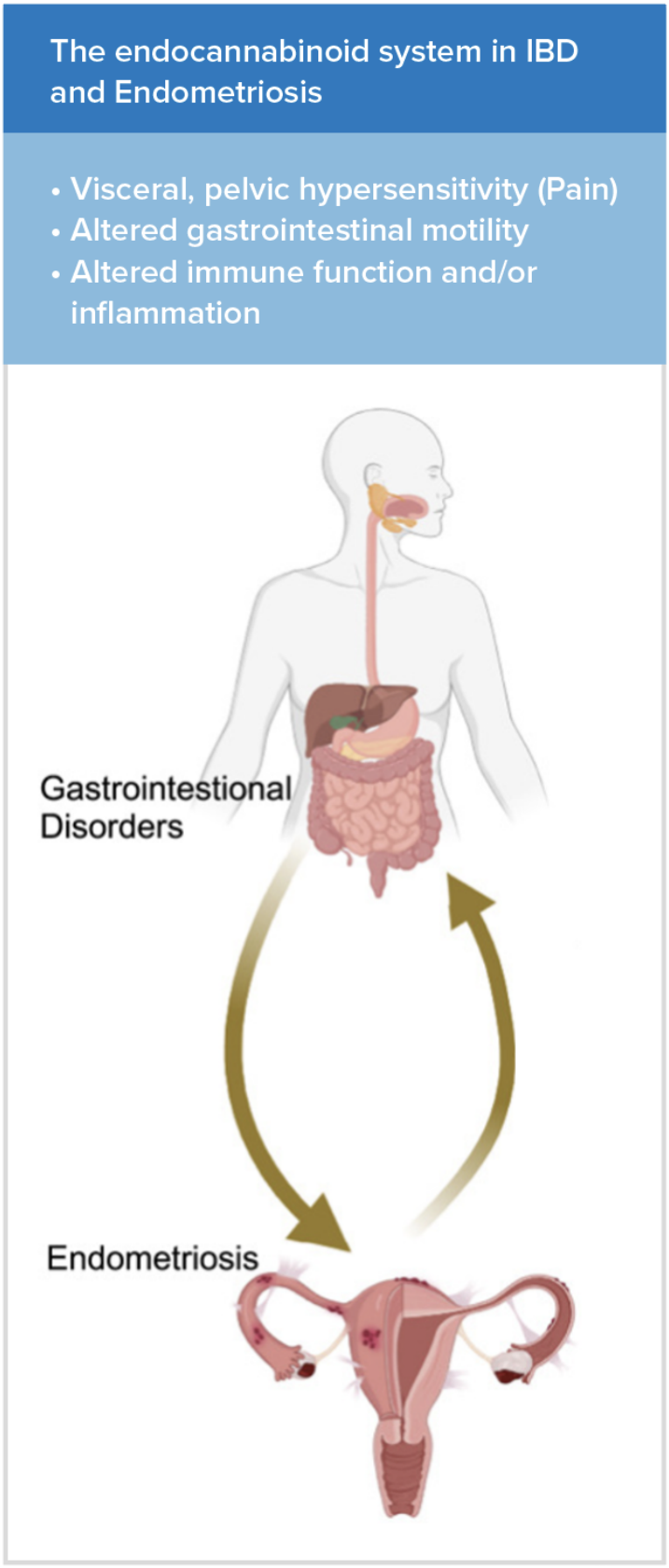

Figure 2: The Endocannabinoid system (ECS) acts as a physiological regulator of various processes that affects all of the clinical features of IBD and endometriosis

Pain and gastrointestinal dysfunction are symptoms associated with IBD and endometriosis

Persistent pain is a common and debilitating symptom associated with many inflammatory diseases, including IBD, endometriosis (EM), rheumatoid arthritis (RA), and osteoarthritis (OA).

Patients with IBD and endometriosis often exhibit persistent, local pain and develop pain hypersensitivity. This pain is not correlated with ongoing inflammation or disease severity. [4] In addition to pain, patients with IBD and endometriosis commonly experience symptoms of irritable bowel syndrome, such as diarrhea, bloating, and fatigue. These symptoms are also not correlated with the level of inflammation or disease severity (number and/or size of lesions).

Role of the endocannabinoid system in the pathophysiology of chronic pain

The ECS is involved in shared pathophysiology between IBD and endometriosis, such as in pain (hypersensitivity), inflammation, and gastrointestinal disorders (diarrhea, bloating). [5, 6] The cannabinoid receptors 1 and 2 (CB1 and CB2, respectively) are important in the pathophysiology.

- CB1 is mainly involved in pain (hypersensitivity) and diarrhea or constipation. It is highly expressed on enteric neurons in the gut and in somata and fibers in endometriosis lesions.
- CB2 is expressed predominantly on immune cells such as macrophages and mast cells, which mediate the anti-inflammatory effects of endocannabinoids in the GI tract or the peritoneal cavity.

Targeting the endocannabinoid system in IBD and endometriosis

The modulation of the ECS has been shown to produce analgesic and/or anti-inflammatory effects in animal models of IBD, endometriosis, and visceral hypersensitivity. [7] Various pharmacological strategies were used: enhancing endocannabinoid levels by inhibition of endocannabinoid degradation (FAAH, NAAH, MAGL inhibitors,…) or direct activation of CB1 and CB2 (CB1 and/or CB2 agonists). [7]

While symptoms of IBD are thus a high burden to patients and society, there is no targeted therapy available nor, to our knowledge, in development. Standard of care for abdominal pain, the lead symptom, includes paracetamol (acetaminophen) and opioids. The former is not sufficiently effective; the latter is addictive and must not be used chronically (cf. opioid epidemic in the US). Non-steroidal anti-inflammatory drugs (NSAIDs) are seen as controversial in IBD as they may provoke flares. Regarding endometriosis, pain is treated by NSAIDs, and more than 50% of patients with clinically or laparoscopically diagnosed endometriosis take opioids. [8, 9, 10]

Promising treatment for inflammatory diseases

As presented in this article, the ECS is involved in the shared pathophysiology between IBD and endometriosis and could offer a promising therapeutic approach to treating pain and gastrointestinal disorders in these diseases. Peripheral restriction and/or selectivity for specific tissue response is deemed essential to promote beneficial therapeutic responses while avoiding central cannabimimetic side effects.

Despite current preclinical evidence, further characterization of the role of the ECS in patients regarding disease activity, severity, and phenotype is warranted to facilitate the development of novel drugs that target the pathway. Conducting translational research to understand the role of the ECS in the pathogenetic mechanisms of human IBD and endometriosis remains crucial for effectively treating these multifactorial diseases.

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