



## EDITORIAL

# Cannabinoid-induced relief of hypermotility in a rat model of the irritable bowel syndrome

$\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC) produced by the cannabis (marijuana) plant is responsible for the multiple effects associated with marijuana use.  $\Delta^9$ -THC produces its effects via activation of cannabinoid-1 (CB1) and cannabinoid-2 (CB2) receptors which are G-protein coupled receptors (GPCRs). The CB1 receptor is expressed by neurons, and activation of this receptor mediates the psychotropic, analgesic, orexigenic, and anti-nausea effects of  $\Delta^9$ -THC.<sup>1</sup> CB2 receptors mediate the anti-inflammatory effects of  $\Delta^9$ -THC.<sup>2</sup> However, the paper by Lin et al in this issue of *Neurogastroenterology and Motility* shows that  $\Delta^9$ -THC acting at CB2 receptors can alter gastrointestinal motility and sensation in a rat model of the irritable bowel syndrome (IBS).<sup>3</sup> These studies confirm previous work showing that CB2 receptors are expressed by enteric neurons<sup>4</sup> and by mesenteric afferent nerves supplying the gut.<sup>5,6</sup> Lin and colleagues used water avoidance stress (WAS)<sup>7</sup> for 10 days to induce visceral hypersensitivity, decreased intestinal transit time (increased propulsive motility), and increased fecal water content. These effects mimic human diarrhea-predominant irritable bowel syndrome (dIBS).<sup>8</sup> Using immunohistochemical methods, Lin and colleagues found that WAS caused an increase in CB2 receptor expression by macrophages in the intestinal lamina propria and by myenteric neurons. In addition, treatment of WAS rats with AM1241, a CB2 receptor agonist, increased intestinal transit time (decreased propulsive motility), decreased fecal water content, and decreased spontaneous contractions of the longitudinal muscle in distal colon segments *ex vivo*. WAS also increased p38 phosphorylation which is linked to stimulation of mitogen-activated protein kinase (MAPK). Increased phospho-p38/MAP kinase activity caused downregulation of nitric oxide synthase NOS expression and AM1241 treatment restored NOS levels and NO production and release. This is important as NO is an inhibitory neurotransmitter in the myenteric plexus that causes the smooth muscle relaxation need for propulsion of gastrointestinal content.<sup>9</sup>

The data summarized above support a key role for p38-MAPK signaling in causing increased propulsive motility and fecal output in WAS-treated rats. Lin et al followed up on these studies by treating control and WAS exposed rats with BIRB796, a p38-MAPK inhibitor. They found that inhibition of p38-MAPK slowed intestinal transit, decreased fecal water content, and inhibited spontaneous contractions of the longitudinal muscle in colon segments *ex vivo*. It is important to note that BIRB796 did not affect intestinal transit, fecal water content, or colonic contractility in control (unstressed) rats suggesting that upregulation of CB2 receptors (and p38-MAPK) is a response to chronic stress.

Functional gastrointestinal motility and sensation disorders, including irritable bowel syndrome (IBS), are common, and drug treatments are not widely effective. Studies, such as the one by Lin et al in this issue, suggest that cannabinoids especially agonists at CB2 receptors might be helpful for some patients with IBS. It is well established that CB2 receptor agonists have anti-inflammatory effects, and there are studies showing that CB2 receptor stimulation can reduce inflammation and improve quality of life in inflammatory bowel disease patients.<sup>10,11</sup> CB1 receptors are expressed widely in the enteric nervous system and agonists at these receptors inhibit propulsive motility in the gut and therefore CB1 receptor agonists slow gastrointestinal transit.<sup>12</sup> However, as shown by Lin et al in this issue, CB2 receptor agonists can also be effective in slowing GI transit and this would occur without the psychotropic effects caused by CB1 receptor activation.

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## DISCLOSURES

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