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Modulating endogenous cannabinoids to treat pain and affective disorders

The endocannabinoids are a family of biologically active lipids that activate cannabinoid (CB) receptors, the G protein-coupled receptors targeted by ∆9-tetrahydrocannabinol (∆9-THC) in marijuana. The term encompasses several derivatives of the polyunsaturated fatty acid arachidonic acid, including anandamide (arachidonylethanolamide), and 2-arachidonoylglycerol (2-AG). The endocannabinoids are thought to operate primarily as paracrine mediators—substances that are generated on demand by neurons and other cells in response to physiological stimuli and act in the vicinity of their sites of synthesis (Piomelli, 2003).

In brain, the endocannabinoids may mediate localized signaling mechanisms through which neurons modify the strength of incoming synaptic inputs. For example, evidence indicates that 2-AG is generated in the hippocampus by activation of postsynaptic metabotropic glutamate mGlu5 receptors and travels backwards across the synapse to inhibit glutamate and GABA transmission, a process called ‘retrograde signaling’ (Hohmann et al, 2005). Other data suggest that local release of anandamide in the dorsal raphe nucleus, locus coeruleus, and periaqueductal gray matter regulates the activity of ascending and descending aminergic pathways to influence stress responses, pain, and affect (Hohmann et al, 2005; Gobbi et al, 2005).

The proposed role of the endocannabinoids in the control of pain and emotion has both theoretical and clinical interest and it could be exploited to develop novel anagelsic, antinociceptive, and antidepressant drugs. However, the psychotropic properties and abuse liability of direct-acting CB receptor agonists such as ∆9-THC pose a major obstacle in the realization of this therapeutic potential. One possible way to circumvent such an obstacle might be to develop drugs that prevent the biological deactivation of the endocannabinoids and, by doing so, amplify their intrinsic effects in a site- and context-restricted manner.

Anandamide and 2-AG are rapidly eliminated through a two-step process, consisting of uptake into cells and enzymatic hydrolysis. The two endocannabinoids share what appears to be a functionally similar transport mechanism, but follow distinct routes of intracellular degradation. Inside cells, anandamide is metabolized by fatty acid amide hydrolase (FAAH), a membrane-bound serine hydrolase that is found in neuronal cell bodies throughout the cortex. 2-AG hydrolysis is catalyzed instead by monoacylglycerol lipase, a cytosolic serine hydrolase that is localized in presynaptic terminals. Agents that target these deactivating reactions might display a more selective pharmacological profile than direct CB agonists. For example, inhibitors of intracellular FAAH activity were shown to exhibit marked anxiolytic, antidepressant, and anagelsic effects in rodents (Gobbi et al, 2005; Kathuria et al, 2003; Russo et al, 2007). These behavioral effects are accompanied by augmented brain levels of anandamide and are prevented by CB1 cannabinoid receptor blockade, but are not associated with overt psychotropic or rewarding actions (Gobbi et al, 2005). FAAH inhibitors have recently entered clinical trials, and data regarding their efficacy in patients should become available in the next few years. Discovery efforts targeting other endocannabinoid-deactivating pathways are also underway.

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