Serine Hydrolase Monoacylglycerol Lipase Inhibitor ABX-1431

National Cancer Institute

Source

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An orally bioavailable inhibitor of the serine hydrolase monoacylglycerol lipase (MGLL), with potential use for the treatment of various central nervous system (CNS) diseases and with potential analgesic and anti-neuroinflammatory activities. Upon oral administration, MGLL inhibitor ABX-1431 targets and binds to MGLL, thereby inhibiting MGLL activity and preventing the breakdown and inactivation of endogenous 2-arachidonoylglycerol (2-AG). Increased 2-AG levels results in enhanced activation of the cannabinoid receptor 1 (CB1) in the CNS and enhanced CB1 endocannabinoid signaling in active neural circuits. Activation of CB1 helps modulate the endocannabinoid system and reduce neurotransmitter release, thereby decreasing overactive neural signaling. This induces analgesic, anti-inflammatory and various neurological effects that are caused by dysregulation of the endocannabinoid system and overactive neural signaling, including anxiolytic effects, reduced spasticity and decreased neurodegenerative effects. In addition, MGLL inhibition by ABX-1431 depletes the supply of the inflammatory signaling molecule arachidonic acid, thereby further alleviating pain and inflammation. CB1 plays a key role in the regulation of neurotransmission; increased CB1 activation decreases overactive neural signaling. MGLL, an enzyme that catalyzes the breakdown of 2-AG, regulates the activation of CB1 and CB2 to modulate neurotransmission and inflammatory signaling, respectively.