Ischemia

Excerpt from www.webmd.com:

What is ischemia?

Ischemia is the medical term for what happens when your heart muscle doesn't get enough oxygen. Ischemia usually happens because of a shortage of blood and oxygen to the heart muscle. It is usually due to narrowing or blockage of one or more of the coronary arteries (which supply blood to the heart muscle). In many cases ischemia is a temporary problem. Your heart may be able to get enough blood through your diseased coronary arteries while you are resting but may suffer from ischemia during exertion or stress.

What is chronic ischemia?

Your coronary arteries may become so narrowed that they limit the flow of blood to your heart all the time, even when you are at rest. If this happens, ischemia can become an ongoing (chronic) condition that can progressively weaken your heart.

What is angina?

When your heart suffers from ischemia, you will typically experience pain or discomfort in your chest. Angina is the medical term for this chest sensation, which is the most common symptom of coronary artery disease (CAD).

It's important to know that people with CAD who experience angina often describe the sensation as "tightness," "discomfort," "squeezing," and "heaviness." The pain or discomfort of angina tends to start under your breastbone but may also travel, often to your shoulder, arm, neck, or jaw. Often people also have shortness of breath, sweating, and a feeling of nausea along with the anginal chest pain or discomfort. Occasionally ischemia causes these other symptoms without causing chest pain or discomfort.

What is silent ischemia?

For reasons that doctors don't fully understand, some people have ischemia but do not feel chest pain or discomfort or any other symptoms. This condition is called silent ischemia. Silent ischemia occurs most often in people with diabetes, women, and older people.

People with silent ischemia typically find out that they have it when their doctor notices that their routine electrocardiogram (EKG), ambulatory EKG, or stress test results indicate that their hearts aren't getting enough blood. Silent ischemia is a particular concern after a heart attack, because it increases the chance of another heart attack.

Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment

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Abstract

Activation of the cannabinoid 2 receptor (CB_2) reduces ischemic injury in several organs. However, the mechanisms underlying this protective action are unclear. In a mouse model of ischemic stroke, we show that the CB_2 agonist JWH-133 (1 mg · kg^{-1} · d^{-1}) decreases the infarct size measured 3 d after onset of ischemia. The neuroprotective effect of JWH-133 was lost in CB_2-deficient mice, confirming the specificity of JWH-133. Analysis of bone marrow chimeric mice revealed that bone marrow-derived cells mediate the CB_2 effect on ischemic brain injury. CB_2 activation reduced the number of neutrophils in the ischemic brain as shown by FACS analysis and by measuring the levels of the neutrophil marker enzyme myeloperoxidase. Indeed, we found in vitro that CB_2 activation inhibits adherence of neutrophils to brain endothelial cells. JWH-133 (1 μM) also interfered with the migration of neutrophils induced by the endogenous chemokine CXCL2 (30 ng/ml) through activation of the MAP kinase p38. This effect on neutrophils is likely responsible for the neuroprotection mediated by JWH-133 because JWH-133 was no longer protective when neutrophils were depleted. In conclusion, our data demonstrate that by activating p38 in neutrophils, CB_2 agonists inhibit neutrophil recruitment to the brain and protect against ischemic brain injury.—Murikinati, S., Jüttler, E., Keinert, T., Ridder, D. A., Muhammad, S., Waibler, Z., Ledent, C., Zimmer, A., Kalinke, U., Schwaninger, M. Activation of cannabinoid 2 receptors protects against cerebral ischemia by inhibiting neutrophil recruitment.

http://www.fasebj.org/content/24/3/788.abstract

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Role of cannabinoids and endocannabinoids in cerebral ischemia.

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Source

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Abstract

The human costs of stroke are very large and growing; it is the third largest cause of death in the United States and survivors are often faced with loss of ability to function independently. There is a large need for therapeutic approaches that act to protect neurons from the injury produced by ischemia and reperfusion. The goal of this review is to introduce and discuss the available data that endogenous cannabinoid signaling is altered during ischemia and that it contributes to the consequences of ischemia-induced injury. Overall, the available data suggest that inhibition of CB1 receptor activation together with increased CB2 receptor activation produces beneficial effects.

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Cannabinoids and Neuroprotection in Global and Focal Cerebral Ischemia and in Neuronal Cultures

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Abstract

Marijuana and related drugs (cannabinoids) have been proposed as treatments for a widening spectrum of medical disorders.*R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-yl]-(1-naphthalenyl)methanone mesylate *(R*(+)-WIN 55212-2), a synthetic cannabinoid agonist, decreased hippocampal neuronal loss after transient global cerebral ischemia and reduced infarct volume after permanent focal cerebral ischemia induced by middle cerebral artery occlusion in rats. The less active enantiomer*S*(−)-WIN 55212-3 was ineffective, and the protective effect of *R*(+)-WIN 55212-2 was blocked by the specific central cannabinoid (CB_1) cannabinoid receptor antagonist*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide-hydrochloride.*R*(+)-WIN 55212-2 also protected cultured cerebral cortical neurons from *in vitro* hypoxia and glucose deprivation, but in contrast to the receptor-mediated neuroprotection observed *in vivo*, this *in vitro* effect was not stereoselective and was insensitive to CB_1 and CB_2 receptor antagonists. Cannabinoids may have therapeutic potential in disorders resulting from cerebral ischemia, including stroke, and may protect neurons from injury through a variety of mechanisms.

http://www.jneurosci.org/content/19/8/2987.abstract

Activation of Cortical Type 2 Cannabinoid Receptors Ameliorates Ischemic Brain Injury

*Reported in The American Journal of Pathology***Philadelphia, PA, February 21, 2013** – A new study published in the March issue of *The American Journal of Pathology* suggests that cortical type 2 cannabinoid (CB2) receptors might serve as potential therapeutic targets for cerebral ischemia.Researchers found that the cannabinoid trans-caryophyllene (TC) protected brain cells from the effects of ischemia in both *in vivo* and *in vitro* animal models. In rats, post-ischemic treatment with TC decreased cerebral infarct size and edema. In cell cultures composed of rat cortical neurons and glia exposed to oxygen-glucose deprivation and reoxygenation (OGD/R), TC decreased neuronal injury and mitochondrial depolarization, specifically through type 2 cannabinoid receptor (CB2R) pathways.“

To our knowledge, novel data presented in this study provide evidence for the first time supporting a previously unappreciated role of cortical CB2R, especially neuronal CB2Rs, in ischemia,” says lead investigator Won-Ki Kim, PhD, of the Department of Neuroscience, College of Medicine, Korea University in Seoul. “This study suggests that further investigation is warranted to establish the clinical usefulness of TC as a preventative and therapeutic agent for treatment of stroke.”

Results presented in the study shed light on the anatomy and mechanism of action of CB2R-mediated neuroprotection. In the *in vivo* study, which was performed in rats, the right middle cerebral artery was occluded for 1.5 hours to mimic an ischemic stroke; blood flow was allowed to return for the next 24 hours. Three hours after the occlusion began, the animals were treated with TC; some animals also received AM630, a CB2R antagonist. The next day, the brains were removed, and the volume of the infarct and extent of cerebral edema were measured.

Using immunocytochemistry, the investigators found evidence of CB2Rs in the cortex of both control and ischemic brains, mostly in cortical neurons but also to a lesser extent in some glial cells. This finding in itself is important because the question of whether CB2Rs are present in the cortex has long been a matter of debate, say the authors.Post-ischemic treatment with TC reduced infarct size by 53.8% and reduced edema by 51.9%. However, co-administration of the CB2R antagonist AM630 completely blocked the protective effect of TC.

Further analysis indicated that CB2R activation is involved in the ability of TC to induce cAMP responsive element-binding protein (CREB) phosphorylation and increase the expression of brain-derived neurotrophic factor (BDNF) in ischemic tissue.

Cell-culture studies of embryonic rat cortical neurons and glia exposed to OGD/R to simulate ischemic insult confirmed some of the findings of the *in vivo* studies

and contributed to further understanding about cellular effects of ischemia and TC treatment. In the cultures, TC decreased neuronal injury, intracellular oxidative stress, and mitochondrial depolarization following OGD/R, and the effects were reversed by AM630 but not by a CB1R antagonist, AM251. Western blot analysis demonstrated that TC enhanced the phosphorylation of AMP protein kinase (AMPK) and CREB, while selective AMPK and CREB inhibitors blocked TC's neuroprotection. Other findings indicated that the anti-ischemic effect of TC was not mediated by NMDA receptor antagonism or antioxidant activity.

TC is a major cannabinoid derived from the essential oil of the flowering plant *Cannabis sativa*, but has a fundamentally different structure from classical cannabinoids. Unlike agents which activate CB1 receptors, selective CB2R receptor agonists do not have psychoactive side effects.

TC appears to maintain CB2R agonist activity when administered orally and is a common ingredient found in many food additives and folk medicines. The intriguing results of the present study suggest that the anti-ischemic benefits of TC deserve further exploration.

http://www.elsevier.com/about/press-releases/research-and-journals/activation-of-cortical-type-2-cannabinoid-receptors-ameliorates-ischemic-brain-injury

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Cannabinoid 1 receptor mediation of spinal cord ischemic tolerance induced by limb remote ischemia preconditioning in rats

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Objective: The aim of this study was to examine the influence of endogenous cannabinoids on neuroprotection of the spinal cord afforded by limb remote ischemic preconditioning.

Methods: In experiment 1 (RIPC group), 3 cycles of limb remote ischemic preconditioning within different episodes (2, 3, or 5 minutes) were induced before spinal cord ischemia in rats (N = 5, n = 8). In experiment 2, animals were pretreated intravenously by the vehicles, cannabinoid 1 (AM251, 1 mg/kg) or cannaboid 2 (AM630, 1 mg/kg) receptor antagonist 15 minutes before remote ischemic preconditioning, or else they were subjected to a sham operation. Thirty minutes after the pretreatment, spinal cord ischemia was induced (N = 8, n = 8). In experiment 3, the arachidonylethanolamide and 2-arachidonoylglycerol contents in the spinal cord after remote ischemic preconditioning and spinal cord ischemia were detected in rats (N = 2, n = 12). Spinal cord ischemia was induced by 12 minutes of thoracic aorta occlusion in rats. Neurologic function was assessed 24 and 48 hours after reperfusion. Histopathologic examination was performed and the number of normal neurons in anterior spinal cord were counted.

Results: In experiment 1, 3 cycles of limb remote ischemic preconditioning (3 minutes of ischemia/3 minutes of reperfusion) induced ischemic tolerance on the spinal cords of the rats. The RIPC group showed a significant reduction in motor deficit index ($P < .01$) as well as an increase in the number of normal neurons ($P < .01$). In experiment 2, the cannabinoid 1 receptor antagonist AM251 pretreatment abolished the protective effects of remote preconditioning. In experiment 3, arachidonylethanolamide content in spinal cord was elevated by remote ischemic preconditioning in rats.

Conclusion: These results indicated that endogenous cannabinoids, through acting on cannabinoid 1 receptors, were involved in the neuroprotective phenomenon on spinal cords of limb remote ischemic preconditioning.

http://jtcs.ctsnetjournals.org/cgi/content/abstract/138/6/1409