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ROLE OF CANNABINOIDS IN THE TREATMENT OF TINNITUS

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ABSTRACT

Tinnitus is a frequent symptom in audiological clinical practice characterized by an abnormal noise perceived in one or both ears or in the head, in which a patient has a conscious hearing percept in absence of external sound. Tinnitus might be caused by a homeostatic response of central dorsal cochlear nucleus auditory neurons that makes them hyperactive in compensation to auditory input loss. One hypothesis suggests that tinnitus is a sensory form of epilepsy that involves the cochlear nucleus and the inferior colliculus, which display impairment in the electrical activity in the auditory system. This alteration determines a synaptic plasticity in the dorsal cochlear nucleus that becomes a target for pharmacological compounds able to treat tinnitus. There is no effective drug treatment for tinnitus, but different studies propose the use of cannabinoid receptors agonist for their anti-epileptic activity, although their practical effects are still unclear. In this review, we want to analyze the emerging pharmacological approaches of cannabinoid receptor agonists to the therapy of tinnitus.

***Key words**: cannabinoids, tinnitus, dorsal cochlear nucleus.*

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Introduction

Tinnitus is a frequent symptom in audiological clinical practice, it happens alone, or in combination with other systemic or otologic diseases[1-3]. It is defined as an abnormal noise perceived in one or both ears or in the head in which a patient has a conscious hearing percept in absence of external sound. The causes of the onset of disease can arise from damage to the inner ear as a results of physical trauma, excessive noise, vascular insufficiency, viral or bacterial infection and exposure to some toxic drugs, such as aspirin and chemotherapeutics, or as a result of aging[4-6].

The mechanisms underlying the development of tinnitus are still not fully understood, the most likely cause of tinnitus is changes in neural activity in the brain, which is supported by both animal and human studies. It has been reported that exposure to intense sound, a manipulation able to modify the functional status of the ear, can induce plastic physiological changes which are more complex from those occurring peripherally[4,7-10]. Sound induced injury have been correlated with an increase in hyperactivity in the dorsal cochlear nucleus (DCN)[11,12] the inferior colliculus and the primary auditory cortex[13-15]. Many researchers focused out the attention on the modifications that occur in

DCN following intense sound exposure inasmuch, this area, is prominent as primary auditory center that projects its output to the contralateral inferior colliculus[16-20]. Fusiform cells of the DCN are responsible of tinnitus-related hyperactivity in the cochlear nucleus. Moreover, recent studies show that stimulation of the trigeminal nerve or ganglion can modulate spontaneous activity fusiform cells in DCN[21]. These cells have higher levels of spontaneous activity in sound exposed animals than in the unexposed controls[22, 23]. In particular exposure to salicylate as well as quinine cause increases in spontaneous activity at several levels of the auditory system and induced transient tinnitus[24-31]. Evidence that hyperactivity in the DCN represents a source of tinnitus-generating signals comes from studies in which electrophysiological recordings from the DCN were complemented by behavioral tests for tinnitus, suggesting that noise-exposure conditions can also cause the development of tinnitus-like percepts[31-33]. Moreover, when behavioral and electrophysiological tests were conducted in the same animals, a significant correlation was found between the level of activity in the DCN and the behavioral evidence for tinnitus[34].

Many pharmacological treatments are targeted to control the activity of neurotransmitters, neuromodulators and voltage-gated channels that play a pivotal role in the modulation of neuronal excitability. Furthermore, because of several co-morbidities of tinnitus, including anxiety, depression, dysfunction of the temporomandibular joint and modification of neuronal excitability, other drugs have been employed including antidepressants, benzodiazepines, antispasmodic drugs, drugs for neuropathic pain, local anesthetics, voltage-gated sodium channel blockers, antiepileptics[35-37].

Currently, no drugs exists with an indication for tinnitus treatment, although many researches pointed out the attention on the antiepileptic effects played by the endocannabinoidergic system in some parts of the CNS that might be useful in the treatment of auditory injury.

Materials and methods

The author's search targeted evidence-based guidelines, evidence-based summaries, systematic reviews and recent experimental research on the hyperactivity of tinnitus-generating signals and endocannabinoidergic system. The keywords used were "Tinnitus" or "Tinnitus in the cochlear nucleus" or "Pharmacological treatment of tinnitus" or "Endocannabinoidergic system" or "Cannabinoid receptors". Through this simple strategy we identified more than 300 using two primary sources for identify relevant information: PubMed and SCOPUS (last accessed via PubMed and SCOPUS on December 2015)

Cannabinoid receptors distribution

Two types of cannabinoid receptors have been identified, distributed in different tissues. CB1 and CB2 receptors are distributed in many different cells, with different mechanisms of signaling. It is known that CB1 receptors are expressed mainly in the central nervous system (CNS), while the CB2 receptors are localized primarily in cells to the immune system[38], peripheral nervous system, testes and retina, but recently their presence has been detected in the brain, in particular microglial cells, though at low concentrations[39]. Both receptors are coupled with Gi or Go protein, negatively to adenylyl cyclase and positively to mitogen-activated protein (MAP) kinase. CB1 receptors, are represented by two subtypes: CB1A and CB1B[40,41]. CB1 receptors are localized predominantly on pre-synaptic terminals[42] and expressed in areas involved in motor coordination and movement, such as cerebellum, basal ganglia and substantia nigra; attention and complex cognitive functions (cerebral cortex), learning, memory and emotions (amygdala and hippocampus)[43,44]. This receptor is coupled to ion channels through Gi/o proteins, positively to A-type and inwardly rectifying potassium channels, and negatively to N-type and P/Q-type calcium channels and to D-type potassium channels[45], in fact CB1 activation inhibits cAMP-dependent protein kinase (PKA), due to the decrease of cAMP.

Therefore, his mechanism causes inhibition of calcium influx at presynaptic terminals, inhibiting the release of classical neurotransmitters, such as gamma-aminobutyric acid (GABA), acetylcholine, noradrenaline and glutamate. It suggests how this mechanism preserves the CNS from over-stimulation or over-inhibition that may be caused by other neurotransmitters. Upon which, the presynaptic inhibition of neurotransmitter release by cannabinoids may turn out to be a key neuronal effect of cannabinoids. Based on the distribution of cannabinoids receptors, different studies focused the attention on the spatial distribution of CB1 receptors in

the auditory brain regions, in particular in the CN[21]. There is only a small literature on cannabinoid receptors in these regions and how they might affect auditory function. Different studies have been shown that CB1 receptor are expressed in both Dorsal and Ventral Cochlear Nuclei (DCN and VCN, respectively), modulating synaptic plasticity in auditory nuclei[46-47] also reported the localization of CB2 receptor CN, in spite of this second subtype of cannabinoid receptor expression in the brain is controversial[32,48]. DCN fusiform cells are the principal output neurons of the DCN, which project to the contralateral inferior colliculus.

Therefore, hyperactivity of these neurons could influence functional properties of inferior colliculus neurons that could influence activity in order structures such as the medial geniculate body and auditory cortex[16-20]. Fusiform cells receive excitatory glutamatergic input via parallel fibers from the granule cells of the DCN, as well as inhibitory glycinergic input from cartwheel cells. In this manner, fusiform cell hyperactivity associated with tinnitus could result from an increase in glutamatergic excitation from the granule cells or a reduction in glycinergic inhibition from the cartwheel cells, or some combination of both. Zhao et al.[47] demonstrated that both fusiform and cartwheel cells expressed diacylglycerol lipase (DAGL) a and b, enzymes necessary for the production of the endocannabinoid, 2- arachidonyl glycerol (2-AG). The two forms of DAGL were found in the dendritic spines of cartwheel but not fusiform cells. It suggests that the production of 2-AG is closer to parallel fiber synapses in cartwheel cells compared to fusiform cells. Tzounopoulos and colleagues[49] demonstrated that CB1 receptors localized to parallel fibers inhibited the release of glutamate onto cartwheel and fusiform cells, but they also inhibit the release of glycine on cartwheel cells (from other cartwheel cells) and from cartwheel cells on fusiform cells[23, 36] Zhao et al.[47] also showed that glutamatergic terminals in the DCN expressed more CB1 receptors on glutamatergic terminals than glycinergic terminals, suggesting that the effects of activation of CB1 receptors in the DCN would be due to the increasing of excitation signals of fusiform cells over their inhibition and that endocannabinoid signaling might be a major factor affecting the balance of excitation and inhibition in this part of the central auditory system.

Moreover the increased activation of CB1 receptors in the DCN could lead to an increased excitation of fusiform cells and to a possible hyperactivity in the inferior colliculus (36). This increase in multiunit spontaneous activity (hyperactivity) in the DCN could be play a significant role in the onset of tinnitus-generating signals.

Endocannabinoids and the neurotrasmission in the Brain

Endocannabinoids (ECs), lipid-derived molecules, produced on demand, activate CB receptors, operating as retro negative feedback system[50,51] via a Ca2+- dependent activation of endocannabinoid synthesizing enzymes. These enzymes induce the activation of pre-synaptic CB1[52-55], that, upon activation, attenuate Ca2+ influx into the pre-synaptic terminal and thus transmitter release by blocking vesicle fusion[56]. This feedback mechanism is called depolarization-induced suppression of inhibition[57-58] (DSI) or depolarization-induced suppression of excitation (DSE)[59], whether the released neurotransmitter exerts an inhibitory or an excitatory action on the post-synaptic neurons[58]. DSI and DSE have been observed throughout the brain for GABAergic and glutamatergic synapses to provide a means for a cell to down-regulate its inputs in an activity-dependent manner. In this way ECs modulate the neurotransmission in the brain, inducing suppression of inhibitory and excitatory inputs[60, 61, 62-64]. CB1 receptors in the DCN regulate the development of DSI and DSE, as well as Long-Term Depression (LTD), indicating that the endocannabinoid system is involved in the control of plasticity in this part of the central auditory system[47, 65]. Little is known about the organization and function of ECs signaling on auditory circuits[66, 67], despite the knowledge of the effects of cannabinoids in the regulation of acoustic discrimination and auditory perception. Some studies have been reported that CB1, CB2 receptors, and the endogenous cannabinoid, 2-arachidonylglycerol (2-AG), are expressed in the cochlear nucleus and that they are involved in the regulation of plasticity[68].

Cannabinoid drugs might be useful in the treatment of tinnitus

Several studies showed that the DCN is involved in the modulation of tinnitus in humans, playing an important role in the etiology of this disease. Studies conducted in hamsters, displayed that neurons become hyperactive in the DCN following

exposure to intense sound[69]. This hyperactivation was originally observed as increase in spontaneous activity at the multiunit level, although more recent studies have demonstrated sound exposure, induced hyperactivity in the DCN at the single unit level[33]. Respect to the evidence that the DCN is a possible source of tinnitus-generating signals, as reported by different studies[70]; and consider the hyperactivation of it, following exposure to intense noise, it is suitable investigate upon the role of cannabinoids in the treatment of tinnitus. Based on theories that tinnitus is a form of sensory epilepsy that occurs as a result of neuronal hyperactivity in certain parts of the auditory CNS, particularly in CN and IC, increasing evidences suggest the use of cannabinoid drugs in the treatment of tinnitus. Lutz[71] reported that cannabinoid drugs have antiepileptic effects in some parts of the CNS and he has been demonstrated that in the hippocampus, CB1 receptor agonists have anticonvulsant activity and exert antiepileptic effects[36,72,73].

In this way, it is conceivable consider the use of cannabinoids in the treatments of tinnitus, because of their antiepileptic effects. Current studies confirm that many neurons in the DCN and VCN have CB1 receptors and that therefore this receptor type may be significant for auditory function. Subjective tinnitus and Cannabis have had a long relationship and it has been suggested to cause tinnitus, but anecdotal evidence suggests that tinnitus sufferers sometimes use it to relieve the condition. There are very few publications on this subject. Kempel et al.[66] reported that Cannabis reduced the ability of humans to discriminate target tones of specific frequency, location and duration. Hajos et al.[67] reported that agonists at the cannabinoid CB1 receptor caused impairment in auditory sensory gating in rats. About the treatment of tinnitus in human, it had been published only one case report, in which tinnitus was treated and eliminated by the administration of Dronabinol, a CB1 receptor agonist, at a dose of 10 mg twice a day and then reduced to 5 mg twice a day[74,75] investigate the relationship between CB1 receptor and tinnitus, using an animal model of tinnitus, in which it had been induced by salicylate injections. Rats displayed a significant decrease in the number of neurons expressing CB1 receptor and in one of the only two studies, the authors investigated the effects of two synthetic CB1 receptor agonist, WIN55,212-2 and CP-55940.[76].

CB1 receptors appear to negatively regulate the release of glutamate and it is possible that their down-regulation during the development of tinnitus is responsible for the neuronal hyperactivity associated with the condition. WIN55,212-2, and CP55,940 could inhibit the behavioral manifestations of salicylate-induced tinnitus in rats in a conditioned suppression task, but neither WIN55, 212-2 (3.0 mg/kg s.c) nor CP55, 940 (0.1 or 0.3 mg/kg s.c), significantly reduced conditioned behavior associated with tinnitus. However, both 3 mg/kg WIN55, 212-2 and 0.3 mg/kg CP55,940 did significantly increase tinnitus-related behavior compared to the vehicle control groups. To investigate tinnitus-related behavior, that realistically simulates the common form of tinnitus in humans, it had been caused by an acoustic injury. This study examined the effect of 1:1 ratio of delta-9-THC (1.5mg/Kg, s.c) and cannabidiol (1.5mg/kg, s.c),[77]. All these studies on experimental animal model displayed an exacerbation of tinnitus and not a relieve. These results suggest that CB receptors agonists may not be useful in the treatment of tinnitus and that at certain doses; they could actually exacerbate the condition[76].

Conclusion

The practical effects of cannabinoids for the treatment of tinnitus, such a central injury, are still unclear. Based on the hypothesis that tinnitus is a form of sensory epilepsy that arise from neuronal hyperactivation in auditory regions of the brain, researchers focus their attention on the antiepileptic mechanisms of cannabinoids on CB1 receptors, that are very abundant in some areas of the brain. Although cannabinoids exert anti-epileptic effects, in the circuit of DCN, they facilitate an increase of the excitation, rather than an inhibition, suggesting that this hyperactivity is part of the cause of tinnitus, such as it is still not clear whether the down-regulation of CB1 receptors, might be part of a hyperactivity or compensatory response to it. Nevertheless, study of model of partial epilepsy in adult male rats, prompt the possibility to use antagonists/inverse agonist CB receptors in co-administration with agonists to increase their antiepileptic effects[78, 79]. This prompt the possibility to use antagonists or inverse agonists CB1 receptors might relieve the hyperactivity in the DCN and then relieve tinnitus.

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