Cannabis, Cannabinoids and Tinnitus

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Abstract

It has been hypothesized that tinnitus is a form of sensory epilepsy, arising partly from neuronal hyperactivity in auditory regions of the brain such as the cochlear nucleus and inferior colliculus. Although there is currently no effective drug treatment for tinnitus, anti-epileptic drugs are used in some cases as a potential treatment option. There is increasing evidence to suggest that cannabinoid drugs, i.e. cannabinoid receptor agonists, can also have anti-epileptic effects, at least in some cases and in some parts of the brain. It has been reported that cannabinoid CB1 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. This review explores the question of whether cannabinoid receptor agonists are likely to be pro- or anti-epileptic in the cochlear nucleus and therefore whether cannabinoids and Cannabis itself are likely to make tinnitus better or worse.

Abbreviations: Delta-9-tetrahydrocannabinol (Delta-9-THC), 2-arachidonylglycerol (2-AG), diacylglycerol lipase (DAG), cochlear nucleus (CN), dorsal cochlear nucleus (DCN), ventral cochlear nucleus (VCN)

Introduction

Subjective tinnitus is the perception of a sound that does not physically exist, i.e. a ‘phantom’ sound. These phantom sounds can take the form of ringing, buzzing, or sometimes hissing, grinding or roaring. Many people experience tinnitus transiently; however, for some it becomes a chronic, debilitating condition. Subjective tinnitus is reported to affect approximately 25% of the population in the USA at some stage in their life, with 8% of people experiencing persistent or chronic tinnitus [1]. Approximately 50% of tinnitus sufferers also suffer from depression [2]. A recent health cost study in the Netherlands reported that the mean annual tinnitus-related health care costs were €10,561 per patient and that the estimated total societal cost of tinnitus in the population was €6.8 billion in 2009 [3]. This cost is expected to increase with the increasing use of portable listening devices such as MP3 players.

Tinnitus can be caused by exposure to loud noise, as well as head and neck injuries; it can also develop as a result of inner ear infection, drug toxicity (e.g., aminoglycoside antibiotics) or as a result of aging [2,4]. The specific neural changes underlying tinnitus are poorly understood. However, subjective tinnitus is regarded as a disorder of the brain, i.e. even though the stimulus for tinnitus may be damage to the peripheral auditory system, once the condition has developed, it is maintained by maladaptive plasticity in auditory brain regions [4]. One theory is that tinnitus is a form of sensory epilepsy that occurs as a result of neuronal hyperactivity in certain parts of the auditory central nervous system (CNS), such as the cochlear nucleus (CN) and inferior colliculus (IC) [4-7]. Treatment options for tinnitus are very limited [2]. For some patients, auditory habituation therapy, a masking device or counselling and relaxation may help. For others, drug treatment is the only option, although the drugs used are often ineffective in many patients and some result in substantial adverse side effects [2]. Based partly on the evidence that tinnitus is caused by neuronal hyperactivity in auditory regions of the brain, anti-epileptic drugs, such as carbamazepine, gabapentin and lamotrigine are sometimes used; however, their side effects can be substantial because they may not act specifically on the mechanisms of tinnitus [2, 8].

Cannabis and subjective tinnitus have had a long relationship. Cannabis has been suggested to cause tinnitus, but anecdotal evidence suggests that it is also sometimes used by tinnitus...
Cannabis

9-tetrahydrocannabinol (delta-9-THC), there are many other has tended to focus on the key psychoactive ingredient, delta-

Wallace et al. [25] demonstrated that the endogenous cannabin-

inverse agonist AM251 [23] blocked the anticonvulsant effect.

[24] reported that the CB1 receptor agonist ACPA increased

the seizure threshold, whereas the CB1 receptor antagonist/inverse agonist rimonabant [23] in the rat pilocarpine model of epilepsy. On the other hand, WIN55,212, completely blocked spontaneous seizure activity

For example, Nakatsuka et al. [27] reported that activation of CB1 receptors could suppress inhibitory synaptic activity in the human dentate gyrus. The CB1 receptor agonist WIN55212-2 suppressed the frequency of spontaneous Inhibitory Post-Synaptic Currents (IPSCs) as well as reducing their ampli-
tude, while the antagonist/inverse agonist AM251 completely blocked these effects. It is conceivable that the activation of CB1 receptors on presynaptic GABAergic terminals resulted in a decrease in GABA release, which resulted in a reduction in IPSC frequency and amplitude.

Endocannabinoids and cannabinoid receptors in the cochlear nucleus

There is only a small literature on cannabinoid receptors in auditory brain regions and how they might affect auditory function. CB1 receptors were first identified in the Cochlear Nucleus (CN) in early autoradiographic studies [28]; however, the density was quite low compared to other brain regions and this may have discouraged researchers from further investigat-

CG1 receptors in the CN were reported by Zheng et al. [30] and Tzounopoulos et al. [31]. Using immunohistochemistry, Zheng et al. [30] quantified CB1 receptor expression in both the Dorsal and Ventral Cochlear Nuclei (DCN and VCN, respec-

there have been some reports of anti-epileptic effects of the synthetic cannabinoid, dronabinol [17].

There are two classes of cannabinoid receptors, the CB1 and CB2 receptors. The general view is that CB1 receptors are ex-

pressed mainly in the central nervous system (CNS), while the CB2 receptors are localized primarily to the immune system, peripheral nervous system, testes and retina [18]. Although, over recent years, studies have emerged of CB2 receptor mRNA and protein expression in various brain regions, in some cases associated with pathology and in other cases even in the normal brain, controversy still surrounds the issue of whether the CB2 receptor is expressed under normal circumstances in the intact CNS or whether it is induced only in response to injury

Zhao et al. [35] demonstrated that both fusiform and cart-

wheel cells expressed diacylglycerol lipase (DAGL) α and β, the two enzymes necessary for the production of the endo-
cannabinoid, 2-arachidonyl glycerol (2-AG) [35]. Both forms of DAGL were found in the dendritic spines of cartwheel cells but not fusiform cells, suggesting that the production of 2-AG is closer to parallel fiber synapses in cartwheel cells compared to fusiform cells. This was the very first evidence for a complete

sufferers to relieve the condition. There are very few publica-
tions on this subject. Kempel et al. [9] reported that Cannabis reduced the ability of humans to discriminate target tones of specific frequency, location and duration. Hajas et al. [10] re-

ported that agonists at the cannabinoid CB1 receptor caused impairment in auditory sensory gating in rats. However, there has been no controlled study of the effects of Cannabis on tinnitus itself. Cannabis itself contains over 400 different chemicals, with 66 unique to the genus. Although attention has tended to focus on the key psychoactive ingredient, delta-

Cannabinoi receptor agonists have been reported to have pro-
or anti-convulsant effects under various circumstances

Epidemiological evidence indicates that Cannabis use is common amongst people with epilepsy because users be-

lieve that it has anticonvulsant actions [16]. However, Gordon and Devinsky[14] reviewed the literature and concluded that although Cannabis use can reduce seizure frequency in some cases and provoke it in others, it probably has no effect in most cases. Nonetheless, there have been some reports of anti-epileptic effects of the synthetic cannabinoid, dronabinol [17].

CB2 receptors are localized primarily to the immune system,

spectively) and found substantial labeling on many different cell types, such as stellate cells, giant cells, fusiform cells, and corn cells in the DCN, as well as globular bushy cells, elongate cells, and octopus cells in the VCN [Figure 1] [32]. Some labeling was cytoplasmic, which first appeared inconsistent with the reported presynaptic localization of CB1 receptors; however, it has since been reported that the CB1 receptor un-
dergoes extensive trafficking between the cytoplasm and the presynaptic terminals, in brain regions where it is very active

These results were extended by Tzounopoulos et al. [31], who reported CB1 receptors in the DCN at the parallel fiber/ cartwheel cell, parallel fiber/fusiform cell synapses, and on the dendritic spines of cartwheel cells, using electron microscopy (Figure 2). Baek et al. [34] also reported CB2 receptor labeling in the CN; however, the expression of this second subtype of cannabinoid receptor in the brain is controversial and substan-
tial doubts have been raised about the specificity of the CB2 receptor antibody used in that study [19].

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endocannabinoid system in the DCN, involving, at the minimum, 2-AG acting on CB1 receptors.

In the DCN, granule cells in the molecular layer give rise to parallel fibres that release glutamate onto fusiform cells, and cartwheel cells, and the latter are interneurons that release glycine onto each other, as well as fusiform cells (Figure 2). Tzounopoulos and colleagues demonstrated that CB1 receptors localized to parallel fibres inhibited the release of glutamate onto cartwheel and fusiform cells, but that they also inhibit the release of glycine onto cartwheel cells (from other cartwheel cells) and from cartwheel cells onto fusiform cells [31,35]. Zhao et al. [35] also showed that glutamatergic terminals in the DCN expressed more CB1 receptors on glutamatergic terminals than glycineric terminals, suggesting that the net effect of activation of CB1 receptors in the DCN would be to increase excitation of fusiform cells over their inhibition and that endocannabinoid signalling might be a major factor affecting the balance of excitation and inhibition in this part of the central auditory system. Increased activation of CB1 receptors in the DCN could lead to increased excitation of fusiform cells and possibly hyperactivity in the inferior colliculus [37].

Zhao et al. [35] have shown that CB1 receptors in the DCN regulate the development of Depolarization-Induced Suppression of Inhibition (DSI) and Excitation (DSE), as well as Long-Term Depression (LTD) [31], indicating that the endocannabinoid system is involved in the control of plasticity in this part of the central auditory system [38]. Their more recent studies indicate an interaction between endocannabinoid signaling and cholinergic inputs [39].

Cannabinoids, cannabinoid receptors and tinnitus

Only two studies to date have investigated the relationship between CB1 receptors in the CN and tinnitus. Zheng et al. [30] studied the expression of CB1 receptors in the DCN and VCN in rats in which tinnitus had been induced using salicylate injections, which is one of the main animal models of tinnitus. Tinnitus was confirmed in these animals using a modification of a conditioned behavioral paradigm developed by Jastreboff et al. [40]. In animals with tinnitus, there was a significant decrease in the number of neurons expressing CB1 receptors in the VCN compared to control animals. However, there was no significant difference in the DCN (Figure 3). It is conceivable that if increased activation of CB1 receptors through up-regu-
Figure 4:
Top: Effects of salicylate (SA, 350 mg/kg) on the lick suppression ratio (SR) in an animal model of tinnitus compared to the effects of SA + vehicle, WIN55,212-2 (3 mg/kg) + SA, WIN55,212-2 (3 mg/kg) + saline and vehicle + saline. SA significantly increased the SR compared to vehicle + saline and WIN55,212-2 + SA did not decrease it. However, WIN55,212-2 + saline significantly increased the SR without SA. * p < 0.05, vehicle + saline compared with SA 350 mg/kg; † p < 0.05, each group compared with vehicle + saline. From [42] with permission from Elsevier.

Bottom: Effects of salicylate on the SR compared to the effects of SA + vehicle, CP55,940 (0.1 mg/kg) + SA, CP55,940 (0.3 mg/kg) + SA, CP55,940 (0.1 mg/kg) + saline, CP55,940 (0.3 mg/kg) + saline and vehicle + saline. SA significantly increased the SR compared to vehicle + saline and CP55,940+ SA did not decrease it. However, CP55,940 (0.3 mg/kg) + saline significantly increased the SR without SA. Bars represent means ± SE. * p < 0.05, vehicle + saline compared with SA 350 mg/kg; † p < 0.05, each group compared with vehicle + saline. From [42] with permission from Elsevier.

Conclusions
The effects of Cannabis itself on tinnitus in humans and animals are still unclear. However, CB1 receptors do exist in the CN and they are functional. Although cannabinoids have been shown to exert anti-epileptic effects in many parts of the brain, the function of CB1 receptors in the circuitry of the DCN, at least, suggests that they might have the potential to facilitate increased excitation rather than inhibit it, which, if neuronal hyperactivity is part of the cause of tinnitus, might exacerbate
tinnitus rather than relieve it. Along those lines, the only animal study of the effects of cannabinoid receptor agonists in tinnitus suggests that tinnitus might be aggravated [42]. Although another study showed that CB1 receptors were down-regulated in the VCN in an animal model of tinnitus [30], it is not clear whether this might be part of the cause of tinnitus-related neuronal hyperactivity or a compensatory response to it. Therefore, at this stage, it is very unclear whether cannabinoid drugs that activate the CB1 receptor would make tinnitus worse or better. Determining this will require a much greater understanding of the functional significance of the endocannabinoid system in the CN and elsewhere in the central auditory system.

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References


