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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

sufferers to relieve the condition. There are very few publications 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. Hajos et al. [10] reported 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-9-tetrahydrocannabinol (delta-9-THC), there are many other cannabinoids in *Cannabis* such as cannabinol and cannabidiol (CBD).Therefore *Cannabis* cannot be considered one drug but a plant containing hundreds of drugs that may have different actions. In addition to synthetic cannabinoid receptor agonists such as dronabinol and nabilone, which are used for the treatment of nausea, vomiting [11] and wasting [12], natural *Cannabis* extracts such as a 1:1 ratio of delta-9-THC and CBD (Sativex™), are now being used for the treatment of spasticity and chronic pain in multiple sclerosis [13].

Cannabinoid receptor agonists have been reported to have pro- or anti-convulsant effects under various circumstances [14,15]. Epidemiological evidence indicates that *Cannabis* use is common amongst people with epilepsy because users believe 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].

There are two classes of cannabinoid receptors, the CB1 and CB2 receptors. The general view is that CB1 receptors are expressed 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 [18,19]. Nevertheless, CB1 receptors are localized presynaptically in many cases, and, as a result of the inhibition of calcium influx at presynaptic terminals, can inhibit the release of classical neurotransmitters, including glutamate [20,21]. For example, Wallace et al. [22] reported that delta-9-THC, as well as the synthetic cannabinoid receptor agonist R(+) WIN55,212, completely blocked spontaneous seizure activity in the rat pilocarpine model of epilepsy. On the other hand, the CB1 receptor antagonist/inverse agonist rimonabant [23] potentiated seizure duration and frequency, suggesting that endocannabinoids were suppressing seizure activity. Using the pentylenetetrazole model of epilepsy in mice, Shafaroodi et al. [24] reported that the CB1 receptor agonist ACPA increased the seizure threshold, whereas the CB1 receptor antagonist/inverse agonist AM251 [23] blocked the anticonvulsant effect. Wallace et al. [25] demonstrated that the endogenous cannabinoid, anandamide, and its analogue, O-1812, had potent anticonvulsant effects in the maximal electroshock seizure model in mice, which were blocked by rimonabant. However, where CB1 receptors are localized to GABAergic terminals, cannabinoids could potentially facilitate epileptiform activity [26]. 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 amplitude, 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 investigating CB1 receptors in the CN. However, Brievogel et al. [29] reported that CB1 receptors in many brainstem regions have greater coupling to their G proteins (i.e., greater efficacy) than those in limbic and neocortical areas.

The first systematic studies focusing on the spatial distribution of CB1 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, respectively) 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 undergoes extensive trafficking between the cytoplasm and the presynaptic terminals, in brain regions where it is very active [33]. 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 substantial doubts have been raised about the specificity of the CB2 receptor antibody used in that study [19].

Zhao et al. [35] demonstrated that both fusiform and cartwheel cells expressed diacylglycerol lipase (DAGL) α and β, the two enzymes necessary for the production of the endocannabinoid, 2-arachidonyl glycerol (2-AG) [35]. Both forms of DAGL were found in the dendritic spines of cartwheel 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

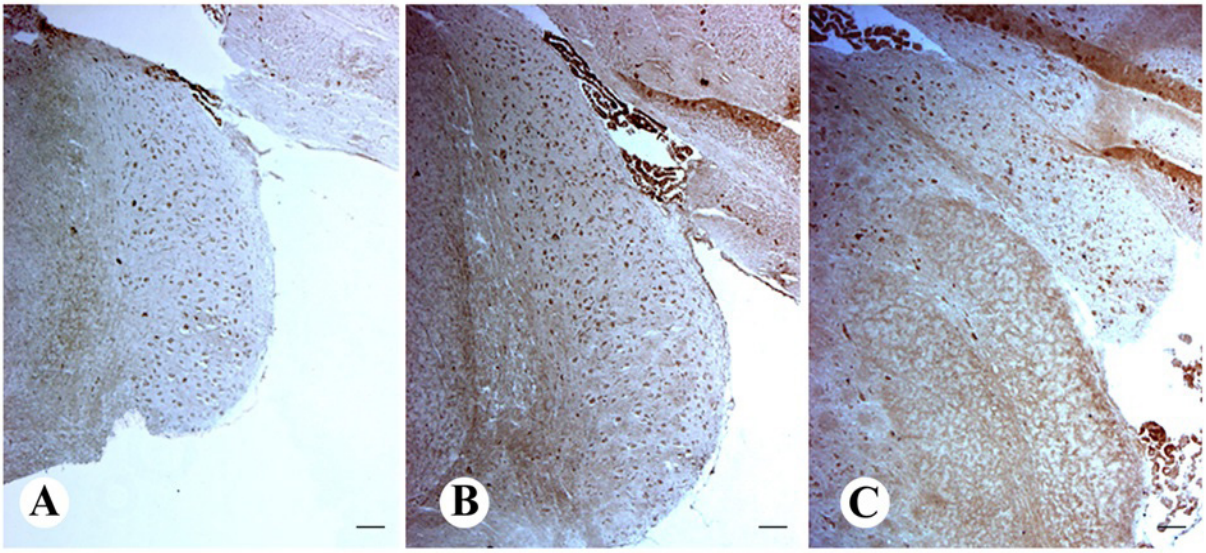

Figure 1: CB1 receptor immunoreactivity in the rat cochlear nuclei. From [30] with permission from Elsevier.

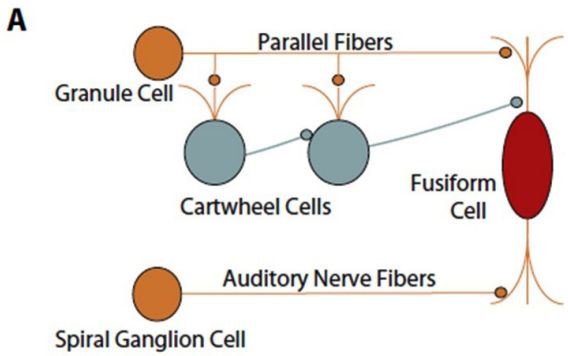

Figure 2: Circuitry of the DCN. From [43] with permission from Elsevier.

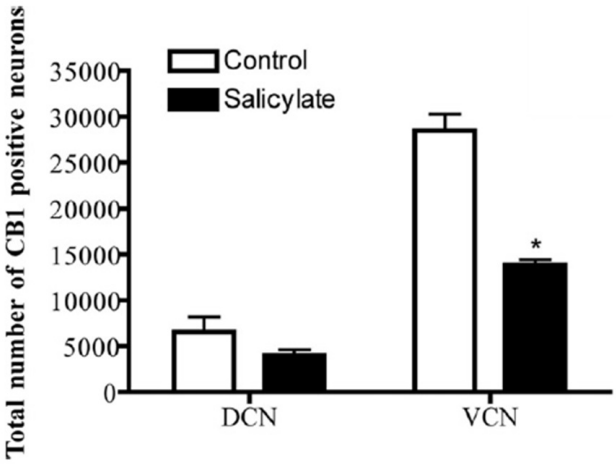

Figure 3: Down-regulation of CB1 receptor-positive neurons in the dorsal and ventral cochlear nuclei (DCN and VCN) in control (open bars) and salicylate-treated (filled bars) rats. Data are expressed as means and bars as 1 SEM. * $P < 0.01$ compared to the control group. From [30] with permission from Elsevier.

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 fusiforms 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 glycinergic 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-

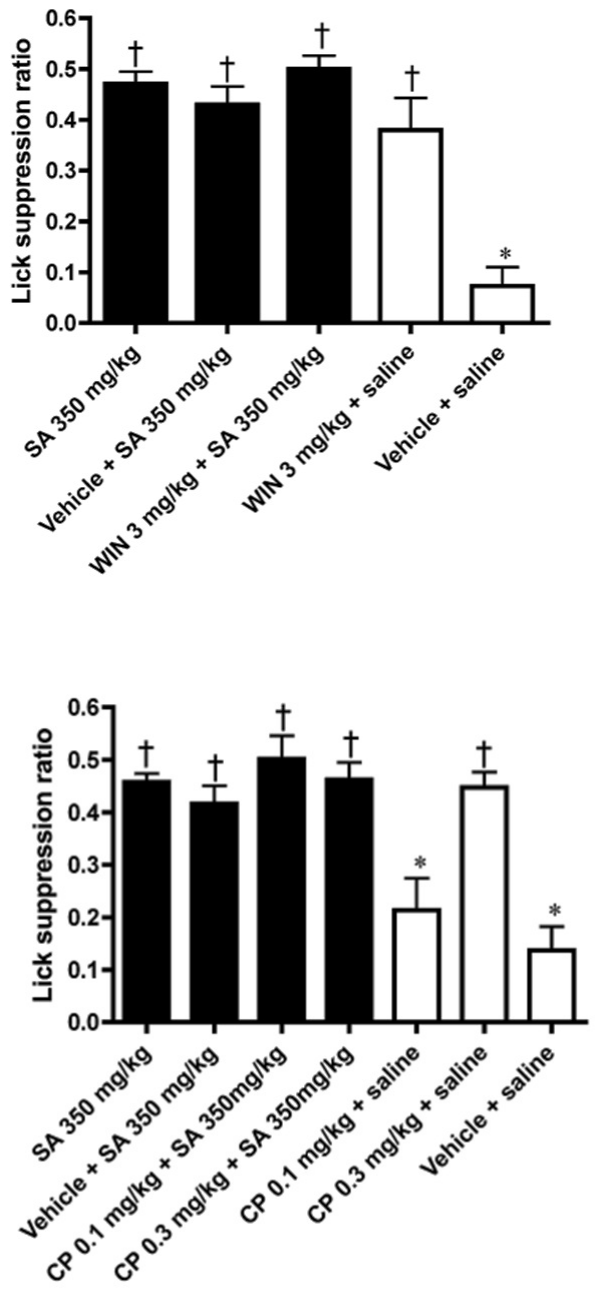

Figure 4:
Top: Effects of salicylate (SA, 350 mg/kg) on the lick suppression ratio (SR) in an animal model of tinnitus compared to the effects of SA + vehicle, WIN55,212-2 (3 mg/kg) + SA, WIN55,212-2 (3 mg/kg) + saline and vehicle + saline. SA significantly increased the SR compared to vehicle + saline 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. **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.

lation, increased affinity or efficacy, or increased activation by 2-AG, amplified the increased excitation of fusiform cells relative to their inhibition, this would lead to hyperexcitability of these neurons. Unfortunately, the nature of the study by Zheng et al. [30] made it impossible to specifically localize the CB1 receptors in the DCN.

Unfortunately, there have been no systematic studies to date of the effects of cannabinoids on tinnitus, in humans. One case report was published in which tinnitus was eliminated by administration of the cannabinoid, dronabinol [41]. However, the patient had intracranial hypertension with many other symptoms and had been previously using *Cannabis*. In the only animal study, Zheng et al. [42] investigated the effects of two CB1 receptor agonists, WIN55,212-2 and CP-55940 on tinnitus induced by salicylate injections in rats. Neither WIN55,212-2 (at 3 mg/kg s.c.) nor CP55,940 (at 0.1 or 0.3 mg/kg s.c.) significantly reduced the conditioned behaviour associated with tinnitus. However, 3 mg/kg WIN55,212-2 and 0.3 mg/kg CP55,940 did significantly increase this behaviour in normal control animals, suggesting that these cannabinoids might induce tinnitus-related behaviour (Figure 4). This result is consistent with the evidence that cannabinoid receptor agonists can have anti- or pro-convulsant effects in different areas of the brain, depending on the specific neural circuitry on which they act. It also suggests the possibility that an antagonist/inverse agonist at CB1 receptors (e.g., rimonabant or AM251) might relieve neuronal hyperactivity in the DCN and therefore relieve tinnitus. However, these drugs could have pro-convulsant effects elsewhere.

Future directions

One of the most pressing issues in this field of research is to determine the effects of specific cannabinoids on tinnitus. Given that *Cannabis* itself contains so many different cannabinoids, it is conceivable that the effects of delta-9-THC on tinnitus could be quite different from other cannabinoids such as CBD and cannabinol. The combined effect of many different cannabinoids in *Cannabis* could be far more complex than any individual agent; for example, there may be synergistic effects. In addition to the effects of clinically available natural *Cannabis* extracts such as Sativex™ (a 1:1 ratio of delta-9-THC and CBD), it will be important to compare the effects of full versus partial agonists, especially the available synthetic agonists [23], and this would best be done using the acoustic trauma model of tinnitus, which is a better animal model of tinnitus in humans. These studies need to be done with a dose-response analysis and an attempt to block their effects with antagonists, in order to confirm receptor specificity.

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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