# Epilepsy and Tinnitus: Characteristic of Disease

Epilepsy is a chronic neurological condition with a predisposition of producing recurrent epileptic seizures unprovoked by any immediately identifiable cause. Epileptic seizures occur due to abnormal, excessive and synchronous neuronal activity in the brain resulting in a wave of depolarization called paroxysmal depolarizing shift (PDS). Epileptogenesis is the gradual process of the brain developing epilepsy after an injury or insult leading to neurons becoming hyperexcitable and producing spontaneous seizures.

Generally, epilepsy can be classified as two main types: generalised seizures including tonic-clonic and typical absence, and focal (partial) seizures including simple and complex partial seizures which can lead to secondary generalised seizures. Focal epilepsy accounts for around 60% of epilepsies and has a complex symptomatic aetiology, for example, can cause cortical damage through a stroke or trauma. Generalised seizure epilepsy accounts for around 40% of epilepsies and has mainly idiopathic aetiology. However, genetics can also play a role as mutations can occur in ion channels such as voltage-gated sodium channels and GABAA receptors.

Tinnitus is an auditory phantom sensation or ringing of the ears experienced when no external sound is present. It is viewed as a symptom of an underlying condition rather than a single disease entity. Most cases are due to noise-induced hearing loss or by ageing. Generally, there are two types of tinnitus: subjective and objective tinnitus. Subjective tinnitus is the phantom perception of sound in the absence of auditory stimulus experienced only by the patient. Objective tinnitus is the noise generated by structures near the ear.

Epilepsy and tinnitus both result from neuronal excitability and therapeutic approaches used to treat epilepsy may also benefit the treatment of tinnitus.Epilepsy is a complicated disorder and the exact mechanism is unknown, however, little is known about the cellular and network mechanism involving neuronal excitability. Epileptic activity can be induced by doing experiments on animal models by blocking inhibitory conductance or activating excitatory conductance.

Excitatory drive (depolarisation) occurs through glutamatergic signalling through the excitatory neurotransmitter glutamate acting at NMDA, AMPA and kainate receptors (glutamate receptors), whilst inhibitory drive (hyperpolarisation) occurs via GABAergic signalling using GABAA receptor antagonists such as GABA. GABA is the main inhibitory neurotransmitter that compensates for neuronal excitation. At the synapse, it binds to two receptors, GABAA and GABAB. GABAA is responsible for fast inhibitory neurotransmission, allowing entry of chloride into the cell, and GABAB causes an increase in potassium conductance, decreases the entry of calcium and inhibits the release of neurotransmitters from the presynaptic terminal resulting in a longer inhibitory postsynaptic current.

Thus, decreasing this inhibition, by reducing levels of GABA and sensitivity to GABAA receptors, can lead to neuronal excitability causing seizures and epilepsy. However, seizures can be blocked by increasing inhibition or decreasing excitation. Thus, experimental work has created a theory that seizures occur due to the interrupted balance between inhibitory and

excitatory conductances at the synaptic level in normal brain tissues. Epilepsies occurring from genetic causes portrayed a causal loss of mutations in inhibitory conductances with loss of function mutations also observed in excitatory conductances.

Further studies revealed interictal spikes could be observed from epilepsy patients using an electroencephalogram. There were large depolarisations and bursts of action potentials within individual neurons. The cerebral cortex layer of the brain is a highly organised structure with lamina cell layers that allows the flow of normal neuronal processing. In epilepsy, this region can be susceptible to abnormal synchronous activity leading to the generation of seizures.

In a normal brain, excitatory synaptic activity is regulated by inhibitory interneurons but insults such as trauma and genetic mutations can upset this regulation causing cortical networks to become hyperexcitable. PDS can also lead to seizures. Depolarisation is dependent on AMPA/NMDA receptor activation by glutamate and voltage-dependent calcium channels causing voltage-gated sodium channels to open initiating action potentials and enhancing excitability. In seizures, there is elevated levels of extracellular glutamate causing excitotoxicity and cell death.

Tinnitus can have many causes but results most commonly from ageing and otologic disorders such as noise-induced hearing loss. In tinnitus, damage to inner hair cells (IHCs) and outer hair cells (OHCs) in the cochlea occurs from noise exposure and ototoxic agents which increases the gain of the central auditory system (CAS). Damage can cause hyperactivity in the CAS leading to increased neuronal spontaneous firing rates in auditory structures such as dorsal cochlear nucleus (DCN), ventral cochlear nucleus (VCN) and inferior colliculus (IC) (Baguley, 2002), (Han et al., 2009). The CAS attempts to increase its neural gain to compensate for reduced input or decrease of gain at the level of the cochlea.

The upregulation in spontaneous activity is thought to be caused by changes in the normal balance between excitatory and inhibitory nerve transmission that occurs due to loss of inhibition and so an increase of excitation leads to increased firing rates and excitability. A recent study in mice showing behavioural tinnitus found that downregulating GABAergic inhibition leads to the development of hyperactivity in the DCN (Middleton et al., 2011). Additionally, there was also increased activity in the VCN after cochlear damage.

Fusiform cells are principal cells of the DCN that project to the IC. Therefore, the same circuits that provide inhibition to projection neurons of DCN also project to the VCN. Noise trauma can cause hyperactivity in specific cell types in the VCN which contributes to hyperactivity expressed at higher levels of the auditory pathway including the IC. This hyperactivity is due to increased spontaneous activity that may be related to reduced IC inhibitory neurotransmission in tinnitus. Furthermore, there is increased bursting firing of action potentials and increased neuronal synchrony observed in tinnitus.

This is linked to downregulation of Kv3 potassium currents that are involved in membrane repolarisation. In neuronal cells, membrane repolarisation is impaired leading to longer depolarisation periods producing bursting activity. Noise exposure causes irregular bursting activity in the auditory nerve, DCN and IC. Moreover, map reorganisation or tonotopy changes occur in tinnitus linked with changing the response properties of auditory neurons. In summary, intense noise exposure causes cochlear damage and so fewer hair cells are expressed leading to deafferentation (between hair cells and auditory nerves).

This leads to neuronal changes such as an alteration in the balance of excitation and inhibition in auditory cortical networks, increased spontaneous activity of neurons in CAS, increased burst firing, changes in the gain of auditory cortical neurons and increased neural synchronous activity. All are linked to decreased inhibition and increased excitation, hence causing neuronal excitability (figure 2) (Henry et al., 2014). The main way of treating epilepsy is with the use of anticonvulsants or conventional antiepileptic drugs (AEDs). Such drugs primarily aim to control the seizures over a longer-term such that the quality of life improves. The main targets in treating epilepsy are enhancement of GABA action, inhibition of sodium channel function and inhibition of calcium channel function. Examples of conventional AED include phenytoin, carbamazepine, and sodium valproate.

Phenytoin can be used in focal and generalised seizures and is a sodium channel blocker. Carbamazepine is effective in treating complex partial seizures by blocking voltage-gated sodium and calcium channels as well as impairing glutamate-induced excitation. Sodium valproate, a monocarboxylic acid, is useful in most epilepsies by increasing GABA content of the brain. It inhibits two enzymes that metabolise GABA, GABA transaminase (GABA-T) and succinic semi-aldehyde dehydrogenase.

Thus, this prevents GABA from being broken down and increases its concentration (Czuczwar and Patsalos, 2001). In epileptogenesis, GABA inhibition is lost. Newer AEDs such as tiagabine can be used to treat seizures as it blocks GABA reuptake transporter 1 (GAT-1) and so increases GABA at the synaptic cleft and receptors. Tiagabine can cross the blood-brain barrier inhibiting the reuptake of GABA into neurons and glia (Salvi, Lobarinas and Sun, 2009). Vigabatrin is an effective new AED that works against generalised and focal seizures to irreversibly inhibit enzyme GABA-T which increases GABA levels in the presynaptic nerve terminal.

There is more GABA around so more inhibition occurs (figure 3) (Beyenburg, 2004). Tinnitus and epilepsy both result from changes in neuronal excitability. Voltage-gated Kv7 potassium (KCNQ) channels are activated at resting membrane potentials to reduce neuronal excitability. Under normal circumstances, KCNQ channels help to shut down sodium-induced electrical potentials when electrical potentials are too long. The channel causes potassium ion efflux, shifting the voltage more negative. Therefore, a reduction of KCNQ channel 2/3 can lead to neuronal excitability disorders like tinnitus and epilepsy.

Retigabine is a small molecule AED which can activate KCNQ channels 2-5 as it shifts voltage dependence opening to more negative values. It aids in opening more KCNQ potassium channels shutting down signalling in overexcited neurons. In some epilepsy types, the KCNQ channel may not open and so cannot prevent hyperexcitability, hence drugs like retigabine can enable these channels to open. However, the side effects of this drug hinder its clinical use. Kalappa et al. (2015) developed a new specific KCNQ 2/3 small molecule activator called SF0034. This was produced by integrating a fluorine substituent into position 3 of the tri-aminophenyl ring of retigabine.

The new SF0034 molecule was five times more potent at shifting the voltage dependence of KCNQ 2/3 channels to more negative voltages when compared to retigabine. In addition, this drug was selective for KCNQ 2/3 channels only and did not shift KCNQ4 or 5 channel voltage dependence hence producing fewer side effects. Furthermore, SF0034 is less toxic, more effective at lower doses and shows stronger anticonvulsant activity in comparison to retigabine.

Administrating retigabine to mice who have tinnitus prevents its development. SF0034 also prevents tinnitus development and does not affect temporal processing or hearing thresholds. Reducing the KCNQ2/3 channel activity in the DCN is linked to hyperexcitability of the DCN and this induces tinnitus hence SF0034 was able to prevent tinnitus. Both drugs were able to increase the KCNQ channel activity. However, SF0034 has improved efficacy, is safer and is more effective in treating patients with mild or severe tinnitus. Thus, it can be used to treat epilepsy and tinnitus.

The two AEDs vigabatrin and tiagabine can also be used in treating tinnitus. Vigabatrin inhibits GABA breakdown, which increases GABA levels as well as causing GABA transporter to work in reverse mode to release GABA. Brozoski, Spires and Bauer (2007) found that in rats vigabatrin decreases tinnitus by restoring central inhibitory function and causing increased GABA availability. Chronic tinnitus causes loss of inhibition of the central auditory pathway and decreased function of GABA as a way of decreasing inhibition. Using vigabatrin, it can increase GABA levels increasing inhibition thus counteracting chronic tinnitus.

Tiagabine also increases GABA levels by blocking GAT-1. Tinnitus occurs due to loss of inhibition in the CNS by cochlear deafferentation as a result of damage caused by excess noise. Therefore, tiagabine can increase inhibition in the CNS by increasing GABA concentrations. Both vigabatrin and tiagabine are effective in treating epilepsy and tinnitus. Furthermore, AED carbamazepine can also be used in tinnitus. The drug can bind to voltage-gated sodium channels and stabilises these channels into their inactive conformation state. It reduces excitation by blocking another repolarisation from occurring thus preventing the repetitive and sustained firing of the action potential, reducing neural firing and bursting.

Epilepsy and tinnitus are common disorders with complex mechanisms resulting from changes in neuronal excitability. Treating epilepsy is the primary objective but being able to treat or prevent tinnitus is a secondary objective. Some therapeutic approaches used to treat epilepsy can also be applied to tinnitus as they aim to increase the inhibition and reduce the excitation thus restoring the neuronal balance and preventing hyperexcitability. Drugs such as SF0034 are crucial in helping to understand the mechanistic similarities between both conditions and develop drugs that can treat epilepsy and tinnitus.