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Tinnitus: a CNS disorder

Opportunities and needs of a big market

The Tinnitus Research Initiative (TRI) is a private organization dedicated to the development of effective treatments for all types of tinnitus. Founded in 2006, this organization is sponsored by one private person, who is suffering from tinnitus. Under the motto "*together for a cure"* TRI funds more than 40 research projects, it has organized two international tinnitus meetings and has established a multinational and multidisciplinary network of clinicians and scientists, leading to a book dealing with tinnitus published by Progress in Brain Research *(Tinnitus: Pathophysiology and Treatment; ed. by Langguth et al. Progress in Brain Research 2007;166).*

Jose Miguel Lainez, chair of the neurologic department in Valencia/Spain pointed out that with a prevalence of 5-10 % tinnitus is a frequent disorder and thus represents a huge market *(Vio and Holme; Hearing loss and tinnitus: 250 million people and a US$10 billion potential market. Drug Discov Today. 2005;10(19):1263-5)*. Whereas tinnitus research traditionally focussed on the ear, where tinnitus is perceived, neuroimaging and electrophysiology findings within the last decade have clearly demonstrated that chronic tinnitus is the consequence of alteration of neural activity in the central nervous system. In more detail, it is assumed, that hearing loss, which is frequently occurring in tinnitus patients, results in a dysbalance between inhibitory and facilitatory mechanisms in the central auditory system, which in turn gives rise to increased neural activity throughout the central auditory pathways. The activity in the auditory pathways is additionally modulated by other brain areas, such as the limbic system. So it is assumed that tinnitus is perceived, when increased activity in the auditory pathways is not sufficiently reduced due to impaired function of the limbic system.

The fact that tinnitus is related to changes in neuronal activity in the brain, suggests that drugs which act on the central nervous system, might potentially also influence tinnitus. In principle this counts for all drugs, which are used for diseases such as pain, headache, epilepsy, depression, anxiety, Parkinson, restless-legs-syndrome, dementia, sleep disorders, schizophrenia or attention deficit and hyperactivity disorder (ADHD) As pointed out by *Berthold Langguth*, neurologist and psychiatrist in Regensburg/Germany, several central-acting drugs have been shown to influence tinnitus, among them lidocaine, benzodiazepines, antidepressants and anticonvulsants. However no drug is approved for tinnitus and no drug has shown efficacy as evidenced by replicated positive findings in at least two well conducted

trials. At the same time initiative and investment of the pharmaceutical industry is still very limited.

There might be several reasons for this unsatisfactory situation, among them the incomplete knowledge of the pathophysiology of tinnitus, the lack of high throughput assays and the lack of well established animal models. However detailed knowledge of the pathophysiology of tinnitus is growing rapidly and several animal models for drug screening have been developed in the last years.

Other difficulties might involve outcome measurement, since tinnitus is a pure subjective condition and patient assessment, since there are different forms of tinnitus, which differ in their pathophysiology and in their response to specific treatments In an attempt to overcome these limitations, TRI aimed at establishing consensus among tinnitus researchers concerning patient assessment and outcome measurement *(Consensus in patient assessment and outcome measurement, Progress in Brain Research 2007;166:525-36).* and is establishing an international patient database for patient subtyping. Summarizing, Berthold Langguth stated that TRI actively addresses current limitation in drug development for tinnitus and that all compounds, which are approved or under development for CNS disorders might represent potential candidates for tinnitus treatment.

Similarities in phenomenology and pathophysiology between tinnitus and pain have been presented by *Dirk de Ridder*, neurosurgeon in Antwerp/Belgium. Both tinnitus and phantom pain arise as a consequence of increased neuronal firing and increased synchroneous neural activity together with reorganization of the tonotopic respective somatotopic maps Successful treatment of both conditions by transcranial magnetic stimulation and electrical epidural stimulation of the sensory cortices clearly demonstrates that tinnitus research can benefit from advancements in related fields and vice versa. Pathophysiological theories of pain, epilepsy, depression or other CNS disorders, might at least partly be valid also for tinnitus and therefore helpful to identify promising treatment options. Thus, for a new compound, which is under development for any of these conditions, the additional testing for tinnitus can be an attractive spin-off with high proceeds at low investment.

In summary there already exists a huge market for a tinnitus drug, which will further grow and which is currently still untapped. Similarities between tinnitus and other CNS disorders suggest synergistic effects. Recent advances in tinnitus research indicate, that the problems which might have hampered the field in the past, are solvable in the near future.