Expert Opinion on Therapeutic Targets

ISSN: 1472-8222 (Print) 1744-7631 (Online) Journal homepage: http://www.tandfonline.com/loi/iett20

Potassium channels as promising new targets for pharmacologic treatment of tinnitus: Can Internet-based 'crowd sensing' initiated by patients speed up the transition from bench to bedside?

Berthold Langguth, Ana Belén Elgoyhen & Winfried Schlee

To cite this article: Berthold Langguth, Ana Belén Elgoyhen & Winfried Schlee (2016) Potassium channels as promising new targets for pharmacologic treatment of tinnitus: Can Internet-based 'crowd sensing' initiated by patients speed up the transition from bench to bedside?, Expert Opinion on Therapeutic Targets, 20:3, 251-254, DOI: 10.1517/14728222.2016.1125884

To link to this article: http://dx.doi.org/10.1517/14728222.2016.1125884

Accepted author version posted online: 26 Nov 2015.
Published online: 22 Jan 2016.

EXPERT OPINION ON THERAPEUTIC TARGETS, 2016
VOL. 20, NO. 3, 251–254
http://dx.doi.org/10.1517/14728222.2016.1125884

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Potassium channels as promising new targets for pharmacologic treatment of tinnitus: Can Internet-based 'crowd sensing' initiated by patients speed up the transition from bench to bedside?

1. Introduction

Tinnitus, the perception of sound in the absence of a corresponding sound source is a frequent disorder. Many pharmacological compounds have been investigated, but for none of these is there convincing evidence for a beneficial effect on tinnitus intensity or loudness.[1]

Despite the large impairment on quality of life and the high socioeconomic burden, only little public funding is allocated to tinnitus research. Also, the pharmaceutical industry has largely neglected the tinnitus field.[2] As the understanding of tinnitus pathophysiology is still incomplete and as there have not been serendipitous discoveries of pharmaceutical compounds that reliably reduce tinnitus intensity, no reliable targets for pharmaceutical treatment have yet been identified.

1.1. Kv7 (KCNQ) potassium channels

Kv7 (KCNQ) channels are voltage-dependent potassium channels that regulate excitability in neuronal, sensory and muscular cells. K^+ channels have a crucial role as regulators of intrinsic electrical properties in excitable cells. Moreover, they control cell volume, proliferation, differentiation and survival.[3] This heterogeneity of functions is accomplished through the expression of a specific pattern of K^+ currents, each with distinct subcellular localization, biophysical properties, modulation and pharmacological profile. Among voltage-gated K^+ channels, the Kv7 (KCNQ) family comprises five different forms (Kv7.1 – Kv7.5). Kv7 proteins are associated with subunits (KCNE) which enhance channel diversity.[4] While Kv7.1 is mainly expressed in the heart, Kv7.2, Kv7.3, Kv7.4 and Kv7.5 channels contribute to the M-current in the nervous system. Reduction of Kv7.2/3 activity has been shown to be linked with hyperexcitability disorders such as epilepsy.[3]

2. Kv7 (KCNQ) potassium channels and tinnitus

In mice it has been shown that tinnitus generation after noise exposure is related to increased spontaneous firing of fusiform cells within the dorsal cochlear nucleus.[5] This hyperactivity is caused, at least in part, by decreased Kv7.2/3 (KCNQ2/3) potassium currents.[6] However, only those mice with an ongoing Kv7.2/3 activity reduction develop tinnitus, whereas mice that are able to reestablish Kv7.2/3 channel activity are resistant to tinnitus.[6]

2.1. Pharmacological modulation of Kv7 potassium channels and tinnitus

Kv7.2/3 channel activity can be pharmacologically modulated. Application of the potassium channel opener retigabine prevents behavioral signs of tinnitus in mice.[5] Retigabine has been approved in 2011 by the FDA as an adjunctive treatment for partial epilepsies. By shifting the voltage-dependent opening of Kv7 channels to more negative voltages [7] retigabine increases channel activity, which leads to reduced excitability and seizure activity.[8] As the clinical use of retigabine is limited by its side effects, efforts have been made to develop improved Kv7.2/3 activators. By incorporating a fluorine substituent the compound SF0034 has been synthesized, which acts more specifically and more potently on Kv7.2/3 channels.[9] Similar to retigabine, SF0034 prevents the development of tinnitus in mice after noise trauma.[9] As SF0034 is less toxic than retigabine, it might represent a candidate for tinnitus treatment with a more favorable side effect profile.[9]

The potential involvement of potassium channels in tinnitus pathophysiology has been the subject of several further studies. The potassium ion channel modulators Maxipost and its R-enantiomer (R-Maxipost), which have opposite effects on Kv7.2 – Kv7.5 channels, but act concordantly on Kv7.1 and BK channels, were investigated in rats with behavioral evidence of salicylate-induced tinnitus.[10] As both compounds abolished behavioral evidence of tinnitus in a dose-dependent manner, it has been assumed that the effects of Maxipost and R-Maxipost for reduction of salicylate-induced tinnitus

are mediated via inhibition of Kv7.1 channels or activation of BK channels.[10]

A comparison of Maxipost and retigabine in rats with salicylate-induced hearing loss revealed that Maxipost prevented hearing loss at high frequencies, whereas retigabine prevented hearing loss at low frequencies.[11] These effects seem to be mediated by potassium channels in the cochlea, since Maxipost and retigabine have a differential effect on Kv7 and BK potassium channels and since the expression of these channels varies on the cochlear hair cells along the tonotopic gradient.[11]

In another recent study ICA-105665, a novel small molecule that opens Kv7.2/3 and Kv7.3/5 channels, has been investigated in rats.[12] Hearing reduction after salicylate application could be prevented by ICA-105665 and it was hypothesized that it may also be effective in the prevention of salicylate-induced tinnitus.[12]

2.2. Genetic variability of Kv7 potassium channels and tinnitus in humans

In patients with chronic tinnitus, the potential influence of genetic variations of potassium channels in tinnitus has been explored,[13,14] based on findings that mutations in Kv7 genes are related to hearing disorders and neuronal hyperexcitability.[4] Two pilot investigations with relatively limited statistical power could neither confirm nor rule out effects of KCNE1 [14] and KCNE3 [13] on the risk for developing chronic tinnitus and on its severity.

2.3. Pharmacological modulation of Kv7 potassium channels in tinnitus patients

Very few studies have investigated the effect of drugs that act on Kv7 channels on tinnitus patients. The analgesic flupirtine exerts an effect on neuronal Kv7 channels which is similar to that of retigabine.[8] In one open trial, in which the effect of flupirtine was investigated on tinnitus severity and loudness, only one out of 24 investigated patients reported a positive effect after 3 weeks of flupirtine intake at a dosage of 200 mg/day.[15] No results from retigabine treatment in tinnitus have been published in the scientific literature and no ongoing trial with retigabine is registered for this application at ClinicalTrials.gov. Currently, the experimental Kv3 modulator AUT00063 is under investigation for tinnitus. Thus, in summary there is very limited clinical data and yet no evidence in humans for an effect of Kv7 channel modulation on tinnitus.

3. Retigabine: transition of animal results into clinical practice

Up to now the usefulness of Kv7 modulation for tinnitus prevention and treatment has only been demonstrated in animal studies. As retigabine is available on the market, one would have expected that the reported effects of this Kv7.2/3 channel opener in animal models of tinnitus [5] would have prompted the initiation of clinical trials in tinnitus patients. However, 2 years down the road from the first available animal study, no clinical trial for retigabine has been registered, indicating that both industry and public funding agencies are hesitant. This may have several reasons. First, clinical trials with sufficient power require large samples and are costly. Because of the heterogeneity of tinnitus, the performance of smaller trials with homogeneous subgroups has been proposed, but it is unclear according to which criteria patients should be stratified and to which extent a homogeneous subgroup would be representative for the total patient population.

Second, the predictive value of positive results in animal studies for efficacy in humans is still unclear. Finally, the unfavorable side effect profile of retigabine would limit its widespread use for tinnitus treatment, even if it turned out to be effective. Nevertheless, pilot data concerning the efficacy of retigabine for tinnitus treatment would be highly desirable since it would provide a first hint regarding the effectiveness of Kv7 potassium channel modulation for tinnitus treatment. Given the present scenario, it would seem reasonable to perform a small clinical trial with retigabine. Such a pilot trial could provide information about the effect size of retigabine in patients with tinnitus and about possible clinical predictors for treatment response (e.g. tinnitus etiology, tinnitus duration, perceptual characteristics, etc.). Such information would enable a realistic sample size calculation and could be used to enhance success chances of a clinical trial by focusing on specific subgroups of tinnitus. A similar approach is currently being promoted by the National Institute of Mental Health with the Fast-Fail-Trial initiative for the identification of new compounds and new targets for psychiatric disorders.

4. Expert opinion

In the case of retigabine, the promising findings from animal studies and its availability as an approved drug for adjunctive treatment of epilepsy have motivated patients to push further investigations of this potassium channel modulator for tinnitus treatment. Communicating via an Internet-based tinnitus forum (Tinnitustalk), these tinnitus patients have encouraged themselves to try retigabine for compassionate use and thereafter share their experience. Thus, within the forum they have provided information concerning their demographic (age, gender) and tinnitus characteristics (etiology, laterality, duration, perceptual characteristics), retigabine dosage used, side effects and the effect of the drug on tinnitus intensity. Eighteen people with tinnitus took at least one dosage of retigabine and shared their experience with the compound (data from 13 January 2015).

The so far collected data have many limitations, which make it very difficult to draw any firm conclusions. First, with the lack of specific inclusion or exclusion criteria the group of participants is expected to be highly heterogeneous. Second, neither the treatment nor the time points of assessment were standardized and there were large variations in the starting dose, dose change, duration of treatment, maximum dose and frequency of reporting. Third, there is only limited information about the reasons for decision-making concerning dose change, treatment termination or reporting on a given day. Fourth, since all information relies on participant reports, there is no possibility to validate whether the reported information is correct or it encountered a reporting bias. Fifth, as there was no control group, it cannot be concluded whether the observed effects were specific or unspecific. Unspecific effects may be particularly large as there was an ongoing interaction and feedback of the patients via the forum. Sixth, patients who are active in Internet forums may not be representative of the entire patient population. With so many potential sources of bias, these data have a significant risk to reveal more noise than information.

Nevertheless, the medical field should become aware of this form of 'patient empowerment' driven by the possibilities of modern communication technologies, as it bears chances and risks – as all new technologies. On one side this patient-initiated effort bears significant risks, as patients may motivate each other to try drugs with still unknown efficacy and potentially dangerous side effects. As most drugs require prescriptions, such patient activities challenge medical doctors who have to be able to make informed decisions if patients ask for compassionate use treatment with specific drugs. Moreover, it has to be made sure that compassionate use treatment with a given drug is uniquely motivated by the patient's clinical situation.

On the other hand, the collection of experiences from compassionate use treatment may speed up the translation from animal research into clinical trials. The collection of data based on the power of the crowd ('crowd-sensing') may have the potential for fast and inexpensive acquisition of knowledge that can motivate the initiation of prospective randomized placebo-controlled clinical trials and inform their design. However – because of all the mentioned limitations – 'crowd-sensing' will never become an alternative to large controlled trials in order to make firm conclusions about safety, tolerability and efficacy of a given drug for a specific indication.

Declaration of interest

B Langguth is supported by the Deutsche Forschungsgemeinschaft, the American Tinnitus Association and the Tinnitus Research Initiative. He received consultancy and speaker honoraria from Autifony, ANM, Astra Zeneca, Merz, Novartis, Pfizer, Lundbeck and Servier.

AB Elgoyhen and W Schlee are supported by the Tinnitus Research Initiative. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Langguth B, Elgoyhen AB. Current pharmacological treatments for tinnitus. Expert Opin Pharmacother. 2012;13(17):2495–2509.
2. Cederroth CR, Canlon B, Langguth B. Hearing loss and tinnitus: are funders and industry listening? Nat Biotechnol. 2013;31(11):972–974.
   - **In this editorial the funding of tinnitus research is compared with other disorders with comparable socioeconomic relevance.**
3. Soldovieri MV, Miceli F, Taglialatela M. Driving with no brakes: molecular pathophysiology of Kv7 potassium channels. Physiology (Bethesda). 2011;26(5):365–376.
4. Jentsch TJ. Neuronal KCNQ potassium channels: physiology and role in disease. Nat Rev Neurosci. 2000;1(1):21–30.
5. Li S, Choi V, Tzounopoulos T. Pathogenic plasticity of Kv7.2/3 channel activity is essential for the induction of tinnitus. Proc Natl Acad Sci U S A. 2013;110(24):9980–9985.

6. Li S, Kalappa BI, Tzounopoulos T. Noise-induced plasticity of KCNQ2/3 and HCN channels underlies vulnerability and resilience to tinnitus. elife. 2015;4:e07242.
•• **The first study that demonstrates the relevance of Kv7.2/3 channels for tinnitus pathophysiology.**
7. Tatulian L, Delmas P, Abogadie FC, et al. Activation of expressed KCNQ potassium currents and native neuronal M-type potassium currents by the anti-convulsant drug retigabine. J Neurosci. 2001;21(15):5535–5545.
8 Wu C, Gopal KV, Lukas TJ, et al. Pharmacodynamics of potassium channel openers in cultured neuronal networks. Eur J Pharmacol. 2014;732:68–75.
9. Kalappa BI, Soh H, Duignan KM, et al. Potent KCNQ2/3-specific channel activator suppresses in vivo epileptic activity and prevents the development of tinnitus. J Neurosci. 2015;35(23):8829–8842.
• **In this study it has been shown that a novel pharmacological compound can prevent tinnitus after noise trauma by effectively activating KCNQ2/3 channels.**
10. Lobarinas E, Dalby-Brown W, Stolzberg D, et al. Effects of the potassium ion channel modulators BMS-204352 Maxipost and its R-enantiomer on salicylate-induced tinnitus in rats. Physiol Behav. 2011;104(5):873–879.
11. Sheppard AM, Chen GD, Salvi R. Potassium ion channel openers, Maxipost and Retigabine, protect against peripheral salicylate ototoxicity in rats. Hear Res. 2015;327:1–8.
12. Sun W, Liu J, Zhang C, et al. Potassium channel activator attenuates salicylate-induced cochlear hearing loss potentially ameliorating tinnitus. Front Neurol. 2015;6:77.
13. Sand PG, Langguth B, Kleinjung T. Deep resequencing of the voltage-gated potassium channel subunit KCNE3 gene in chronic tinnitus. Behav Brain Funct. 2011;7:39.
14. Sand PG, Luettich A, Kleinjung T, et al. An examination of KCNE1 mutations and common variants in chronic tinnitus. Genes (Basel). 2010;1(1):23–37.
15. Salembier L, De Ridder D, Van De Heyning PH. The use of flupirtine in treatment of tinnitus. Acta OtolaryngolSuppl. 2006;556:93–95.

Berthold Langguth
Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany
Interdisciplinary Tinnitus Clinic, University of Regensburg, Regensburg, Germany
Berthold.Langguth@medbo.de

Ana Belén Elgoyhen
Instituto de Investigaciones en Ingeniería Genética y Biología Molecular Dr Héctor N Torres, Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina
Department of Pharmacology, University of Buenos Aires, School of Medicine, Buenos Aires, Argentina

Winfried Schlee
Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany
Interdisciplinary Tinnitus Clinic, University of Regensburg, Regensburg, Germany

Received 30 September 2015; accepted 25 November 2015
Published online 20 January 2016