Small Molecule-GIRK Potassium Channel Modulators Are Anxiolytic Therapeutics

VANDERBILT UNIVERSITY
CTTC Center for Technology Transfer & Commercialization

Summary

The G-protein activated, inward-rectifying potassium (K+) channels, "GIRKs", are a family of ion channels that has been the focus of intense research interest for nearly two decades. GIRK has been shown to play important roles in the pathophysiology of diseases such as anxiety, epilepsy, Down's syndrome, pain perception and drug addiction. Here scientists at Vanderbilt developed the first truly potent, effective, and selective GIRK activator, ML297 (VU0456810) and demonstrated that ML297 is active in animal models of epilepsy. While the group is using ML297 to continue to explore the therapeutic benefits of GIRK modulation, they are continuing to develop more selective and druggable GIRK inhibitors from different scaffolds.

Addressed Need

- GIRK channels comprised of four subunits, GIRK1−4 (aka Kir3.1−3.4), which can form homo and hetero-tetramers with unique biophysical properties, regulation, and distribution. GIRK1/2 subunit combination is the most common and widely expressed GIRK.
- GIRK channels hyperpolarize neurons in response to activation of many different G protein-coupled receptors and thus control the excitability of neurons.
- Pharmacological investigations of GIRK channels and studies in animal models suggest that GIRK activity has an important role in physiological responses, including pain perception, memory modulation, addiction, anxiety, spatial learning/memory and predisposition toward seizure activity.
- Although GIRKs have long been the focus of basic research efforts, there are very few pharmacological tools that have been reported. This lack of tools has limited the understanding of GIRKs' potential as targets for therapeutic intervention.

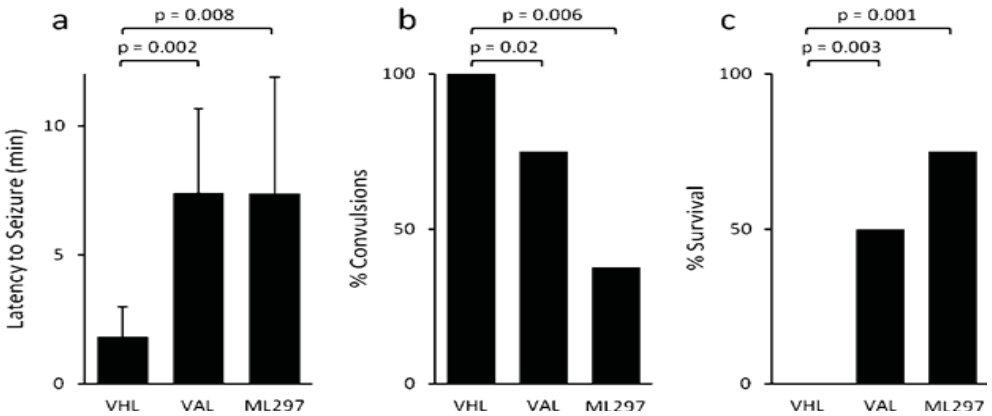

Figure 1. ML297 is active in two models of epilepsy. Shown are ata obtained from mice after intraperitoneal dosing with ML297 (60 mg/kg) or sodium valproate (150 mg/kg). In (a) are the measured latencies before seizure onset in mice exposed to a lethal electrical shock. Both the antiepileptic positive control, sodium valproate (VAL), and ML297 showed highly significant delays in seizure onset. In (b) and (c) are the data obtained from mice injected with the GABAA inhibitor, PTZ. Shown in (b) are the percentage of animals tested that experienced convulsions from PTZ treatment and in (c) the percentage of animals that survived PTZ treatment. In both cases VAL and ML297 showed significant decreases in the number of animals experiencing convulsions and surviving PTZ treatment compared to vehicle (VHL)-treated controls.

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VU REFERENCE: VU13070

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Proof of Concept Tool Compound ML297 Description & Novel features

- ML297 (VU0456810) is a small molecule compound identified from a high-throughput screening (HTS)-compatible thallium flux assay for Gi/o-coupled GPCRs using GIRK as a readout. It is the first potent, subtype-selective small molecule activator of a GIRK channel.
- ML297 shows a preference for the GIRK1/GIRK2 subunit combination compared to GIRK1/GIRK4 and is inactive on GIRK2/GIRK3 and a number of other potassium channels. This represents a major advance in this field, as the only other known small molecule activators of GIRK channels are simple alcohols and the natural product, naringin, all of which are very low potency and non-selective with respect to GIRK subtype.
- ML297 possesses favorable physiochemical and dystrophia myotonica protein kinase (DMPK) properties (ML297 is centrally penetrant, affording good CNS exposure in rats), making it a useful tool to selectively probe GIRK1-containing GIRK function in vitro and in vivo.
- In two different animal models of epilepsy, regardless of whether epilepsy was initiated chemically with PTZ or via electroshock, ML297 showed equal or greater efficacy compared to a clinically active anti-seizure medication, sodium valproate (Figure 1).
- Additional Anxiolytic animal models have shown efficacy with the tool compound ML297 as well.from PTZ treatment and in (c) the percentage of animals that survived PTZ treatment. In both cases VAL and ML297 showed significant decreases in the number of animals experiencing convulsions and surviving PTZ treatment compared to vehicle (VHL)-treated controls.

Intellectual Property Status:

- A provisional patent application has been filed.
- Published in journal: ACS Chem. Neurosci., 2013, 4 (9), pp 1278–1286.

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