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COMMENTARY

Improving K_v7 targeting anticonvulsants - will repurposing save the day?

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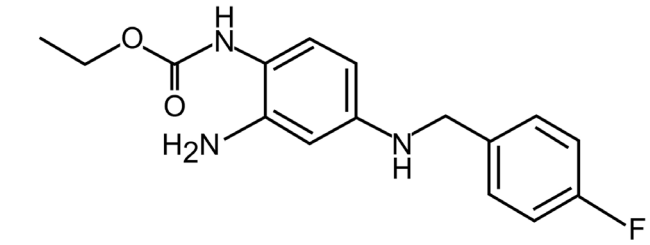
Among the molecular targets for treating disorders of neuronal excitability, such as epilepsy, chronic pain and conditions involving excitotoxicity (e.g. stroke or traumatic brain injury), the **K_v7 (KCNQ) family** of voltage-gated potassium channels stands out as particularly promising. Several biophysical properties make K_v7 channels well-suited for this role. They have activation voltage threshold near the resting membrane potential of many neurons, they do not inactivate and have slow activation and deactivation kinetics (Jones et al., 2021). Owing to these characteristics, a fraction of K_v7 channels remains conductive in a neuron at rest, controlling firing threshold and rheobase. Gradual increase of K_v7 channel activity during sustained depolarization or continuous firing introduces self-tuning or 'accommodation' in firing patterns.

There are five K_v7 subunits in mammals, **$K_v7.1$–$K_v7.5$**, and these are encoded by *KCNQ1-KCNQ5* genes. $K_v7.1$ is mainly expressed in the cardiovascular system and epithelia, while **$K_v7.2$**–$K_v7.5$ are mostly neuronal, responsible for so-called M-type K^+ current in these cells (Jones et al., 2021). Generic mutations causing loss of K_v7 function often result in pathological hyperexcitability (epilepsies, cardiac arrhythmias and pain) (Jones et al., 2021). Conversely, pharmacological activation or enhancement of K_v7 activity is widely recognised therapeutic strategy for management of hyperexcitability symptoms. Two K_v7 activators have been clinically used as a painkiller (**flupirtine**) and anticonvulsant (**retigabine**), and a number of other clinically used drugs may have K_v7 activation among their mechanisms of action. These include painkillers, **celecoxib** (Du et al., 2011) and **paracetamol** (Ray et al., 2019) and a vasodilator, **fasudil** (Zhang et al., 2016).

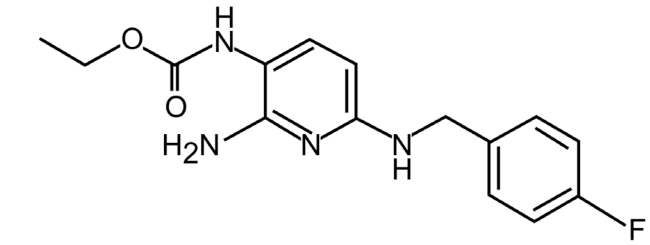
Although flupirtine and retigabine initially demonstrated clinical promise, both compounds were ultimately withdrawn from the market, mostly due to adverse effects. Retigabine was associated with blue skin discolouration, retinal pigmentation and urinary retention, while flupirtine carried a risk of hepatotoxicity. Current efforts in drug development are focused on identifying next-generation K_v7 channel activators with superior pharmacological selectivity and safety. Yet, development of a new drug from scratch is a costly and time-consuming undertaking. In this context, screening libraries of already approved (or close to approval) drugs for potential repurposing represents a promising alternative strategy, offering the advantages of accelerated market entry and reduced development costs.

A new study by Lidia Carotenuto and co-authors, published in the British Journal of Pharmacology (Carotenuto et al., 2025), reports the efforts on identifying new K_v7 activators through the repurposing pipeline. The authors performed a high-throughput screening of ~8000 compounds from the Fraunhofer repurposing Library and the EU-Openscreen Pilot Bioactive Library in hope to identify safe and potent K_v7 activators for treatment of epilepsy. The screen returned one such promising compound, **JNJ-37822681** (Figure 1), a fast-dissociating **D_2 receptor** antagonist, originally developed by Johnson & Johnson for the treatment of schizophrenia (Langlois et al., 2012). The molecule has a good bioavailability, good general toxicological and safety profiles, and it is currently undergoing advanced stages of clinical development.

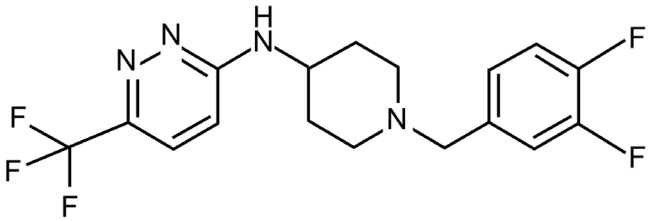
Abbreviations: iPSC, induced pluripotent stemcells; KCNQ, potassium voltage-gatedchannel subfamily Q; KCNQ2-DEE, *KCNQ2*-developmentaland epileptic encephalopathy; PDB, protein data bank; PTZ, pentylenetetrazole.



Retigabine



Flupirtine



JNJ-37822681

FIGURE 1 Chemical structures of retigabine, flupirtine and JNJ-37822681.

The authors first used a fluorescence thallium assay to screen the compound libraries against Chinese hamster ovary (CHO) cells stably overexpressing a $K_v7.3$ channel isoform mutated for enhanced macroscopic current ($K_v7.3$ A315T). Retigabine was used as a positive control. The screen identified about a dozen of candidates, among which were retigabine and another known K_v7 activator, **ML213**. Most of the novel candidates were disqualified in further patch clamp experiments for their low potency and/or efficacy. However, JNJ-37822681 survived the verification, demonstrating potency and efficacy comparable to that of retigabine for $K_v7.2$, **$K_v7.4$** and $K_v7.5$ homomers and $K_v7.2/K_v7.3$ heteromers, with slightly weaker effects on $K_v7.3$. As an example, retigabine and JNJ-37822681 induced hyperpolarizing shift of the half-voltage of $K_v7.2/K_v7.3$ activation of −40 and −37 mV respectively, with EC_{50} of 2.5 and 1.2 μM, respectively. Similar to retigabine, JNJ-37822681 had little effect on $K_v7.1$ channels.

Using cryo-EM structures of $K_v7.2$ in complex with retigabine (PDB: 7CR2) and molecular docking simulations, authors were able to fit JNJ-37822681 into the retigabine binding pocket of $K_v7.2$. Moreover, mutation of tryptophan at the position 236 in $K_v7.2$ (W236L), which is critical to retigabine binding, abolished the K_v7 activation effect of JNJ-37822681, confirming modelling predictions.

The authors then utilised induced pluripotent stem cells (iPSC) technology to test the effect of JNJ-37822681 on the excitability of human iPSC-derived cortical glutamatergic neurons. They used cortical-like glutamatergic neurons differentiated from two patients with a genetic form of epilepsy due to the loss-of-function mutations in *KCNQ2* (*KCNQ2*-developmental and epileptic encephalopathy; KCNQ2-DEE), as well as CRISPR/Cas9-corrected isogenic cell lines as a control. In these experiments, JNJ-37822681 and retigabine were similarly effective in reducing excitability and firing frequency (measured using the patch clamp recordings and extracellular recordings with multielectrode array system) in both control and DEE neurons. Both compounds also comparably augmented the M current amplitude in isogenic control neurons.

Finaly, the authors utilised two mouse models of epileptic seizures: pentylenetetrazole (PTZ) model of generalised tonic–clonic seizures and audiogenic reflex seizures in genetically epilepsy-prone DBA/2 mice. In both models, retigabine and JNJ-37822681 significantly reduced clonic and tonic seizures with JNJ-37822681 displaying similar (PTZ) or slightly higher (DBA/2) potency, as compared to retigabine.

Taken together, the study identified and characterised novel K_v7 activator with a good safety profile, which is currently being advanced towards clinical use as an antipsychotic. The molecule binds to the retigabine binding pocket in K_v7 channels and has a comparable selectivity profile. The absence of activity on $K_v7.1$ is advantageous, as this subunit is predominantly expressed in cardiac and vascular tissues. Consequently, modulators exhibiting significant $K_v7.1$ interaction may present cardiovascular risk. JNJ-37822681 reduced neuronal excitability *in vitro* and seizure severity *in vivo* with potency and efficacy comparable to that of retigabine. Presumably, JNJ-37822681 would not have the blue skin discoloration issue, which is unique to retigabine due to the formation of pigmented dimers. However, JNJ-37822681 may still have some other on-target side-effects of retigabine, such as dizziness, confusion, somnolence and urinary retention. Additionally, since JNJ-37822681 is a D_2 receptor antagonist, it may elicit side-effects commonly associated with this pharmacological class, including extrapyramidal symptoms and metabolic issues. It is also important to note that, according to UK.GOV, GlaxoSmithKline cited limited clinical use as the primary reason for discontinuing retigabine (Trobalt/Potiga) in 2017, rather than concerns related to the efficacy or safety. Hence, it is yet to be established if a similar compound would achieve greater market viability. Nevertheless, the study by Carotenuto and co-authors exemplifies a thorough and comprehensive strategy for identifying and characterising new clinically relevant K_v7 channel openers for treatment of excitability disorders.

AUTHOR CONTRIBUTIONS

N.G. wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

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