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G Protein-Gated Inwardly Rectifying Potassium (GIRK) Channels in Epilepsy: From Channelopathy to Subunit-Selective Therapeutics

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Systematic Review

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G Protein-Gated Inwardly Rectifying Potassium (GIRK) Channels in Epilepsy: From Channelopathy to Subunit-Selective Therapeutics

Abstract

Epilepsy affects roughly 70 million people worldwide, and about a third of patients remain refractory to current antiseizure medications, which act mainly on sodium channels, calcium channels, GABA receptors, and synaptic release machinery. G protein-gated inwardly rectifying potassium (GIRK) channels convert inhibitory G protein-coupled receptor signaling into membrane hyperpolarization and are therefore an attractive, mechanistically distinct target. This review summarizes the molecular biology and neuronal physiology of GIRK channels; evidence from knockout, chemoconvulsant, and Down syndrome mouse models; human variants in the GIRK subunit genes (KCNJ3, KCNJ6, KCNJ9) and in genes along the same signaling pathway (GABBR1, GABBR2, GNB1); and the development of subunit-selective activators such as ML297, GAT1508, and GiGA1, together with the observation that the antiseizure drug ethosuximide inhibits GIRK channels. We discuss the central translational problem: both loss and gain of GIRK function can cause neurological disease, so the direction of therapy may need to match the underlying genotype, and cardiac GIRK channels impose a safety constraint on non-selective activation. GIRK channels link inhibitory neurotransmission to intrinsic neuronal excitability, and the data support them as a candidate target for seizure control. Clinical translation will depend on brain-selective activators, genotype-guided patient selection, and cardiac safety profiling.

Keywords: GIRK; Kir3; KCNJ3; KCNJ6; GNB1; epilepsy; potassium channel; channelopathy; GABA-B receptor; ML297

Introduction

Epilepsy is a chronic neurological disorder defined by recurrent seizures, and it affects roughly 70 million people worldwide [1]. Despite the growth of the antiseizure medication (ASM) portfolio, about a third of people with epilepsy have drug-resistant epilepsy, and the availability of newer ASMs has not clearly improved the likelihood of seizure freedom [2]. The International League Against Epilepsy defines drug resistance as failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules to achieve sustained seizure freedom [3]. This persistent treatment gap shows that mechanistically distinct targets are still needed.

Ion channels are among the best validated targets in epilepsy, and many monogenic epilepsies are channelopathies. Within the potassium channel superfamily, voltage-gated Kv7 (KCNQ) channels have already yielded an approved antiseizure drug, retigabine (ezogabine), which has since been withdrawn. Inwardly rectifying (Kir) channels are expressed in neurons and glia, control cell volume and excitability, and have been reviewed as contributors to epileptogenesis across their subfamilies [1]. The clearest human example outside the GIRK family is loss of function of the glial channel Kir4.1 (KCNJ10), which causes the autosomal recessive EAST/SeSAME syndrome of seizures, ataxia, sensorineural deafness, intellectual disability, and a salt-wasting tubulopathy [4,5].

GIRK (Kir3) channels are the Kir subfamily most directly coupled to synaptic inhibition. They hyperpolarize neurons in response to activation of many different G protein-coupled receptors (GPCRs),

and they therefore control excitability through self-inhibition and slow inhibitory postsynaptic currents [6]. Pharmacological and animal studies have implicated them in pain perception, memory modulation, Down syndrome, Parkinson's disease, psychiatric disorders, drug addiction, and epilepsy [6,7], and knockout mouse models have provided extensive insight into their roles [7].

The receptor input most relevant to epilepsy is the GABA-B receptor, whose postsynaptic form opens GIRK channels to produce the slow phase of inhibition [6]. Mice lacking the $GABA_B$ (1) subunit are viable but have spontaneous seizures, hyperalgesia, hyperlocomotor activity, and memory impairment, with loss of all $GABA_B$ responses [8], and $GABA_B$ (2)-deficient mice show a similar phenotype [9]. In humans, variants in GABBR2 have been associated with a Rett-like phenotype, epileptic encephalopathy, and milder developmental delay with absence epilepsy, and de novo GABBR1 variants have been linked to neurodevelopmental delay and epilepsy [10]. Functional studies of these receptor variants show both gain-of-function and loss-of-function effects [11], which already hints at a theme developed in this review: the relationship between inhibitory signaling and seizure risk is not simply monotonic.

Four developments make a focused review of GIRK channels timely: newly described human variants in the GIRK subunit genes; the finding that variants in GNB1, which encodes a G protein subunit that gates GIRK channels, cause epilepsy through altered GIRK signaling; the first subunit-selective GIRK activators with in vivo anticonvulsant activity; and evidence that an established ASM, ethosuximide, inhibits GIRK channels. These are discussed in the sections that follow, with the supporting studies cited there.

This narrative review asks a focused question: what is the evidence that GIRK channel dysfunction contributes to epilepsy, and can the channel be targeted safely? We (1) summarize GIRK channel biology, (2) review animal-model evidence, (3) review human genetic evidence for GIRK subunits and pathway genes, (4) evaluate the pharmacology of GIRK activators and inhibitors, and (5) identify gaps and priorities for translation.

Methods

Review design

This is a narrative review. It was not conducted as a systematic review, and PRISMA reporting standards were not applied, because the aim was interpretive rather than exhaustive. The domains covered here use incompatible outcome measures, ranging from ion currents and seizure thresholds in animal models to variant effects in patients, so quantitative pooling was neither possible nor intended.

Search strategy

A literature search was conducted in November 2026 using web-based search engines and open-access repositories, including PubMed and PubMed Central, with the terms "GIRK", "Kir3", "KCNJ3", "KCNJ6", "KCNJ9", "KCNJ5", "GNB1", "GABA-B", "epilepsy", and "seizure".

Eligibility criteria

Studies were included if they reported experimental or clinical data on GIRK subunits, on genes in the GABA-B receptor–G protein–GIRK pathway, or on GIRK-targeting compounds in relation to seizures or epilepsy. Studies from other contexts, such as Down syndrome, were included where they informed

mechanism. Peer-reviewed original studies, reviews, and case reports were eligible. Preprints, conference abstracts, and reports without a seizure-, epilepsy-, or pathway-related question were excluded, except where noted in the text.

Study selection

Selection was purposive. Where several studies addressed the same question, preference was given to primary studies with direct functional validation (for example, patch-clamp recordings of variant channels) and to studies with a design that could address confounding. The reference lists of key reviews were hand-searched. In total, 35 sources are cited in this review. Sixteen key primary studies, which bear most directly on the question, are summarized in Table 2. The remaining sources provide background (reviews, consensus definitions, a doctoral dissertation, and a gene database entry) or supporting primary data. The number of records retrieved and screened was not tracked, because the search was not designed as a systematic retrieval, and for the same reason no flow diagram is presented. Because selection was purposive, the studies reviewed should be read as an argued sample of the literature rather than a complete inventory, and selection bias cannot be excluded.

Data extraction and synthesis

For each included study, the model or population, the GIRK subunit or pathway gene involved, the key finding, and the direction of GIRK function implicated were recorded (Table 2). Findings were synthesized narratively across five domains: channel biology, animal models, human genetics, pharmacology, and translational challenges. No formal risk-of-bias appraisal was performed; methodological concerns are raised where they bear on interpretation and are collected in the limitations.

Results

The reviewed evidence is presented in four groups: channel biology, animal models, human genetic evidence, and pharmacological studies. The principal studies are then summarized in Table 2.

Molecular biology and expression of GIRK channels

Four mammalian GIRK subunits exist: GIRK1 (Kir3.1), GIRK2 (Kir3.2), GIRK3 (Kir3.3), and GIRK4 (Kir3.4), encoded by KCNJ3, KCNJ6, KCNJ9, and KCNJ5, respectively [7,12]. Subunits assemble as homo- or heterotetramers with distinct biophysical properties, regulation, and distribution [6]. In the brain, the GIRK1/GIRK2 heteromer is the most common and widely expressed combination, although there are exceptions, and the precise subunit composition of neuronal GIRK channels is still being worked out [13]. GIRK1/GIRK4 heteromers form the muscarinic-gated atrial channel that mediates parasympathetic regulation of heart rate, which is the origin of the cardiac liability discussed below [12].

Channel opening is triggered when a GPCR releases G protein beta-gamma subunits that bind the channel directly, increasing potassium permeability. The resulting potassium efflux hyperpolarizes the neuron and shunts excitatory input. Channel gating also depends on the membrane lipid PIP2 [13,14], and neuronal GIRK activity is further sensitive to phosphorylation, regulators of G protein signaling, intracellular sodium and calcium, and cholesterol [13]. Function is shaped not only by biophysics but also by localization: GIRK channels are distributed mainly in the somatodendritic compartment, including

perisynaptic sites where they mediate the slow inhibitory postsynaptic current that follows GABA-B receptor activation [6,12].

Evidence from animal models

Genetic models

The strongest early evidence came from mouse genetics. The weaver mouse, which shows ataxia, tremor, male infertility, and spontaneous seizures, carries a point mutation in Girk2 [15,16]. Mice lacking GIRK2 are morphologically normal but develop spontaneous seizures and are more susceptible to seizures induced by a GABA antagonist, without the neuronal death seen in weaver, which suggests that the weaver phenotype reflects abnormal rather than absent GIRK2 function [15]. Together these observations established Girk2 as a seizure-control gene, and subsequent knockout work extended the link between GIRK subunits and hyperexcitability, anxiety, and cognition [7].

Activity-dependent regulation during seizures

GIRK expression is not static during epileptogenesis. In cultured hippocampal neurons, high-frequency epileptiform discharges first increase surface expression of GIRK1 and GIRK2 within about 20 minutes, a homeostatic response that counteracts excessive activity [17]. When seizure-like activity is prolonged beyond about 30 minutes, caspase-3 cleaves the cytoplasmic C-termini of GIRK1 and GIRK2; the cleaved GIRK2 loses an endoplasmic reticulum export motif, binds G protein beta-gamma subunits poorly, and cannot assemble with GIRK1, and kainate-induced status epilepticus produced the same cleavage in rat hippocampus [18]. This suggests a time-dependent window: early compensatory upregulation may be protective, while later caspase-mediated loss of channels may sustain hyperexcitability and neuronal injury [17,18].

This pattern fits the broader view that temporal lobe epilepsy involves both homeostatic and maladaptive ion channel changes, which are cell-type specific [19]. It is also not uniform across preparations: in a rat status epilepticus model, HCN channel expression fell in dorsal CA1 neurons, whereas M-channel and GIRK expression were unchanged [20]. The timing, cell type, and model therefore matter when interpreting GIRK expression data.

GABA-B signaling and generalized epilepsy

GIRK channels are the main postsynaptic effector of GABA-B receptors, and their activation shapes the oscillatory behavior of thalamic and hippocampal networks [13]. Loss of the receptor itself produces seizures in mice [8,9], which is consistent with a protective role for the effector. Direct evidence from absence-epilepsy models is limited, however, and the direction of the GABA-B/GIRK contribution to spike-wave discharges remains an open question. As discussed below, GIRK gain of function can also be pro-epileptic in a G protein mutation model, so more GIRK current is not automatically more protection.

GIRK2 gene dosage and Down syndrome

Because KCNJ6 lies on chromosome 21, trisomy 21 raises GIRK2 gene dosage, and GIRK2 overexpression has therefore been studied in Down syndrome models. Mice carrying three copies of Kcnj6 alone show deficits in hippocampus-dependent learning and memory, altered reward responses, hampered depotentiation, and accentuated long-term depression [21]. In the Ts65Dn model, reducing Kcnj6 to two copies restored hippocampal Kir3.2 levels and rescued behavioral and dentate gyrus

plasticity deficits, and the Kir3.2-suppressing drug fluoxetine increased synaptic plasticity in slices from trisomic mice [22]. These studies address cognition rather than seizures, so a direct contribution of GIRK2 dosage to the seizure burden in Down syndrome remains to be shown.

Human genetic evidence

The human literature is much smaller than the animal literature, but it has grown in recent years and now shows that both loss and gain of GIRK function can be pathogenic. It also extends beyond the channel genes to genes that act upstream of the channel in the same signaling pathway.

KCNJ3 (GIRK1)

An early mutation screen of KCNJ6 and KCNJ3 in 38 patients with juvenile myoclonic epilepsy found only synonymous changes, which did not support a major role for this gene pair in that syndrome [16]. More recently, trio exome sequencing identified two de novo missense variants in KCNJ3 (p.Leu333Ser and p.Arg313Gln) in two unrelated families with early-onset epilepsy. Both variants lie in the C-terminal domain, were absent from gnomAD, and reduced channel current in whole-cell patch-clamp recordings [23]. This is the clearest direct human evidence that reduced GIRK function can cause epilepsy.

KCNJ9 (GIRK3)

Trio exome sequencing in a newborn who developed generalized convulsive seizures in the first days of life revealed a de novo KCNJ9 variant (p.Phe326Ser) with no previously described disease association. The authors suggest that the substitution may disrupt local hydrophobic contacts and impair GIRK2/GIRK3 tetramer formation, but they stress that further patients and functional work are needed [24].

KCNJ6 (GIRK2)

KCNJ6 lies on chromosome 21 in the Down syndrome critical region. Exome sequencing of three unrelated individuals with Keppen-Lubinsky syndrome, a rare disorder with severe developmental delay, intellectual disability, microcephaly, an aged appearance, and generalized lipodystrophy, found de novo variants near the selectivity filter (p.Thr152del in two individuals and p.Gly154Ser in one), which established the syndrome as a channelopathy [25]. A further patient with a de novo p.Leu171Arg variant had a severe hyperkinetic movement disorder (dystonia and ballismus) and developmental delay without lipodystrophy. The mutant channel produced an aberrant basal inward current that lacked G protein activation, lost potassium selectivity, and gained calcium permeability, similar to the mouse weaver mutation. Epilepsy was not present in that patient [26]. A p.Gly154Cys variant at the same selectivity-filter residue was reported in an adult with a milder phenotype that included mild intellectual disability and pathological startle responses [27]. Gene databases list epilepsy among the associations of KCNJ6 [28], but the evidence is weaker than for the developmental and movement phenotypes.

GNB1 (Gβ1)

GIRK channels are gated by G protein beta-gamma subunits, so variants in the genes that encode these subunits can produce GIRK-related epilepsy. De novo GNB1 variants cause an autosomal dominant neurodevelopmental disorder (GNB1 encephalopathy) characterized by developmental delay and hypotonia, with epilepsy in nearly 60% of patients [29]. Three recurrent variants (K78R, I80N, and I80T) did not alter GPCR–Gi/o coupling or Gβγ regulation of the neuronal calcium channel CaV2.2, but they profoundly altered Gβγ regulation of GIRK channels, with gain of function for K78R and loss of function for I80T and I80N, in a GIRK-subunit-specific manner [30]. Gnb1 K78R/+ mice recapitulate developmental delay and generalized seizures; their cultured cortical neurons show aberrant bursting and increased GABA-B-induced GIRK activity, and the antiseizure drug ethosuximide, a known GIRK blocker, suppresses their spike-and-wave discharges [29]. Whether loss-of-function variants such as I80T also drive epilepsy through reduced GIRK signaling has not yet been established in peer-reviewed work, which makes this an important open question.

GABBR1 and GABBR2

As noted in the Introduction, variants in the GABA-B receptor genes are linked to epileptic encephalopathy, Rett-like phenotypes, and neurodevelopmental delay with epilepsy, and functional studies reveal both gain- and loss-of-function effects [10,11]. Because postsynaptic GABA-B receptors signal through GIRK channels [6], these disorders are likely to involve GIRK signaling, although the contribution of the channel has not been isolated in patients.

Interpretation

The human data point to a bidirectional relationship. Too little GIRK current (KCNJ3 loss of function) has been linked to early-onset epilepsy [23]. Too much or dysregulated current (KCNJ6 gain of function) has been linked to developmental and hyperkinetic phenotypes in which epilepsy is not a defining feature [25,26], whereas in GNB1 encephalopathy, which includes both gain-of-function (K78R) and loss-of-function (I80T, I80N) variants, epilepsy has been tied mechanistically to GIRK gain of function in a mouse model [29,30]. This matters for therapy, because indiscriminate activation could be unhelpful or harmful in some genetic contexts. It is a reasonable hypothesis, not yet tested, that the best intervention may be an activator in one genotype and an inhibitor in another.

Pharmacological studies

For many years the only known GIRK activators were simple alcohols and the natural product naringin, which are low-potency and non-selective [31]. The field changed with the discovery of ML297 (VU0456810), the first potent and selective small-molecule GIRK activator. It prefers GIRK1-containing channels and is inactive on GIRK2/GIRK3 channels [31]. In mice, ML297 (60 mg/kg intraperitoneally) was active in both the maximal electroshock and the pentylenetetrazole seizure models, with efficacy reported as equal to or greater than that of sodium valproate [31]. ML297 also reduces anxiety-related behavior in a GIRK1-dependent manner, and, unlike receptor-mediated activation, it does not require G protein beta-gamma subunits [14].

ML297 is a probe rather than a drug candidate. First-generation GIRK1/2 activators suffer from poor brain penetration and only modest selectivity over the cardiac GIRK1/4 channel [32], and ML297 shows high intrinsic clearance in mouse liver microsomes [31]. A newer ether-based series improved metabolic stability, and its lead compound activated GIRK1/2 more potently than GIRK1/4 (EC50 about 137 nM versus 702 nM) [32].

GAT1508

A bromothiophene-substituted derivative of ML297, is selective for brain GIRK1/2 channels over cardiac GIRK1/4 channels in oocyte recordings. It activated GIRK currents in the basolateral amygdala, facilitated conditioned fear extinction in rodents, and lacked cardiac and behavioral side effects in the original report [33]. Its antiseizure efficacy has not yet been reported in peer-reviewed work, which is a clear gap given its improved selectivity profile.

A further chemotype, GiGA1, is a GIRK1-selective activator that acts on the alcohol-binding hydrophobic pocket in the cytoplasmic domain, independently of G proteins. It activates GIRK1/2 in vitro and in vivo and mitigates the effects of a convulsant in an acute mouse seizure model, supporting structure-based design of subunit-specific modulators [34].

GIRK inhibition and existing antiseizure medications

Pharmacology also points in the opposite direction. Ethosuximide, classically described as a T-type calcium channel blocker, inhibited GIRK channels at clinically relevant concentrations in Xenopus oocytes and in cerebellar granule cells, whereas phenytoin, valproic acid, carbamazepine, phenobarbital, gabapentin, topiramate, and zonisamide had no significant effect even at toxic concentrations [35]. In the Gnb1 K78R mouse, ethosuximide suppressed spike-and-wave discharges and normalized network behavior in vitro, and part of its action appears to be through GIRK inhibition [29]. These findings suggest that GIRK modulation may already contribute to the action of one established ASM and support a genotype-matched strategy.

Table 1. Compounds that modulate GIRK channels and have been tested in seizure-related settings.

Compound	Mechanism	Reported preclinical effect	Main limitation
ML297	GIRK1-selective activator	Anticonvulsant in MES and PTZ mouse models [31]	Poor brain penetration, high clearance, limited GIRK1/2 vs GIRK1/4 selectivity [31,32]
GAT1508	Brain-selective GIRK1/2 activator	Fear extinction in rodents [33]	Antiseizure efficacy not yet shown in peer-reviewed studies; no human data
GiGA1	G-protein-independent GIRK1-selective activator at the alcohol pocket	Reduced convulsant effects in an acute mouse model [34]	Early-stage; chronic efficacy and safety unknown

Compound	Mechanism	Reported preclinical effect	Main limitation
Ethosuximide	GIRK inhibitor (in addition to other proposed actions)	Inhibits GIRK in vitro [35]; suppresses spike-and-wave discharges in Gnb1 K78R/+ mice [29]	Benefit expected only where GIRK activity is increased; not generalizable
Alcohols, naringin	Direct, non-selective activators	None of therapeutic relevance	Low potency, no selectivity [31]

Summary of the evidence

Table 2 collects the principal studies discussed in this review, grouped by the direction of GIRK function that each study implicates. Three observations stand out. First, loss of GIRK function is supported by human genetics (KCNJ3), by knockout mice, and by seizure-induced channel cleavage. Second, gain of function is supported by KCNJ6 and GNB1 K78R data, although epilepsy is a defining feature only in the latter. Third, the pharmacological antiseizure evidence is almost entirely preclinical and comes mainly from acute mouse models.

Table 2. Summary of key studies included.

Study	System	Key finding	GIRK function implicated
Signorini et al., 1997 [15]	Girk2 knockout mice	Spontaneous seizures; higher susceptibility to GABA-antagonist seizures	Loss
Schuler et al., 2001 [8]	$GABA_B(1)$ knockout mice	Spontaneous seizures; loss of all GABAB responses	Loss (upstream)
Gassmann et al., 2004 [9]	$GABA_B(2)$ knockout mice	Spontaneous seizures similar to $GABA_B(1)$ knockout	Loss (upstream)
Baculis et al., 2017 [18]	Cultured neurons; kainate status epilepticus in rats	Prolonged seizure activity causes caspase-3 cleavage of GIRK1 and GIRK2	Acquired loss
Cooper et al., 2012 [21]	Kcnj6 triploid mice	Learning, memory, and plasticity deficits	Increased dosage
Kleschevnikov et al., 2017 [22]	Ts65Dn mice	Reducing Kcnj6 dose rescues behavioral and plasticity deficits	Increased dosage
Li et al., 2024 [23]	Two families; patch clamp	De novo KCNJ3 variants in early-onset epilepsy	Loss
Kochetkova et al.,	One neonate	De novo KCNJ9 p.Phe326Ser with	Unknown

Study	System	Key finding	GIRK function implicated
2023 [24]		neonatal seizures	
Masotti et al., 2015 [25]	Three individuals; exome sequencing	De novo KCNJ6 variants cause Keppen-Lubinsky syndrome	Gain
Horvath et al., 2018 [26]	One patient; functional assays	KCNJ6 p.Leu171Arg; hyperkinetic movement disorder, no epilepsy	Gain
Colombo et al., 2023 [29]	Gnb1 K78R/+ mice	Generalized seizures; ethosuximide suppresses spike-wave discharges	Gain
Reddy et al., 2021 [30]	Heterologous expression	GNB1 variants alter GIRK regulation; K78R gain, I80T and I80N loss	Gain or loss
Kaufmann et al., 2013 [31]	Mouse seizure models	ML297 is anticonvulsant	Activation
Xu et al., 2020 [33]	Oocytes and rodents	GAT1508 favors GIRK1/2 over GIRK1/4	Activation
Zhao et al., 2020 [34]	Acute mouse seizure model	GiGA1 reduces convulsant effects	Activation
Kobayashi et al., 2009 [35]	Oocytes; cerebellar slices	Ethosuximide inhibits GIRK; other tested ASMs do not	Inhibition

Discussion

Principal findings

Four findings emerge from the studies reviewed. First, mouse, human, and cell-based evidence converge on the idea that reduced GIRK function can be pro-epileptic: Girk2 deletion causes seizures [15], loss-of-function variants in KCNJ3 are associated with early-onset epilepsy [23], loss of the upstream GABA-B receptor causes seizures in mice [8,9], and prolonged seizure activity cleaves GIRK1 and GIRK2 [18]. Second, the relationship is not monotonic: gain-of-function variants in KCNJ6 cause developmental and hyperkinetic disorders [25,26], and epilepsy in a Gnb1 K78R mouse is linked to excess GIRK activity and is suppressed by a GIRK blocker [29]. Third, pharmacology operates in both directions, with activators such as ML297 and GiGA1 showing anticonvulsant effects in acute mouse models [31,34] and ethosuximide acting as a GIRK inhibitor [35]. Fourth, human evidence is sparse and mostly confined to single families, and no GIRK modulator has been tested in patients.

A working model: GIRK balance rather than GIRK strength

These findings can be organized, as a hypothesis, around the idea that seizure risk depends on the balance of GIRK signaling in a given cell type and circuit rather than on its absolute strength. At the low end, genetic loss of function (KCNJ3), loss of the receptor input (GABBR1 and GABBR2 deficiency), and acquired loss through caspase-mediated cleavage during prolonged seizures [18] all weaken the slow

inhibition that GIRK channels provide. At the high end, excess Gβγ-driven GIRK activity (GNB1 K78R) is associated with generalized seizures [29,30]. The cellular mechanism by which too much GIRK current produces seizures has not been resolved. Plausible candidates, which need to be tested and are not established by the studies cited here, include excessive hyperpolarization of inhibitory interneurons with secondary disinhibition of circuits, and de-inactivation of T-type calcium channels in thalamocortical neurons, which promotes burst firing.

This model has two practical implications. The first is that therapy should be matched to the direction of dysfunction: an activator in conditions of reduced GIRK function and an inhibitor in conditions of excess function, as the ethosuximide data in the Gnb1 K78R mouse illustrate [29,35]. The second is that acquired loss of GIRK channels during prolonged seizures [18] points to a different strategy, preserving existing channels, which has not yet been tested. Neither implication has been evaluated in patients.

Clinical translation

The first challenge is subunit selectivity and cardiac safety. GIRK1/4 channels in atrial myocytes mediate parasympathetic slowing of heart rate [12], so non-selective activators risk cardiac effects. ML297 has only modest selectivity over GIRK1/4 [32], and GAT1508 was developed to address this [33]. However, the antiseizure efficacy of GAT1508, the most selective brain-targeted activator described so far, has not been reported in peer-reviewed studies [33], so its promise remains untested in seizure models.

A second challenge is that GIRK-related disease is bidirectional. The KCNJ3, KCNJ6, and GNB1 data show that both under- and over-activity of GIRK signaling can be associated with disease [23,25,26,29,30], so genotype-guided or biomarker-guided patient selection is likely to be necessary.

Third, the evidence base is limited in several ways. Most efficacy data come from acute chemoconvulsant or electroshock models in mice, which test seizure threshold rather than epileptogenesis or drug-resistant epilepsy. Only a handful of KCNJ3, KCNJ9, and KCNJ6 families have been described, mostly with limited functional validation, and the contribution of GIRK to GABBR1 and GABBR2 disorders has not been isolated. Finally, regulation of GIRK channels changes across the course of seizures and epileptogenesis and differs between brain regions and models [17,18,20], so the optimal timing and site of intervention are unknown.

Future directions and limitations

Several steps would move the field forward. Screening KCNJ3, KCNJ6, KCNJ9, and GNB1 in early-onset and unexplained epilepsy cohorts, including under-represented populations, with functional characterization of every novel variant, would clarify how common GIRK-related epilepsy is. Chronic and spontaneous-seizure models, such as kindling, post-injury temporal lobe epilepsy, and genetic absence models, are needed to test whether GIRK modulation changes epileptogenesis and not only acute thresholds. On the pharmacological side, the antiseizure efficacy of GAT1508 needs to be tested and compared head-to-head with ML297 and GiGA1 for efficacy, brain exposure, and cardiac safety, together with further medicinal chemistry that favors GIRK1/2 over GIRK1/4 [32,33].

Because the direction of dysfunction differs between genotypes, genotype-matched preclinical trials in GNB1 models should test GIRK inhibitors for gain-of-function variants and activators for loss-of-function variants [29,30]. GIRK inhibitors or repurposed drugs could also be explored for gain-of-function channelopathies such as KCNJ6-related disorders. It remains to be defined whether GIRK inhibition contributes to the clinical efficacy of ethosuximide and whether this predicts which patients

respond [35]. Finally, integrating GIRK-related variants into gene panels would allow precision-medicine strategies to be tested in clinical trials.

This review has several limitations. It is a narrative review with purposive study selection, so selection bias cannot be excluded. The search was run once, mainly through web-based engines and open-access repositories and was not repeated across multiple bibliographic databases. Preprints were deliberately excluded, so very recent findings may be missing. The studies are heterogeneous in model, preparation, and outcome, which prevented pooling, and no formal risk-of-bias assessment was performed. Finally, much of the mechanistic evidence comes from heterologous expression systems and acute mouse models, whose translation to human epilepsy is uncertain.

Conclusions

GIRK channels are an effector of GABA-B and other inhibitory signaling pathways, a determinant of neuronal excitability, and a gene family whose variants cause human neurological disease. Animal evidence supports a seizure-suppressing role, newly identified human loss-of-function variants in KCNJ3 link reduced GIRK function to early-onset epilepsy, and variants in GNB1 show that both gain and loss of GIRK function can arise within a single disease gene. First-generation selective activators show anticonvulsant activity in mice, and the established drug ethosuximide may act in part through GIRK inhibition. The principal barriers to clinical translation are cardiac selectivity, pharmacokinetics, the bidirectional nature of GIRK-related disease, and the limited peer-reviewed evidence for antiseizure efficacy of the newest compounds. GIRK channels are therefore best viewed as a promising but early-stage target, and the most plausible route to clinical benefit is a genotype-matched strategy rather than indiscriminate channel activation.

List of abbreviations

ASM: antiseizure medication; CaV: voltage-gated calcium channel; ETX: ethosuximide; GABA: gamma-aminobutyric acid; GIRK: G protein-gated inwardly rectifying potassium channel; GNB1: gene encoding the G protein beta-1 subunit; GPCR: G protein-coupled receptor; HCN: hyperpolarization-activated cyclic nucleotide-gated channel; Kir: inwardly rectifying potassium channel; MES: maximal electroshock; PIP2: phosphatidylinositol 4,5-bisphosphate; PTZ: pentylenetetrazole.

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