Book Section:
Al-Owais, M.M. orcid.org/0000-0001-9122-7873, Ozsoy, N. and Dallas, M.L. (2024) The Voltage-Gated Potassium Channel Kv2.1 as a Multicellular Drug Target. In: Stephens, G. and Stevens, E., (eds.) Ion Channels as Targets in Drug Discovery. Springer , pp. 221-237. ISBN 978-3-031-52196-6

https://doi.org/10.1007/978-3-031-52197-3_7

The voltage-gated potassium channel $K_v2.1$ as a multicellular drug target

Moza M. Al-Owais[2], Nagihan Ozsoy[1] and Mark L Dallas[1]

[1]Reading School of Pharmacy, University of Reading, Reading RG6 6AP, UK.

[2]School of Biomedical Sciences, University of Leeds, Leeds LS2 9JT, UK.

Corresponding author(s): Dr Mark L. Dallas (m.dallas@reading.ac.uk) and Dr Moza M. Al-Owais (m.al-owais@leeds.ac.uk)

Keywords: potassium ion channel, $K_v2.1$, electrophysiology, voltage-gated, drug target

Abstract

Voltage-gated potassium (K^+; K_v) channels are critical homeostatic regulators of ionic equilibrium. The diversity of channel subtypes and expression profiles makes them interesting drug targets. The $K_v2.1$ channel, encoded by the KCNB1 gene, has a multitude of physiological roles from setting neuronal firing frequency to influencing viral replication. Here we look at the biophysical fingerprint of the $K_v2.1$ channel and its role in a variety of unique cellular systems. These cellular systems provide a wealth of evidence for modulating $K_v2.1$ to offer novel avenues to treat a range of disease from neurological disorders to diabetes. Existing pharmacological compounds that target $K_v2.1$ function are highlighted, along with presenting differential pharmacological approaches to modulate $K_v2.1$ function. This chapter reveals the $K_v2.1$ channel to be an exciting drug target that could afford treatment options in complex diseases affecting ionic homeostasis, future research should be dedicated to delivering the drug in the appropriate manner to provide novel compounds and repurpose existing medicines.

Introduction

Voltage-gated K^+ channels

Voltage-gated K^+ (K_v) channels, which belong to the six-transmembrane domain family of K^+ channels, activate upon depolarisation of the cell membrane and deactivate upon repolarisation, promoting the efflux of K^+ ions. 40 genes encoding K_v channels have been identified in humans, forming 12 families, each then divided further into subfamilies. Based on their sequence identity, the classification is usually given as $K_vm.n$ where m denotes the family and n is the subfamily, which display multiple physiological roles (see Gamper et al., this volume).

The K_v2, or Shab-related, K^+ channel family consists of $K_v2.1$ and $K_v2.2$ (Gutman et al. 2003). The kinetics of these channels are distinct from other K_v channels, with slow activation and with inactivation that takes up to several seconds, characterising the currents carried by the Shab-related channels as delayed rectifier (Frech et al. 1989; Hwang et al. 1992).

The Shab gene was initially identified in Drosophila (Butler et al. 1989) and its product has subsequently been shown to maintain the electrical excitability of neurons and muscle cells (Frech et al. 1989).

K_v2.1 Function and Structure

K_v2.1 is encoded by the KCNB1 gene and consists of α-subunits that share the structural characteristic of six-transmembrane helices, designated as S1-S6, like other K_v channels, with two long intracellular domains known as the N-terminus and carboxyl terminus (Figure 1). A highly conserved tetramerization T1 domain is located at the N-terminus, playing a major role in determining the compatibility of different K_v subunits. A recent study investigating the crystal structure of the human K_v2.1 T1 domain found that the domain forms a pentamer structure (Xu et al. 2022; Figure 1)

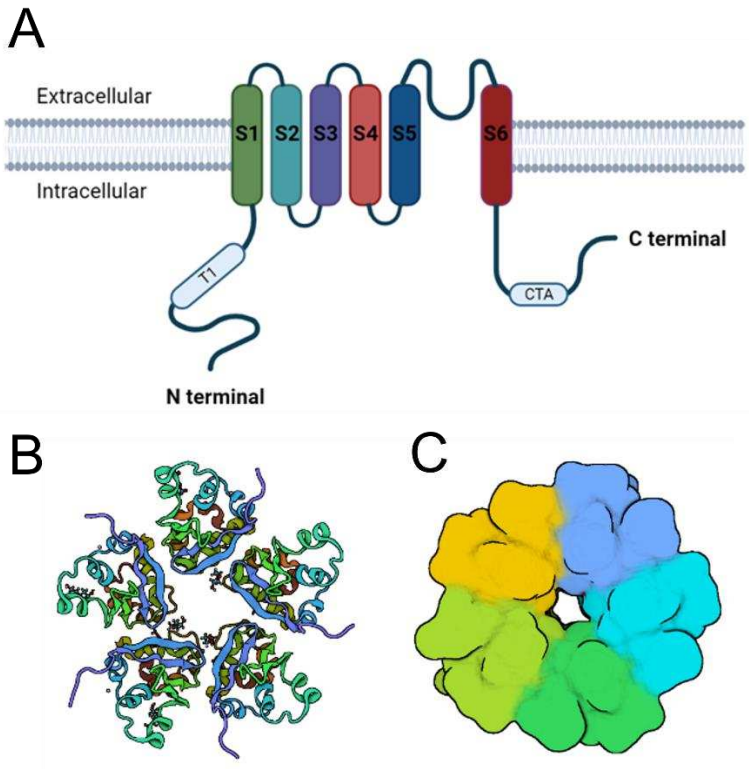

Figure 1. Proposed architecture for K_v2.1. A. K_v α-subunits consist of six transmembrane segments (S1-S6). S4 form the voltage sensor domain of the channel, and account for the channel gating where, in response to depolarisation, movement of positively charged amino acids results in opening of the channel. S5-S6 form the electrical pore. The N- and C-termini that are located intracellularly contain a T1 tetramerization domain and CTA domain that is mainly responsible for activation of the channel with T1 domain. **B.** Pentameric assembly of the K_v2.1 tetramerization domain viewed in cartoon form. **C.** Pentameric assembly of the K_v2.1 tetramerization domain viewed in quick surface form. Figure made in Biorender.com and retrieved using PDB ID 7SPD.

The carboxy terminus tail of the K_v2.1 channel protein contains a motif representing the C terminal activation (CTA) domain (Ju et al. 2003) and has been associated with the targeting and localization of the channel (Lim et al. 2000; Tamkun et al. 2007). Changes in the phosphorylation level have been attributed to changes in the channel's gating and surface expression (Grizel et al. 2014).

Highly conserved positively charged residues are located on the S4 domain, which acts as the main voltage sensor, and contains the main components of the gating charge for the channel. The selectivity filter loop is characteristically located between the S5 and S6 transmembrane helices and includes the signature sequence of the K_v channel selectivity filter; TXXTXGYG (Heginbotham et al. 1994).

In its open state when the channel activated, the pore opening step is distinct. This step is weakly voltage-dependent leading, to slow activation of $K_v2.1$ with unique kinetics supporting K^+ ion flux and therefore forming its physiological role in membrane excitability. In the channel's inactivating state, the channel remains dormant via two separate inactivation pathways and does not response to voltage changes across the membrane. Firstly, a very rapid inactivation pathway that involves conformational change of the N-terminus in the main subunit, leading to pore blocking of the channels, this known as an N-type inactivation or '*ball and chain*' inactivation (Rettig et al. 1994). However, the channel also undergoes a slower C-type inactivation mechanism, regulated at the selectivity filter, which involves the narrowing of outer mouth of the channel. An additional U-type rapid inactivation mechanism, involving a voltage-dependent recovery has also proposed (Klemic et al. 2001).

$K_v2.1$ as a drug target

Neurological

There is an array of evidence to support the targeting of $K_v2.1$ to manage a range of neurological conditions, arising from its expression profile throughout the brain (Uhlen et al. 2015) and in discreet neuronal loci (Maletic-Savatic et al. 1995; Misonou and Trimmer, 2004). This pattern allows the $K_v2.1$ protein to regulate neuronal excitability (Du et al. 1998; 2000) by its contribution to the delayed rectifier K^+ currents (Murakoshi and Trimmer, 1999). For example, within the hippocampus, $K_v2.1$ channels are reported to carry 50% of recorded delayed rectifier K^+ currents (Murakoshi and Trimmer, 1999). Genetic deletion of $K_v2.1$ leads to a hyperactive phenotype, characterised by accelerated seizure progression and increased sensitivity to anticonvulsants (Speca et al. 2014). Therefore, a clear therapeutic strategy would be to modify $K_v2.1$ activity under conditions of hyperexcitability. This role is supported further by human genetic studies indicating that mutations in $K_v2.1$, result in changes in activity and expression, leading to epilepsy (Bersell et al. 2014).

Alzheimer's Disease

The characteristic feature of Alzheimer's Disease (AD) is the plaques which form in the brain by the accumulation of fragments of β-amyloid (Aβ) protein (Selkoe, 1991). A result of this accumulation is the disruption of ionic homeostasis; while changes in Ca^{2+} have been extensively studied, a role for changes in K^+ homeostasis has also been proposed. In relation to $K_v2.1$, studies have identified altered levels of $K_v2.1$ channel mRNA expressed in cultured rat hippocampal neurons, which had been incubated *in vitro* with Aβ fragments (Jin et al. 2002); these studies are supported by comparable observations *in vivo* in drug-induced memory deficiency in the rat hippocampus (Zhong et al. 2005). While these are animal studies and link to accumulation of the amyloid beta peptide, they still demonstrates the sensitivity of K^+

channels to disease modification. More physiological research has demonstrated a link between the phosphorylation state of the $K_v2.1$ channel and neuronal hyperexcitability in hypoxia and ischemic stroke, where augmentation of the K^+ currents carried by the $K_v2.1$ channel results in suppression of hyperexcitability (Misonou et al. 2004; 2005). Interestingly the phosphorylation of $K_v2.1$ is regulated by AMPK, which is a master energy regulator in cellular metabolism (Ikematsu et al. 2011).

Cell death

Evidence suggests that the $K_v2.1$ channel has a distinct role in neuronal apoptosis, as demonstrated *in vitro* in cortical neurons, where the expression of $K_v2.1$ channels increased cellular susceptibility to apoptosis, when compared to dominant negative $K_v2.1$-transfected neurons (Pal et al. 2003). Moreover, a surge in $K_v2.1$ channel activity was observed in both HEK293 cells and CHO cells undergoing apoptosis following induced oxidative stress (Pal et al. 2006; Al-Owais et al. 2012). This apoptotic surge is mediated through p38 phosphorylation at the serine 800 site of the $K_v2.1$ channel (Redman et al. 2007) following Zn^{2+} activation of signal-regulating kinase 1 (ASK-1) (Aras and Aizenman, 2005). The requirement for Zn^{2+} mediated phosphorylation was also determined for the N-terminal residue tyrosine at position 124 of the channel (Redman et al. 2009). In fact, dual phosphorylation of S800 and Y124 aids trafficking of the $K_v2.1$ channels protein delivery to the plasma membrane (He et al. 2015), highlighting the channel's role in the apoptotic cascade.

Multiple signalling mechanisms are responsible for modulation of the $K_v2.1$ channel's activity: in hippocampal neurons; SUMOylation has been demonstrated to regulate the firing of cell excitability, by shifting the half-maximal activation voltage (Plant et al. 2011). While a reduction in the phosphorylation status of the channel alters the voltage-dependence of activation and location of $K_v2.1$ (Murakoshi et al. 1997; Mohapatra et al. 2007). Several amino acid residues on the carboxy terminal domain of the $K_v2.1$ channel are highly phosphorylated in neurons and rapid phosphorylation mediated by cyclin-dependent kinase 5 can restore neuronal excitability (Cerda and Trimmer, 2011), or can indeed suppress excitability, influencing hyperpolarizing shifts in the voltage-dependence of activation, when mediated by AMP-activated protein kinase (Ikematsu et al. 2011). Recently, S-sulfhydration, the post-translational modification of proteins by hydrogen sulfide (H_2S), has been shown to play a role in neuronal excitability surges, by increasing the action potential firing rate (Dallas et al. 2021).

To assess the therapeutical potential of prompting a decrease in pro-apoptotic $K_v2.1$ surges, and K^+ loss, thus increasing neuronal survival, the *in vitro* inhibition of $K_v2.1$ channel activity following ischemic insult resulted in suppression of hyperexcitability in neurons (Misonou et al. 2005). Additionally, *de novo* experiments using syntaxin-1A-mimicking peptides, which target the control of membrane trafficking insertion of the $K_v2.1$ channel protein, preventing the channel's clustering and disrupting its location on the plasma membrane, reduced cell death and enhanced the neurological outcome in an ischemic stroke model (Yeh et al. 2017). Indeed, recent *in vivo* observations of therapeutic peptides designed to disrupt the association between $K_v2.1$ and the vesicle-associated membrane protein-associated protein-A (VAP-A), thus reducing

the channel's trafficking to the membrane, have shown promising neuroprotection following administration in ischemic stroke mice. However, *in vitro* these peptides do not bind to VAP-A directly, suggesting another trafficking delivery mechanism may be involved (Schulein et al. 2020).

Alternatively, K^+ channel blockers such as tetraethylammonium and 4-aminopyridine could provide protection against apoptosis accelerated by a range of insults, including oxidative stress (Redman et al. 2007). Cholinesterase inhibitors, for example, donepezil, rivastigmine and galantamine, are approved drugs for use in early and mild stages of AD. These drugs have been shown to inhibit $K_v2.1$ (Zhang et al. 2004; Pan et al. 2003; Yuan et al. 2011) with donepezil, exhibiting beneficial effects on neuronal damage and on cognitive deficits following ischemic insults (Yuan et al. 2011). However, those blockers can also act on other K^+ channels, such as $K_v1.5$ and hERG (Li et al. 2017; Chae et al. 2015), thus producing detrimental side effects. Clearly, the development of a therapeutic agent that selectively acts on the $K_v2.l$ channel, without affecting other ion channels, would be advantageous. Research on 48F10, a norbornyl catechol derivative, which selectively inhibits the $K_v2.1$ channel with an IC_{50} value of 60μM, has shown to prevent oxidants-induced apoptosis in cortical neurons (Zaks-Makhina et al. 2004).

Metabolic

$K_v2.1$ is expressed in the pancreas (Yan et al. 2004), specifically, in the β-cells, playing a role in regulating membrane excitability, with a demonstrated role in regulating membrane repolarisation, consecutively controlling glucose-stimulated insulin secretion (Roe et al. 1996). Pancreatic β cells respond to high concentrations of glucose through membrane depolarization, in response to K^+ induced Ca^{2+} influx (Dawson et al. 1984), followed by rapid repolarisation when the K_v channels are active. The $K_v2.1$ channel has been found to be the main contributor to the voltage-dependent outward K^+ currents (MacDonald et al. 2001), thus its impact on insulin secretion has been extensively investigated.

In isolated rat islets, dominant negative knockout of $K_v2.1$ resulted in extensive reduction of the delayed rectifier K^+ currents and caused an increase in insulin production, following stimulation by glucose (MacDonald et al. 2002). This role was further highlighted by use of the specific $K_v2.1$ channel blocker hanatoxin, a toxin peptide isolated from Chilean rose tarantula venom (Swartz and MacKinnon, 1995). The inhibition of the $K_v2.1$ channel resulted in an increase in membrane potential, elevated intracellular Ca^{2+} oscillation in response to glucose, and improved glucose dose dependent insulin secretion (Tamarina et al. 2005). These results suggest that $K_v2.1$ could serve as a potential target in the treatment of type 2 diabetes, where the $K_v2.1$ channel is shown to be reduced in human β-cells isolated from type 2 diabetic patients (Fu et al. 2017).

Interestingly, the depolarization duration through outward K^+ currents can influence insulin exocytosis from cell plasma membrane (Figure 2), through membrane clustering of the $K_v2.1$ channels (Greitzer-Antes et al. 2018; Fu et al. 2019).

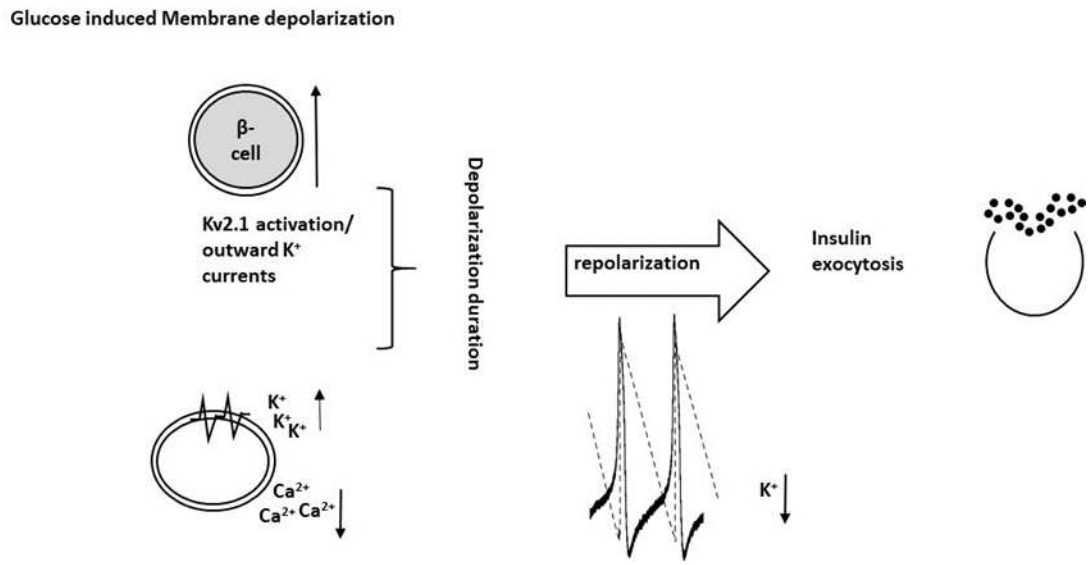

Figure 2. Schematic representation of glucose induced changes in β-cell membrane potential. Dynamic ionic flux resulting in an increase in membrane potential triggering rapid depolarization followed by rapid repolarization phase to restore the K^+ efflux via the opening of $K_v2.1$ channels influencing action potential duration and the subsequent firing of APs and insulin secretion.

$K_v2.1$ clustering aids in insulin exocytosis and contribute to rescuing dysfunctional human β-cell function (Fu et al. 2017). SNARE syntaxin1A and syntaxin-3 proteins are required for delivering these $K_v2.1$ clusters to the plasma membrane (Dai et al. 2012; Greitzer-Antes et al. 2018; Fu et al. 2019) and regulated through the SUMOylation-mediated $K_v2.1$ channels and thus regulation of pancreatic β-cell excitability (Plant et al. 2011). Glucose activation of β-cells results in action potential (AP) initiation. Following rapid depolarization, K_v channel activation facilitates the rapid repolarization phase of β-cell APs, restoring K^+ efflux via the opening of the channel, thus affecting the duration and the subsequent firing of APs (Jacobson and Philipson, 2007). Consequently, blocking the $K_v2.1$ channel in diabetic patients would contribute to inhibition of β-cell over-excitability and delay repolarisation of the action potential, therefore minimising K^+ loss and sustaining cytosolic Ca^{2+} (MacDonald and Wheeler, 2003).

However, the precise role of $K_v2.1$ in repolarization of the AP in human β cells is still unclear. It has been proposed that the large conductance Ca^{2+} activated K^+ channels (BK channels) are the main contributors to the repolarization phase in these cells, as stromatoxin inhibition of $K_v2.1$ had no effect on stimulated electrical activity in human β cells obtained from non-diabetic donors (Braun et al, 2008). Nevertheless, the significance of the $K_v2.1$ channel's role in human β-cells was demonstrated using *in vitro* studies; tetramers of the $K_v2.1$ channel were found to be clustered on the plasma membrane of human β cells and $K_v2.1$ knockdown had an adverse effect on the depolarization-induced exocytosis in human β-cells (Fu et al. 2017).

In addition, examination of the structure of β-cells, obtained from type 2 diabetic human donors revealed abnormalities in granule fusion, compared with non-diabetic donors. The density of these membrane-attached granules is regulated by clusters of K_v2, the relative proportion of these granule fusions are determined by SUMOylation at two $K_v2.1$ residues; K145 and K470 (Fu et al. 2019). Moreover, dual blocking of BK and $K_v2.1$ channel activities, during glucose triggered AP, resulted in an increase in amplitude, duration, and latency of the AP, indicating that the repolarizing phase involves multiple K^+ channels and does indeed include the $K_v2.1$ channel (MacDonald et al. 2002).

In further studies, $K_v2.1$ gene disruption in animal models resulted in the modification of β-cell electrical activity, including reduced firing frequency and the prolongation of AP duration, as well as enhanced insulin secretion (Jacobson et al. 2007), confirming the important role of $K_v2.1$ in modulating glucose-induced APs.

Furthermore, application of the pan K_v2 channel inhibitor, RY796, which selectively inhibits the $K_v2.1$ and $K_v2.2$ channels, lead to the enhancement of glucose-stimulated insulin secretion *in vitro* in both isolated mouse and human islets (Li et al. 2013). These effects were supported by the inhibition of the $K_v2.1$ channel using further pharmacological $K_v2.1$-specific blockers such as SP6616, and the small molecule inhibitor 4-ethoxy-N-{[6-(2-thienyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl]methyl}aniline (ETA) ameliorates hyperglycaemia and promotes β cell survival in diabetic mice (Zhou et al. 2016, Yao et al. 2013, Zhou et al. 2018). Even a modest inhibition of $K_v2.1$ channels can sustain cytosolic Ca^{2+} and stimulate insulin production, thus improving glucose tolerance in diabetic mice treated with glucagon-like peptide-1 based drugs; such observations have opened a new avenue to reduce the doses of such drugs and potentially the associated adverse effects, while attaining the same glycaemic control in type 2 diabetics (Sukma Rita et al. 2015).

In addition to improving glucose tolerance and enhancing insulin secretion, inhibition of $K_v2.1$ by the selective inhibitor, SP6616 in diabetic mice has been shown to improve the diabetic peripheral neuropathy-like pathology of the mice (Zhu et al. 2020), a summary of selected $K_v2.1$ inhibitors and their proposed role are listed in Table 1. For a more comprehensive picture of $K_v2.1$ pharmacological tools readers are signposted to the International Union of Basic and Clinical Pharmacology (IUPHAR) database (Attali et al., 2021).

Virology

Anti-apoptotic strategies are also employed by viruses and there is growing evidence that viruses manipulate K^+ homeostasis to their advantage for a number of processes from infection to replication (Gazzarrini et al. 2003; Gargan et al. 2021). There is also a body of evidence that supports the idea that a viral-encoded K^+ protein might be the K^+ channel protein evolutionary progenitor (Thiel et al. 2013). Modulating K^+ efflux through manipulation of $K_v2.1$ has been proposed to be an effective strategy used by the hepatitis C virus to maintain infectivity (Mankouri et al. 2009). This original observation indicated that the $K_v2.1$ channel had viral anti-apoptotic properties, and this has been developed further to indicate specific signalling mechanisms (Amako et al. 2013; Clemens et al. 2015). These observations have been used in generating a

novel neuroprotective strategy involving the interaction of the hepatitis C protein (NS5A) and the K_v2.1 protein (Justice et al. 2018).

Pharmacological approaches to influence K_v2.1 activity

Given the diverse array of physiological processes that K_v2.1 are involved in, there is a need for distinct pharmacological tools to modulate channel activity in an appropriate manner to offer therapeutic potential. Here we consider some options available that could be used to target diseases where K_v2.1 activity has been shown to regulate pathophysiology (see above).

Channel blockers

K^+ channel blockers such as tetraethylammonium (TEA) and 4-aminopyridine (4-AP) have been used to inhibit K_v2.1 to achieve an array of therapeutic goals. For example, direct channel blockade offered protection against apoptosis accelerated by a range of insults, including oxidative stress (Redman et al. 2007). In addition, 4-AP has been used in the management of multiple sclerosis (Henney & Blight. 2012) so there is a place for pan K_v blockers in the clinical but how much of the 4-AP effect is mediated by K_v2.1 inhibition is unclear. So, while pan K_v channel blockers have their place in the clinical they are likely to report a clinical benefit based on multiple drug-target interactions. Therefore, more selective tools are required to influence K_v2.1 channels to offer clinical potential. Here, more specific K_v2.1 tools have been used in highlighting discreet roles for the K_v2.1 protein (e.g., 48F10, Zaks-Makhina et al. 2004; Table 1). Of note here is that the 48F10 compound showed some selectively against other K_v channels (K_v1.5) 48F10 demonstrated inhibitory actions on the Kir2.1 channel. However, most of these new chemical entities are still experimental compounds, and further research is needed to explore their full target profiles.

Channel modulators

Channel blockade may afford therapeutic potential for broad spectrum conditions; however, another more targeted strategy would be the modulation of individual K_v2.1 channels. There are several approaches that have been tested that range from channel trafficking to channel gating modifications. K_v2.1 protein trafficking is an important determinant of channel assembly and insertion of operational channels into the plasma membrane. Removal of K^+ conductance pathways via K_v2.1 could be achieved by disrupting channel clustering that appear to act as supply platform for the channel's trafficking to the plasma membrane (Fox et al. 2015). Indeed, research has highlighted that this approach, targeted by calcineurin-mediated dephosphorylation, disrupted K_v2.1 channel clustering, and afforded greater neuroprotection (Misonou et al. 2004; Shepherd et al. 2012).

Small molecule mediated gating modification has also been demonstrated to offer therapeutic potential. This has been reported for experimental compounds such as the tarantula guangxitoxin-1E (GxTx) which modulates K_v2.1 activity by increasing time in the closed state (Tilley et al. 2019). This has led to the development of high throughput screens looking to identify novel gating modifiers (Schmalhofer et al, 2009. While the search for novel gating modifiers is underway, existing medicines have been reported to act through K_v2.1 dependent mechanisms. Evidence suggests that existing the anti-tumour drug perifosine can alter the inactivation gate with the K_v2.1 channel complex

leading to a hyperpolarising shift in the voltage dependence of $K_v2.1$ (Delgado-Ramirez et al., 2016). This $K_v2.1$ modulation may underpin the anti-tumour effects in tandem with the more widely reported perifosine mediated Akt inhibition (Taniguchi et al. 2021).

In summary, the $K_v2.1$ channel is a promising drug target in a range of cell types to address distinct therapeutic areas. The work exploring modulation of $K_v2.1$ in diabetes has provided a pathway to research and development programmes. Evidence indicates that blockade of $K_v2.1$ channels in β-cells could promote insulin release with a lower risk of hypoglycaemic events compared with the more appreciated K_{ATP} channel blockers (e.g., sulfonylureas). Suppression of channel activity to a level above the reported IC_{50} threshold would be more advantageous as opposed to full blockade, and depending on the route of administration could mitigate other disease related pathology, such as diabetes associated neuropathy (Xu et al, 2020). This chapter also indicates interesting datasets about drug repurposing and some previously unreported effects on the $K_v2.1$ channel that could enhance clinical benefits of currently approved medicines. With respect to the other therapeutic areas highlighted in this chapter (e.g., neurological) more detailed structural and functional studies to provide the cell and channel specific reagents are needed to realise $K_v2.1$ targeted therapies.

References

Al-Owais MM, Scragg JL, Dallas ML, Boycott HE, Warburton P, Chakrabarty A, Boyle JP, Peers C. (2012) Carbon monoxide mediates the anti-apoptotic effects of heme oxygenase-1 in medulloblastoma DAOY cells via K+ channel inhibition. J Biol Chem. 287: 24754-64. DOI: 10.1074/jbc.M112.357012

Amako Y, Igloi Z, Mankouri J, Kazlauskas A, Saksela K, Dallas M, Peers C, Harris M. (2013) Hepatitis C virus NS5A inhibits mixed lineage kinase 3 to block apoptosis. J Biol Chem. 288(34):24753-63. DOI: 10.1074/jbc.M113.491985

Attali B, Chandy KG, Giese MH, Grissmer S, Gutman GA, Jan LY, Lazdunski M, Mckinnon D, Nerbonne J, Pardo LA, Robertson GA, Rudy B, Sanguinetti MC, Stühmer W, Trimmer JS, Wang X. (2019) Voltage-gated potassium channels (K_v) in the IUPHAR/BPS Guide to Pharmacology Database. IUPHAR/BPS Guide to Pharmacology CITE. 2019(3). DOI: https://doi.org/10.2218/gtopdb/F81/2021.3

Bersell KR, Jorge BS, Kearney JA, GeorgeJr, AL. (2014) Epilepsy-Associated Point Mutation in the Pore Domain of K_v2.1. Biophysical Journal. 106; 2. Supp1, pg 433a

Braun M, Ramracheya R, Bengtsson M, Zhang Q, Karanauskaite J, Partridge C, Johnson PR, Rorsman P. (2008) Voltage-gated ion channels in human pancreatic beta-cells: electrophysiological characterization and role in insulin secretion. Diabetes. 57: 1618-28. DOI: 10.2337/db07-0991

Butler A, Wei AG, Baker K, Salkoff L A. (1989) family of putative potassium channel genes in Drosophila. Science. 243: 943-947. DOI: 10.1126/science.2493160

Cerda O, Trimmer JS. (2011) Activity-dependent phosphorylation of neuronal K_v2.1 potassium channels by CDK5. J Biol Chem. 286: 28738-28748. DOI: 10.1074/jbc.M111.251942

Chae YJ, Lee HJ, Jeon JH, Kim IB, Choi JS, Sung KW, Hahn SJ. (2015) Effects of donepezil on hERG potassium channels. Brain Res. 1597: 77-85. DOI: 10.1016/j.brainres.2014.11.057

Clemens K, Yeh CY, Aizenman E. (2015) Critical role of Casein kinase 2 in hepatitis C NS5A-mediated inhibition of K_v2.1 K(+) channel function. Neurosci Lett. 609:48-52. DOI: 10.1016/j.neulet.2015.10.021

Dai XQ, Manning Fox JE, Chi$K_v$ashvili D, Casimir M, Plummer G, Hajmrle C, Spigelman AF, Kin T, Singer-Lahat D, Kang Y, Shapiro AM, Gaisano HY, Lotan I, Macdonald PE. (2012) The voltage-dependent potassium channel subunit K_v2.1 regulates insulin secretion from rodent and human islets independently of its electrical function. Diabetologia. 55: 1709-20. DOI: 10.1007/s00125-012-2512-6

Dallas ML, Al-Owais MM, Hettiarachchi NT, Vandiver MS, Jarosz-Griffiths HH, Scragg JL, Boyle JP, Steele D, Peers C. (2021) Hydrogen sulfide regulates hippocampal neuron excitability via S-sulfhydration of K_v2.1. Sci Rep. 11: 8194. DOI: 10.1038/s41598-021-87646-5

Dawson CM, Atwater I, Rojas E. (1984) The response of pancreatic beta-cell membrane potential to potassium-induced calcium influx in the presence of glucose. Q J Exp Physiol. 69: 819-30. DOI: 10.1113/expphysiol.1984.sp002871

Delgado-Ramírez M, Morán-Zendejas R, Aréchiga-Figueroa IA, Toro-Castillo C, Ramírez-Martínez JF, Rodríguez-Menchaca AA. (2016) Modulation of the voltage-gated potassium channel $K_v2.1$ by the anti-tumor alkylphospholipid perifosine. Pharmacol Rep. 68(2):457-61. DOI: 10.1016/j.pharep.2015.11.006

Du J, Haak LL, Phillips-Tansey E, Russell JT, McBain CJ. (2000) Frequency-dependent regulation of rat hippocampal somato-dendritic excitability by the K^+ channel subunit $K_v2.1$. J Physiol. 522: 19-31. DOI: 10.1111/j.1469-7793.2000.t01-2-00019.xm

Du J, Tao-Cheng JH, Zerfas P, McBain CJ. (1998) The K+ channel, $K_v2.1$, is apposed to astrocytic processes and is associated with inhibitory postsynaptic membranes in hippocampal and cortical principal neurons and inhibitory interneurons. Neuroscience. 84: 37-48. DOI: 10.1016/S0306-4522(97)00519-8

Fox PD, Haberkorn CJ, Akin EJ, Seel PJ, Krapf D, Tamkun MM. (2015) Induction of stable ER-plasma-membrane junctions by $K_v2.1$ potassium channels. J Cell Sci. 128: 2096-105. DOI: 10.1242/jcs.166009

Frech GC, VanDongen AM, Schuster G, Brown AM, and Joho RH. (1989) A novel potassium channel with delayed rectifier properties isolated from rat brain by expression cloning. Nature. 340: 642-645. DOI: 10.1038/340642a0

Fu J, Dai X, Plummer G, Suzuki K, Bautista A, Githaka JM, Senior L, Jensen M, Greitzer-Antes D, Manning Fox JE, Gaisano HY, Newgard CB, Touret N, MacDonald PE. (2017) $K_v2.1$ Clustering Contributes to Insulin Exocytosis and Rescues Human β-Cell Dysfunction. Diabetes. 66: 1890-1900. DOI: 10.2337/db16-1170

Fu J, Githaka JM, Dai X, Plummer G, Suzuki K, Spigelman AF, Bautista A, Kim R, Greitzer-Antes D, Fox JEM, Gaisano HY, MacDonald PE. (2019) A glucose-dependent spatial patterning of exocytosis in human β-cells is disrupted in type 2 diabetes. JCI Insight. 5: e127896. DOI: 10.1172/jci.insight.127896

Gargan S, and Stevenson NJ. (2021) Unravelling the Immunomodulatory Effects of Viral Ion Channels, towards the Treatment of Disease. Viruses. 27;13(11):2165. DOI: 10.3390/v13112165

Gazzarrini S, Severino M, Lombardi M, Morandi M, DiFrancesco D, Van Etten JL, Thiel G, Moroni A. (2003) The viral potassium channel Kcv: structural and functional features. FEBS Lett. 18;552(1):12-6. DOI: 10.1016/s0014-5793(03)00777-4

Greitzer-Antes D, Xie L, Qin T, Xie H, Zhu D, Dolai S, Liang T, Kang F, Hardy AB, He Y, Kang Y, Gaisano HY. (2018) $K_v2.1$ clusters on β-cell plasma membrane act as reservoirs that replenish pools of newcomer insulin granule through their interaction with syntaxin-3. J Biol Chem. 293: 6893-6904. DOI: 10.1074/jbc.RA118.002703

Grizel A, Popinako A, Kasimova MA, Stevens L, Karlova M, Moisenovich MM, Sokolova OS. (2014) Domain structure and conformational changes in rat $K_v2.1$ ion channel. J Neuroimmune Pharmacol. 9:727-39. DOI: 10.1007/s11481-014-9565-x

Grishin A, Ford H, Wang J, Li H, Salvador-Recatala V, Levitan ES, Zaks-Makhina E. (2005) Attenuation of apoptosis in enterocytes by blockade of potassium channels. Am J Physiol Gastrointest Liver Physiol. 289(5):G815-21.DOI: 10.1152/ajpgi.00001.2005

Gutman GA, Chandy KG, Adelman JP, Aiyar J, Bayliss DA, Clapham DE, Covarriubias M, Desir GV, Furuichi K, Ganetzky B, Garcia ML, Grissmer S, Jan LY, Karschin A, Kim D, Kuperschmidt S, Kurachi Y, Lazdunski M, Lesage F, Lester HA, McKinnon D, Nichols CG, O'Kelly I, Robbins J, Robertson GA, Rudy B, Sanguinetti M, Seino S, Stuehmer W, Tamkun MM, Vandenberg CA, Wei A, Wulff H, Wymore RS (2003) International Union of Pharmacology. XLI. Compendium of voltage-gated ion channels: potassium channels. Pharmacol Rev. 55: 583-586. DOI: 10.1124/pr.55.4.9

Gupta P, Tiwari S, Singh A, Pal A, Mishra A, Singh S. (2021) Rivastigmine attenuates the Alzheimer's disease related protein degradation and apoptotic neuronal death signalling. Biochem J. 478(7):1435-1451. DOI: 10.1042/BCJ20200754

He K, McCord MC, Hartnett KA, Aizenman E. (2015) Regulation of Pro-Apoptotic Phosphorylation of $K_v2.1$ K+ Channels. PLoS One. 10: e0129498. DOI: 10.1371/journal.pone.0129498

Heginbotham L, Lu Z, Abramson T, MacKinnon R. (1994) Mutations in the K+ channel signature sequence. Biophys. J. 66: 1061-1067. DOI: 10.1016/S0006-3495(94)80887-2

Henney HR 3rd, Blight AR. (2012) Walking impairment in patients with multiple sclerosis - a new therapeutic approach and clinical potential of dalfampridine extended release tablets. Degener Neurol Neuromuscul Dis. 2:53-64. DOI: 10.2147/DNND.S19839

Hwang PM, Glatt CE, Bredt DS, Yellen G, and Snyder SH. (1992) A novel K+ channel with unique localizations in mammalian brain: molecular cloning and characterization. Neuron. 8: 473-481. DOI: 10.1016/0896-6273(92)90275-i

Ikematsu N, Dallas ML, Ross FA, Lewis RW, Rafferty JN, David JA, Suman R, Peers C, Hardie DG, Evans AM. (2011) Phosphorylation of the voltage-gated potassium channel $K_v2.1$ by AMP-activated protein kinase regulates membrane excitability. Proc Natl Acad Sci U S A. 108: 18132-7. DOI: 10.1073/pnas.1106201108

Jacobson DA, Philipson LH. (2007) Action potentials and insulin secretion: new insights into the role of K_v channels. Diabetes Obes Metab. 9: 89-98. DOI: 10.1111/j.1463-1326.2007.00784.x

Jacobson DA, Kuznetsov A, Lopez JP, Kash S, Ammälä CE, Philipson LH. (2007) $K_v2.1$ ablation alters glucose-induced islet electrical activity, enhancing insulin secretion. Cell Metab. 6: 229-35. DOI: 10.1016/j.cmet.2007.07.010

Jin HW, Zhang W, Wang XL. (2002) Effects of chronic exposure to beta-amyloid-peptide25–35 on the mRNA expressions of voltage-gated outward potassium channel subunits in cultured rat hippocampal neurons. Acta Pharmaceutica Sinica. 37: 598–602.

Ju M, Stevens L, Leadbitter E, Wray D. (2003) The Roles of N- and C-terminal determinants in the activation of the K_v2.1 potassium channel. J. Biol. Chem. 278: 12769-12778. DOI: 10.1074/jbc.M212973200

Justice JA, Manjooran DT, Yeh CY, Hartnett-Scott KA, Schulien AJ, Kosobucki GJ, Mammen S, Palladino MJ, Aizenman E. (2018) Molecular Neuroprotection Induced by Zinc-Dependent Expression of Hepatitis C-Derived Protein NS5A Targeting K_v2.1 Potassium Channels. J Pharmacol Exp Ther. 367(2):348-355. DOI: 10.1124/jpet.118.252338

Klemic KG, Kirsch GE, Jones SW. (2001) U-type inactivation of K_v3.1 and Shaker potassium channels. Biophys. J. 81:814–826. DOI: 10.1016/S0006-3495(01)75743-8

Kyle B, Bradley E, Ohya S, Sergeant GP, McHale NG, Thornbury KD, Hollywood MA. (2011) Contribution of K_v2.1 channels to the delayed rectifier current in freshly dispersed smooth muscle cells from rabbit urethra. Am J Physiol Cell Physiol. 301(5):C1186-200. DOI: 10.1152/ajpcell.00455.2010

Li K, Cheng N, Li XT. (2017) Inhibitory effects of cholinesterase inhibitor donepezil on the K_v1.5 potassium channel. Sci Rep. DOI: 10.1038/srep41509

Li X, Herrington J, Petrov A, Ge L, Eiermann G, Xiong Y, Jensen MV, Hohmeier HE, Newgard CB, Garcia ML, Wagner M, Zhang BB, Thornberry NA, Howard AD, Kaczorowski GJ, Zhou YP. (2013) The role of voltage-gated potassium channels K_v2.1 and K_v2.2 in the regulation of insulin and somatostatin release from pancreatic islets. J Pharmacol Exp Ther. 344: 407-16. DOI: 10.1124/jpet.112.199083

Lim ST, Antonucci DE, Scannevin RH, Trimmer JS. (2000) A novel targeting signal for proximal clustering of the K_v2.1 K+ channel in hippocampal neurons. Neuron. 25: 385-97. DOI: 10.1016/s0896-6273(00)80902-2

MacDonald PE, Ha XF, Wang J, Smukler SR, Sun AM, Gaisano HY, Salapatek AM, Backx PH, Wheeler MB. (2001) Members of the K_v1 and K_v2 voltage-dependent K(+) channel families regulate insulin secretion. Mol Endocrinol. 15: 1423-35. DOI: 10.1210/mend.15.8.0685

MacDonald PE, Sewing S, Wang J, Joseph JW, Smukler SR, Sakellaropoulos G, Wang J, Saleh MC, Chan CB, Tsushima RG, Salapatek AM, Wheeler MB. (2002) Inhibition of K_v2.1 voltage-dependent K+ channels in pancreatic beta-cells enhances glucose-dependent insulin secretion. J Biol Chem. 277:44938–44945. DOI: 10.1074/jbc.M205532200

MacDonald PE, Wheeler MB. (2003) Voltage-dependent K(+) channels in pancreatic beta cells: role, regulation and potential as therapeutic targets. Diabetologia. 46: 1046-62. DOI: 10.1007/s00125-003-1159-8

Maletic-Savatic M, Lenn NJ, Trimmer JS. (1995) Differential spatiotemporal expression of K+ channel polypeptides in rat hippocampal neurons developing in situ and in vitro. J Neurosci. 15: 3840-51. DOI: 10.1523/JNEUROSCI.15-05-03840.1995

Mankouri J, Dallas ML, Hughes ME, Griffin SD, Macdonald A, Peers C, Harris M. (2009) Suppression of a pro-apoptotic K+ channel as a mechanism for hepatitis C virus persistence. Proc Natl Acad Sci U S A. 106(37):15903-8. DOI: 10.1073/pnas.0906798106

Misonou H, Mohapatra DP, Menegola M, Trimmer JS. (2005) Calcium- and metabolic state-dependent modulation of the voltage-dependent $K_v2.1$ channel regulates neuronal excitability in response to ischemia. J Neurosci. 25: 11184-93. DOI: 10.1523/JNEUROSCI.3370-05.2005

Misonou H, Mohapatra DP, Park EW, Leung V, Zhen D, Misonou K, Anderson AE, Trimmer JS. (2004) Regulation of ion channel localization and phosphorylation by neuronal activity. Nat Neurosci. 7: 711-8. DOI: 10.1038/nn1260

Misonou H, Trimmer JS. (2004) Determinants of voltage-gated potassium channel surface expression and localization in Mammalian neurons. Crit Rev Biochem Mol Biol. 39: 125-45. DOI: 10.1080/10409230490475417

Mohapatra DP, Park KS, Trimmer JS. (2007) Dynamic regulation of the voltage-gated $K_v2.1$ potassium channel by multisite phosphorylation. Biochem Soc Trans. 35: 1064-8. DOI: 10.1042/BST0351064

Murakoshi H, Shi G, Scannevin RH, Trimmer JS. (1997) Phosphorylation of the $K_v2.1$ K+ channel alters voltage-dependent activation. Mol Pharmacol. 52: 821-8. DOI: 10.1124/mol.52.5.821

Murakoshi H, Trimmer JS. (1999) Identification of the $K_v2.1$ K+ channel as a major component of the delayed rectifier K+ current in rat hippocampal neurons. J Neurosci. 19: 1728-35. DOI: 10.1523/JNEUROSCI.19-05-01728.1999

Pal S, Hartnett KA, Nerbonne JM, Levitan ES, Aizenman E. (2003) Mediation of neuronal apoptosis by $K_v2.1$-encoded potassium channels. J Neurosci. 23: 4798-802. DOI: 10.1523/JNEUROSCI.23-12-04798.2003

Pal SK, Takimoto K, Aizenman E, Levitan ES. (2006) Apoptotic surface delivery of K+ channels. Cell Death Differ. 13: 661-7. DOI: 10.1038/sj.cdd.4401792

Pan Y, Xu X, Wang X. (2003) Rivastigmine blocks voltage-activated K+ currents in dissociated rat hippocampal neurons. Br J Pharmacol. 140: 907-12. DOI: 10.1038/sj.bjp.0705503

Park HW, Song MS, Sim HJ, Ryu PD, Lee SY. (2021) The role of the voltage-gated potassium channel, $K_v2.1$ in prostate cancer cell migration. BMB Rep. 54(2):130-135. DOI: 10.5483/BMBRep.2021.54.2.210

Plant LD, Dowdell EJ, Dementieva IS, Marks JD, Goldstein SA. (2011) SUMO modification of cell surface $K_v2.1$ potassium channels regulates the activity of rat hippocampal neurons. J Gen Physiol. 137: 441-54. DOI: 10.1085/jgp.201110604

Redman PT, Hartnett KA, Aras MA, Levitan ES, Aizenman E. (2009) Regulation of apoptotic potassium currents by coordinated zinc-dependent signaling. J Physiol. 587: 4393-404. DOI: 10.1113/jphysiol.2009.176321

Redman PT, He K, Hartnett KA, Jefferson BS, Hu L, Rosenberg PA, Levitan ES, Aizenman E. (2007) Apoptotic surge of potassium currents is mediated by p38 phosphorylation of $K_v2.1$. Proc Natl Acad Sci U S A. 104: 3568-73. DOI: 10.1073/pnas.0610159104

Rettig J, Heinemann SH, Wunder F, Lorra C, Parcej DN, Dolly JO, Pongs O. (1994) Inactivation properties of voltage-gated K+ channels altered by presence of beta-subunit. Nature. 369(6478):289-94. DOI: 10.1038/369289a0

Roe MW, Worley JF III, Mittal AA, Kuznetsov A, DasGupta S, Mertz RJ, Witherspoon SM 3rd, Blair N, Lancaster ME, McIntyre MS, Shehee WR, Dukes ID, Philipson LH. (1996) Expression and function of pancreatic beta-cell delayed rectifier K+ channels. Role in stimulus-secretion coupling. J. Biol. Chem. 271: 32241-32246. DOI: 10.1074/jbc.271.50.32241

Schulien AJ, Yeh CY, Orange BN, Pav OJ, Hopkins MP, Moutal A, Khanna R, Sun D, Justice JA, Aizenman E. (2020) Targeted disruption of K_v2.1-VAPA association provides neuroprotection against ischemic stroke in mice by declustering K_v2.1 channels. Sci Adv. 1;6(27):eaaz8110. DOI: 10.1126/sciadv.aaz8110

Schütter N, Barreto YC, Vardanyan V, Hornig S, Hyslop S, Marangoni S, Rodrigues-Simioni L, Pongs O, Dal Belo CA. (2019) Inhibition of K_v2.1 Potassium Channels by MiDCA1, A Pre-Synaptically Active PLA2-Type Toxin from Micrurus dumerilii carinicauda Coral Snake Venom. Toxins (Basel). 11(6):335. DOI: 10.3390/toxins11060335

Schmalhofer WA, Ratliff KS, Weinglass A, Kaczorowski GJ, Garcia ML, Herrington (2009) A K_v2.1 gating modifier binding assay suitable for high throughput screening. J.Channels (Austin). 3(6):437-47. DOI: 10.4161/chan.3.6.10201

Selkoe DJ. (1991) The molecular pathology of Alzheimer's disease. Neuron. 6: 487–498. DOI: 10.1016/0896-6273(91)90052-2

Shepherd AJ, Loo L, Gupte RP, Mickle AD, Mohapatra DP. (2012) Distinct modifications in K_v2.1 channel via chemokine receptor CXCR4 regulate neuronal survival-death dynamics. J Neurosci. 32: 17725-39. DOI: 10.1523/JNEUROSCI.3029-12.2012

Speca DJ, Ogata G, Mandikian D, Bishop HI, Wiler SW, Eum K, Wenzel HJ, Doisy ET, Matt L, Campi KL, Golub MS, Nerbonne JM, Hell JW, Trainor BC, Sack JT, Schwartzkroin PA, Trimmer JS. (2014) Deletion of the K_v2.1 delayed rectifier potassium channel leads to neuronal and behavioral hyperexcitability. Genes Brain Behav. 13(4):394-408. DOI: 10.1111/gbb.12120

Sukma Rita R, Dezaki K, Kurashina T, Kakei M, Yada T. (2015) Partial blockade of K_v2.1 channel potentiates GLP-1's insulinotropic effects in islets and reduces its dose required for improving glucose tolerance in type 2 diabetic male mice. Endocrinology. 156: 114-23. DOI: 10.1210/en.2014-1728

Suzuki T, Takimoto K. (2004) Selective expression of HERG and K_v2 channels influences proliferation of uterine cancer cells. Int J Oncol. 25(1):153-9.

Swartz KJ, and MacKinnon R. (1995) An inhibitor of the K_v2.1 potassium channel isolated from the venom of a Chilean tarantula. Neuron. 15: 941-9. DOI: 10.1016/0896-6273(95)90184-1

Tamarina NA, Kuznetsov A, Fridlyand LE, Philipson LH. (2005) Delayed-rectifier (K_v2.1) regulation of pancreatic beta-cell calcium responses to glucose: inhibitor specificity and modeling. Am J Physiol Endocrinol Metab. 289: E578-85. DOI: 10.1152/ajpendo.00054.2005

Tamkun MM, O'connell KM, Rolig AS. (2007) A cytoskeletal-based perimeter fence selectively corrals a sub-population of cell surface K_v2.1 channels. J Cell Sci. 120: 2413-23. DOI: 10.1242/jcs.007351

Taniguchi K, Suzuki T, Okamura T, Kurita A, Nohara G, Ishii S, Kado S, Takagi A, Tsugane M, Shishido Y. (2021) Perifosine, a Bioavailable Alkylphospholipid Akt Inhibitor, Exhibits Antitumor Activity in Murine Models of Cancer Brain Metastasis Through Favorable Tumor Exposure. Front Oncol. 11:754365. DOI: 10.3389/fonc.2021.754365

Thiel G, Moroni A, Blanc G, Van Etten JL. (2013) Potassium ion channels: could they have evolved from viruses? Plant Physiol. 162(3):1215-24. DOI: 10.1104/pp.113.219360

Tilley DC, Angueyra JM, Eum KS, Kim H, Chao LH, Peng AW, Sack JT. (2019) The tarantula toxin GxTx detains K^+ channel gating charges in their resting conformation. J Gen Physiol. 151(3):292-315. DOI: 10.1085/jgp.201812213

Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, Olsson I, Edlund K, Lundberg E, Navani S, Szigyarto CA, Odeberg J, Djureinovic D, Takanen JO, Hober S, Alm T, Edqvist PH, Berling H, Tegel H, Mulder J, Rockberg J, Nilsson P, Schwenk JM, Hamsten M, von Feilitzen K, Forsberg M, Persson L, Johansson F, Zwahlen M, von Heijne G, Nielsen J, Pontén F. (2015) Proteomics. Tissue-based map of the human proteome. Science. 23;347(6220):1260419. DOI: 10.1126/science.1260419

Wei L, Yu SP, Gottron F, Snider BJ, Zipfel GJ, Choi DW. (2003) Potassium channel blockers attenuate hypoxia- and ischemia-induced neuronal death in vitro and in vivo. Stroke. 34(5):1281-6. DOI: 10.1161/01.STR.0000065828.18661.FE

Xu Z, Khan S, Schnicker NJ, Baker S. (2022) Pentameric assembly of the K_v2.1 tetramerization domain. Acta Crystallogr D Struct Biol. 78: 792-802. DOI: 10.1107/S205979832200568X

Xu X, Xu X, Hao Y, Zhu X, Lu J, Ouyang X, Lu Y, Huang X, Li Y, Wang J, Shen X. (2020) Antispasmodic Drug Drofenine as an Inhibitor of K_v2.1 Channel Ameliorates Peripheral Neuropathy in Diabetic Mice. iScience. 23(10):101617. DOI: 10.1016/j.isci.2020.101617

Yan L, Figueroa DJ, Austin CP, Liu Y, Bugianesi RM, Slaughter RS, et al. (2004) Expression of voltage-gated potassium channels in human and rhesus pancreatic islets. Diabetes. 53: 597-607. DOI: 10.2337/diabetes.53.3.597

Yao XG, Chen F, Li P, Quan L, Chen J, Yu L, Ding H, Li C, Chen L, Gao Z, Wan P, Hu L, Jiang H, Shen X. (2013) Natural product vindoline stimulates insulin secretion and efficiently ameliorates glucose homeostasis in diabetic murine models. J Ethnopharmacol. 150: 285-97. DOI: 10.1016/j.jep.2013.08.043

Yeh CY, Bulas AM, Moutal A, Saloman JL, Hartnett KA, Anderson CT, Tzounopoulos T, Sun D, Khanna R, Aizenman E. (2017) Targeting a Potassium Channel/Syntaxin

Interaction Ameliorates Cell Death in Ischemic Stroke. J Neurosci. 37: 5648-5658. DOI: 10.1523/JNEUROSCI.3811-16.2017

Yuan H, Wang WP, Feng N, Wang L, Wang XL. (2011) Donepezil attenuated oxygen-glucose deprivation insult by blocking K_v2.1 potassium channels. Eur J Pharmacol. 657: 76-83. DOI: 10.1016/j.ejphar.2011.01.054

Yu SP, Yeh CH, Sensi SL, Gwag BJ, Canzoniero LMT, Farhangrazi ZS, Ying HS, Tian M, Dugan LL, Choi DW. (1997) Mediation of neuronal apoptosis by enhancement of outward potassium current. Science.278: 114–117. DOI: 10.1126/science.278.5335.114

Zaks-Makhina E, Kim Y, Aizenman E, Levitan ES. (2004) Novel neuroprotective K+ channel inhibitor identified by high-throughput screening in yeast. Mol Pharmacol. 65: 214-9. DOI: 10.1124/mol.65.1.214

Zhang HX, Zhang W, Jin HW, Wang XL. (2004) Galantamine blocks cloned K_v2.1, but not K_v1.5 potassium channels. Brain Res Mol Brain Res. 131: 136-40. DOI: 10.1016/j.molbrainres.2004.08.010

Zhong CB, Pan YP, Tong XY, Xu XH, Wang XL. (2005) Delayed rectifier potassium currents and K_v2.1 mRNA increase in hippocampal neurons of scopolamine-induced memory-deficient rats. Neurosci Lett. 373: 99-104. DOI: 10.1016/j.neulet.2004.09.069

Zhou T, Du M, Zhao T, Quan L, Zhu Z, Chen J. (2018) ETA as a novel K_v2.1 inhibitor ameliorates β-cell dysfunction and hyperglycaemia. Clin Exp Pharmacol Physiol. 45: 1257-1264. DOI: 10.1111/1440-1681.13011

Zhou TT, Quan LL, Chen LP, Du T, Sun KX, Zhang JC, Yu L, Li Y, Wan P, Chen LL, Jiang BH, Hu LH, Chen J, Shen X. (2016) SP6616 as a new K_v2.1 channel inhibitor efficiently promotes β-cell survival involving both PKC/Erk1/2 and CaM/PI3K/Akt signaling pathways. Cell Death Dis. 7: e2216. DOI: 10.1038/cddis.2016.119

Zhu X, Chen Y, Xu X, Xu X, Lu Y, Huang X, Zhou J, Hu L, Wang J, Shen X. (2020) SP6616 as a K_v2.1 inhibitor efficiently ameliorates peripheral neuropathy in diabetic mice. EBioMedicine. 61:103061. DOI: 10.1016/j.ebiom.2020.103061

Compound	Reported physiological role	Concentration	System tested	In vitro/In vivo	Ref
Tetraethylammonium	Blocked excessive pro-apoptotic K^+ efflux	5 mM	Murine cortical cultures	*In vitro*	Yu et al. 1997; Wei et al. 2003
	Reduced cerebral infarct volume	5 µg/kg	Ischemic rats	*In vivo*	Wei et al. 2003
Donezepil	Reduced oxygen-glucose deprivation-induced apoptosis	30 µM	HEK293 expressing $K_v2.1$	*In vitro*	Yuan et al. 2011
Rivastigmine	Improved proteasome activity contributing to amyloid aggregation removal	2 mg/kg	Rat cortex and hippocampus	*In vivo*	Gupta et al, 2021
MiDCA1 Toxin	Induced hydrolysis of phosphatidylcholine	1 µM	Isolated murine dorsal root ganglion neurons	*In vitro*	Schütter et al. 2019
			Xenopus oocyte expressing $K_v2.1$	*In vitro*	
Hanatoxin	Blocked K^+ channels	0.5 µM	Xenopus oocyte expressing $K_v2.1$	*In vitro*	Swartz and MacKinnon. 1995
	Reduced proliferation	0.2-1 µM	Uterine cancer cells	*In vivo*	Suzuki and Takimoto. 2004
48F10	Supressed oxidative induced apoptosis	1-3 µM	Rat cortical neurons	*In vitro*	Zaks-Makhina et al. 2004
		IC_{50} 1 µM	CHO cells expressing $K_v2.1$	*In vitro*	
		10 µM	IEC-6 enterocytes	*In vitro*	Grishin et al. 2005
SP6616	Promoted glucose-stimulated insulin secretion (GSIS); Promoted β-cell survival	1–10 µM	INS-1 832/13 Rat Insulinoma Cell Line	*In vitro*	Zhou et al., 2016
	Ameliorated hyperglycaemia and β-cell dysfunction	IC_{50} 2.58 µM	CHO cells expressing $K_v2.1$	*In vitro*	
	Ameliorated peripheral neuropathy	20 and 40 mg/kg	Diabetic mice	*In vivo*	Zhou et al., 2020
ETA	Ameliorated hyperglycaemia and improved β-cell dysfunction	20 mg/kg/day	Type 2 diabetic mice	*In vivo*	Zhou et al., 2018

		20 μM	INS-1 832/13 Rat Insulinoma Cell Line	*In vitro*	
Vindoline	Stimulates insulin secretion and enhanced GSIS	20 mg/kg	Diabetic models (mice) type 2 diabetic (rats)	*In vivo*	Yao et al., 2013
		IC_{50} 50 μM	MIN6 mouse insulinoma cell line and primary mice islets	*In vitro*	
Stromatoxin-1	Modulated insulin secretion	100 nM	Human β-cells	*In vitro*	Braun et al, 2008
	Modulation of myogenic contraction in concert with BK channels	300 nM	Rabbit urethral smooth muscle cells	*In vitro*	Kyle et al, 2011
	Blockade of channel pore	150 nM	HEK293 expressing $K_v2.1$	*In vitro*	
	Reduced proliferation	600 nM	Prostate cancer cells	*In vitro*	Park et al, 2021
Perifosine	Inactivation gate modifier	0.3 μM	HEK293 expressing $K_v2.1$	*In vitro*	Delgado-Ramírez et al. 2016

Table 1. Selected summary list of investigated $K_v2.1$ inhibitors and their proposed/reposted physiological role.