Kv7 channels a potential therapeutic target in fibromyalgia: A hypothesis

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INTRODUCTION

Adequate relief with current pharmacological approaches for persistent pain is often unmet, with up to two-thirds of patients remaining refractory to treatment and reporting dissatisfaction with current therapies[1]. Further, the drug treatments are often liable to various central side effects because therapeutic targets are often within the central nervous system (CNS)[2]. Persistent pain remains a significant unmet medical need as a consequence of the understanding of the underlying mechanisms involved in the pathophysiology being limited with the complex interplay among those mechanisms having not been resolved. Preclinical research investigations of several potential targets for drug discovery involving mechanisms associated with the development and maintenance of persistent pain are offering urgently needed novel approaches for analgesic drug design[2].

Potassium (K^+) channels, a diverse and widely distributed family of ion channels, play a crucial role in the cellular physiology of neuronal activity throughout the nervous system, and have a prominent involvement in nociceptive processing, particularly in regulating peripheral hyperexcitability[3]. As a consequence of differential channel subtype expression and function in the nociceptive pathways, K^+ channels are important regulators of a number of physiological processes, such as membrane potential, peripheral nerve terminal action potential initiation, firing adaption in excitable tissues, axonal conduction and neurotransmitter release. Activation of K^+ channels in the peripheral and CNS has been associated with a range of anti-nociceptive drugs[4]. The anti-nociception induced by agonists of G-protein-coupled receptors such as α2-adrenoceptors, opioid, $GABA_B$, muscarinic M2, adenosine, serotonin and cannabinoid receptors has been associated with the opening of particular K^+ channel subtypes[4,5]. Mutations in K^+ channel genes leading to complete or partial loss of function through dominant-negative suppression or subtle functional disturbances have been suggested to contribute to altered physiological processing in nociceptive pathways or inherited pain syndromes[6,7]. Ionic mechanisms underlying persistent pain are often mediated by the upregulation or enhancement of depolarizing ion channels[8]. Consequently depolarizing ion channels have often been the focus of research for novel analgesics, with studies into the role of K^+ channels as therapeutic targets in pain being less abundant. K^+ channel activators constitute interesting candidates as novel analgesics which depending on the channel subtype targeted can demonstrate peripheral and/or central actions[9-11].

Kv7 CHANNELS

Voltage-gated K^+ channels on the basis of homology and ability to assemble into hetero-multimeric channels have been divided into several Kv subfamilies (Kv1 to Kv12)[12]. The Kv7 subfamily encompasses five members termed Kv7.1 to Kv7.5, of which Kv7.2-Kv7.5 channels are expressed and distributed throughout peripheral nerves and the CNS, and have been investigated as novel drug targets for the treatment of neuronal hyper-excitability disorders[13-15]. Kv7.1 is expressed in cardiac muscle. Nociceptive pathways contain Kv7 channel subunits with expression in both peripheral and central systems, such as central terminals of primary afferents, dorsal horn neurons, and motor neurons within the spinal cord[15]. A decrease in Kv7 channel expression has been reported to contribute to an increased excitability of sensory neurones in the peripheral nervous system, such as Adelta and C fibres, following injury[16,17]. This change in Kv7 channels which is linked to a down regulation of the relevant genes is a feature of remodelling of the injured nerves and neighbouring uninjured fibres leading to neuropathic pain. Further, in models of nerve injury associated with peripheral neuromas an excitability compensating increase in Kv7.2 channels has been observed[18]. Kv7 channels are also inhibited by the inflammatory mediator bradykinin, and stimulation of protease-activated receptor 2 and Mas-related G-protein coupled receptor member D contributing to neuronal excitability and inflammatory pain[19]. Importantly the channel expression and function in these pathologies are reduced, but not abolished. Thus, Kv7 channels play a fundamental role in the regulation of neuronal excitability, as would be observed in persistent pain conditions and recovering or enhancing the activation of these channels would lead to suppression of aberrant neuronal activity.

A complex formed of Kv7.2 and Kv7.3 subunits is a molecular correlate of the M-current, a voltage-sensitive K^+ current which is inhibited by stimulation of muscarinic acetylcholine receptors and controls neuronal excitability[20] (Figure 1). The subthreshold membrane potential is stabilized towards the potassium equilibrium potential following activation of the Kv7.2/Kv7.3 channel complex resulting in reduced neuronal firing. Expression of Kv7.2 and Kv7.3 channels has been reported in key locations in the pain pathway, including the thalamus, cerebral cortex and the nociceptive dorsal root ganglia neurons in the spinal cord[21]. Thalamic Kv7.2 and Kv7.3 channel activation increases the occurrence of burst firing of thalamocortical neurons which may interfere with tonic action potential generation which is fundamental for relaying sensory stimuli to the cortex[22]. Thus, activation of thalamic Kv channels leads to delays in behavioural and electrophysiological correlates of pain responses[22]. Kv7.3 subunits can also co-assemble with Kv7.4 or Kv7.5 subunits to produce K^+ currents with properties similar to those of the M-currents[23,24]. Further, Kv7 channel activity associated with suppression of hyperactivity of the amygdala and the dorsal raphe nucleus is linked to an anxiolytic effect[25,26]. Dysfunction of Kv7 channels within the hippocampal function is linked to memory deficit and reduction of channels

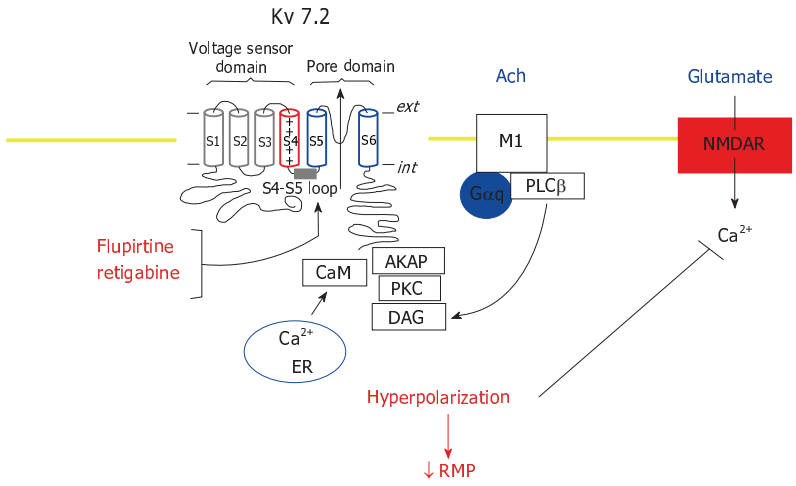

Figure 1 Schematic of a Kv7.2 subunit with activators flupirtine and retigabine. Flupirtine and retigabine activate Kv7.2/7.3 channel complexes resulting in efflux of K^+ leading to hyperpolarization and concomitant decrease in the resting membrane potential. Kv7.2/7.3 channel complexes are inhibited due to the release of calcium from the endoplasmic reticulum and the activation of M1-type muscarinic receptors by acetylcholine. Excessive levels of glutamate activating N-methyl-D-aspartic acid receptors which leads to an influx of Ca^{2+} ions into neurones is indirectly antagonised by the retigabine- or flupirtine-induced hyperpolarization suppressing free intracellular Ca^{2+} ion levels reducing neuronal excitability. AKAP: A-kinase anchoring protein; CaM: Calmodulin; NMDAR: N-methyl-D-aspartic acid receptor; PKC: Protein kinase C; PLCβ: Phospholipase C.

has been reported to mediate age-dependent memory decline[27].

Thus, utility of activators of Kv7 channels as a treatment approach in pain conditions, which are often refractory to current available therapies, is consistent with the expression and function of Kv7 channel subunits in peripheral and central nociceptive pathways such as the central terminals of primary afferents, dorsal horn neurons, and motor neurons within the spinal cord[10,15,21].

The triaminopyridines, flupirtine and retigabine, activate all Kv subunits, except Kv7.1, by stabilizing the channel in the open confirmation with a resulting negative shift in the membrane potential[28-31] (Figure 1). Although flupirtine and retigabine express limited selectivity between the Kv7 subunits, Kv7.3 appears to be more sensitive to their actions. The binding site of retigabine is situated within the cytosolic region of the S5 transmembrane domain of Kv7 channels which involves a critical tryptophan residue (W236 in Kv7.2)[29,30] (Figure 1). Structure-activity relationship studies have produced compounds with greater potency and subunit selectivity than retigabine. PF-05020182 and NS15370 are 10-30 fold more potent than retigabine at Kv7.2-Kv7.5 channels, whilst RL648_81 is 15 times more potent than retigabine at Kv7.2/Kv7.3 channels but does not affect Kv7.4 and Kv7.5 and ICA-069673 displays selectivity for Kv7.2 over Kv7.3[32-35]. The benzanilide ICA-27243 demonstrates selectivity for Kv7.2/Kv7.3 channels over Kv7.4 or Kv7.3/Kv7.5 heteromultimers and has a binding site within the Kv7 channels distinct from that of retigabine[36]. Identification that Kv7 channels are activated by flupirtine, retigabine and related analogues has also led to the investigation of a range of new chemical scaffolds exhibiting activation properties. Acrylamides such as (S)-1 and (S)-2 appear to share the same site of action and thereby the same specificity profile as retigabine[37]. A QO series which activate all Kv7 channels except Kv7.3 and a benzimidazoles series which are selective for Kv7.2 over Kv7.3, Kv7.4 and Kv7.5 do not require the residue W236 to exhibit activation properties[38,39].

The availability of compounds offering different selectivity profiles will be valuable in the understanding of the importance of the Kv7 channel subtypes as targets for the management of pain conditions. In addition, the lack of discrimination between Kv7 subunits may be responsible for "on-target" side effects.

FIBROMYALGIA

Persistent diffuse pain, fatigue, sleep disturbance and cognitive dysfunction are the primary characteristic symptoms of fibromyalgia[40]. The American College of Rheumatology (ACR) 1990 criteria of widespread pain (for at least 3 mo) in all 4 quadrants of the body and pain in 11 of 18 tender point sites have been used to classify fibromyalgia[41]. Revisions of the criteria were introduced in 2010 to include the assessment of somatic symptom (sleep disturbance, cognitive disturbance and fatigue) severity and widespread pain, thereby reflecting the range of symptoms and avoid reliance on tender points[42]. Further revision in 2016, comparing the 2010 criteria with the ACR 1990 classification, limits potential misclassification and introduced the use of a fibromyalgia symptom scale[43]. A worldwide prevalence of fibromyalgia has been reported to be 0.4%-8% of the population based on the application of the ACR 1990 criteria with the condition being 7 times more common in females than males[44,45]. Recognition of fibromyalgia is often complicated by the occurrence of co-morbidities exhibiting similar symptoms[40,46,47].

Alteration of sensory processing in the brain, dis-

Table 1 Examples of current pharmacological treatments of fibromyalgia[40,46]

Drug class	Drug
Tricyclic antidepressants	Amitriptyline
Serotonin-noradrenaline re-uptake inhibitors	Duloxetine
	Milnacipran
Selective serotonin re-uptake inhibitor	Fluoxetine
	Citalopram
Dopamine receptor agonist	Pramipexole
α2delta	Gabapentin
	Pregabalin
Analgesics	Dihydrocodeine
	Morphine
	Tramadol
	Paracetamol

turbances in neurotransmitters such as glutamate, substance P, dopamine and serotonin, reduced reactivity of the hypothalamus-pituitary-adrenal axis to stress, increased pro-inflammatory and reduced anti-inflammatory cytokine profiles, and small fiber pathology have been associated with the pathophysiology of fibromyalgia[40,46,47]. Central sensitization (CS) is believed to underlie the neuronal excitability associated with the amplified responses of the CNS to peripheral input observed in patients with fibromyalgia[40,46,47] (Figure 1). The peripheral sensory generators reported to play a role in the heightened activity of the CNS leading to the range of symptoms include nerve pathologies, neuro-inflammation, skeletal muscle abnormalities and ischaemia[48,49]. The CS in patients with fibromyalgia reflects an altered neurotransmitter (glutamine, serotonin, substance P, dopamine) functioning and possible neuroplasticity leading to augmented sensory processing consistent with an enhanced excitation and reduced inhibition within the CNS[48]. Systemic stress-related effects have also been proposed to enhance or underlie the symptoms of fibromyalgia due to alterations in the hypothalamic pituitary adrenal axis (HPA), and autonomic and cardiovascular systems[40,47,48].

Pharmacological and non-pharmacological therapeutic approaches, as with many persistent pain conditions, are often required as treatments of the challenges associated with fibromyalgia[40]. Drug therapies, however, often involve an empiric approach resulting in a focus towards individual symptoms, in particular pain[40,48]. The lowering of levels of pronociceptive excitatory neurotransmission or/and increasing antinociceptive neurotransmission in the CNS is a primary aim of many of the pharmacological treatments, consequently the management of symptoms other than pain is often limited. The current options as therapeutic approaches of fibromyalgia include drugs, usually given as oral therapies, that target serotonin and noradrenaline levels, *e.g.*, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, or voltage-gated calcium channel α2delta subunit ligands, *e.g.*, gabapentin and pregabalin[40,48] (Table 1). The role of peripheral sensory generators within the pathophysiology of fibromyalgia would support the use of topical medicines as a treatment approach. Topical treatments would limit the occurrence of adverse effects or toxicity that may be related to oral therapy of drugs such as retigabine and flupirtine.

FIBROMYALGIA AND POTASSIUM CHANNELS

Characteristic symptoms of fibromyalgia demonstrate commonality with certain clinical features consistent with altered functioning of K^+ channels that present in channelopathies (*i.e.*, conditions as a consequence of channel mutations)[50]. For example, persistent and neuropathic pain are associated with acquired and inherited channelopathies involving altered expression and/or activity of voltage-gated K^+ channels (Kv)[21,51]. Kv channels have been proposed to underlie the pathogenesis of neuromyotonia, where the clinical features of fatigue, insomnia and skeletal muscle hyperactivity can be observed[52]. Further, several of the commonly used treatments of fibromyalgia have been reported to alter K^+ channel activity.

The persistent pain attributed to fibromyalgia has been proposed to possibly belong to a spectrum of hyperexcitability disorders caused by autoantibodies targeting voltage-gated potassium channel (VGKC) complexes and the implicated autoimmunity[53-55]. A positive VGKC-complex immunoglobulin G status, and specifically Contactin-associated protein 2 (Caspr 2)-IgG sero-positivity, correlated significantly with pain prevalence in a range of persistent pain conditions which included fibromyalgia. In the VGKC-complex seropositive patients, immune modulation therapy was reported to evoke an improvement in pain[53-55]. Consequently, a diagnostic method and therapeutic approach for fibromyalgia related to an anti-VGKC complex antibody has been proposed[56].

The sleep disturbance in patients with fibromyalgia is characterised by a high incidence of alpha-delta sleep resulting from the intrusion of alpha activity into the delta activity that occurs during slow-wave sleep[57]. Alpha-delta sleep has been suggested to arise following alterations in conductance of K^+ currents leading to

selective depolarization of thalamocortical cells or of the entire somato-sensory thalamus[58]. Delta sleep can be restored from alpha-delta sleep by simultaneously increasing K^+ currents and $GABA_B$ currents. The alpha-delta sleep may exacerbate and/or be the source of pain in patients with fibromyalgia[57]. An abnormal thalamic activity and a lower stimulus threshold for the activation of the pain pathway have been associated with fibromyalgia[58]. The incidence of alpha-delta sleep in fibromyalgia has been shown to be reduced by sodium oxybate which acts on K^+ channels, $GABA_B$ currents, and a non-specific ionic current[59,60]. The restoration of delta sleep by sodium oxybate is associated with modulation of molecular targets in the thalamocortical cells[58].

Thus, drugs with actions on K^+ currents within the peripheral nervous system and the CNS, could be effective treatments of the multifaceted disorder fibromyalgia that involves peripheral sensory generators and multiple brain circuits.

Kv7 CHANNEL ACTIVATORS AND FIBROMYALGIA

The Kv7 channel activators flupirtine and retigabine exhibit pharmacological profiles that are consistent with the management of symptoms of fibromyalgia. Flupirtine and retigabine exert analgesic properties by activation of Kv7 channels leading to hyperpolarization of neuronal membranes, indirectly reducing *N*-methyl-D-aspartate (NMDA) receptor activity[13,61,62]. Affinity of flupirtine for NMDA receptors has not been demonstrated, however the drug by Kv7 channel activation suppressed glutamate-induced rise in cortical neuron Ca^{2+} levels consistent with indirect NMDA receptor antagonism[63-65]. In addition to restoration of normal sensitivity of over-excitable nociceptive pathways, flupirtine and retigabine have been shown to inhibit the stimulation of nociceptive neurons by inflammatory mediators such as bradykinin[19,66,67]. Consequently effective analgesia of persistent pain by flupirtine has been demonstrated in conditions such as musculoskeletal pain, postoperative pain, migraine and neuralgia[61,62,68]. Retigabine has been shown to evoke analgesic efficacy in preclinical pain models of temporomandibular joint pain, visceral pain, bradykinin-induced hind-paw pain and carrageenan-induced hyperalgesia systemic[13,66,69,70]. Further, retigabine selectivity reduces the activity of axotomized Adelta/C fibres, but not uninjured axons and human C-fibre axons, and suppresses responses to dorsal root stimulation[71-73]. The analgesic and anti-allodynic effects exhibited by retigabine in neuropathic pain models are comparable to those of the treatments of fibromyalgia, tramadol and gabapentin[74,75].

Flupirtine also evokes a reduction in skeletal muscle rigidity and akinesia by the suppression of spinal mono- and polysynaptic reflexes mediated by NMDA receptors[76,77]. The muscle relaxant and analgesic properties of flupirtine are demonstrated in the same dose range, and thus would be applicable treatment of the pain and muscle stiffness observed with fibromyalgia[40,47,48]. NMDA receptors, particularly those within the dorsal horn of the spinal cord, are fundamental in nociceptive transmission and synaptic plasticity, and may play a role in CS[78]. In patients with fibromyalgia glutamate levels are elevated in key pain-processing areas of the brain, which change in response to treatment that reduce pain[79,80]. The heightened activity of glutamatergic transmission may also be responsible for raised cerebrospinal levels of nerve growth factor and brain-derived neurotrophic factor reported in FM patients[81,82]. Mechanisms that regulate NMDA receptor activity, such as Kv channels, phosphorylation sites, and interacting kinases (*e.g.*, casein kinase 2, Src-NADH dehydrogenase) offer an alternative therapeutic target for the management of glutamatergic processes that may play a role in the pathophysiology of fibromyalgia[78].

Flupirtine has also been shown to prevent acute stress-induced impairment of spatial memory retrieval and hippocampal long-term potentiation[83]. Activation of Kv7 channels by flupirtine reduced stress-induced activation of glycogen synthase kinase-3β which appears to be responsible for impaired memory formation[83]. Thus, flupirtine could target the symptoms of fibromyalgia that are associated with stress-related effects, such as cognitive dysfunction.

Preliminary evidence from an open-label study supports the use of flupirtine as a treatment approach in patients with fibromyalgia where a reduction of pain, sleep disturbance, fatigue and depressive symptoms was observed[84]. Retigabine has been proposed as a treatment of neuropathic pain and fibromyalgia and in a phase IIa clinical trial for the treatment of post-herpetic neuralgia improvements in pain scores and Patient Global Impression of Change scores were observed but not statistically analysed[85]. During the post-herpetic neuralgia trial, but not in epilepsy trials, of retigabine proteinuria was unexpectedly reported which may have influenced continuation of the study[86]. Controlled clinical studies in fibromyalgia however are required for the confirmation of the utility of flupirtine and retigabine.

The expression of Kv7 channel subunits throughout the CNS and their involvement in various central processes however raises the potential of adverse effects and limitations to activators of this molecular target. Development of Kv channel activators exhibiting subunit selectivity (*e.g.*, Kv7.2/7.3) could avoid possible centrally or peripherally generated unwanted effects. For example, benzimidazole derivatives have been synthesized that lack activity at Kv7.4, the main Kv7 channel expressed in vascular smooth muscle[87]. The unwanted effects related to central actions of Kv7 activators could also be contained by the availability of openers that do not cross the blood-brain barrier and target peripherally located Kv7 channels[3] (Figure 2).

CONCLUSION

Fibromyalgia is a multifaceted disorder that remains a major unmet medical need with current therapies being

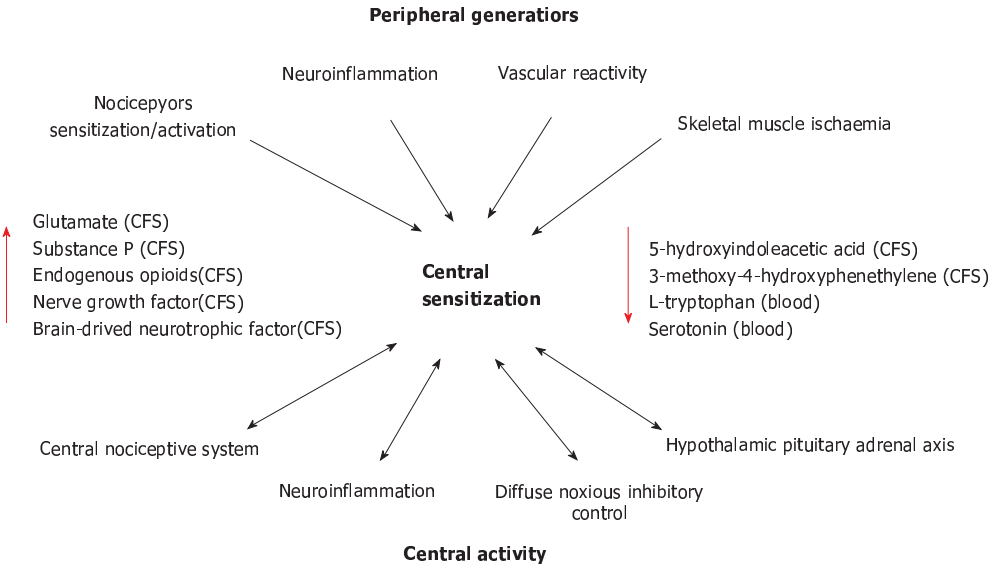

Figure 2 Pathophysiology of fibromyalgia. Neuronal excitability due to amplified and altered central nervous system functioning linked to peripheral generators is associated with central sensitization. The central sensitization reflects the altered biochemistry and neurotransmitter levels. Up arrow: Raised levels relative to healthy subjects; Down arrow: Lowered levels relative to healthy subjects; CFS: Cerebrospinal fluid.

limited in the control of the condition. The physiological changes responsible for the diverse symptoms characteristic of fibromyalgia support the need to target multiple events to evoke effective therapeutic control. Consequently, a standard approach for the treatment of fibromyalgia is combination therapy involving drugs and non-pharmacological therapies that act through diverse mechanisms. An involvement of K^+ channels in the pathophysiology of fibromyalgia and the related symptoms is emerging and supported by drug treatments for this condition exhibiting action at these molecular targets. The important role of Kv7 channels as regulators of many physiological processes has generated interest in these molecule targets for the development of drugs that would be relevant to the treatment of fibromyalgia. The distribution of Kv7 subunits, in both the CNS and PNS, is consistent with the physiological components implicated in the pathophysiology of fibromyalgia and the Kv7 channel activators, flupirtine and retigabine, have exhibited pharmacological profiles in preclinical and clinical studies compatible to the requirements needed for use as a therapeutic approach. The complexity of the pathophysiology of fibromyalgia however involves several components consequently the contribution of K channels and activators of these targets may be limited. Thus, Kv7 activators, such as flupirtine and retigabine or related drugs, may not provide complete resolution of the symptoms of fibromyalgia, but may offer an additional treatment approach to those currently available. Outcomes from preclinical studies and clinical trials in other pain states, however, may not be reliable predictors for efficacy in the multidimensional challenges of fibromyalgia where specific investigations of K channel drugs are required and focused clinical trials are awaited.

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