

Review

Identification of the Involvement of Potassium Channels in Fibromyalgia

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Abstract

Fibromyalgia is a central sensitivity syndrome that presents with chronic pain, fatigue, cognitive dysfunction, and disordered sleep. The pathophysiology which due to multisensory hypersensitivity of the central nervous system involves neuronal excitability leading to central sensitization. Treatments of the challenges associated with the complexities of fibromyalgia involve combinations of pharmacological and non-pharmacological therapeutic approaches which often offer limited benefit. Potassium (K^+) channels play a fundamental role in establishing and maintaining stability of neuronal activity. The large molecular diversity and distribution of K^+ channels support involvement in a broad range of physiological functions. In nociceptive pathways, neuronal hyperexcitability leading to pain sensation has been associated with reduced function of K^+ channels and loss of cellular control. This article reviews the evidence of involvement of K^+ channels in fibromyalgia. A potential role both in the pathophysiological processes responsible for the symptoms of fibromyalgia and as therapeutic targets for the management of the condition is considered.

Keywords: fibromyalgia; potassium channels; pathophysiology; pharmacology; channelopathies

1. Introduction

Fibromyalgia is part of the spectrum of central sensitivity syndromes characterized by persistent widespread idiopathic or “nociceptive” pain which is accompanied by fatigue, cognitive and mood disturbances, and disordered sleep [1–3]. Diffuse hyperalgesia (heightened responses to painful stimuli) and allodynia (painful responses to non-painful stimuli) with lowered pressure pain thresholds are characteristics of the pain associated with fibromyalgia. The diagnosis is often complicated by co-morbidities, *e.g.*, chronic fatigue syndrome, with similar symptoms. Fibromyalgia, dependent on the diagnostic criteria and methods of classification, is estimated to affect 0.4–8% of the population worldwide with prevalence greater in females and increasing with age [4]. The pathophysiology of fibromyalgia involves amplified responses of the central nervous system (CNS) to peripheral stimuli associated with neuronal excitability leading to central sensitization (CS) [1]. The heightened activity of the CNS responsible for the characteristic fibromyalgia symptoms is initiated by a range of peripheral sensory generators.

Neuronal activity within the CNS and peripheral nervous system (PNS) is suppressed and stabilized by potassium (K^+) channel activity regulating the membrane potential, action potential initiation, axonal conduction and neurotransmitter release. K^+ channels play a fundamental role in nociceptive processing linking disturbances of their expression and function to the generation of pain due to peripheral and central hyperexcitability [5–9]. In addition, the

pharmacology of certain anti-nociceptive drugs has been associated with K^+ channel modulation within the PNS and CNS [6–9]. K^+ channels are a diverse family of ion channels that are widely distributed in excitable and non-excitable cells and are involved in the regulation of the resting membrane potential and level of excitation of cells. The large molecular diversity that has been identified and characterized supports involvement of K^+ channels in a broad range of physiological functions. More than 78 genes in humans are responsible for the diversity of K^+ channels which are organized into four structural types, voltage-gated (K_v), inward rectifier (K_{ir}), Ca^{2+} -activated (K_{Ca}) and tandem-pore domain K^+ channels [7,8,10]. An α -subunit containing gating and selectivity filter apparatus forms the K^+ ion-conduction pore which can be co-located with auxiliary β -subunits responsible for modulating function and interaction with cellular signalling pathways. The activation of K^+ channels facilitates rapid transmembrane K^+ efflux repolarizing or hyperpolarizing the cell membrane and limiting action potential generation. Neuronal hyperexcitability in nociceptive pathways leading to development of pain sensation due to complete or partial loss of cellular control has been associated with reduced function of K^+ channels whether inherited or acquired. Dominant-negative suppression of function of K^+ channels has been described due to gene mutations and altered expression contributing to the development of pain conditions [7,8].

Clinical features related to altered K^+ channel function present in channelopathies, *i.e.*, conditions due to ion



channel dysfunction, have demonstrated similarity to the characteristic fibromyalgia symptoms [11]. This narrative review will consider evidence of involvement of K^+ channels in the pathophysiology of fibromyalgia and as therapeutic targets for treatment of this condition.

2. Pathophysiology of Fibromyalgia

Evidence in patients with FM predicts responses to augmented sensory input evokes disturbed neurotransmitter functioning and neuroplasticity leading to neuronal hyperexcitability and hypersensitivity in the CNS due to enhanced excitatory and reduced inhibitory processes [1,2,12]. These findings are consistent with the development of central sensitization (Fig. 1) [1,12]. Although heightened activity of the CNS can be initiated by peripheral sensory generators, such as nerve pathologies, neuroinflammation, skeletal muscle abnormalities and ischaemia, constant nociceptor activation due to a comorbid condition can also evoke secondary fibromyalgia [2,3,12]. Pain associated with fibromyalgia is characterized by neuropathic components in that it is chronic and intractable and unlike nociceptive pain, which serves to protect from potential or actual injury, persists after tissue healing has taken place. Even in the apparent absence of sensory stimulus symptoms of pain can present indicating that it is maladaptive and has no obvious biological purpose [2,12].

In brain spectroscopy studies of patients with fibromyalgia severity of pain correlated with raised levels of neurotransmitters glutamate, glutamine, and glycine in regions of the brain associated with pain processing [1,2,13]. Consequently, in the spinal cord and brain the glutamate N-methyl-D-aspartate (NMDA) receptors are exposed to elevated glutamate levels. In addition, the cerebrospinal fluid (CSF) of patients with fibromyalgia has elevated levels of substance P, endogenous opioids, nerve growth factor, brain-derived neurotrophic factor and attenuated levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin, and 3-methoxy-4-hydroxyphenylglycol, a metabolite of noradrenaline [1,2,13]. Serum serotonin and L-tryptophan are also suppressed relative to healthy subjects in people with fibromyalgia [1,2,13]. Consistent with these findings, the activity of descending serotonergic-noradrenergic efferent pathways in people with fibromyalgia has been observed to be reduced resulting in altered diffuse noxious inhibitory control (DNIC) of pain pathways [14]. DNIC is the descending, from the CNS to the spinal cord, control of nociception which relies on painful conditioning stimulation of one part of the body to inhibit pain in another part and inefficiency has been implicated in the development of chronic pain [14].

A characteristic of fibromyalgia is non-restorative sleep associated with poor sleep quality [15–17]. Superficial, fragmented and non-restorative sleep with restless leg syndrome and morning fatigue are common complaints amongst people with fibromyalgia. Diminished slow-wave

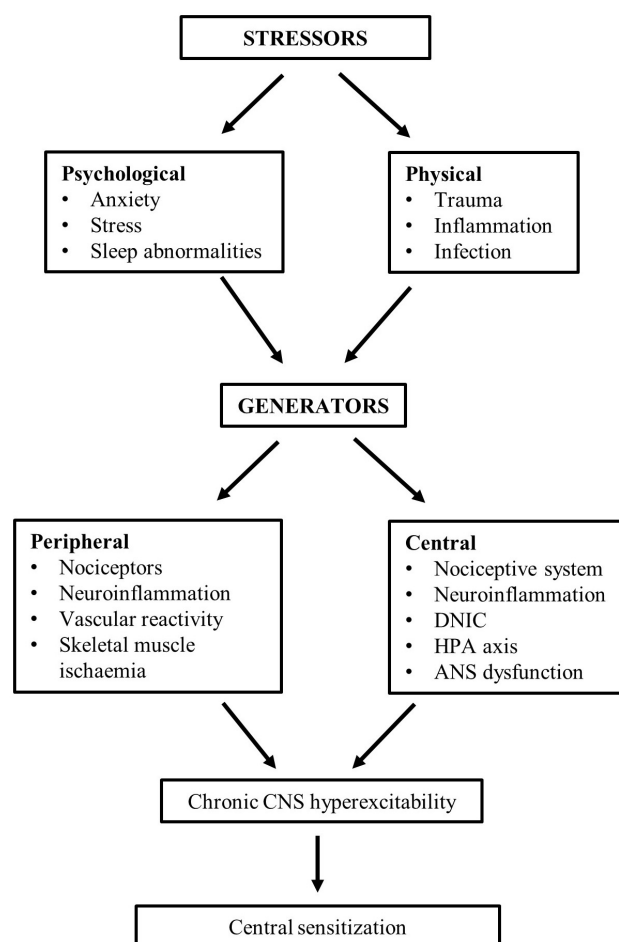


Fig. 1. Model of the pathophysiology of fibromyalgia. Postulated relationship between hypersensitivity due to stressors activating generators of neuronal hyperexcitability resulting in the development of central sensitization a characteristic of fibromyalgia.

sleep, which is essential to feeling refreshed upon awakening, during non-rapid eye movement sleep (NREM) is often reported [15–17]. Persistent pain related to heightened states of arousal has been linked to lower sleep efficiency and patterns of sleep discontinuity [18]. Altered production of melatonin has also been reported in patients with fibromyalgia with lower secretion in dark hours related to sleep disturbance and raised secretion in daytime contributing to pain, fatigue and mood symptoms [19].

Dysautonomia, neuroinflammation, increased pro-inflammatory with reduced anti-inflammatory cytokine profiles and reduced reactivity to stress of the hypothalamic pituitary adrenal axis have also been proposed to be involved in the genesis and enhancement of symptoms of fibromyalgia [2,12,13].

3. Fibromyalgia and Potassium Channels

3.1 Pathophysiology

3.1.1 Sensory Axonal Excitability

Investigation of sensory axonal excitability in patients with fibromyalgia revealed enhanced superexcitability relative to healthy controls [20]. The technique used measured membrane polarization, ion channel function and paranodal/internodal condition of peripheral nerves. Superexcitability is influenced by the conductance of paranodal fast K^+ channels with increased conductance reducing intensity and period of superexcitability, and reduced conductance contributing to increased superexcitability [21,22]. The symptoms of fibromyalgia assessed by the Fibromyalgia Impact Questionnaire (FIQ), an evaluation instrument of fibromyalgia patient status, progress, and outcomes, negatively correlated with the increased subexcitability suggesting compensatory K^+ channel activity attenuating the severity of the condition. Neuronal cell excitability can be monitored by creating subthreshold depolarizing or hyperpolarizing currents within the membrane, *i.e.*, threshold electrotonus (TE). In patients with fibromyalgia a slight increase in sensory hyperpolarizing TE was observed which would also be consistent with instability of K^+ channels [20]. The dysregulated K^+ channel conductance observed in, at least, the nociceptive pathway would be consistent with the hypersensitivity underlying symptoms in patients with fibromyalgia.

3.1.2 Thalamic Cells

Although findings have been inconsistent, some studies have suggested an abnormal intrusion of alpha activity (8–13 Hz oscillations) into the delta activity (1–4 Hz oscillations) that occurs during slow-wave sleep in people with fibromyalgia [15–17,23]. The pain experienced by patients with fibromyalgia may be exacerbated by these sleep abnormalities. Depolarization of cells within the thalamus due to alterations in conductance of K^+ currents has been suggested to underlie alpha-delta sleep [24]. Increasing thalamic K^+ currents was suggested to lead to the restoration of delta sleep. The drug sodium oxybate, which has been shown to improve quality of sleep and levels of pain in patients with fibromyalgia [25], restores delta sleep following modulation of molecular targets, including K^+ channels, in the thalamocortical cells [24].

3.1.3 KCHN2 Protein

Lower plasma levels of KCHN2 protein, which forms the Kv11.1 subtype of the hERG (Ether-a-go-go-related gene) Kv channel were observed in patients with fibromyalgia compared to healthy controls [26]. In contrast, the levels of the proteins KCHN6 and KCHN7 that form the Kv11.2 and Kv11.3 subtypes of the hERG channel were not different in patients with fibromyalgia and healthy controls. Kv11 channels are expressed in the CNS and are thought

to contribute to adaptive firing of neurons [27,28]. At the spinal cord level Kv11.1 channels have been demonstrated to be involved in nociceptive modulation [29]. Hyperexcitable states due to a lack of accommodation of nerve cells to repetitive stimuli may occur due to altered hERG expression. A relationship between the plasma levels of KCHN2 and the symptoms of fibromyalgia has not yet been established.

3.1.4 Kv Channel Autoantibodies

Autoantibodies targeting Kv channels associated with contactin-associated protein-2 (CASPR2)-IgG-positivity have been observed to contribute to hyperexcitability which could be responsible for persistent pain experienced by people with fibromyalgia [30]. CASPR2 is a member of the neurexin family that is expressed in the PNS and CNS and colocalizes with Kv1 subtype channels. In people with persistent pain conditions, such as fibromyalgia, the prevalence of symptoms correlated with a positive Kv channel-complex immunoglobulin status. Disruption of Kv localization at paranodal axons may be involved in the link between CASPR2 autoimmunity and pain. Immune modulation therapy, prednisone, methylprednisolone, intravenous immune globulin, methotrexate or hydroxychloroquine, reduced the state of pain in Kv channel-complex seropositive patients allowing the discontinuation of opioid analgesics in some cases [30].

3.1.5 Substance P

Substance P (SP) levels are elevated in the CSF of people with fibromyalgia [1,2]. SP is a mediator of pain involved in the generation and transmission of pain signalling which can also exhibit antinociceptive properties [31]. CS results due to SP activating excitatory post-synaptic potential in the CNS, whilst peripheral neurogenic inflammation is caused by the release of SP from nociceptive nerve fibres [32,33]. SP decreases the activity of Kir channels in locus coeruleus and nucleus basalis neurons, and IK_{Ca} subtype channels in stellate ganglion neurons leading to neuronal excitation [34–36]. Within the PNS SP has been suggested to sensitize nociceptors due to a decrease of low-threshold K^+ channel (Kv4 subtype) activity in addition to activating excitatory mechanisms [37]. Thus, raised levels of SP observed in people with fibromyalgia will lead to suppression of the inhibitory K^+ channel activity within peripheral sensory small neurons (nociceptors) resulting in neuronal excitation and increased nociceptive responses. In contrast, SP enhances the current of Kv7 subtype channels in the PNS and the afferent dorsal root ganglion neurons whilst inhibiting T-type calcium currents which dampen neuronal excitability and evokes an anti-nociceptive effect [38,39]. The balance between pro- and anti-nociception in people with fibromyalgia will be dependent on the distribution and concentration of the elevated SP levels.

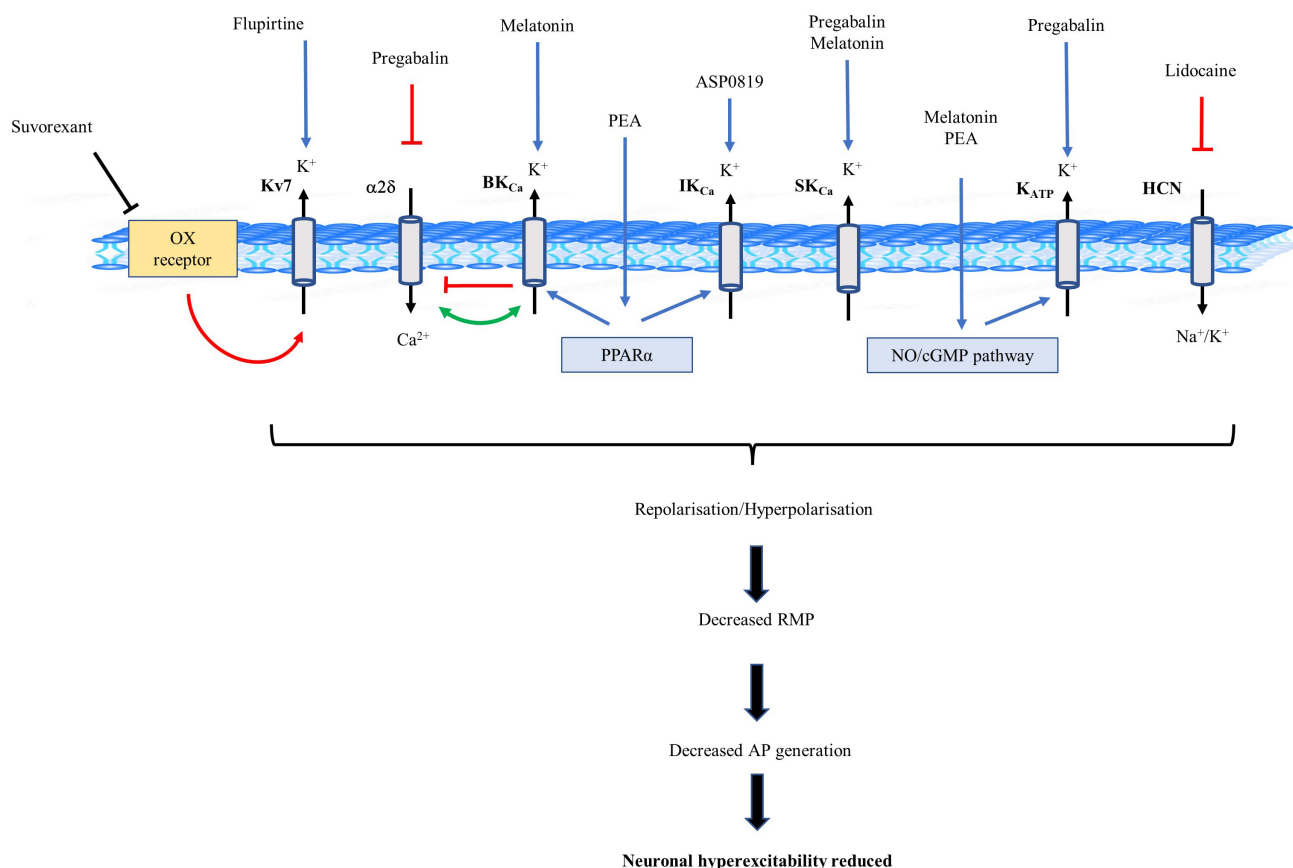


Fig. 2. Schematic diagram of potassium (K^+) channel involvement in pharmacological treatments of fibromyalgia. ASP0819, flupirtine, melatonin and pregabalin have direct K^+ channel activating properties leading to increased K^+ ion efflux. Melatonin and PEA exhibit indirect channel activating properties through involvement of the NO/cGMP pathway and PPAR α . Pregabalin inhibitory action on $\alpha 2\delta$ subunits of the Ca^{2+} channel evokes an interaction with BK_{Ca} channels leading to suppression of Ca^{2+} channel expression and Ca^{2+} ion influx. Suvorexant evokes antagonistic activity at the OX receptor reducing receptor-induced suppression of Kv7 channel expression. Lidocaine inhibits influx of K^+ ions through HCN channels. The altered transmembrane ion movement will lead to suppression of neuronal hyperexcitability associated with central sensitization characteristic of fibromyalgia. Blue lines indicate activating properties, red lines indicate inhibitory properties, black line indicates antagonistic properties and green line indicates channel-channel interaction. Abbreviations: $\alpha 2\delta$, alpha2delta subunit; AP, action potential; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; K_{ATP} , ATP-dependent potassium channel; BK_{Ca} , large conductance calcium-activated potassium channel; IK_{Ca} , intermediate conductance calcium-activated potassium channel; SK_{Ca} , small conductance calcium-activated potassium channel; Kv, voltage-gated potassium channel; NO/cGMP, nitric oxide/cyclic guanosine monophosphate; OX, orexin; PEA, palmitoylethanolamide; PPAR α , peroxisome proliferator-activated receptor; RMP, resting membrane potential.

3.2 Pharmacological Treatment

3.2.1 Pregabalin

The gabapentinoid pregabalin has demonstrated clinically significant improvements of core symptoms in patients with fibromyalgia and is a recommended treatment of the condition [40]. The benefits reported have been dose-related pain alleviation with improvement in quality of life and sleep [40]. The efficacy exhibited by pregabalin as a treatment of pain is a consequence of preventing sensory propagation with reduction of neuronal excitability. Alpha-2-delta ($\alpha 2\delta$) subunits of the voltage-activated calcium channels, which are expressed in pain processing areas of the spinal dorsal horn, periaqueductal gray, ante-

rior cingulate cortex, insula and amygdala, have been the focus of the mechanism of action of pregabalin leading to inhibition of neurotransmitter, such as glutamate and glutamine, release, and pain control [41]. Evidence, however, supports the involvement of K^+ channels in the action of pregabalin on pain processing and analgesia. Pregabalin activated ATP-dependent K^+ channels (K_{ATP}) in isolated hippocampal neuron-derived cells and an anti-nociceptive effect in a formalin-induced pain rat model involved the activation of K_{ATP} channels by pregabalin [42,43]. Suppression of the $\alpha 2\delta$ subunit function by the extracellular N terminus region of the BK_{Ca} channel in dorsal root ganglion neurons reducing calcium ion influx and neuronal excita-

tion could be enhanced by pregabalin binding to the $\alpha 2\delta$ subunit [44]. Pregabalin has also been reported to enhance apamin-sensitive SK_{Ca} currents in rat dorsal root ganglion neurons [45].

3.2.2 Lidocaine

Intravenous lidocaine has been demonstrated to reduce hyperalgesia, pain intensity and FIQ scores in people with fibromyalgia [46]. Although inhibition of sodium channels is considered the primary mechanism of action, lidocaine suppresses neuronal activity within the dorsal horn due to hyperpolarization following blockade of Kv channels [47,48]. Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which are related to Kv channels and generate inward K⁺ current producing rhythmic electrical activity in specialized peripheral sensory and CNS neurons, are inhibited by lidocaine at a concentration range for systemic use [49,50]. Thus, the activity of HCN channel activity evoking repetitive firing of nociceptive neurons leading to pain is suppressed by lidocaine [50].

3.2.3 Flupirtine

Patients with fibromyalgia reported an improvement in their symptoms, particularly pain and physical activity, following flupirtine treatment [51]. Flupirtine evokes hyperpolarization and stabilization of neuronal membranes due to activation of Kv7 subtype channels, with subsequent NMDA receptor activity reduction [52]. Kv7 channels are present in central terminals of primary afferents and spinal cord dorsal horn neurons and involved in the regulation of peripheral and central nociceptive pathway activity [52,53]. Activation of neuronal Kv7 channels evokes stabilization of membrane excitability producing inhibition of action potential initiation and thereby these channels are a therapeutic target for the treatment of diseases involving neuronal hyperexcitability [54,55]. The location of Kv7 channels in other neuronal areas responsible for the pharmacological properties of flupirtine are relevant to the management of the spectrum of symptoms characteristic of fibromyalgia [52,53]. Thus, K⁺ channel activation, at least in nociceptive pathways, by flupirtine appears to be responsible for the benefit to patients with fibromyalgia.

3.2.4 Melatonin

Melatonin regulates the sleep-awake cycle due to synchronization of circadian rhythm which impacts on fatigue and mood levels and enhances pain inhibition [56,57]. Some studies in patients with fibromyalgia have reported altered levels of melatonin with secretion during dark hours being lowered contributing to disordered sleep leading to daytime pain and fatigue and raised daytime secretion enhancing the pain, fatigue, and mood symptoms further disturbing sleep quality [19]. Although such findings could suggest abnormal secretion of melatonin being involved in the pathophysiology of fibromyalgia, inconsistencies have

been reported where studies have observed no difference in the melatonin levels in patients with fibromyalgia and healthy controls [19]. Administration of melatonin as a treatment of fibromyalgia reduced pain and fatigue, and improved sleep quality and quality of life measurements [19]. The anti-nociceptive effects of melatonin following stimulation of melatonergic receptors have been associated with the activation of SK_{Ca}, BK_{Ca}, K_{ATP} and G-protein coupled Kir3 channels [58,59]. Cell hyperpolarization due to efflux of K⁺ ions in regions of the nervous system such as the suprachiasmatic nucleus and cerebellar cells contribute to the anti-nociceptive effect of melatonin [59,60].

3.2.5 ASP0819

In rat reserpine-induced myalgia and vagotomy-induced myalgia models that mimic pain features of fibromyalgia, such as hyperalgesic symptoms, the activator of IK_{Ca} (also known as K_{Ca}3.1) channels ASP0819 reduced responses of neuronal excitation in peripheral nerve fibres at the dorsal root responsible for pain [61]. Increases in cytosolic calcium evokes opening of K_{Ca} channels regulating calcium-signalling and membrane potentials in excitable and non-excitable cells. The IK_{Ca} subtype is a voltage-insensitive channel widely expressed in numerous cell types and tissues, including dorsal root ganglion [62,63]. Activation of IK_{Ca} channels leads to a period after each action potential of reduced excitability and thereby evokes cellular stability [63]. ASP0819 improved sleep, pain and FIQ scores in people with fibromyalgia consistent with IK_{Ca} channels being a therapeutic target in such a clinical condition that involves unregulated nerve excitation [64].

3.2.6 Palmitoylethanolamide

Palmitoylethanolamide (PEA) is a peroxisome proliferator-activated receptor (PPAR α) agonist that improved pain and FIQ quality of life scores in people with fibromyalgia [65,66]. Interestingly the analgesic effects of PEA in a formalin-induced pain mouse model have been demonstrated to involve the activation of IK_{Ca}, BK_{Ca} and K_{ATP} channels [67]. In a prostaglandin E₂-induced hyperalgesia rat paw model peripheral antinociception due to PEA treatment involved the activation of K_{ATP} channels, but not Kv, IK_{Ca} or BK_{Ca} channels [68]. In addition to exhibiting PPAR α agonist properties PEA, which is an endocannabinoid-like structurally related N-acylethanolamine, has been shown to stimulate cannabinoid receptors which may be responsible for the K⁺ channel activation. Plasma levels of PEA were reported to be elevated in patients with fibromyalgia and thereby may be part of a compensatory mechanism involving K⁺ channel activation within the complex pathophysiology of this condition [69].

Table 1. Summary of evidence of potassium channel involvement in fibromyalgia.

	Target channel	Model	Outcomes	Comments	References
Pathophysiology					
Peripheral axonal function	Fast K ⁺ channel	Patients with fibromyalgia.	Testing nerve excitability and nerve conduction indicated axonal superexcitability increased in fibromyalgia relative to healthy controls.	Indicating dysfunction of paranodal channels.	[20]
Thalamic neuron activity	Potassium leak (KL) channel	Imaging studies in fibromyalgia patients.	Biophysically realistic mathematical model indicating increased I _{KL} conductance restoring delta sleep.		[24]
KCHN2 protein	Kv11.1	Patients with fibromyalgia.	Plasma levels of KCHN2 protein lower in patients than healthy controls.	KCHN2 protein widely expressed in the CNS and forms hERG voltage-gated potassium channel.	[26]
VGKC-complex-immunoglobulin G (IgG)–seropositive patients	Kv1	Patients with persistent pain, including fibromyalgia.	Autoimmunity, autoantibodies to channel complex.		[30]
Substance P	Kv4, IK _{Ca} ; Kir	Dorsal root ganglion neurons, locus coeruleus neurons, nucleus basalis neurons (rat); Stellate ganglion neurons (guinea pig).	Decreased channel activity led to increased afferent nerve excitability, sensitized nociceptors.		[34–37]
	Kv7 (M-type), K _{Ca}	Dorsal root ganglion neurons (rat and mouse). Trigeminal nociceptors (rat). Vagal sensory (PNS) neurons (ferret).	Enhanced channel activity leading to hyperpolarization and suppression of excitability.	Substance P levels raised in patients with fibromyalgia.	[38,39,73]
Treatment					
Pregabalin	K _{ATP} , BK _{Ca} , SK _{Ca}	Patients with fibromyalgia.	Reduction of pain, and improvement in quality of life and sleep.	Activation of K _{ATP} channels in hippocampal neuron-derived cells and a rat formalin-induced pain model. BK _{Ca} channel activity enhanced. Kv currents in dorsal root ganglion neurons and neocortical tissue enhanced.	[42–45]
Lidocaine	Kv, HCN	Patients with fibromyalgia.	Hyperalgesia, pain and FIQ score reduced.	Neuronal activity suppressed in dorsal horn due to Kv blockade.	[46–48]
Flupirtine	Kv7 (M-type)	Patients with fibromyalgia.	Reduced pain and improved physical activity.	Flupirtine activates Kv7 (M-type) channels.	[51]
Melatonin	SK _{Ca} , BK _{Ca} , K _{ATP} , Kir3	Patients with fibromyalgia.	Reduced pain and fatigue, and improved sleep quality and quality of life.	Anti-nociceptive effects due to stimulation of melatonergic receptors involve activation of K ⁺ channels.	[58–60]
ASP0819	IK _{Ca} (K _{Ca} 3.1)	Rat myalgia models of fibromyalgia. Patients with fibromyalgia.	Reduced excitation in dorsal root peripheral nerve fibres. Improved FIQ score, sleep and pain.	ASP0819 is an activator of K _{Ca} 3.1 channels.	[61,64]
Palmitoylethanolamide (PEA)	IK _{Ca} , BK _{Ca} , K _{ATP}	Patients with fibromyalgia.	Improved pain and FIQ scores.	PEA evokes channel activation.	[66–68]
Suvorexant	Kv7 (M-type)	Patients with fibromyalgia.	Improved sleep and reduced pain sensitivity.	Suvorexant, an orexin receptor antagonist, reversed the decreased channel function due to action of hypocretin/orexin neuron hyperexcitability.	[70]

FIQ, Fibromyalgia Impact Questionnaire; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; hERG, human ether-a-go-go-related gene; K_{ATP}, ATP-dependent potassium channel; K_{Ca}, calcium-activated potassium channel; KCHN2, potassium voltage-gated channel subfamily H member 2 isoform; Kir, inward rectifier potassium channel; Kv, voltage-gated potassium channel; PEA, palmitoylethanolamide; PNS, peripheral nervous system; VGKC, voltage-gated potassium channel.

3.2.7 Suvorexant

In patients with fibromyalgia treatment with the orexin receptor antagonist suvorexant, which would allow recovery of Kv7 channel activity, resulted in an improved sleep time and subsequent reduced pain sensitivity [70]. The hypocretin/orexin neurons within the lateral hypothalamus are involved in sleep-wake control where stimulation of neuronal activity leads to sleep-to-wake transition, whilst suppression induces NREM sleep [71]. Hyperexcitability in hypocretin/orexin neurons in a mouse model leading to destabilized sleep involved a decreased density and impaired functioning of Kv7 channels [72]. When the Kv7 channel activity was augmented with flupirtine the resulting hyperpolarization suppressed the activity of the hypocretin/orexin neurons, increased NREM sleep and restoration of sleep stability. Interestingly, the flupirtine enhanced sleep quality was related to an improvement in cognitive function in the mice, a characteristic of fibromyalgia that was not assessed during the clinical trial of suvorexant.

4. Conclusions

Evidence is presented demonstrating involvement of K^+ channels in the chronic pain condition fibromyalgia, which is summarized in Table 1. Hyperexcitability and increased sensitivity of cells, particularly neurons, is proposed to be the basis of the pathophysiology of fibromyalgia, however a full understanding of the underlying processes is currently not available. The limited knowledge regarding the pathophysiology has often hindered the development of specific diagnostic tools, resulting in a reliance on symptom profiling, and the identification of effective therapeutic approaches.

Modulation of K^+ channel expression and function has been identified in patients with fibromyalgia which would be consistent with an altered inhibitory mechanism to regulate cell activity. The absence of damping mechanisms related to K^+ channel activity leads to enhanced cell excitation that would be responsible for the characteristics of fibromyalgia, such as pain initiation and processing, sleep disturbance and cognitive dysfunction. Activation of K^+ channels is a component of the mechanism of action of several pharmacological treatments that have demonstrated efficacy in the management of fibromyalgia (Fig. 2).

Identification of the role K^+ channels play within the pathophysiology and/or as a therapeutic target for drugs will provide clues to an understanding of the cause(s) of and processes within the altered biology responsible for fibromyalgia. The diversity and abundance of K^+ channels offer a breadth of functions that are consistent with the characteristic complexity of fibromyalgia.

Abbreviations

CASPR2, contactin-associated protein-2; CNS, central nervous system; CS, central sensitization; CSF, cerebrospinal fluid; DNIC, diffuse noxious inhibitory control; FIQ, Fibromyalgia Impact Questionnaire; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; hERG, human ether-a-go-go-related gene; K_{ATP} , ATP-dependent potassium channel; K_{Ca} , calcium-activated potassium channel; KCHN2, potassium voltage-gated channel subfamily H member 2 isoform; Kir, inward rectifier potassium channel; Kv, voltage-gated potassium channel; NMDA, N-methyl-D-aspartate; NREM, non-rapid eye movement; PEA, palmitoylethanolamide; PNS, peripheral nervous system; $PPAR\alpha$, peroxisome proliferator-activated receptor; SP, substance P; TE, threshold electrotonus; VGKC, voltage-gated potassium channel.

Author Contributions

KL is solely responsible for all the work leading to and resulting in this paper, including researching, writing and editing the paper.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

References

- [1] Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience*. 2016; 338: 114–129.
- [2] Borchers AT, Gershwin ME. Fibromyalgia: a critical and comprehensive review. *Clinical Reviews in Allergy & Immunology*. 2016; 49: 100–151.
- [3] Lawson K. Emerging pharmacological strategies for the treatment of fibromyalgia. *World Journal of Pharmacology*. 2017; 6: 1–10.
- [4] Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatology International*. 2017; 37: 1527–1539.
- [5] Abd-Elseyed A, Jackson M, Gu SL, Fiala K, Gu J. Neuropathic pain and Kv7 voltage-gated potassium channels: The potential role of Kv7 activators in the treatment of neuropathic pain. *Molecular Pain*. 2019; 15: 1744806919864256.
- [6] Du X, Gamper N. Potassium channels in peripheral pain pathways: expression, function and therapeutic potential. *Current Neuropharmacology*. 2013; 11: 621–640.
- [7] Tsantoulas C, McMahon SB. Opening paths to novel analgesics: the role of potassium channels in chronic pain. *Trends in Neuroscience*. 2014; 37: 146–158.

- [8] Ciotu CI, Tsantoulas C, Meents J, Lampert A, McMahon SB, Ludwig A, *et al.* Noncanonical Ion Channel Behaviour in Pain. *International Journal of Molecular Sciences*. 2019; 20: 4572.
- [9] Alles SRA, Smith PA. Peripheral Voltage-Gated Cation Channels in Neuropathic Pain and Their Potential as Therapeutic Targets. *Frontiers in Pain Research*. 2021; 2: 750583.
- [10] Coetzee WA, Amarillo Y, Chiu J, Chow A, Lau D, McCormack T, *et al.* Molecular diversity of K⁺ channels. *Annals of the New York Academy of Sciences*. 1999; 868: 233–285.
- [11] Lawson K. Are the symptoms of Fibromyalgia Syndrome related to abnormal potassium channel function? *Myalgias International*. 2002; 2: 25–30.
- [12] Clauw DJ. Fibromyalgia: a clinical review. *Journal of the American Medical Association*. 2014; 311: 1547–1555.
- [13] Siracusa R, Paola RD, Cuzzocrea S, Impellizzeri D. Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update. *International Journal of Molecular Sciences*. 2021; 22: 3891.
- [14] Staud R, Robinson ME, Vierck CJ Jr, Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain*. 2003; 101: 167–174.
- [15] Diaz-Piedra C, Catena A, Sánchez AI, Miró E, Martínez MP, Buéla-Casal G. Sleep disturbances in fibromyalgia syndrome: The role of clinical and polysomnographic variables explaining poor sleep quality in patients. *Sleep Medicine*. 2015; 16: 917–925.
- [16] Wu YL, Chang LY, Lee HC, Fang SC, Tsai PS. Sleep disturbances in fibromyalgia: A meta-analysis of case-control studies. *Journal of Psychosomatic Research*. 2017; 96: 89–97.
- [17] Lawson K. Sleep Dysfunction in Fibromyalgia and Therapeutic Approach Options. *OBM Neurobiology*. 2020; 4: 049.
- [18] Finan PH, Goodin BR, Smith MT. The association of sleep and pain: An update and a path forward. *Journal of Pain*. 2013; 14: 1539–1552.
- [19] Lawson K. Is there a role for melatonin in fibromyalgia? *AIMS Molecular Science*. 2019; 6: 73–86.
- [20] Teng HW, Tani J, Chang TS, Chen HJ, Lin YC, Lin CS, *et al.* Altered sensory nerve excitability in fibromyalgia. *Journal of the Formosan Medical Association*. 2021; 120: 1611–1619.
- [21] Lin CS, Kiernan MC, Burke D, Bostock H. Assessment of nerve excitability properties in peripheral nerve disease. In Kimura J (ed.) *Handbook of Clinical Neurophysiology* (pp. 381–399). Elsevier: Edinburgh, Scotland. 2006.
- [22] David G, Modney B, Scappaticci KA, Barrett JN, Barrett EF. Electrical and morphological factors influencing the depolarizing after-potential in rat and lizard myelinated axons. *Journal of Physiology*. 1995; 489: 141e57.
- [23] Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis & Rheumatism*. 2001; 44: 222–230.
- [24] Vijayan S, Klerman EB, Adler GK, Kopell NJ. Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia. *Journal of Neurophysiology*. 2015; 114: 1923–1930.
- [25] Spaeth M, Bennett RM, Benson BA, Wang YG, Lai C, Choy EH. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. *Annals of the Rheumatic Diseases*. 2012; 71: 935–942.
- [26] Tas A, Hayta E, Karadag A, Zontul C, Ozmen E, Aydin S, *et al.* Potassium Ion Channel Protein (KCNH) Levels in Patients with Fibromyalgia Syndrome. *Cellular and Molecular Biology*. 2022; 67: 451–457.
- [27] Chiesa N, Rosati B, Arcangeli A, Olivetto M, Wanke E. A novel role for HERG K⁺ channels: spike-frequency adaptation. *Journal of Physiology*. 1997; 501: 313–318.
- [28] Heide J, Vandenberg JI, Shannon Weickert C. Expression of KCNH2-3.1 mRNA is increased in small neurons in the dorsolateral prefrontal cortex in patients with schizophrenia. *The European Journal of Psychiatry*. 2015; 29: 85–103.
- [29] Pan Z, Zhang M, Ma T, Xue ZY, Li GF, Hao LY, *et al.* Hydroxymethylation of microRNA-365-3p Regulates Nociceptive Behaviors via Kcnh2. *Journal of Neuroscience*. 2016; 36: 2769–2781.
- [30] Klein CJ, Lennon VA, Aston PA, McKeon A, Pittock SJ. Chronic pain as a manifestation of potassium channel-complex autoimmunity. *Neurology*. 2012; 79: 1136–1144.
- [31] Chang C-T, Jiang B-Y, Chen C-C. Ion Channels Involved in Substance P-Mediated Nociception and Antinociception. *International Journal of Molecular Sciences*. 2019; 20: 1596.
- [32] De Koninck Y, Henry JL. Substance P-mediated slow excitatory postsynaptic potential elicited in dorsal horn neurons *in vivo* by noxious stimulation. *Proceedings of the National Academy of Science U S A*. 1991; 88: 11344–11348.
- [33] Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiological Reviews*. 1993; 73: 229–308.
- [34] Nakajima Y, Nakajima S, Inoue M. Pertussis toxin-insensitive G protein mediates substance P-induced inhibition of potassium channels in brain neurons. *Proceedings of the National Academy of Science U S A*. 1988; 85: 3643–3647.
- [35] Takano K, Yasufuku-Takano J, Kozasa T, Singer WD, Nakajima S, Nakajima Y. Gq/11 and PLC-beta 1 mediate the substance P-induced inhibition of an inward rectifier K⁺ channel in brain neurons. *Journal of Neurophysiology*. 1996; 76: 2131–2136.
- [36] Gilbert R, Ryan JS, Horackova M, Smith FM, Kelly ME. Actions of substance P on membrane potential and ionic currents in guinea pig stellate ganglion neurons. *American Journal of Physiology*. 1998; 274: C892–903.
- [37] Sculptoreanu A, Artim DE, de Groat WC. Neurokinins inhibit low threshold inactivating K⁺ currents in capsaicin responsive DRG neurons. *Experimental Neurology*. 2009; 219: 562–573.
- [38] Linley JE, Ooi L, Pettinger L, Kirton H, Boyle JP, Peers C, *et al.* Reactive oxygen species are second messengers of neurokinin signaling in peripheral sensory neurons. *Proceedings of the National Academy of Science U S A*. 2012; 109: E1578–1586.
- [39] Lin CC, Chen WN, Chen CJ, Lin YW, Zimmer A, Chen CC. An antinociceptive role for substance P in acid-induced chronic muscle pain. *Proceedings of the National Academy of Science U S A*. 2012; 109: E76–83.
- [40] Tzadok R, Ablin JN. Current and Emerging Pharmacotherapy for Fibromyalgia. *Pain Research and Management*. 2020; 2020: 6541798.
- [41] Alles SRA, Cain SM, Snutch TP. Pregabalin as a Pain Therapeutic: Beyond Calcium Channels. *Frontiers in Cellular Neuroscience*. 2020; 14: 83.
- [42] Huang CW, Huang CC, Wu SN. The opening effect of pregabalin on ATP-sensitive potassium channels in differentiated hippocampal neuron-derived H19-7 cells. *Epilepsia*. 2006; 47: 720–726.
- [43] Kweon TD, Kim JY, Kwon IW, Choi JB, Lee YW. Participation of K(ATP) Channels in the Antinociceptive Effect of Pregabalin in Rat Formalin Test. *Korean Journal of Pain*. 2011; 24: 131–136.
- [44] Zhang F-X, Gadotti VM, Souza IA, Chen L, Zamponi GW. BK potassium channels suppress *cav* α 2 δ subunit function to reduce inflammatory and neuropathic pain. *Cell Reports*. 2018; 22: 1956–1964.
- [45] McClelland D, Evans RM, Barkworth L, Martin DJ, Scott RH. A study comparing the actions of gabapentin and pregabalin on the electro-physiological properties of cultured DRG neurons from neonatal rats. *BMC Pharmacology*. 2004; 4: 14.
- [46] Tully J, Jung JW, Patel A, Tukan A, Kandula S, Doan A, *et al.*

Utilization of Intravenous Lidocaine Infusion for the Treatment of Refractory Chronic Pain. *Anesthesiology and Pain Medicine*. 2021; 10: e112290.

- [47] Wolff M, Schnobel-Ehehalt R, Mühling J, Weigand MA, Olschewski A. Mechanisms of lidocaine's action on subtypes of spinal dorsal horn neurons subject to the diverse roles of Na⁺ and K⁺ channels in action potential generation. *Anesthesia and Analgesia*. 2014; 119: 463e70.
- [48] Olschewski A, Hempelmann G, Vogel W, Safronov BV. Blockade of Na⁺ and K⁺ currents by local anesthetics in the dorsal horn neurons of the spinal cord. *Anesthesiology*. 1998; 88: 172–179.
- [49] Meng Q, Xia Z, Liu J, Bayliss DA, Chen X. Local anesthetic inhibits hyperpolarization-activated cationic currents. *Molecular Pharmacology*. 2011; 79: 866–873.
- [50] Ramírez D, Zúñiga R, Concha G, Zúñiga L. HCN Channels: New Therapeutic Targets for Pain Treatment. *Molecules*. 2018; 23: 2094.
- [51] Lawson K, Singh A, Kantsedikas I, Jenner CA, Austen DK. Flupirtine as a potential treatment for fibromyalgia. *Journal of Exploratory Research in Pharmacology*. 2021; 6: 5363.
- [52] Lawson K. Pharmacology and clinical applications of flupirtine: current and future options. *World Journal of Pharmacology*. 2019; 8: 1–13.
- [53] Lawson K. Kv7 channels a potential therapeutic target in fibromyalgia: A hypothesis. *World Journal of Pharmacology*. 2018; 7: 1–9.
- [54] Robbins J. KCNQ potassium channels: physiology, pathophysiology, and pharmacology. *Pharmacology & Therapeutics*. 2001; 90: 1–19.
- [55] Wickenden AD, McNaughton-Smith G. Kv7 channels as targets for the treatment of pain. *Current Pharmaceutical Design*. 2009; 15: 1773–1798.
- [56] Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin – A pleiotropic, orchestrating regulator molecule. *Progress in Neurobiology*. 2011; 93: 350–384.
- [57] Srinivasan V, Lauterbach EC, Ho KY, Acuna-Castroviejo D, Zakaria R. Melatonin in antinociception: its therapeutic applications. *Current Neuropharmacology*. 2012; 10: 167–178.
- [58] Hernandez-Pacheco A, Araiza-Saldana CI, Granados-Soto V, Mixcoatl-Zecuatl T. Possible participation of the nitric oxide-cyclic-GMP-protein kinase G-K⁺ channels pathway in the peripheral antinociception of melatonin. *European Journal of Pharmacology*. 2008; 596: 70–76.
- [59] van den Top M, Buijs RM, Ruijter JM, Delagrange P, Spanswick D, Hermes ML. Melatonin generates an outward potassium current in rat suprachiasmatic nucleus neurones in vitro independent of their circadian rhythm. *Neuroscience*. 2001; 107: 99–108.
- [60] Wang LM, Suthana NA, Chaudhury D, Weaver DR, Colwell CS. Melatonin inhibits hippocampal long-term potentiation. *European Journal of Neuroscience*. 2005; 22: 2231–2237.
- [61] Takeshita N, Oe T, Kiso T, Kakimoto S. A KCa3.1 channel opener, ASP0819, modulates nociceptive signal processing from peripheral nerves in fibromyalgia-like pain in rats. *Journal of Pain Research*. 2021; 14: 23–34.
- [62] Mongan LC, Hill MJ, Chen MX, Tate SN, Collins SD, Buckby L, *et al.* The distribution of small and intermediate conductance calcium-activated potassium channels in the rat sensory nervous system. *Neuroscience*. 2005; 131: 161–175.
- [63] Wulff H, Kolski-Andreaco A, Sankaranarayanan A, Sabatier JM, Shakkottai V. Modulators of small- and intermediate-conductance calcium-activated potassium channels and their therapeutic indications. *Current Medicinal Chemistry*. 2007; 14: 1437–1457.
- [64] Arnold LM, Blauwet MB, Tracy K, Cai N, Walzer M, Blahunka P, *et al.* Efficacy and Safety of ASP0819 in Patients with Fibromyalgia: Results of a Proof-of-Concept, Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Pain Research*. 2020; 13: 3355–3369.
- [65] Schweiger V, Martini A, Bellamoli P, Donadello K, Schievano C, Balzo GD, *et al.* Ultramicronized Palmitoylethanolamide (um-PEA) as Add-on Treatment in Fibromyalgia Syndrome (FMS): Retrospective Observational Study on 407 Patients. *CNS & Neurological Disorders - Drug Targets*. 2019; 18: 326–333.
- [66] Del Giorno R, Skaper S, Paladini A, Varrassi G, Coaccioli S. Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies. *Pain and Therapy*. 2015; 4: 169–178.
- [67] LoVerme J, Russo R, La Rana G, Fu J, Farthing J, Mattace-Raso G, *et al.* Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor- α . *Journal of Pharmacology and Experimental Therapeutics*. 2006; 319: 1051–1061.
- [68] Romero TRL, Duarte IDG. N-palmitoyl-ethanolamine (PEA) induces peripheral antinociceptive effect by ATP-sensitive K⁺ channels activation. *Journal of Pharmacological Sciences*. 2012; 118: 156–160.
- [69] Stensson N, Ghafouri N, Ernberg M, Mannerkorpi K, Kosek E, Gerdle B, *et al.* The relationship of Endocannabinoidome lipid mediators with pain and psychological stress in women with fibromyalgia: A case-control study. *The Journal of Pain*. 2018; 19: 1318–1328.
- [70] Roehrs T, Withrow D, Koshorek G, Verkler J, Bazan L, Roth T. Sleep and pain in humans with fibromyalgia and comorbid insomnia: double-blind, crossover study of suvorexant 20 mg versus placebo. *Journal of Clinical Sleep Medicine*. 2020; 16: 415–421.
- [71] Sakurai T. The neural circuit of orexin (hypocretin): Maintaining sleep and wakefulness. *Nature Reviews Neuroscience*. 2007; 8: 171–181.
- [72] Li SB, Damonte VM, Chen C, Wang GX, Kebschull JM, Yamaguchi H, *et al.* Hyperexcitable arousal circuits drive sleep instability during aging. *Science*. 2022; 375: eabh3021.
- [73] Jafri MS, Weinreich D. Substance P hyperpolarizes vagal sensory neurones of the ferret. *Journal of Physiology*. 1996; 493: 157–166.