K_v7 (KCNQ) Channel Modulators and Neuropathic Pain

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Received August 16, 2006

Introduction

Neuropathic pain can arise as a result of direct trauma to nerves or indirectly as a secondary consequence of a diverse range of disease states including metabolic disorders (diabetes), cancer, chemotherapy, autoimmune disease (multiple sclerosis, AIDs), viral infection (postherpetic neuralgia), and stroke. Patients with neuropathic pain can present any number of positive symptoms as typified by spontaneous pain, pain evoked by normally innocuous sensory stimuli (allodynia), or exacerbated pain in response to noxious stimuli (hyperalgesia). Paradoxically, negative symptoms are also common and generally include loss of sensation around the area of injury.[1] Preclinical studies have clearly demonstrated that altered functioning of voltage-activated Na^+ and Ca^{2+} ion channels are key mediators of injury-induced hyperexcitability within pain processing pathways.[2] These findings are mirrored in the clinical treatment of patients where antiepileptic drugs such as the Na^+ channel blocker lamotrigine and gabapentin (which binds to the Ca^{2+} channel $\alpha_2\delta$ subunit) have proven to be variably effective in alleviating signs and symptoms of pain.[1,3] Nevertheless, a significant number of patients receive inadequate treatment from these drugs and from other medications that include opiates and antidepressants.[1,4] Therefore, novel mechanism of action drugs must be developed to help fulfill the unmet needs of patients. To this end, drugs capable of modulating voltage-activated K_v7 channels are particularly appealing,[5,6] given that these channels play a key role in controlling the excitability status of neurons within the nervous system.[7]

K_v7 Channels and the M Current

K_v7 (KCNQ) channels are a family of six transmembrane domain voltage-gated K^+ channels consisting of five family members ($K_v7.1$− $K_v7.5$).[8] Four K_v7 subunits are required to form functional K_v7 channels. Whereas all five K_v7 channel subunits can form homomeric channels in vitro, the formation of heteromeric channels appears to be restricted to certain combinations.[7] In rodents, $K_v7.2$−$K_v7.5$ channels are expressed in various cells of the peripheral and central nervous systems including dorsal root ganglion (DRG[a]) cells, hippocampal cells, and cortical cells (reviewed in ref 9). In contrast, $K_v7.1$ channels are expressed in cardiac tissue and peripheral epithelial and smooth muscle cells.[8,9] The biophysical properties, pharmacological sensitivity to the selective blockers (also termed negative modulators) linopirdine and XE991 (**1** and **2**, respectively; Figure 1), and distribution pattern of $K_v7.2$ and $K_v7.3$ subunits enabled David McKinnon and colleagues to conclude that heteromeric $K_v7.2 + K_v7.3$ channels are the molecular correlate

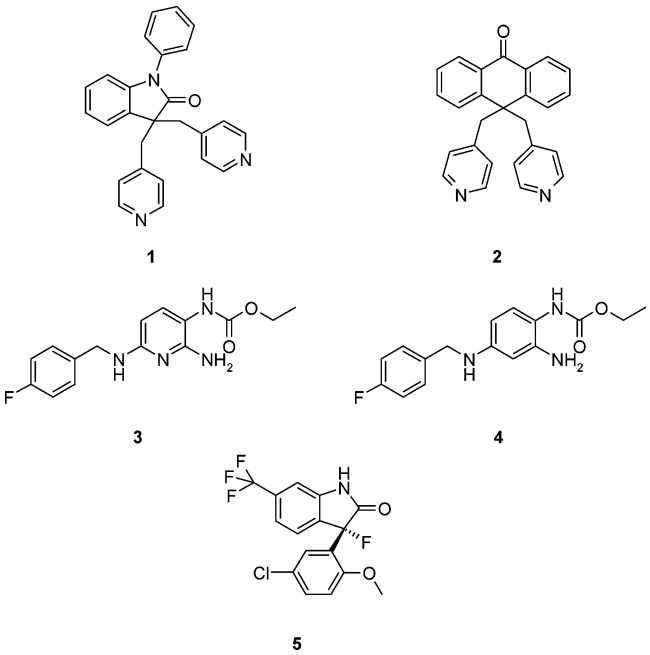

Figure 1. First-generation modulators of K_v7 channels: **1**, linopirdine; **2**, XE991; **3**, flupirtine; **4**, retigabine; **5**, BMS204352.

of the M channel;[10] notably, $K_v7.4$, $K_v7.5$, and $K_v7.5 + K_v7.3$ subunits also constitute functional M channels. The M current was first described in frog sympathetic neurons as a noninactivating K^+ current that could be slowly activated by depolarization and inhibited by muscarinic acetylcholine receptor activation.[11] The M channel is activated at membrane potentials that are more negative than the action potential threshold, at which few other ion channels are active. This enables M channels to act as excitability "brakes" to ultimately prevent repetitive firing of neuronal action potentials. Subsequently, the flupirtine [D-9998, 2-amino-6-(4-fluoro-benzylamino)-pyridin-3-yl)-carbamic acid ethyl ester, **3**) derivative retigabine [D23129, *N*-(2-amino-4-(4-fluorobenzylamino)-phenyl)carbamic acid ethyl ester), **4**] (Figure 1) was reported to activate cloned $K_v7.2 + K_v7.3$ channels by shifting their voltage sensitivity to more hyperpolarized membrane potentials.[12−14] Somewhat predictably, retigabine is also an opener (also termed positive modulator) at homomerically expressed $K_v7.4$ and $K_v7.5$ channels and $K_v7.5 + K_v7.3$ heteromultimeric channels.[15−17]

Epilepsy is a common neurologic condition encompassing a number of different syndromes that are characterized by a predisposition to recurrent unprovoked seizures.[18] In accordance with the recognition of epilepsy as a neuronal hyperexcitability disorder, treatment of epilepsy is directed toward resolving the imbalance between inhibitory and excitatory synaptic neurotransmission. However, it has been estimated that in the U.S.A. more than 30% of patients remain inadequately treated with available drugs. To this end, the potential for using K_v7/M

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[a] Abbreviations: CCI, chronic constriction injury; DRG, dorsal root ganglion; ED_{50}, dose of drug required to produce 50% antinociceptive effect; ip, intraperitoneal; iv, intravenous; MED, minimum effective dose; po, per os (oral); SNL, spinal nerve ligation.

10.1021/jm060989l CCC: $37.00 © 2007 American Chemical Society
Published on Web 05/10/2007

channel openers as a novel pharmacotherapy in seizure prevention has been highlighted by multiple studies from Chris Rundfeldt's group who have shown that retigabine possesses a broad spectrum of activity in animal models of electrically induced and chemically induced epileptic seizures.[19−21] Retigabine is currently being developed by Valeant Pharmaceuticals Inc., which is evaluating its antiepileptic potential in two multinational phase III trials in patients with partial-onset seizures.[22]

As already mentioned, hyperexcitability mechanisms also contribute to the injury-induced manifestation of behavioral symptoms in neuropathic pain. Peripherally, these can include spontaneous action potential discharges arising from lesioned sensory neurons.[2] Centrally, activity-dependent and transcription-dependent changes occurring within spinal cord pain-processing neurons contribute to amplification of peripheral sensory input and to a process termed central sensitization.[23] So what evidence exists to suggest that K_v7 channels are involved in the processing of nociceptive signaling within pain transmission pathways?

K_v7 Channel Distribution and Function in Pain Pathways

Peripheral sensory neurons have their cell bodies located within the DRG and traverse either side of the spinal cord outside of the central nervous system. They act as an interface, enabling both low (innocuous touch and thermal) and high (noxious mechanical and thermal) threshold sensory information to be relayed from their terminals, which reside within peripheral tissues including the skin and visceral structures, to central neurons within the spinal dorsal horn. From here, pain signals ascend via multiple pathways to various brainstem, thalamic, and cortical regions to initiate in parallel, the sensory (duration, location, intensity) and affective (emotion, arousal) qualities of pain.[24] Importantly, preliminary observations suggest that K_v7 channels appear to be localized in many of these key structures.[25,26] Passmore and colleagues have reported that $K_v7.2$, $K_v7.3$, and $K_v7.5$ subunits are all variably expressed within both small and large cell bodies of rat DRG sensory neurons.[27] Their overlapping distribution patterns suggest that the M current in these cells likely comprises both $K_v7.2 + K_v7.3$ and $K_v7.3 + K_v7.5$ heteromultimeric complexes. Correspondingly, $K_v7.2$ channels are present in peripheral myelinated nerve fibers, where their localization with nodal Na^+ channels in the narrow unmyelinated part of the nodes of Ranvier suggests that they are a major contributor to fast action potential propagation.[26]

At a functional level, Passmore and colleagues have used a standard deactivation voltage protocol to identify the M current in isolated small-diameter sensory neurons, 70% of which were responsive to capsaicin, identifying them as nociceptors. Predictably, the M channel blocker linopirdine inhibited the M current and reduced the threshold of firing. In contrast, retigabine hyperpolarized the resting membrane potential and increased the threshold of firing in sensory neurons.[27] In extension of these experiments, Rivera-Arconada and Lopez-Garcia have used an isolated rat spinal cord preparation to demonstrate that retigabine application produces a strong and long-lasting hyperpolarization of sensory neuron inputs.[28,29] This indicates that functional M channels are also present at the first central synapse of the pain transmission pathway, a not unexpected finding given their expression pattern within DRG cells. A similar picture has recently been reported for K_v7 channel expression and functionality within visceral sensory neurons suggesting that these channels might also participate in nociceptive transmission relayed from deeper, internal body structures.[30,31] Collectively, these morphological and electrophysiological observations suggest that pathological changes in K_v7 channel function within pain transmission pathways might potentially contribute to neuropathic pain. Therefore, what evidence exists to suggest that K_v7 openers might prove to be effective analgesics in pain conditions associated with nerve injury?

K_v7 Openers and Neuropathic Pain

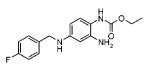
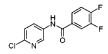
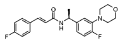
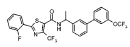
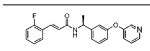
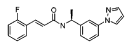
Animal models of neuropathic pain invariably entail some form of damage to a peripheral nerve innervating the hind limb, with subsequent injury-induced sensitization of pain transmission signals, which manifests behaviorally as hind paw allodynia and hyperalgesia.[32] Altered expression of voltage-activated Na^+ and Ca^{2+} channels within pain signaling pathways has been clearly shown to underly such signs and symptoms of neuropathic pain.[33] Increasingly, a number of studies have reported that voltage-gated K^+ currents and K^+ channel subunit expression (principally K_v1 and K_v2 family subunits) are reduced within DRG cells after axotomy and/or peripheral nerve injury.[34−38] Although a preliminary study has suggested that DRG $K_v7.2$ and $K_v7.3$ subunit expression is increased after spinal nerve ligation as an adaptive response to neuropathic injury, this has not been rigorously confirmed.[39]

Thus, a primary line of evidence for specific K_v7 channel involvement in neuropathic pain is based on electrophysiological recordings made from anesthetized neuropathic rats.[27] These have revealed direct inhibitory actions of spinally administered retigabine (10−90 μg) on spinal dorsal horn neuron firing rate activated by mechanical stimulation of their peripheral receptive fields within the injured hind limb. Furthermore, retigabine also appears to be extremely effective at reducing a mechanistic process referred to as "wind-up", which reflects increased neuronal plasticity of dorsal horn neurons in response to repetitive input stimulation.[27]

The confirmatory line of evidence for K_v7 channel involvement in neuropathic pain comes from behavioral studies in animal pain models. The formalin test is initiated by injection of the chemical algogen (pain-producing) formalin into the rat or mouse hind paw. It involves sensitization of peripherally mediated nociceptive events with subsequent amplification of the afferent input within the spinal dorsal horn. Systemically (intraperitoneal (ip) and oral (po)) administered retigabine markedly reduces formalin-induced pain hypersensitivity in rats (ED_{50} = 6.6 and 47.6 mg/kg, respectively; Table 1). Importantly, this effect is completely reversed by coadministration of the selective K_v7 channel blocker **2**, indicating a mechanism of in vivo action selectively mediated by K_v7 channels.[40] Retigabine also diminishes behavioral hypersensitivity to mechanical and cold stimulation of the injured hind paw in the chronic constriction injury and spared nerve injury models of neuropathic pain.[40] Again, the crucial aspect of K_v7 channel specificity has been confirmed by Dost and colleagues who have reported that the antiallodynic actions of retigabine in the spinal nerve ligation model of neuropathic pain could be abolished by coadministration of the K_v7 blocker linopirdine.[41] Although not widely regarded as a neuropathic disorder per se, fibromyalgia is characterized by widespread muscoskeletal pain in humans, together with altered spinal processing of sensory information and activation of brain structures implicated in pain appraisal.[42] Although no animal model of fibromyalgia currently exists, retigabine has been reported to attenuate mechanical allodynia in a rat model of acid-induced muscoskeletal pain.[43]

Collectively, these behavioral findings suggest that K_v7 openers have major potential as novel mechanism of action

Table 1. Effects of K_v7 Modulators in Animal Models of Experimental Pain[a]

Structure	Clinical pain condition	Preclinical pain model	Analgesic efficacy	Ref.
	Persistent pain	Formalin test	ED_{50} = 48 mg/kg (p.o.)	40
	Neuropathic pain	CCI and SNL nerve injury models	MED = 10 mg/kg (p.o.)	40,41
	Persistent Pain	Formalin test	MED = 30 mg/kg (p.o.)	69
	Inflammatory pain	Carrageenan model	MED = 30 mg/kg (p.o.)	69
	Neuropathic pain	SNL nerve injury model	ED_{50} = 25 mg/kg (p.o.)	69
	Neuropathic pain	SNL nerve injury model	MED = 10 mg/kg (i.v.)	92
	Diabetic polyneuropathy	Streptozotocin-induced diabetic pain	MED = 10 mg/kg (i.v.)	92
	Neuropathic pain	SNL nerve injury model	MED = 10 mg/kg (i.v.)	85
	Diabetic polyneuropathy	SNL nerve injury model	MED = 10 mg/kg (i.v.)	85
	Neuropathic pain	SNL nerve injury model	MED = 10 mg/kg (i.v.)	77
	Neuropathic pain	SNL nerve injury model	MED = 10 mg/kg (i.v.)	80

[a] Data from preclinical experiments were obtained from rats.

analgesics. However, a major limiting factor in assessing retigabine efficacy in animal pain models is its neurotoxic profile. Retigabine impairs motor function in both mice and rats as assessed by exploratory motility and rotarod testing paradigms.[21,44] This translates to a therapeutic index (calculated as (ED_{50} in rotarod test)/(ED_{50} in pain model)) in rats of approximately 1−4 after ip or po administration. Fortunately, retigabine is reasonably well tolerated in humans, although it is perhaps no surprise that the most common adverse events reported by patients leading to its discontinuation are ataxia, dizziness, and somnolence.[22] Until proven otherwise, it remains feasible that the development of subtype-selective K_v7 channel openers may circumvent this issue.

One particularly exciting aspect of K_v7 channel involvement in chronic pain states remains to be tested. The physical and psychological stress of living with chronic pain entails that patients have a high risk of developing anxiety and depressive disorders.[45] While the preclinical efficacy of retigabine in attenuating reflex sensory nociceptive responses has been clearly demonstrated, nothing is known in relation to K_v7 channel involvement in affective (emotional) pain processing. Retigabine has been shown to possess an anxiolytic profile in the mouse zero maze and marble burying models of anxiety.[44] Thus, K_v7 openers might conceivably attenuate both sensory *and* affective pain responses in appropriate preclinical testing paradigms.[46] In chronic pain patients, this might translate as improved pain relief at the time of drug administration and, in addition, improved pain coping mechanisms with continued use of drug.

Developments in K_v7 Modulators

Negative and positive modulators (blockers and openers respectively) of the K_v7 channel were known before the ion channel itself was identified and cloned. Linopirdine (and second-generation compounds **2** and DMP543[47]) originated from research efforts at DuPont aimed at optimizing compounds for the treatment of Alzheimer's disease. However, the pharmaceutical industry ceased to show interest in negative K_v7 modulators about a decade ago, precluding further development in this area. The positive modulator and desazaflupitine derivative retigabine, in turn, originated from the NIH Antiepileptic Drug Development Program and, as previously mentioned, was subsequently developed by Asta Medica where epilepsy was the primary indication.[19,20] While the relative merits of retigabine's use as a tool compound with some $K_v7.2$ selectivity have already been mentioned,[21] more recently MaxiPost (BMS204352, **5**) has been reported to selectively potentiate $K_v7.4$, $K_v7.5$, and $K_v7.3 + K_v7.5$ channel function.[44,48,49]

Retigabine may also interact with GABA and kainate receptor induced currents as well as voltage-activated Na^+ and Ca^{2+} channels.[43] Although the GABA receptor modulating properties have been regarded as significant enough for Valeant Pharmaceuticals Inc. and others to consider that retigabine may possess a dual mechanism of action,[51] the potentiation of GABA induced currents in rat cortical neurons by retigabine is observed at concentrations 100-fold greater than those required for K^+ channel opening.[50] Thus, the contribution of this mechanism to the anticonvulsant activity of retigabine is probably a minor one. Nevertheless, retigabine has relatively low-potency actions at K_v7 channels ($EC_{50} \cong 1\ \mu M$; patch clamp on cloned Chinese hamster ovary cells (CHO) stably expressing K_v7 channels)[16] and has a complex phase II metabolism subject to glucoronidation by multiple UGT isoenzymes which might render it unsuitable for administration to young children.[21,52] Thus, in combination with the previously mentioned toxicity issues, these further aspects leave considerable scope for the development of more selective, potent, and efficacious K_v7 modulators.

Using retigabine as a first-generation modulator, scientists at Lundbeck A/S have explored the retigabine scaffold in a systematic manner, giving rise to six recent patent applications.[53−58] The structure−activity relationship has yet to be disclosed, but the greatest focus has been given to bioisosters for the primary amine, which might be expected to give rise to glucoronidation problems as discussed above. Nevertheless, more potent compounds (**6**, Figure 2) relative to retigabine with EC_{50} values less than 150 nM have been reported using a ^{86}Rb efflux assay using cloned CHO cells stably expressing $K_v7.2$).[54] The given biological data indicate that epilepsy is the indication of choice, with no pain-related data disclosed.

In 2001, specific oxindole derivates including **5** were found to be potent and efficacious openers of K_v7 channels.[15] Subsequently, it was claimed that these compounds were particularly useful for alleviating neuropathic pain, although no supporting data were presented.[59] The oxindole scaffold was originally designed as part of a BK (maxi-K) channel opener program by Bristol-Myers Squibb, inspired by the classical BK openers NS004 and NS1619.[60] Further development by ring expansion led to a family of 3-substituted quinolin-2-one analogues that were found to modulate K_v7 channel function

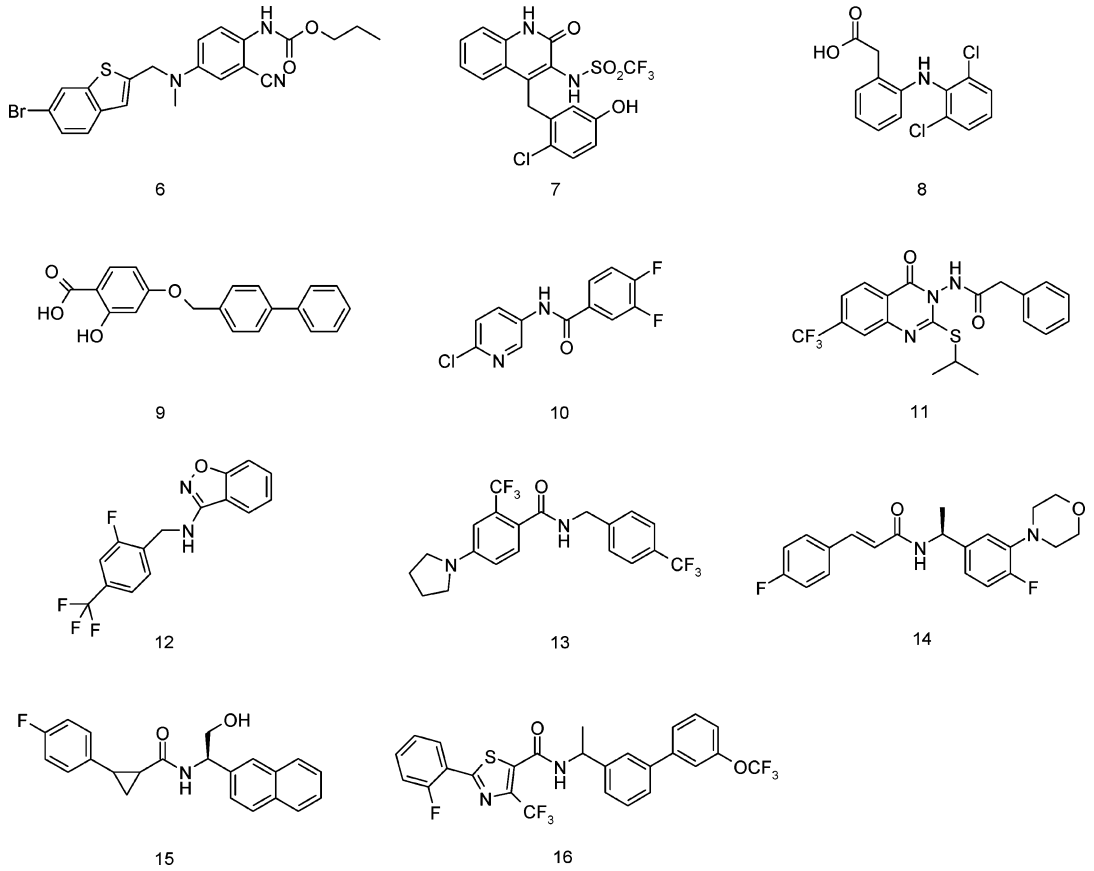


Figure 2. New chemical entities modulating K_v7 channels: **6**, second-generation retigabine analogues from Lundbeck; **7**, 3-substituted quinolin-2-one derivatives inspired by BK modulators from Bristol-Myers Squibb; **8**, diclofenac from Tel Aviv University; **9**, salicylic acid derivatives from NeuroSearch; **10**, benzanilides from Icagen; **11**, 3-aminoquinazolin-ones from Icagen; **12**, benzo[*d*]isoxazole derivatives from Grünenthal; **13**, pyrimidines from Bristol-Myers Squibb; **14**, bisarylacrylamides from Bristol-Myers Squibb; **15**, arylcyclopropylcarboxylic amides from Bristol-Myers Squibb; **16**, 2-arylthiazol derivatives from Bristol-Myers Squibb.

after the introduction of a relatively acidic substituent in the 3-position (**7**, Figure 2).[61] Although a structure−activity relationship has been given, the therapeutic potential for this type of compound remains to be explored.

Attali and co-workers have recently shown that specific fenamates (**8**, Figure 2) also modulate K_v7 channel function.[62] Importantly, the M-current modulating effect of meclofenamic acid was reversed by linopirdine when tested by voltage clamp on cultured rat cortical neurons known to coexpress $K_v7.2$ and $K_v7.3$ subunits, which led the authors to conclude that the effect was K_v7 mediated.[62] Furthermore, diclofenac and, to a lesser extent, meclofenamic acid displayed robust antiepileptic properties in vivo. The fenamates are currently prescribed as analgesics for rheumatic pain, an effect that is at present believed to be mediated by the cyclooxygenase isoforms COX-1 and COX-2. Although the reported pharmacological effects are obtained at relatively high concentrations, the fenamate scaffold may nevertheless serve as a template for novel K_v7 modulators with neuropathic pain as a primary indication.[62]

Another class of compounds, namely, salicylic acid derivatives (**9**, Figure 2), was recently reported to modulate K_v7 channel function, but only limited biological information was specified, and no reference to pain alleviating effects were made presumably as a result of poor brain penetration qualities.[63]

Overall, the classes of compounds mentioned above constitute isolated research efforts that in combination with the limited level of biological and structural data disclosed do not appear to add significantly to our understanding of the therapeutic potential of K_v7 openers for alleviating signs and symptoms of neuropathic pain. However, more information has come from two new series of compounds from Icagen and Bristol-Myers Squibb. In 2001, Icagen published the first of three patent applications relating to a class of compounds collectively referred to as benzanilides (**10**, Figure 2).[64−66] While it was reported that the compounds were effective in animal models of anxiety and pain, no specific structure was revealed. However, 4 years later, in 2005 the structure and biological data for **10** (ICA-27243, previously known as ICA-D1[67]) were eventually disclosed.[68−70] The selectivity over other ion channel families (certain Na^+, Ca^{2+}, GABA, and K^+ channels) and within neuronal K_v7 heteromers (**10** is $K_v7.2 + K_v7.3$ selective) was specifically pointed out with reference made to the less selective actions of retigabine. Furthermore, it was shown that the safety profile was slightly improved compared to that of retigabine. More specifically, the therapeutic index (calculated as (ED_{50} in rotarod test)/(ED_{50} in efficacy model), where roatrod ED_{50} = 40 mg/kg) was reported to range from 4 to 13 in the rat kindling model of epileptic seizures and from 1.6 to 8 in the spinal nerve ligation model of neuropathic pain.[67] The most recent family of K_v7 modulators from Icagen comprises quinazolin-4-one derivatives.[71] These compounds are as potent and efficacious as retigabine, although no in vivo data are yet available (**11**, Figure 2).

Recently, scientists from Grünenthal GMBH disclosed a series of benzo[*d*]isoxazole compounds claimed to positively modulate $K_v7.2 + K_v7.3$ channels. The compounds were identified by FLIPR (using a membrane potential kit) and validated in patch clamp electrophysiology. The compounds are mentioned as

being suitable for pain treatment, but no reference to preclinical animal data is made in the patent application (**12**, Figure 2).[72]

The Bristol-Myers Squibb Company has been active from the very onset in developing new chemical entities for modulating K_v7 channel function, with the initial synthesis of a series of pyrimidines[73] (**13**, Figure 2). However, the best described and most extensive work has been completed within a family of acrylamides by Bristol-Myers Squibb scientists. Numerous articles,[74−76] patent applications,[77−82] and reviews[83,84] describe in detail how a simple bisarylacrylamide was found in a Tl^+ influx assay and how this hit was optimized to give several potent compounds including **14** (BMS-568274, Figure 2). Despite the many potent and efficacious compounds synthesized, there is a general trend that as the potency increases, the efficacy (current flux under voltage clamp) decreases, with the end improvement relative to retigabine being a minor one in vitro. Subsequently, the cinnamic acid fingerprint of these compounds was further developed to contain a cyclopropyl group in place of the double bond (**15**, Figure 2)[84] and an arylthiazole as a bioisoster for styrene (**16**, Figure 2).[85,86] Furthermore, the arylthiazole compounds have been reported to be efficacious in animal models of neuropathic pain (Table 1). To date, the Bristol-Myers Squibb company has primarily focused on using K_v7 modulators for the treatment of migraine. The compounds generally show good efficacy in a migraine model of KCl-induced cortical spreading depressions. Some data are also available from the patent literature, where the acrylamides have been reported to alleviate pain in certain models of neuropathic pain (Table 1).

Future Perspectives for K_v7 Modulators

As yet, no published accounts of retigabine efficacy in the clinical treatment of chronic pain exist. However, numerous open label and double-blind controlled trials have shown that the close structural analogue and K_v7 opener flupirtine (Figure 1) is effective in alleviating pain associated with a diverse range of etiologies.[87] These include chronic myofacial pain, osteoporosis-related pain, cancer pain, and muscoskeletal pain.[88−91] A particular facet of flupirtine-mediated analgesia in humans is that it is obtained at doses associated with plasma concentrations in the low micromolar range, which suggests that K_v7 channel opening is the likeliest pharmacological mechanism to account for this action. Combined with the wealth of newly emerging molecular and pharmacological data obtained from animal pain models, these clinical observations support the concept that drugs capable of targeting K_v7 channels should prove to be effective analgesic agents in the fight against neuropathic pain.

Acknowledgment. We thank Dr. Palle Christophersen for critical reading of the manuscript.

Biographies

Gordon Munro received his Ph.D. in Physiology from the University of Edinburgh in 1994. Following postdoctoral positions in the field of neuroendocrinolgy and then postdoctoral pain research with Susan Fleetwood-Walker at the University of Edinburgh, he joined the Danish biopharmaceutical company NeuroSearch A/S in 2001. He is currently a senior investigator with a research base focused on translating the pharmacology of diverse animal behaviors into mechanisms that contribute to neuropathic pain.

William Dalby-Brown graduated in 2001 with a M.Sc. in Chemistry from the University of Copenhagen, and in the same year he joined the biopharmaceutical company NeuroSearch A/S. Over the years he has been involved as a medicinal chemist in the development of chemical entities modulating different ion channels including ionotropic glutamate receptors, GABA-A receptors, and currently K_v7.

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JM060989L