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Is KCNQ Channel a Mediator of Urinary Bladder Disorders in Multiple Sclerosis ?

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ABSTRACT

The KCNQ encoded channels in such pacemaker cells as well as smooth muscles regulate the excitability and membrane physiology. ICC like cells in the ureter are distributed throughout the ureter with higher distribution in the upper ureter i.e pyeloureteric junction. These cells in the absence of neural input can still maintain peristalsis for propulsion of urine from the kidney to ureter. Ion channels encoded by the KCNQ gene family (K_v7.1–7.5) are major determinants of neuronal membrane potential and the cardiac action potential. This key physiological role is highlighted by the existence of a number of hereditary disorders caused by mutations to KCNQ genes. Recently, KCNQ gene expression has been identified in vascular and non-vascular smooth muscles. In addition, experiments with an array of pharmacological modulators of KCNQ channels have supported a crucial role for these channels in regulating smooth muscle contractility. This article will provide an overview of present understanding in this nascent area of KCNQ research and will offer guidance as to future directions. This hypothetical review examines the possibility of KCNQ channels and their role in urinary bladder disorders in multiple sclerosis.

Keywords: KCNQ, bladder, phospholipase C, multiple sclerosis, smooth muscle

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INTRODUCTION

In the central nervous system (CNS), K_V7 channels form through homo- or heteromeric assembly of $K_V7.2$ to $K_V7.5$ subunits. Thus far, homomeric compositions are shown for $K_V7.2$-5 subunits; heteromeric compositions and are represented by $K_V7.2+3$, $K_V7.3+4$ and $K_V7.3+5$ channels [1,2]. In most neurons native K_V7 channels are composed of $K_V7.2$ and $K_V7.3$ subunits [3,4] or sometimes of homomeric $K_V7.2$ subunits [5], [6], although probably with a contribution by $K_V7.5$ subunits in some neurons [7]; $K_V7.4$ subunits are predominantly expressed in the auditory and vestibular systems, but also probably contribute to K_V7 channels in central dopaminergic neurons [8,9]. On the other hand, functional significance of KCNQ channels in bladder are important in setting vascular tone; Yeung et al [10] demonstrated relaxation of pre-contracted murine aorta with flupirtine and meclofenamic acid. In contrast, KCNQ inhibitors constricted rat mesenteric [11] and rat or mouse intrapulmonary arteries [12]. Here, the putative functional role of KCNQ channels in bladder was demonstrated in bladder strips where myogenic spontaneous contractions were affected by KCNQ drugs, indicating that KCNQ channels are active under these conditions. These findings are consistent with the current-clamp studies of isolated cells, in which KCNQ inhibitors reduced the membrane potential and often elicited transient depolarizations, whereas KCNQ activators induced hyperpolarization and simultaneous cessation of any spontaneous transient depolarizations. It can interpreted that the flupirtine reduction in contractility with a degree of caution however, as this could be partly explained by its effect on L-type Ca2+-currents. The effects of KCNQ channel drugs on bladder strip contractility are reasonably explained by a direct action on SMC and not arising from depolarization of intramural nerves leading to neurotransmitter release, as experiments were performed in the presence of tetrodotoxin. It was noted with interest that KCNQ drugs impacted contraction amplitude and AUC analysis but had no overall significant effect on frequency. Moreover, KCNQ inhibitors did not significantly enhance baseline tone, typical of other phasic smooth muscle tissues such as uterus [13] and colon [14]. Ca2+-experiments demonstrated that at the single cell level and within smooth muscle bundles, XE991 enhanced the frequency of Ca2+-oscillations consistent with the depolarization found in current clamp experiments. Therefore, in normal bladder, KCNQ channels seem to advance our current findings knowledge of the diversity of K+ channel expression in bladder smooth muscle. The roles of BK, SK, delayed rectifier and KATP in bladder electrical activity are well established, yet there are more K+ channels present, including novel TASK [15] and TREK channels [16] in addition to KCNQ. Clearly bladder SMC contain a complement of K+ channels that can be finely tuned to work together in response to the physiological requirements of the organ during filling and micturition. In this hypothetical review we speculate the interaction of KCNQ channels and phospholipase C in bladder muscle tone control. It can be speculated that KCNQ channels may contribute to the bladder incontinence and pathophysiology in multiple sclerosis patients.

Causes of bladder dysfunction in patients of multiple sclerosis

The demyelinization of the nerve tissue in the spinal cord can cause an interruption of nerve signals to the urinary bladder and sphincter muscles between the bladder and the urethra. Demyelinization is the result of the immune system attacking the myelin sheath on

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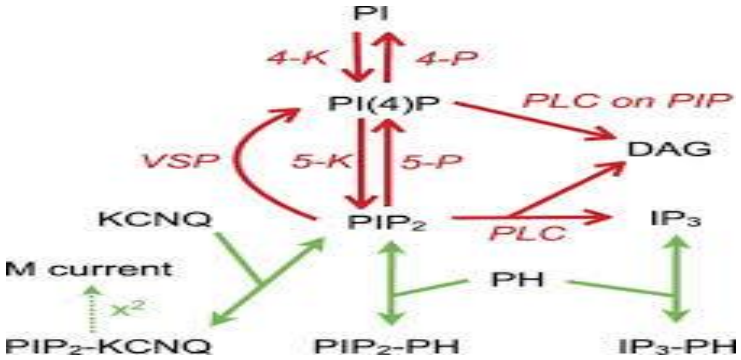
the spinal nerves that innervate the bladder. Due to blocked or delayed nerve signals in the spinal cord, the individual may experience bladder spasms resulting in urinary incontinence. Bladder spasms occur when the sphincter muscle contracts at the wrong times. As a result of spasms of the bladder, the flow of urine may be blocked or restricted. Conversely, the signals supplying the bladder may cause the sphincter to relax when it is supposed to be constricted. If the sphincter is relaxed when the bladder has urine in it, the individual will experience urinary incontinence. Whether the KCNQ channels are involved in the regulatory control of smooth muscles needs to be investigated.

KCNQ and Phospholipid metabolism

The Modulation of KCNQ by muscarinic neurotransmitters in bladder presents an intriguing area of future work; this mechanism is now well established for the neuronal KCNQ M-current where muscarinic stimulation inhibits KCNQ channel activity. Muscarinic receptors are physiologically the most important mechanism mediating urinary bladder contraction [17]. The mammalian bladder (including human) mainly expresses M2 and M3 muscarinic receptors, which coexist in an approximate 3:1 ratio [18,19]. Whereas M2 receptors can contribute to bladder smooth muscle tone under certain conditions, the primary mediator of normal mammalian bladder contraction is the minor population of M3 receptors [20,21]. Muscarinic receptor subtypes can couple to a range of signal transduction pathways, and the primary signaling of M3 receptors is thought to occur by stimulation of a phospholipase C (PLC) to generate inositol-1,4,5-triphosphate (IP3) and diacylglycerol [22]. Muscarinic receptor coupling to PLC activation and IP3 formation in the mammalian urinary bladder also has been reported [23]. On the other hand, when FKBP was joined with PIP_2 5-phosphatase to dephosphorylate PIP_2, the M-current fell precipitously after dimerization. Several control experiments showed that this fall was accompanied by a rapid fall of PIP_2 (seen with the PH-domain translocation probe), was not sensitive to PLC inhibitors and was not accompanied by production of a Ca^{2+} elevation or of DAG (tested with the C1-domain probe). Thus, inhibition of M-current does not require the downstream messengers generated when PLC cleaves PIP_2. Furthermore, the translocated enzyme presumably generated a large bolus of PIP at the plasma membrane, yet the KCNQ current fell. This means that PIP cannot replace PIP_2 as a permissive ligand for KCNQ channels (Figure 1). A more direct approach to the lipid specificity question involves exposing the cytoplasmic face of an excised patch of membrane to different phosphoinositides very similar translocatable PIP_2 5-phosphatase probe was developed by [24].

Figure 1:



Phospholipase C gamma and multiple sclerosis

The Phosphoinositide-specific C phospholipases (PLC) are one of the major group of cell-signaling switch molecules because their role in the formation of the second messenger inositol 1,4,5-trisphospate (IP3) and diacylglycerol (DAG). There are six families of PLC enzymes that differ in their amino acid sequence and structural organization [24,25]. The two members of the branch corresponding to the PLCg family have inserted within the catalytic core, two Src homology 2 (SH2) domains and one SH3 domain. The C-terminal SH2 domain is a critical determinant for auto-inhibition [26], while translocation to lipid membranes is required for full enzymatic activity [27]. PLCg1 is ubiquitously expressed while PLCg2 is most highly expressed in cells of hematopoietic origin and play a critical role in the regulation of the immune system [28], [29]. A gain-of-function mutation in murine PLCg2 enhanced its membrane stability and lead to severe autoimmunity [30]. Recently, a human dominantly inherited phenotype linked to deletions of the autoinhibitory domain of PLCg2 was reported. These deletions lead to constitutive phospholipase activity and autoimmune disease [31]. Thus, mutations of PLCg2 that affect its activity or its temporal location or by extension, variants in associated molecules could lead to complex immunological phenotypes with very different manifestations, such as inflammation, cold urticaria or signs of autoimmunity such as autoantibody formation.PLCg2 may be involved indirectly or directly to the smooth muscle anomalies in multiple sclerosis.

Prospects for therapy with KCNQ channel modulators

The identification of the *KCNQ2* and *KCNQ3* gene products that underlie many M channels [32] from inherited human epileptic syndromes [33] it is not surprising that these channels are under intensive study for new therapeutic modes for a variety of diseases. Thus, specific M channel openers, such as retigabine, are currently being developed as novel antiepileptic drugs and specific blockers, such as XE991 (a linopirdine derivative) [34,35] may find use as 'cognition enhancers' and also in disorder like the MS. Since M current plays such a powerful role in tuning synaptic efficacy and neurotransmitter action, we also predict M channels to be potential targets to ameliorate a variety of psychiatric diseases, as well as new treatments for chronic pains, in accord with the identification of M currents in a variety of nociceptive/sensory neurons [36,37]

CONCLUSION

It appears based on the current research data that KCNQ channels underlie the regulatory control of urinary bladder smooth muscle. Thus KCNQ mediated linkage to phospholipase C may be involved in aetiological basis of urinary bladder and other smooth muscle malfunction in multiple sclerosis.

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