Editorial

Understanding the cardiac role of K$_{2p}$ channels: A new TASK for electrophysiologists

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Received 4 May 2007; accepted 8 May 2007


Two-pore-domain K$^+$ channels (K$_{2p}$ channels) form a newly identified class of 15 K$^+$ channels that possess four transmembrane-spanning domains and two pore domains. Studies in heterologous systems suggest that functional K$_{2p}$ channels are dimers with an overall topology close to that of inward rectifier channels. Heterologous expression of these channels gives rise to instantaneous, non-inactivating K$^+$ currents that display little or no voltage dependence, suggesting that they might contribute to background or leak currents. These channels are sensitive to a large spectrum of physical and chemical factors such as membrane stretch, temperature, oxygen tension, pH, fatty acids, phospholipids, and anesthetics [1]. Many of them are ubiquitously expressed, suggesting that they likely subserve a variety of important physiological and pathophysiological functions. Such a hypothesis is supported by studies regarding the central nervous system. For instance, TREK-1 seems to protect neuronal cells against excessive excitability and is a target for anesthetics [2], whereas TASK-1 contributes to the standing-outward K$^+$ current (I$_{KSO}$) of cerebellar granule neurons [3]. Cardiomyocytes also express several K$_{2p}$ channels, the main ones being TREK-1 (or K$_{2p}2.1$, encoded by KCNK2 gene) and TASK-1 (or K$_{2p}3.1$, encoded by KCNK3), but the contribution of these channels to the cardiac electrical activity has been poorly evaluated. Their properties are relatively similar to those of the so-called “plateau current” (I$_{Kp}$) observed in guinea-pig cardiomyocytes [4] or to the steady-state K$^+$ current (I$_{SS}$) in mouse cardiomyocytes [5].

In this issue of Cardiovascular Research, Putzke and co-workers [6] confirm the high level of expression of TASK-1 in cardiomyocytes and provide the first quantitative description of I$_{TASK}$ contribution to ventricular repolarisation in rats. By measuring the pH-sensitive current and by using a new TASK-1 channel inhibitor that appears to be highly selective, these authors show that TASK-1 contributes significantly to the net current during the plateau phase. Inhibition of this current leads to a robust (≈20%) prolongation of action potential duration. More studies now need to be done. Because of the heterogeneity of ventricular repolarisation, the impact of I$_{TASK}$ on the different subendocardial and subepicardial myocyte populations should be studied more extensively. Future studies will also need to quantify the impact of the current at different, and more physiological, rates. Finally, the role of I$_{TASK}$ in mammals with repolarisation properties close to those in human cardiac myocytes, in which TASK-1 is highly expressed [7], should also be investigated, since previous studies in mice suggest that inhibition of this current could be arrhythmogenic [8]. Indubitably, the new TASK channel blocker used by Putzke and coworkers will facilitate these investigations.

Another important finding of Putzke et al. is that stimulation of a$_{1A}$-adrenergic receptors inhibits I$_{TASK}$. It has been known for a long time that a-adrenergic stimulation prolongs cardiac repolarisation by decreasing different K$^+$ currents, including a steady-state outward current [9] that could be generated by TASK-1 channels based on the present results. The authors
should now determine the relative contribution of ITASK to the overall effect of α1-adrenergic stimulation. This information can be easily obtained by the use of their TASK-1 channel inhibitor. They should also investigate the intracellular pathway involved in α1-adrenergic regulation of ITASK. Such studies are crucial for evaluating the pathophysiological impact of this finding, and one can bet that they are most likely under way. Alpha1-adrenergic receptors can couple to G proteins of the Gn/G11 family. When activated, Gn proteins stimulate phospholipase C (PLC), which then hydrolyzes phosphorylidyinositol 4,5-bisphosphate (PIP2) to produce two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3).

Recently, activation of another Gs-coupled receptor, the M1 muscarinic receptor, has been shown to decrease ITASK via the activation of PLC [10]. Interestingly, though, this study provides strong evidence that the inhibition of TASK-1 is not mediated by DAG or IP3 but rather on PIP2 hydrolysis itself, which causes local reduction of PIP2 levels in the plasma membrane. As for many other K+ channels, PIP2 appears to regulate voltage gating of TASK-1 and other K2P channels. Angiotensin II receptors are also Gs-coupled receptors, and TASK-1 has been shown to be inhibited by angiotensin II in glomerulosa cells of rat adrenal cortex [11,12]. Because there is increasing evidence that angiotensin II plays a crucial role in the development of cardiac electrical dysfunction and arrhythmias in the context of ischemia–reperfusion [13], cardiac hypertrophy, and heart failure [14,15], investigating whether or not angiotensin II regulates TASK-1 in cardiac myocytes would certainly improve our understanding of arrhythmias in these pathophysiological conditions.

More than 10 years after the cloning of the first mammalian K2P channel, the results presented by Putzke and coworkers demonstrate further the need for improving our knowledge of the cardiac function of these channels. Although incomplete, as all pioneering studies can be, the study by Putzke and coworkers is undoubtedly an important milestone toward elucidation of TASK-1 involvement in cardiac electrical activity.

References