EDITORIAL FOCUS

Myriad roles of voltage-activated potassium channel subunit Kvβ1.1 in the heart

Rakesh C. Kukreja
Division of Cardiology, Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia

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ELECTRICAL ABNORMALITIES within the heart can often result in the development of arrhythmias that may further progress into sudden cardiac death; often the origins of these developments remain largely unknown. Atrial fibrillation, which is one of the most common type of heart arrhythmia, affects an estimated 3–6 million people within the United States (Center for Disease Control). Arrhythmic events can arise in atria and or the ventricular regions of the heart, often developing from genetic mutations, in particular, from genes encoding important ion channels such as sodium and/or potassium channels and their auxiliary subunits. Research in the field of arrhythmic study identified key ion channels such as sodium and potassium channels, highlighting the clinical importance of mutations such as in the SCN5A channel (33). However, to date, potassium channel mutations as well as their auxiliary subunits alterations are less known and therefore remain important and clinically relevant targets for investigation. One particular group of potassium channels of interest are the voltage-activated potassium (Kv) channels, which play a critical role in establishing the repolarization phase of cardiac action potentials. In addition, they are one of the key channels affected in action potential prolongation as well as in QT prolongation. The human genome encodes roughly 40 different Kv channels, which are further subdivided into twelve subfamilies (Kv1–Kv12). They share a general channel mechanism, i.e., sensing voltage changes within the cell and responding by activating/inactivating or closing, dependent upon the channel properties. Kv channels open, inactivate, and close in response to voltages, and this synchrony of Kv channel action works in continuous balance to propagate action potentials. Previous research identified that mutations of fast-inactivating Kv currents (murine-Kv4.2 human-Kv4.3 channels) demonstrated significant prolongation in QT durations, resulting in cardiac hypertrophy and even heart failure (4, 23). Mutations in other cardiac relevant Kv channels such as Kv2.1, 1.5, and 1.4 produced similar deleterious effects, altering QT durations with little to no effect demonstrated on cardiac remodeling (16, 17).

Kv channel auxiliary subunit modulation has had profound effects on regulating Kv channel activity, which is sometimes even greater than mutations or deletions of the potassium channel (11, 19, 32). The auxiliary subunits or otherwise known β-subunits Kvβ (Shaker potassium channel subunit) include Kvβ1 (with splice variants Kvβ1.1, Kvβ1.2, and Kvβ1.3) and Kvβ2. These Kvβ subunits are of particular interest in the cardiovascular system because they are highly expressed within the heart and vascular system including the aorta (7, 25). In vitro work has demonstrated profound effects of Kvβ subunits on Kv channel activity, although little is known about the in vivo effects of Kvβ subunit alterations. Kvβ1 subunits have been shown to modulate key Kv channels including Kv1.5, 1.4 and most recently 4.2 all of which play a vital role in the repolarization of cardiac action potentials (8, 25, 31). Kvβ1 knockout mice have significant decrease in $I_{\text{to,f}}$ as well as the $I_{\text{to,s}}$ (1). More recent genetic testing is beginning to reveal the absence of Kvβ1 in numerous disease conditions including schizophrenia, high blood pressure, and sudden cardiac death (3, 5, 12, 14).

Initial discoveries demonstrated high levels of Kvβ subunits in brain and abundant expression in the heart as well as the vascular system (7). The cloning, isolation, purification, and X-ray crystallography work led to the understanding of the sequence and structure of the Kvβ subunits (9). The sequence alignment analysis showed that Kvβ subunits shared similarities with the oxidoreductases, in particular, the aldo-keto reductases (AKR) (15). Because of the closely related sequence to AKR5 and AKR7 subfamilies, the Kvβ subunits were later classified as AKR6 (10). Furthermore, the Kvβ subunits were recognized as the only protein with dual functions, both as an enzyme as well as modulator of Kv channels. These distinct characteristics categorized Kvβ subunits to an elite group of proteins known to us in nature. In addition, the unique ability of Kvβ subunits as reductase enzyme that convert carbonyls (aldehydes or ketones) to their respective alcohols shared the central feature of AKR’s proteins, i.e., the ability to bind pyridine nucleotides (NAD/NADH and NADP/NADPH) with high affinity. In this context, the findings by Tur and colleagues (29), reported in the current issue of the American Journal of Physiology-Heart and Circulatory Physiology, that Kvβ1 interacts with NADH/NAD and alters cardiac electrical activity are highly novel. Subsequent research focused on understanding the Kvβ structure culminating in the crystal structure of a truncated Kvβ2 subunit that remained bound to the NADP molecule during the crystallization process (9). In addition to the pyridine nucleotide binding abilities, the Kvβ1 subunits with their varying NH2-termini demonstrated the potential to rapidly inactivate noninactivating Kv channels (2, 30). Moreover, even fast-inactivating Kv channels such as Kv1.4 as well as Kv4.2/4.3 could be modulated by Kvβ1 subunits (6, 20, 22).

Much like the other oxidoreductases, the Kvβ subunits maintained substrate binding sites and cofactor binding pockets. While it was understood that pyridine nucleotides could
bind to Kvβ subunits at low-micromolar concentrations, little was known as to how this binding altered Kv channel or Kvβ activity in cardiovascular physiology. The binding affinity ($K_d$) of pyridine nucleotides and Kvβ subunits was found to be in the micromolar range (13, 26). In addition, flavin adenine dinucleotide (FAD) and nicotinamide mononucleotide (NMN) also bind to the Kvβ subunits but required significantly higher concentrations (13). To this end, a link between pyridine nucleotide binding, Kvβ subunits, and their modulation of Kv channels remained unknown. Kv1.5 and the addition of Kvβ1 in the presence and absence of pyridine nucleotides significantly altered Kv1.5 channel activity; high levels of NADH increased inactivation rates, whereas high NAD caused the channel to remain active (27). AKR’s catalytic activity uses a hydride transfer and thus requires pyridine nucleotides for modulation (24), while previous research demonstrated the importance of pyridine nucleotides and Kv channel modulation through Kvβ’s aldo-ketoreductase abilities. Mutation of the AKR sites resulted in significant Kv channel kinetic alterations (2). Further work highlighted that reductase ability itself modulated Kv channel kinetics after adding 4-cyanobenzaldehyde in the presence of Kvβ subunits (18).

Recent genomic analysis has suggested the important role of Kvβ subunits in cardiovascular function from familial hypertension to a recent mutation discovery linked to Brugada’s syndrome (21). Knockout of Kvβ1 in mice caused significant decrease in $I_{ss}$, although overt phenotypic changes were not revealed (1). More recently, Tur et al. showed that the deletion of Kvβ1.1 resulted in significant prolongation in action potentials in addition to the prolonged QTc durations in male and female mice (28). Interestingly, female knockout mice had significantly higher blood pressure and aortic pressure that likely resulted in the hypertrophic hearts. Thus, oftentimes, it appears that deletion of a key protein or subunit may not directly impact the cardiac physiology. It is the application of physiologically relevant stress that may provide insightful information revealing the importance of such proteins.

In their recent study, Tur et al. (29) describe the myriad physiological role of Kvβ subunits in the cardiovascular system. Specifically, they show that Kvβ subunits not only are chaperone proteins but are precisely positioned in close proximity for binding to ion channels to modulate physiological roles in the heart. The Kvβ subunits do so by sensing metabolic changes via alterations in $[\text{NAD(P)H}]/[\text{NAD(H)}]$ thereby altering the electrical activity (Fig. 1). These results suggest that Kvβ subunits are key players in the field of ion channels, which were otherwise thought to be a silent partner for many decades. Thus this elegant work by Tur and colleagues brings the Kvβ subunits to the forefront of cardiovascular research and its potential impact in modulating the electrical activity of the heart in a physiologically relevant manner.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

R.C.K. prepared figures and approved final version of manuscript.

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