AJP Editorial Focus

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

Rakesh C. Kukreja

Pauley Heart Center, Division of Cardiology,
Virginia Commonwealth University. Richmond, VA. 23298, U.S.A.

Address correspondence to:
Rakesh C. Kukreja, Ph.D.
Professor of Internal Medicine, Physiology & Biophysics,
Biochemistry & Molecular Biology
Eric Lipman Distinguished Chair of Cardiology
Scientific Director, Pauley Heart Center
Division of Cardiology, Box 980204
Virginia Commonwealth University
1101 East Marshall Street, Room 7-020D
Richmond, VA 23298-0204, U.S.A.
Phone: 804-628-5521
Fax: 804-828-8700
E-mail: rakesh.kukreja@vcuhealth.org

Copyright © 2017 by the American Physiological Society.
Electrical abnormalities within the heart can often result in the development of arrhythmias which 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 (CDC). 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 (32). 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 sub-families (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 in order 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, resulted 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, 31). 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

2
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, 30). Kvβ1 knockout mice have significant decrease in I_{tof} current as well as the I_{to's} current (1). More recent genetic testing is beginning to reveal the absence of Kvβ’s 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 which 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. To this context, the findings by Tur and colleagues reported in the current issue of the journal that Kvβ1.1 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 which 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 non-inactivating Kv channels (2, 29). 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 (Kd) of pyridine nucleotides and Kvβ subunits was found to be in the micro molar 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
while high NAD caused the channel to remain active (27). AKR's catalytic activity utilizes 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 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_to currents although overt
phenotypic changes were not revealed (1). More recently Tur et al showed that 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 KO mice had significantly higher
blood pressure and aortic pressure which likely resulted in the hypertrophic hearts. Thus often
times, 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 which may provide insightful
information revealing the importance of such proteins.

In the current issue of AJP Heart Tur et al describe the myriad physiological role of Kvβ
subunits in the cardiovascular system. Specifically, they show that Kvβ subunits are not only
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 [NAD(P)H]/[NAD(H)] thereby altering the electrical activity (Figure 1). These
results suggest that Kvβ subunits are key players in the field of ion channels which otherwise
were 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.
**Figure legend**

**Figure 1:** The schematic diagram illustrates the link between ion channel modulation by Kvβ subunit in the presence of oxidized (blue) or reduced (red) pyridine nucleotide leading to action potential and ECG changes.

**Acknowledgements.**

Supported by National Institutes of Health (R01HL118808, R01HL134366 and R37HL51045 to R.C.K.).

**References**


Figure 1.

![Diagram showing the transition between open and inactivated states of a channel protein, with associated graphs for current, action potential, and ECG.]