Keeping you healthy: BK channel activation by omega-3 fatty acids

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In the exuberant world of K⁺ channels, the Ca²⁺- and voltage-activated K⁺ (BK, MaxiK, Slo1) channel stands alone. It is coded by a single gene (slo1 or KCNMA1), and the pore-forming α subunit has seven transmembrane segments instead of six as found in voltage-dependent K⁺ channels (Atkinson et al., 1991; Adelman et al., 1992; Butler et al., 1993; Wallner et al., 1996). Being activated by depolarizing voltages and cytoplasmic Ca²⁺, the BK channel is the perfect molecular machine to retard or to simply stop excitatory signals. The negative feedback (hyperpolarization) created by the opening of these K⁺ channels is caused by the perfect tuning between Ca²⁺ and voltage sensors. The communication between these two types of sensors is allosterically established, that is, voltage- or internal Ca²⁺-alone is able to open the BK channel, but channel opening is increasingly facilitated as more Ca²⁺ and voltage sensors are activated (Horrigan and Aldrich, 2002; Horrigan, 2012) (Fig. 1 A). Another important difference between BK channels and Kv channels, where opening is tightly coupled to voltage-sensor activation (Soler-Llavana et al., 2003) (Fig. 1 B), is that, albeit with a very low probability, BK channels can open in a voltage sensor– and Ca²⁺-independent manner (reaction C↔O defined by the equilibrium constant L in Fig. 1 A).

Despite being coded by a single gene, BK channel diversity is large. Alternative splicing, posttranslational modifications, and/or the presence of modulatory β or γ subunits create this diversity (Orio et al., 2002; Salkoff et al., 2006; Yan and Aldrich, 2010, 2012). In particular, modifications induced in BK gating kinetics by the β1, β2, and β4 subunits proved to be of crucial importance in many physiological processes, ranging from shaping neuronal excitability and neurosecretion to smooth muscle tone, and in others not so physiological, such as alcohol tolerance (Brenner et al., 2000; Hu et al., 2001; Gollasch et al., 2002; Grimm and Sansom, 2007; Martin et al., 2008). The expression of β subunits is highly tissue specific; β1 is the only β subunit expressed in smooth muscle, and β4 is mainly expressed in the nervous system (Orio et al., 2002; Wu and Marx, 2010). In vascular smooth muscle cells (SMCs), the presence of β1 plays a vital role in vasoregulation, and its lack leads to hypertension (Brenner et al., 2000; Fernández-Fernández et al., 2004; Nelson and Bonev, 2004). β1 and β2 have been observed to dramatically slow down activation and deactivation kinetics as well as increase the apparent Ca²⁺ sensitivity of the BK channel. Although β4 also decelerates BK activation and deactivation kinetics, even more so than β1, Ca²⁺ sensitivity of channels formed by α/β4 subunits is complex. Channels are less sensitive to Ca²⁺ at low internal Ca²⁺ concentrations (<10 µM) than channels formed by the α subunit alone. However, Ca²⁺ is more effective in activating α/β4 channels at higher Ca²⁺ concentrations (Ha et al., 2004; Wang et al., 2006).

In addition to their effects on channel gating, β subunits grant BK channels sensitivity to several physiologically important compounds, thus making these subunits targets for possible pharmacological interventions. For example, β1-containing BK channels but not channels formed by the α subunit alone appear to be the target of 17β-estradiol and other compounds such as estrogen analogues, anti-estrogens, and the bile salt component lithocholic acid (Valverde et al., 1999; Dick et al., 2001; Bukiya et al., 2009; Maher et al., 2013). The activation of BK channels by 17β-estradiol has been proposed as the possible mechanism that mediates the acute relaxation of vascular smooth muscle induced by the hormone (White et al., 1995; Ruehlmann et al., 1998). On the other hand, stress steroids activate channels formed by the α/β4 complex but not by α/β2 (King et al., 2006). Polyunsaturated fatty acids such as arachidonic acid (AA) are also able to directly activate BK channels, but in this case, AA enhances BK current in the presence of either β2 or β3 (Sun et al., 2007). Findings by Sun et al. (2007) also show that AA is able to remove inactivation, suggesting that this fatty acid is interacting with the β2-inactivating peptide. Tissue specificity of β subunits and their particular capacity to endow BK channels with different pharmacological profiles have greatly increased the importance of BK channels in maintaining the adequate cellular electrical homeostasis in different tissues.

Docosahexaenoic acid (DHA), an omega-3 fatty acid known to be associated with beneficial cardiovascular effects, was reported to be a potent activator of BK currents in rat coronary artery SMCs and to promote dilation of isolated small coronary arteries (Lai et al., 2009;...
DHA, an omega-3 fatty acid found in fish oil (salmon, sardines, herring, etc.) and also in plant seeds, is the most abundant omega-3 fatty acid in the brain. By studying the Greenland Inuit tribe, which consumes large amounts of fat from fish, the conclusion was reached that high levels of omega-3 fatty acids consumed by the Inuit were the cause of their reduced triglycerides and blood pressure. Hence, this study underscores the benefits of consuming this type of lipid (Dyerberg et al., 1975). Below-normal levels of this fatty acid have been also associated with cognitive decline and increase in neural cell death (Serhan et al., 2004; Lukiw et al., 2005). However, the detailed mechanisms underlying the mode of action of this important fatty acid remain unclear.

The work done by Hoshi et al. (2013b) adds to the numerous beneficial effects of DHA by including the possibility that this fatty acid could be clinically relevant if targeted to BK channels, because of its blood pressure-lowering effects. In wild-type mice, but not in Slo1 knockout (SLO1−/−) mice, DHA injections have been observed to reversibly reduce blood pressure and produce a significant increase in BK-mediated K+ currents in isolated aortic vascular SMCs, a current enhancement that was absent in SMCs dissociated from SLO1−/− mice. When applied to the intracellular side of inside-out membrane patches, DHA was able to quickly activate α/β1 channels in a reversible manner and with an EC50 of ~500 nM. These findings indicate that the omega-3 fatty acid directly acts on the α/β1 complex with an affinity that is ~20-fold greater than the affinity to a G-coupled receptor associated to the antiinflammatory properties of this fatty acid (Oh et al., 2010). Other important fatty acids like, for example, omega-6 fatty acids, α-linoleic and eicosapentaenoic acid or AA, are also able to activate BK channels, albeit with a lower potency. Because DHA BK channel activation can be elicited with all the voltage sensors at rest and in the absence of internal Ca2+, Hoshi’s group arrived at the conclusion that DHA acts directly on the Ce↔O equilibrium (Fig. 1 A) and destabilizes the channel closed conformation of the pore gate.

The next step in this BK channel saga was to identify the molecular determinants in the β1 subunit that confer BK its ability to be activated by the omega-3 fatty acid (Hoshi et al., 2013a). The effects of DHA were first tested in channel with various subunits (β1, β2 [inactivation removed], β4, and γ1 [LRRC26]), with the result that robust channel activation by DHA was only observed in channels formed by α/β1 and α/β4. β subunits consist of two transmembrane domains connected by a large external loop and with N and C termini oriented toward the cytoplasm. The β1 phenotype can be recovered by creating a chimera containing the N terminus and the N-terminal half of the first transmembrane segment (TM1) of β1 in a β2 background. Two β1 amino acid residues, one in the amino terminus (R11) and the other in TM1 (C18), proved to be enough to recover the full effect of DHA when replacing the corresponding amino acids in β2 (A42L, L49). On the other hand, the corresponding amino acids in β4 are E12 and R19. As in the case of the double mutant β2 A42L/L49C, BK channels formed by α/β2 A42L/L49R subunits have very similar responses to DHA as α/β4 channels. Mechanistically, it is still unclear how these of amino acid residues in β1 and β4 confer DHA sensitivity to the BK channel. However, the fact that the α/β1 as well as the α/β4 channel can be activated by DHA opens the possibility that DHA regulation of neuronal BK channel activity may play an important role in the nervous system.

In this issue of JGP, Hoshi et al. continue dissecting the effects of DHA, and their queries have led them to the identification of a single amino acid residue in the BK S6 transmembrane domain, which has been seen to establish the sensitivity to the omega-3 fatty acid.
The finding that DHA is able to activate BK channels in the absence of β subunits, albeit with about a fivefold loss in potency, led Hoshi et al. (2013c) to search for the molecular determinants of this β subunit–independent mode of action of the lipid, for which the fruit fly came to the rescue. *Drosophila melanogaster* BK channels turned out to be insensitive to DHA, and chimeras created by mixing regions of *Drosophila* and human BK channels made it possible to identify the pore domain (PD; S5-P loop–S6) as the region that is necessary and sufficient to recover the full effect of DHA in the absence of β subunits (about a fourfold increase in ionic currents). From all the point mutations made in the PD, Y318S was the only one capable of dramatically decreasing the DHA effect. Y318 is located toward the C terminus end of S6. However, before continuing with the DHA issue, an overview of certain BK activation gate characteristics having direct implications on the DHA mode of action must be offered. The BK internal vestibule is much wider than the intracellular mouth of Kv channels (Li and Aldrich, 2004; Brelidze and Magleby, 2005; Geng et al., 2011; Zhou et al., 2011). Additionally, large quaternary ammonium ions and the Shaker “ball” peptide can block closed channels, implying that the bundle crossing does not hinder the passage of ions (Wilkins and Aldrich, 2006; Thompson and Begenisich, 2012). Although this evidence strongly suggests that the BK activation gate is not cytoplasmic like in Kv channels (Thompson and Begenisich, 2012), the C terminus of S6 renders the BK channel insensitive to DHA, and chimeras created by mixing regions of *Drosophila* slo locus. Science. 253:551–555. http://dx.doi.org/10.1126/science.1857984

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Latorre and Contreras
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