JGP Journal of General Physiology

RESEARCH NEWS

FMRP differentially regulates BK channels

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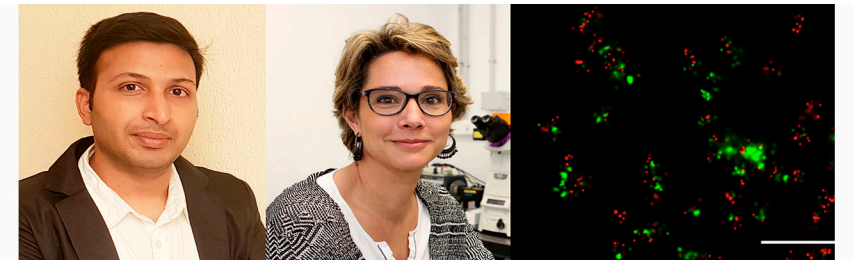
Study suggests that the fragile X syndrome-associated protein FMRP can interact with different types of BK channels and modulate their kinetics in different ways.

Mutations in fragile X mental retardation protein (FMRP) cause fragile X syndrome (FXS), an inherited disorder characterized by seizures and intellectual disability. FMRP is highly expressed in neurons and is best known as a cytosolic RNA-binding protein that regulates translation. More recently, however, the protein has also been shown to bind and regulate various ion channels. For example, FMRP is thought to increase the open probability of type II BK channels by binding to their auxiliary β_4 subunits, thereby modifying neuronal action potentials and neurotransmission (1, 2). In this issue of *JGP*, Kshatri et al. demonstrate that FMRP also regulates type I BK channels lacking β subunits, indicating that the effects of FMRP on BK currents are more complex than originally thought (3).

BK channels are voltage- and Ca^{2+}-activated potassium channels that are widely expressed throughout the nervous system. Composed of four channel-forming α subunits, the properties of BK channels can be modulated by a variety of additional, regulatory subunits, including β_4. FMRP has been proposed to enhance the activity of BK channels by binding and sequestering β_4 subunits (1, 2), and Teresa Giraldez and colleagues at Universidad de La Laguna in Spain were interested in studying the FMRP–β_4 interaction in a heterologous expression system.

"However, when we were setting up the controls for this project, we found, to our surprise, that FMRP had a significant effect on BKα-only channels lacking β_4," Giraldez says.

Giraldez and colleagues, including first author Aravind Kshatri, determined that FMRP alters the properties of BKα-only channels, especially the rate of deactivation, which was eight times slower in the presence of FMRP.



Aravind Kshatri (left), Teresa Giraldez (center), and colleagues reveal that the FXS-related protein FMRP, previously proposed to regulate type II BK channels by binding to the auxiliary β_4 subunits, also regulates type I channels containing BKα subunits only. STORM imaging (right) shows that heterologously expressed FMRP (red) and BKα (green) cluster together in the plasma membrane of HEK293T cells.

After analyzing their data using an established model of BK channel gating (4), Kshatri et al. propose that, in the absence of β_4, FMRP enhances channel activity by favoring both voltage sensor activation and pore opening (3). Super-resolution STORM imaging revealed that FMRP clusters with BKα channels in the plasma membrane, supporting the idea that FMRP modulates channel activity by forming a complex with BKα even in the absence of β_4.

FMRP also clustered with BKαβ_4 channels, but its effects on this type of BK channel were relatively modest, only slowing the rate of deactivation by a factor of ∼2. Kshatri et al. found that, rather than abrogating the effects of β_4 by sequestering it, FMRP potentiates β_4 function: while β_4 enhances voltage sensor activation in BKα channels, FMRP promotes pore opening to further enhance channel activity (3).

Finally, the researchers analyzed a mutant version of FMRP, FMRP-R138Q, linked to FXS. This mutation largely abolished FMRP's effects on the function of both BKα and BKαβ_4 channels.

Though Kshatri et al.'s study was performed in a heterologous expression system, their finding that FMRP can differentially regulate distinct types of BK channel is likely to have important physiological consequences (3). Neurons express a variety of BK channels with diverse subunit compositions, so understanding how FMRP affects neuronal action potentials and neurotransmission, and how this is altered in FXS, will be a complex undertaking.

"We now want to examine the effect of FMRP on BK channels containing other regulatory subunits," Giraldez says. "We are also interested in understanding how FMRP interacts with BK channels and the mechanisms by which it alters their function."

References

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This work is part of the special collection entitled "Electrical Signaling in the Heart and Nervous System: A Joint Meeting of the Society of General Physiologists and Latin American Society of Biophysicists."