Uncorking AMPA receptors

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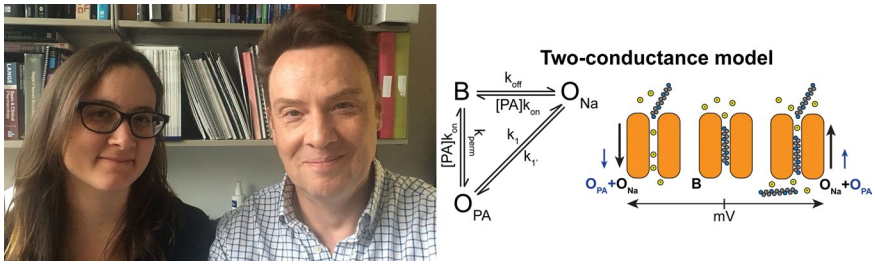
New JGP study explains how auxiliary proteins relieve polyamine block of AMPARs.



First author Patricia Brown (left), senior author Derek Bowie (middle), and co-author Hugo McGuire (not depicted) demonstrate that auxiliary proteins relieve polyamine blockade of AMPARs by enhancing permeation of polyamines (right).

Polyamines are positively charged molecules present inside all cells. They are involved in diverse processes such as protein synthesis, apoptosis, and cell growth. Polyamines also help limit currents through several types of ion channels, including AMPA receptors (AMPARs; 1, 2) and kainate receptors (KARs; 1). In their paper this month in JGP, Brown et al. explain how the auxiliary proteins stargazin and cornichon-3 alleviate blockade of AMPARs by polyamines (3).

Binding of the ligand L-glutamate to AMPARs causes opening of a pore that allows passage of sodium, potassium, and calcium cations across the cell membrane. Excitable cells such as the neurons of our brains maintain a negative voltage across their cell membranes while at rest, so opening of the AMPAR pore rapidly depolarizes the membrane and generates action potentials. However, currents through AMPARs are limited because the climbing membrane potential also drives polyamines such as spermine from the cytoplasm into the channel's pore.

"We basically think it acts like a cork in a bottle. The polyamine is attracted into the electronegative pore and gets stuck on the way through," explains Derek Bowie, a Professor at McGill University and the director of the multi-institution GEPROM group. As a result, polyamines start blocking currents through AMPARs at membrane voltages near 0 mV.

Using experimental techniques such as patch clamping to control voltage across isolated pieces of cell membrane, researchers have found that stuck polyamines can be forced to pass all the way through AMPARs (thereby relieving the channel block), but only by subjecting the membrane to very positive voltages (1, 2). Such voltages are nonphysiological, but prior research has also shown that cells have a way to obtain relief from polyamine blockade of AMPARs at positive—but still physiological—membrane voltages: via expression of the auxiliary proteins stargazin or cornichon-3 (4). These proteins coassemble with AMPARs in the cell membrane and allow AMPARs to pass current even when polyamines are present. Until now, it wasn't known how auxiliary proteins relieve AMPAR polyamine block, but there was one major clue.

"I had this big study in 2016 with kainate receptors where we explored relief of polyamine block by auxiliary proteins," says Patricia Brown, a graduate student in Bowie's laboratory. In that study, the researchers observed that the KAR auxiliary proteins Neto1 and Neto2 relieve polyamine block by making it easier for polyamines to pass through the ion channel (5). Because AMPARs and KARs are closely related, Brown says, "it totally made sense to ask whether this could also be happening with AMPA receptors."

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To do this, the authors expressed AMPARs (composed of the AMPAR subunit GluA2), with or without each of the auxiliary proteins, in HEK293 cells. They then used patch clamping to measure sodium currents in the presence or absence of spermine. Finally, mathematical models were constructed by co-author Hugo McGuire to try to explain the data. The model that best fit the data suggested that spermine itself can carry charge across AMPAR channels when an auxiliary protein is present.

"It's hard to believe, but in the presence of cornichon-3, spermine is actually more permeant than sodium," notes Bowie. Accordingly, when AMPARs were coexpressed with either stargazin or cornichon-3, it was possible to observe currents through AMPARs when only spermine was available to carry charge across the membrane. Therefore, AMPAR auxiliary proteins, like KAR auxiliary proteins, make their partner channel more permeable to spermine.

Brown et al. think that auxiliary proteins alter the characteristics of the AMPAR pore to allow passage of spermine. More studies are needed to understand the molecular mechanism involved. Nonetheless, because auxiliary protein expression is developmentally regulated in the brain, these findings may be important for brain development. In addition, AMPARs are present on cells outside the brain, raising the possibility that auxiliary proteins could help AMPARs act as polyamine transporters. This would have implications for how AMPARs and polyamines affect healthy tissues and disease states such as cancer.

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