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Teamwork: ion channels and transporters join forces in the brain

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Abstract

Voltage-gated potassium (Kv) channels open in response to changes in membrane potential to permit passage of K^+ ions across the cell membrane, down their electrochemical gradient. Sodium-coupled solute transporters utilize the downhill sodium gradient to co-transport solutes, ranging from ions to sugars to neurotransmitters, into the cell. A variety of recent studies have uncovered cooperation between these two structurally and functionally unrelated classes of protein, revealing previously unnoticed functional crosstalk and in many cases physical interaction to form channel-transporter (chansporter) complexes. Adding to this field, Bartolomé-Martín and colleagues now report that the heteromeric KCNQ2/KCNQ3 (Kv7.2/7.3) potassium channel – the primary molecular correlate of the neuronal M-current – can physically interact with two sodium-coupled neurotransmitter transporters widely expressed in the brain, DAT and GLT1 (dopamine and glutamate transporters, respectively). The authors provide evidence that the interactions may enhance transporter activity while dampening the depolarizing effects of sodium influx. Cumulative evidence discussed here suggests that chansporter complexes represent a widespread form of cellular signaling hub, in the CNS and other tissues.

Keywords

DAT1; GLT1; KCNQ1; KCNQ2; KCNQ3; SMIT1; SMIT2; NIS

In the current issue of Neuropharmacology, Bartolomé-Martín and colleagues report their discovery that specific KCNQ (Kv7) subfamily potassium channels expressed in the brain can interact with the DAT dopamine transporter and the GLT1 glutamate transporter (Bartolome-Martin et al., 2019). Here we discuss the implications and place the new findings in the context of an expanding field.

The neuronal M-current is well known for its role in regulating neuronal excitability. Generated by members of the KCNQ family of voltage-gated potassium (Kv) channels, the M-current has several key properties that define and shape its influence on the nervous system, as follows. The primary molecular correlate of the M-current is the heteromeric KCNQ2/KCNQ3 (Kv7.2/Kv7.3) potassium channel complex (Schroeder et al., 1998; Wang et al., 1998). In addition, KCNQ5 channels are important in specific regions of the brain; heteromeric KCNQ3/KCNQ5, and homomeric KCNQ2, 3 and 5 channels may also

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contribute to the M-current in some neuronal subsets and other locations (Tzingounis et al., 2010; Tzingounis and Nicoll, 2008).

KCNQ2/3 channels are enriched at the axon initial segment of neurons, where they are considered to acts a "gatekeepers" or band-pass filters that can regulate axonal transmission and tune neuronal firing based on their gating state. Activated KCNQ2/3 channels impede firing, deactivated KCNQ2/3 channels facilitate firing. Rather than their role being to repolarize cells once an action potential has fired, it is thought that KCNQ2/3 channels, because of their ability to open at potentials around -60 mV, are more important in determining whether or not action potentials fire in the first place, and if so at what rate they can be sustained (Hill et al., 2008; Pan et al., 2006; Shah et al., 2008). KCNQ2/3 channels, and/or KCNQ2 or KCNQ3 homomers, are also enriched at nodes of Ranvier and paranodal regions in, for example, sciatic nerves, where they may serve a similar gatekeeper role (Devaux et al., 2004; Schwarz et al., 2006).

The M-current is so-called because it is inhibited by activation of muscarinic acetylcholine receptors, a process that is permissive to neuronal firing because the KCNQ2/3 channels are no longer passing repolarizing current that slows or prevents neurons reaching threshold. Two different mechanisms are implicated in muscarinic inhibition of M-current, each relying on the specific properties of KCNQ channels. KCNQs are sensitive to regulation by phosphatidylinositol 4,5-bisphosphate (PIP_2), a soluble lipid-derived signaling molecule that favors KCNQ channel activation by binding to the intracellular linker between the voltage sensing domain and the pore to shift the voltage dependence of KCNQ activation to more negative membrane potentials. Muscarinic acetylcholine receptor activation depletes PIP_2 and shifts KCNQ activation more positive, thus allowing action potentials to fire (Suh and Hille, 2002; Winks et al., 2005). In addition, the breakdown of PIP_2 generates diacylglycerol and inositol trisphosphate, respectively activating protein kinase C and increasing cytosolic calcium concentration. This combination of signaling events is thought to synergistically suppress M-current (Kosenko and Hoshi, 2013; Kosenko et al., 2012). When the M-current malfunctions, it can be catastrophic for the central nervous system. KCNQ2, KCNQ3 and KCNQ5 sequence variants that perturb activity (mostly loss of function, but in some cases gain of function) lead to electrical disorders ranging from benign familial neonatal convulsions to the much more severe epileptic encephalopathy that also includes intellectual disability (Lehman et al., 2017; Millichap and Cooper, 2012). Therefore, a full understanding of the signaling events and regulatory processes in which neuronal KCNQ channels participate is crucial for explaining both normal neurophysiology and electrical disorders of the brain.

Over the last several years, KCNQ subunits have been found to participate in an entirely different type of signaling activity. It has long been known that the KCNQ1 subunit, most studied for its roles in the heart and various epithelia, interacts with single transmembrane domain β subunits (KCNE subunits) to alter its functional properties and therefore facilitate a variety of functional roles in diverse excitable and non-excitable cell types (Abbott, 2014). In several polarized epithelial cell types, KCNQ1 interacts with the KCNE2 subunit to produce a constitutively active channel with a relatively small but persistent activity (Abbott, 2015). *Kcne2* knockout mice exhibit increased seizure susceptibility, because of disruption

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of KCNQ1-KCNE2 channels located in the apical membrane of the choroid plexus epithelium, the blood-cerebrospinal fluid (CSF) barrier and primary source of CSF production and secretion. The underlying reason was a surprise: *Kcne2* knockout predisposes to seizures by perturbing CSF levels of the cyclic polyol *myo*-inositol, which is an important osmolyte and also a precursor of signaling molecules such as PIP_2. The mechanism behind this perturbation was just as unexpected: KCNQ1-KCNE2 channels were discovered to form physical complexes with the sodium-coupled *myo*-inositol transporter, SMIT1 (encoded by *SLC5A3*) (Abbott et al., 2014; Roepke et al., 2011).

SMIT1 is a secondary active transporter that uses movement of sodium down its electrochemical gradient to facilitate uphill transport of *myo*-inositol into cells (Berry et al., 1995; Kwon et al., 1992). By regulating CSF *myo*-inositol levels, choroid plexus epithelium KCNQ1-KCNE2-SMIT1 complexes contribute to regulation of neuronal excitability. *In vitro*, SMIT1 can also form complexes with heterologously co-expressed KCNQ1, with or without KCNE2. SMIT1 enhances KCNQ1 currents; KCNQ1 augments SMIT1 transport activity, but co-expression of both KCNE2 and KCNQ1 strongly inhibits SMIT1 activity (Abbott et al., 2014).

As originally observed for KCNQ1, neuronal KCNQ2/3 channels also form physical complexes with SMIT1 and the closely-related SMIT2 *myo*-inositol transporter. This occurs in mouse neuronal axon initial segment, and in rat and mouse sciatic nerve nodes of Ranvier. Even in the absence of extracellular *myo*-inositol, SMIT1 and SMIT2 each enhance KCNQ2 and KCNQ2/3 currents by negative-shifting the voltage dependence of, and speeding, channel activation; in turn, KCNQ2/3 channels inhibit SMIT1 and SMIT2 transport activity *in vitro* although this arises from diminished transporter surface expression and may be specific to heterologous expression systems (Manville et al., 2017; Neverisky and Abbott, 2017). SMIT1 is now known to physically associate with the KCNQ2 channel pore module, actually resulting in a shift in pore conformation that changes ion selectivity, increasing sodium and lithium ion permeability relative to that of K^+ (although the channels still remain selective for K^+ over Na^+) (Manville et al., 2017). The shift in selectivity caused by SMIT1 interaction may have solved a conundrum in the M-current field, explaining a mismatch between the relative ion permeability of cloned KCNQ2/3 versus native M-current (Tzingounis, 2017).

Of course, as *myo*-inositol is a precursor for PIP_2, the effects of *myo*-inositol on KCNQ2/3-SMIT1/2 complexes, beyond the obvious ramifications of physical interaction, cannot be overlooked. The PIP_2 generated from *myo*-inositol entering the cell via SMIT1 was demonstrated to be of sufficient magnitude to functionally regulate KCNQ2 (Dai et al., 2016). The combination of SMIT1 overexpression and *myo*-inositol supplementation increases intracellular stores of PIP_2, in turn augmenting KCNQ2 activity enough to attenuate action potential firing in superior cervical ganglion neurons (Dai et al., 2016). Because SMIT1 expression is increased by extracellular hypotonicity - via the transcription factor tonicity-responsive enhancer binding protein (TonEBP) – the functional and physical interaction between KCNQ channels, SMITs and PIP_2 couples electrical activity, and therefore membrane excitability, to osmotic potential (Dai et al., 2016).

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KCNQ2/3-SMIT1/2 complex formation may be especially important in the confines of axons, where *myo*-inositol and/or PIP_2 diffusion rate could become rate-limiting. We previously found that disrupting the cytoskeleton with cytochalasin D strongly inhibited KCNQ2/3 channel activity but only when SMIT1 was co-expressed, suggesting that when in complexes with SMIT1, KCNQ2/3 is reliant upon locally generated PIP_2, which typically diffuses away very slowly because of the local cytoskeleton (Cho et al., 2005; Neverisky and Abbott, 2017). Conversely, when cells were depolarized by addition of high extracellular K^+, SMIT1 uptake of *myo*-inositol was inhibited, as expected because the depolarization reduced the electrical gradient for sodium influx required for *myo*-inositol co-transport into the cell. However, co-expression of KCNQ2/3 prevented the depolarization-induced inhibition of *myo*-inositol uptake, which we interpreted as evidence that the co-assembled KCNQ2/3 counteracts the depolarizing effects to maintain an electrical gradient sufficient for optimal SMIT1 activity (Neverisky and Abbott, 2017).

Further evidence for functional dependence of transporters upon KCNQ channels was that in the case of both SMIT1 and SMIT2, co-expression with KCNQ1 rendered them sensitive to inhibition by drugs that inhibit KCNQ1, such as XE991 and chromanol 293B (Abbott et al., 2014). In addition, *Kcne2* deletion in mice leads to hypothyroidism, because of reduced activity of another sodium-coupled solute transporter, the sodium-iodide symporter (NIS), in thyroid cells (Roepke et al., 2009). Injection of the KCNQ1-KCNE2 inhibitor (-)-[3*R*,4*S*]-chromanol 293B (C293B) into mice impairs thyroid iodide uptake, measured using positron emission tomography detection of $^{124}I^-$. The inhibitory action of C293B required KCNQ1-KCNE2, as C293B did not inhibit NIS heterologously expressed in COS cells without KCNQ1-KCNE2, but did suppress iodide uptake by NIS in rat thyroid FRTL5 cells, which expresses NIS, KCNQ1 and KCNE2 (Purtell et al., 2012).

Fascinatingly, KCNQ-SMIT complexes also occur in the insect brain, and involve an ex-transporter that has lost its transport capacity. The *Drosophila* dSLC5A11 protein (also named *cupcake*) is a relative of mammalian SMIT2 (SLC5A11) and sugar transporter SGLT1 (SLC5A1) that has lost its ability to transport glucose but is thought to act as a hunger sensor. The dKCNQ K^+ channel is an ortholog of mammalian KCNQs, exhibiting characteristics of both KCNQ1 and KCNQ2 (Park et al., 2016). As we found previously for human SMIT2 with KCNQ1 (Abbott et al., 2014), dSLC5A11 inhibits dKCNQ activity. Upregulation of dSLC5A11 in the vinegar fly brain inhibits neuronal dKCNQ activity, promoting feeding and other hunger-driven behaviors (Park et al., 2016).

The new study by Bartolomé-Martín et al broadens the scope of KCNQ channel-transporter interactions still further, suggesting this class of signaling complex is a common theme in the KCNQ family. Like SMITs and NIS, DAT and GLT1 utilize the sodium gradient to accumulate important signaling components within the cell, in this case neurotransmitters. Similar to KCNQ-SMIT complexes, KCNQ2/3 channels are suggested to counteract the depolarizing force of sodium movement through DAT and GLT1 transporters, enabling efficient function of the transporters and also preventing undue cellular depolarization. As was previously observed for KCNQ-SMIT complexes (Abbott et al., 2014), the KCNQ inhibitor XE991 eliminated the augmenting effects of KCNQ2/3 on DAT and GLT1 activity. DAT and GLT1 complexes with KCNQ2/3 are suggested to form in axons where, again, the

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restrictive confines may necessitate complex formation to minimize delay and maximize signal-to-noise ratio for crosstalk between the two protein types (Bartolome-Martin et al., 2019). It will be fascinating to observe whether or not KCNQ2/3-SMIT complexes can co-exist in the same region as KCNQ2/3-DAT or KCNQ2/3-GLT1 complexes, or whether even mixed complexes can form containing one or more type of transporter associating with a single channel tetramer.

A previous study also uncovered a complex formed of a potassium channel and a neurotransmitter transporter, namely the Ca^{2+}-activated K^{+} channel, MaxiK, with the GABA transporter 3, GAT3 – another sodium-coupled transporter (encoded by *SLC6A11*). This complex was identified from mouse brain lysates and while a functional characterization has yet to be reported, in combination with the latest report it suggests that regulation of neurotransmitter transport by potassium channels could be another common signaling theme (Singh et al., 2016).

Furthermore, another Kv channel, KCNA2 (Kv1.2), was recently discovered to interact with the SLC7A5 (LAT1) neutral amino acid transporter. This complex was discovered by proteomics analysis of the HEK cell KCNA2 interactome. SLC7A5 alters KCNA2 gating and voltage dependence, and the proteins reciprocally affect the impact of disease-associated mutations in one another (gene variants linked to developmental delay and epilepsy, respectively). SLC7A5- and KCNA2-detecting antibodies were found to co-localize in mouse neurons and their co-assembly may therefore represent another example of a neuronal chansporter complex (Baronas et al., 2018).

In the present study, the authors also examine effects of glutamate and dopamine on the activity of KCNQ2/3 channels. As we recently also reported (Manville et al., 2018), in the new study glutamate had no effect on KCNQ2/3 activity. However, dopamine (10 μM) inhibited KCNQ2/3 activity ~50% in the present study (Bartolome-Martin et al., 2019), while we previously observed no effects of dopamine (100 μM) on KCNQ2/3 currents (Manville et al., 2018). This difference may arise from the cell types used; we expressed KCNQ2/3 in *Xenopus* oocytes whereas in the present study the authors used the H22 mouse hepatocarcinoma cell line. This perhaps points to an additional co-factor that might be required for transducing effects of dopamine on KCNQ2/3. Interestingly, we recently showed that the primary inhibitory neurotransmitter, GABA, directly binds to KCNQ3 and KCNQ5 channels (via a binding pocket located between the pore domain and voltage sensor) and regulates their function and also that of KCNQ2/3 channels, potentiating their activity by negative-shifting the voltage-dependence of their activation (Manville et al., 2018). The new work by Bartolomé-Martín and colleagues presents the fascinating possibility that GABA, by binding to KCNQ3 channels, could regulate neuronal uptake of dopamine and/or glutamate via KCNQ3 complex formation with their respective transporters. In addition, dopamine and glutamate uptake could be regulated, via KCNQ2/3, by osmotic potential, muscarinic activity, and by other factors that regulate neuronal PIP_2 levels. The discovery of an expanding array of KCNQ-transporter complexes in neurons and other cell types presents a multitude of potential mechanisms for crosstalk and feedback between different cellular signaling modalities.

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Finally, it is important to emphasize that the phenomenon of channel-transporter complexes is not confined to potassium channels or to neurons. To give a few examples, the cystic fibrosis transmembrane conductance regulator (CFTR) forms complexes with members of the SLC26A solute transporter family that transport (and exchange) chloride and bicarbonate ions (Ko et al., 2004; Shcheynikov et al., 2006). The epithelial sodium channel, ENaC forms complexes with the sodium chloride co-transporter (NCC) in distal convoluted tubules of the kidney and the two partners are functionally co-dependent (Mistry et al., 2016). The Orai1 Ca^{2+} channel forms channel-transporter complexes with secretory pathway Ca^{2+}-ATPase isoform 2 (SPCA2), a Golgi-localized P-type calcium ion transporter; these complexes regulate human mammary Ca^{2+} regulation and tumorigenicity (Feng et al., 2010). Thus, chansporters represent a widespread and evolutionarily conserved class of signaling complex.

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