Generally Physiological

Introducing *Generally Physiological*

Physiology is generally considered to consist of that branch of biology concerned with the function of living organisms and the underlying physicochemical processes, with general physiology specifically concerned with the analytical investigation of the molecular and cellular mechanisms of fundamental physiological processes.

The Journal of General Physiology (the *JGP*) was founded by Jacques Loeb in 1918 with the mission of publishing research elucidating "basic biological mechanisms of broad physiological significance using the tools of chemistry and physics" (Andersen, 2004). The *JGP* has continued to pursue that mission for nearly 100 years. As Andersen noted in "A Brief History of *The Journal of General Physiology*," the initial announcement specified that "the editors invite contributions relating to the physico-chemical explanation of life phenomena, no matter in what field of science they originate." Articles published that first year spanned such varied areas as photosynthesis, respiration, endocrinology, muscle tone in heliotropic insects, bioluminescence, and bacterial decomposition in bread.

The propagating excitement about electrophysiological research that exploded in the 1950s and 1960s—together with a growing appreciation of the crucial and fundamental roles of ion channels in physiological processes—was accompanied by a shift in the focus of the *JGP* toward electrophysiology and the biophysical analysis of ion channel structure and function. Indeed, despite our ongoing publication of outstanding research in many other areas of physiology, the *JGP* has become so well known for its articles on ion channels that a perception has arisen in some quarters that other aspects of physiology may be outside of the Journal's scope.

Although we remain excited about biophysical analyses of ion channels and will certainly continue to publish work in this area, we also welcome submissions of material pertaining to all other aspects of general physiology. As executive editor of the *JGP*, I will be highlighting research that catches my eye—and other matters of interest—in this column. In this first installment of *Generally Physiological*, I'd like to draw your attention to four recent studies that provide insight into disparate aspects of neurophysiology. They concern an unexpected role for vitamin K_2 that may have implications for the therapy of Parkinson's disease, explorations of interactions between calcium and chloride fluxes in vomeronasal sensory neurons and neurons of the thalamic reticular nucleus, and mechanisms whereby an auxiliary calcium channel subunit contributes to synaptic efficacy.

Four recent studies that provide insight into disparate aspects of neurophysiology

Of vitamin K_2 and mitochondrial electron transport

In the first of these studies, Vos et al. (2012) identified a role for vitamin K_2 in mitochondrial electron transport (Bhalerao and Clandinin, 2012). Oxidative damage has been implicated in the pathogenesis of the neurodegenerative disorder Parkinson's disease, and mutations in the gene encoding PTEN-induced putative kinase 1 (PINK1), a mitochondrial protein kinase, are associated with Parkinson's disease in people and affect mitochondrial function in fruit flies. Using a genetic screen for mutations that suppressed or enhanced flight defects in *pink1* mutant flies, Vos et al. (2012) identified *heixuedian* (*heix*), which encodes an enzyme involved in the biosynthesis of vitamin K_2 (menaquinone), as a modifier of *pink1*. Loss of *heix* enhanced defects in flight, ATP abundance, and neuronal mitochondrial membrane potential found in *pink1*-null mutant flies, whereas *heix* overexpression—or dietary supplementation with vitamin K_2—countered *pink1* mutant phenotypes. Although best known for its roles in blood coagulation and bone metabolism, vitamin K_2 functions in electron transport in bacteria, leading the authors to postulate that it might play a similar role in mitochondrial electron transport. Indeed, they found that, like ubiquinone, vitamin K_2 facilitated electron transport in mitochondrial fractions and increased ATP production and oxygen consumption in *pink1* mutant mitochondria. Thus, vitamin K_2 appears to contribute to electron transport in mitochondria, as well as in bacteria; moreover, its ability to antagonize deficits associated with *pink1* mutation in flies suggests that vitamin K_2 may hold promise in the therapy of disorders associated with mitochondrial dysfunction.

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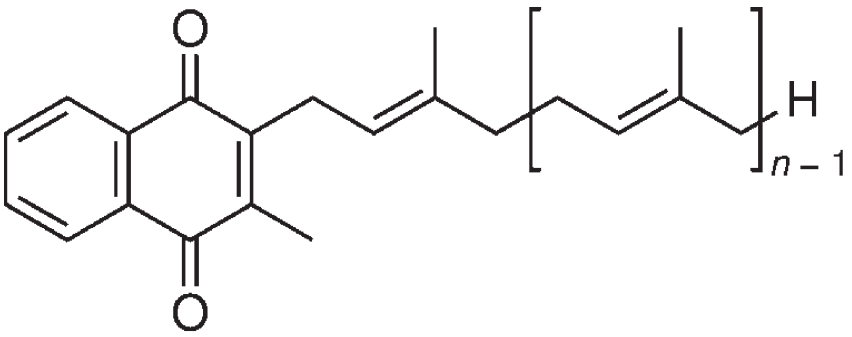


Vitamin K_2 (menaquinone) contributes to electron transport in mitochondria; menaquinone side chains have a variable number of isoprenoid residues, indicated by *n*.

"This is an intriguing new angle on the effects of PINK1 loss-of-function," said neurologist William Dauer, who does research on Parkinson's disease at the University of Michigan and was not involved in the study, "and it will be interesting to learn whether similar results are obtained in vertebrate models."

Participating in pheromone perception?

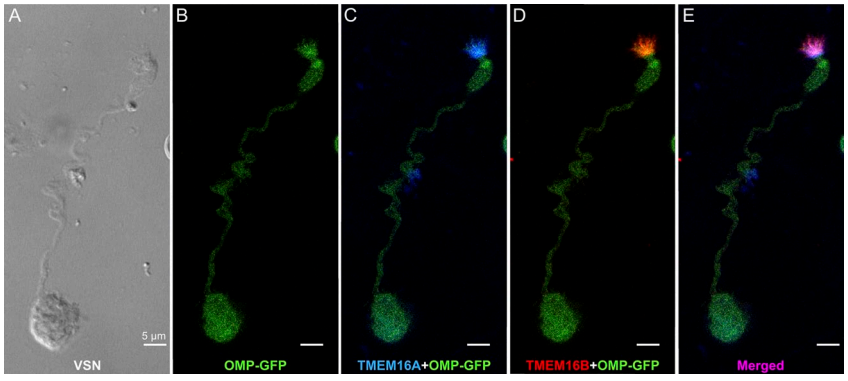
In the second study, Dibattista et al. (2012) explored the mechanisms whereby rodents sense pheromones. Pheromones, interorganismal signaling molecules that mediate various social cues, bind to G protein–coupled receptors in the membranes of microvilli on the apical surface of chemosensory neurons of the vomeronasal organ. This initiates a signaling cascade that leads to the activation of TRPC2 channels and thereby to calcium influx and an increase in microvillar calcium concentration. Dibattista et al. (2012) used flash photolysis of caged calcium to rapidly increase apical calcium concentration in isolated mouse vomeronasal sensory neurons independent of other sequelae of GPCR activation and identified a calcium-activated chloride current. Immunofluorescence analysis revealed the presence of the calcium-activated chloride channels TMEM16A and TMEM16B (also known as anoctamin-1 [ANO1] and anoctamin-2 [ANO2], respectively) on the apical surface of mouse vomeronasal epithelium, where they colocalized with TRPC2, and analyses of isolated vomeronasal sensory neurons showed that TMEM16A and TMEM16B were coexpressed in sensory neuron microvilli. The authors thus conclude that calcium-dependent activation of chloride channels likely plays a role in vomeronasal sensory transduction.

GABA-mediated burst firing

Whereas Dibattista et al. (2012) investigated calcium-activated chloride channels, Sun et al. (2012) found that depolarizing potentials consequent to chloride efflux mediated by the $GABA_A$ receptor (a ligand-activated chloride channel) led to activation of low threshold T-type calcium channels, and thereby burst firing, in neurons of the thalamic reticular nucleus (TRN). GABA (γ-aminobuytric acid) is, of course, known for its role as an inhibitory neurotransmitter in the mature vertebrate central nervous system, and the GABAergic synapses that interconnect neurons of the TRN have been postulated to mediate shunting or hyperpolarizing inhibition. Sun et al. (2012) found, however, that activation of intra-TRN GABAergic synapses in thalamocortical slices from 2–5-week-old mice elicited depolarizing postsynaptic potentials that triggered bursts of action potentials. Pharmacological analysis confirmed that $GABA_A$ receptor activation led to a depolarizing response; moreover, the reversal potential to a $GABA_A$ receptor agonist was positive to the resting potential. Consistent with a high intracellular chloride concentration, expression of the chloride transporter KCC2 was "virtually nonexistent" in the TRN. TRN neurons have abundant dendritic low threshold T-type calcium channels, and pharmacological and electrophysiological analyses, together with calcium imaging, indicated that their activation—by boosting the $GABA_A$-mediated depolarization to threshold for action potential generation—was crucial to the ability of GABA to trigger burst firing in TRN neurons.

Enhancing synaptic efficacy

Although the studies by Dibattista et al. (2012) and Sun et al. (2012) concerned roles for calcium influx in chloride channel activation and in providing a depolarizing boost to achieve firing threshold, respectively,



TMEM16A and TMEM16B colocalize in the microvilli of mouse vomeronasal sensory neurons (from Dibattista et al. 2012. *J. Gen. Physiol.* 140:3–15).

perhaps the best-known role for neuronal calcium influx is in triggering neurotransmitter release. Noting that overexpression of the pore-forming $\alpha 1_A$ subunit of voltage-gated calcium channels fails to increase synaptic strength, Hoppa et al. (2012) expressed labeled $\alpha 1_A$ in rat hippocampal neurons and found that, although $\alpha 1_A$ abundance doubled in the soma, its overall nerve terminal abundance was comparable to that in control neurons. In contrast, overexpression of auxiliary α2δ subunits increased nerve terminal $\alpha 1_A$ abundance and the exocytotic response to an action potential, whereas α2δ depletion decreased them. Surprisingly, α2δ overexpression was associated with a decrease in the synaptic calcium signal in response to an action potential; however, it attenuated the decrease in exocytotic response produced by the calcium chelator EGTA. Mutation of an extracellular α2δ metal ion-dependent adhesion site (MIDAS) motif blocked the ability of α2δ to enhance exocytosis and protect the exocytotic response from EGTA, although its ability to promote synaptic accumulation of $\alpha 1_A$ was retained. Thus, the authors propose that α2δ enhances synaptic efficacy through two distinct mechanisms—one involving $\alpha 1_A$ trafficking to the nerve terminal, and a local MIDAS-dependent interaction that enhances $\alpha 1_A$ coupling to exocytosis despite an overall decrease in calcium influx.

I hope you've enjoyed reading this first installment of *Generally Physiological*. Please feel free to get in touch (eadler@rockefeller.edu) to let me know about must-attend meetings, ground-breaking physiological research, or dynamic researchers—or any other topics of interest to general physiologists—that you'd like to hear more about here.

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