QnAs with Mark T. Nelson

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Mark T. Nelson has long been interested in the mechanisms that control blood flow in the brain in response to neuronal activity. During his research career, he has examined ion channels in smooth muscle and endothelial cells, and how the channels are regulated. Nelson's work has improved researchers' understanding of how cerebral blood flow can be regulated by calcium signaling and potassium channel activation. He has also explored how cerebral blood flow can be disrupted, resulting in small-vessel diseases that contribute to stroke and dementia. Nelson is the Chair of the Department of Pharmacology at the University of Vermont and was elected to the National Academy of Sciences in 2019. In his Inaugural Article (1), Nelson describes the role of a plasma membrane lipid, phosphatidylinositol 4,5-bisphosphate (PIP_2), in the regulation of vascular ion channels in smooth muscle and endothelial cells. He recently spoke to PNAS about his work.

PNAS: How did you become interested in studying the regulation of blood flow?

Nelson: We've been working on calcium signaling and ion channels in blood vessels since the mid-1980s and were particularly interested in the control of blood flow in the brain. In recent years, we've become interested in how neurons tell the blood vessels to dilate and deliver blood in the areas of active neurons. Every time you use part of your brain, blood has

Mark T. Nelson. Image credit: Sally McCay (photographer).

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to be delivered there within seconds to supply oxygen and glucose and nutrients and also to remove waste. So you move your hand, the motor cortex turns on, and blood is delivered there. It's one of these physiological processes—like the beating of your heart—that you don't think about until something starts going wrong. The fundamental question is: How does it work, and what happens when it goes wrong?

PNAS: What have you learned about the role of PIP_2 in the regulation of blood flow?

Nelson: Your brain has about a thousand miles of blood vessels, and the vast majority of them are capillaries. They're composed of one type of cell called endothelial cells, and the diameter of a capillary is about one-twentieth the diameter of your hair. Until recently, most people viewed capillaries as simply the conduit for red blood cells and not a sensing organ. We had a paper a couple of years ago providing evidence that capillaries in the brain are sensors of neural activity (2). We call the capillaries the shadow nervous system, because every capillary endothelial cell is electrically coupled to one another.

So imagine that the thousand miles of blood vessels in the brain are like little wires connected throughout your brain, sending signals in response to neural activity. What we found was that when the neurons become active, they release potassium, which then signals the capillary endothelial cells to turn on and generate an electrical signal that travels to upstream arterioles, and cause them to dilate and deliver blood. The molecular cornerstone of this potassium sensing in the capillaries is an ion channel called the inward rectifier potassium channel. Over the last couple of years, we've discovered that at least in the brain capillaries, the activity of these inward rectifier potassium channels in the endothelial cells is dynamically regulated by PIP_2. The inward rectifier channel, called Kir2.1, requires PIP_2 to be functional and a counteracting ion channel, TRPV4, is inhibited by PIP_2 (3, 4). So dynamic regulation of this simple little lipid molecule PIP_2 appears to be the lynchpin for determining the delivery of blood in response to neural activity.

PNAS: What have you learned about the role of PIP_2 in disease pathology?

Nelson: We noticed that a number of disease processes had a reduction in the activity of these inward-rectifier potassium channels. We found that the electrical signaling through the capillaries—which is responsible for at least half the increase in blood flow during neural activity—is crippled in small-vessel disease in the brain, which is a major contributor to dementia and stroke. This effect is due to a decrease in PIP_2 in the endothelial cells of the capillaries. There are two possible causes for this decrease. One is decreased synthesis of PIP_2, which is tightly linked to metabolism. The other is that when a neuron or an astrocyte releases a substance that activates a receptor on the endothelial cells, it turns on an enzyme that chews up PIP_2. That can happen quite rapidly, and could lead to compromised delivery of blood and therefore oxygen and glucose and nutrients, as well as disruption in getting rid of metabolic byproducts from the brain.

In Andersen–Tawil syndrome, genetic mutations in the inward-rectifier Kir2.1 channel can prevent the binding of PIP_2 and thereby deactivate the channel. The bottom line is, if you disturb the balance between synthesis of PIP_2 and breakdown of PIP_2, this can result in compromised blood flow and compromised delivery of blood to critical areas in the brain. The flipside is, if you can restore the system, you can then improve blood flow. In follow-up work that's not published yet, we've looked at a mouse model of small-vessel disease of the brain. When their neurons become active, only half the blood is delivered that will be normally delivered, and we can restore normal blood flow within 15 minutes by giving PIP_2.

PNAS: What are some implications of your research?

Nelson: During a stroke, part of the brain dies and the surrounding neurons are hanging on for life. We could use what we've learned to potentially improve blood flow to critical areas of the brain when you have a major stroke. In terms of therapeutics, if we can find other ways to reactivate this system, it could help with small-vessel disease in the brain that contributes to dementia. In addition, these concepts may also apply to the cardiac muscle cells of the heart, to skeletal muscle, and to virtually every organ (5).

1 O. F. Harraz, D. Hill-Eubanks, M. T. Nelson, PIP_2: A critical regulator of vascular ion channels hiding in plain sight. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 20378–20389 (2020).

2 T. A. Longden *et al.*, Capillary K^+-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. *Nat. Neurosci.* **20**, 717–726 (2017).

3 O. F. Harraz, T. A. Longden, D. Hill-Eubanks, M. T. Nelson, PIP_2 depletion promotes TRPV4 channel activity in mouse brain capillary endothelial cells. *eLife* **7**, e38689 (2018).

4 O. F. Harraz, T. A. Longden, F. Dabertrand, D. Hill-Eubanks, M. T. Nelson, Endothelial GqPCR activity controls capillary electrical signaling and brain blood flow through PIP_2 depletion. *Proc. Natl. Acad. Sci. U.S.A.* **115**, E3569–E3577 (2018).

5 G. Zhao, H. C. Joca, M. T. Nelson, W. J. Lederer, ATP- and voltage-dependent electro-metabolic signaling regulates blood flow in heart. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 7461–7470 (2020).