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Triskelion channels might bring Star Wars to the global problem of hypertension

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Abstract

In a compelling new report Zeng et al (Science 2018) suggest that neuronal Piezo1 and Piezo2 channels sense blood pressure in major arteries above the heart [1]. The data challenge previous proposed baroreceptor mechanisms and add to prior knowledge of Piezo1 channels as sensors of blood flow and key players generally in cardiovascular biology.

Commentary

Zeng et al [1] address three important topics: blood pressure control; the molecular basis of baroreceptors; and the molecules that lie at the core of mechanical force sensing in mammalian biology.

While we all need blood pressure, we don't need high blood pressure. Surprisingly, given the many anti-hypertensive therapies, this silent killer remains a major global concern, afflicting more than 1 billion people [2, 3]. Mechanisms controlling blood pressure are numerous and of course complex. One is the baroreceptor reflex. It involves special pressure-sensing neurones embedded in arteries above the heart – a fast-acting mechanism: hence the importance in postural control of blood pressure. There is increasing appreciation of this reflex in cardiovascular disease [4].

Determination of the molecular basis of baro (pressure) receptors is important for fundamental knowledge; it might also enable development of new therapies. For over 30 years it has been suspected that the receptors are Ca^{2+}-permeable, Na^{+}-permeable or Ca^{2+}- and Na^{+}-permeable channels. Both lanthanide-sensitive and lanthanide-resistant mechanisms have been suggested, as have specific channel types including ENaC, TRPV1 and TRPC5. Now Piezos vie for position as the origin of pressure-sensing in this system.

There are two Piezo proteins in mammals encoded by distinct genes – Piezo1 and Piezo2 (PIEZO1 and PIEZO2 in human) [5]. Structural information is available for Piezo1. Three Piezo1s assemble to form a big ion channel of about 1MDa – a beautiful triskelion structure that has an ion pore in the middle and which inwardly indents the membrane [6]. The channels are Ca^{2+}-permeable non-selective cationic channels that are inhibited by the lanthanide Gd^{3+}. A striking feature of the Piezo literature is the strong agreement amongst investigators that the channels are activated reliably by mechanical force – particularly increases in membrane tension. They appear to be bona fide force-sensing ion channels – not simply influenced by mechanical force, as many mechanisms are, but with raison d'être to sense force and trigger responses to it. There is shared excitement that these are Real McCoy force sensors of mammalian systems. In contrast there is controversy about whether other channels hold such centrality in mammalian force sensing.

Zeng et al [1] show that neurones of the nodose-petrosal-jugular ganglia express mRNA encoding Piezo1 and/or Piezo2. Intriguingly these mRNA species were rarely together in the same neurones, suggesting distinct sub-populations of neurones expressing one or the other homomeric channel. Also striking is the observation that conditional deletion of Piezo1 or Piezo2 in these ganglia had no effect on blood pressure or baroreceptor reflex. What did have an effect was the double knockout, which abolished reflex decrease in heart rate and increased systolic blood pressure and its variability. Aortic depressor nerve activity in response to phenylephrine was abolished and optogenetic stimulation of Piezo2-positive carotid sinus

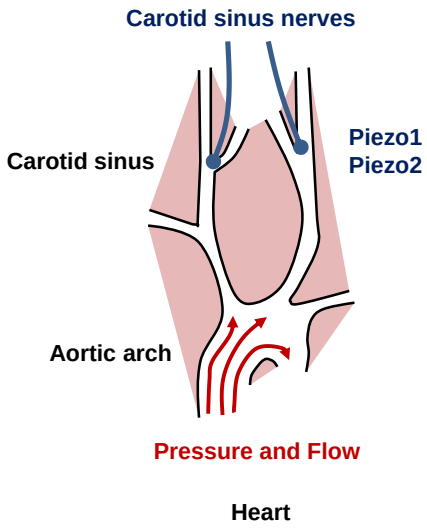
neurones depressed heart rate. Based on these results, Zeng et al [1] suggest that Piezo1 and Piezo2 are the baroreceptor pressure sensors - jointly important for acute blood pressure control (Figure 1).

The baroreceptor data of Zeng et al [1] are persuasive and strongly support their conclusion of a critical role for Piezos in this biology. Like all top-class research, it raises important new questions for future studies. Why would there be two sets of pressure-sensing neurones containing different Piezo channels? Is there a separate lanthanide-resistant pressure sensor [7] and, if so, in which context is it important – given Zeng et al's [1] observation that Piezo1/2 double knockout cleanly ablates the baroreceptor reflex of their mice? Do baroreceptors of other species, especially human, similarly need Piezo channels and are they both important in baroreceptor control of blood pressure in cardiovascular disease?

The new findings add to the bigger picture of the importance of Piezo channels in cardiovascular biology - especially Piezo1 channels (Figure 1). Piezo1 knockout in mice is embryonic lethal because endothelial Piezo1 is required for vascular maturation (major vessel formation) shortly after the heart starts beating at E8.5 [8]. Endothelial Piezo1 channels are flow sensors and it is the sensing of this flow by the nascent endothelial plexus that is thought to mediate vascular maturation proportional to the needs of newly-forming organs [8]. Conditional deletion of endothelial Piezo1 shows importance in flow-sensing of adult mice [9, 10] and requirement for the elevated blood pressure response of whole body physical exercise [9]. Endothelial Piezo1 is also important in angiogenesis, nitric oxide production and atherosclerosis [8, 10, 11]. Smooth muscle Piezo1 is important in vascular remodelling in hypertension and Piezo1 is functional in epithelial cells of the kidney, another key organ of blood pressure determination. Early suggestions of relevance to cardiac myocytes and fibroblasts are appearing and relevance to red blood cells is well established.

Piezo1 channels are flow sensors also in human endothelial cells [8] but the general significance of Piezos in the human cardiovascular system is largely unknown. What is striking, based on the limited research done so far, is that there are people who are Piezo1 null, or at least lack the ion pore domain of Piezo1 [12]. Therefore, for these people, Piezo1 disruption was not embryonic lethal. Because there are so few known cases, however, it is hard to know if these people are exceptions who compensated, perhaps through Piezo2, and thus survived. These people cannot, however, be considered lucky because they have generalized lymphatic dysplasia, which is potentially explained by failure or weakness in flow-sensing of their lymphatic endothelial cells. If baroreceptors operate similarly in humans as in mice, disruption of Piezo1 in people will not affect the baroreceptor reflex. This hints at why Zeng et al [1] had to disrupt Piezo1 and Piezo2 to affect the baroreceptor reflex: because the reflex might be so important in postural control of blood pressure or response to haemorrhage that two separate genes are needed to guarantee it.

Because of the importance of the baroreceptor reflex in cardiovascular disease [4] it is tempting to consider if targeting Piezos might be a route to new important anti-hypertensive agents. This could be possible because we already know that chemicals can modulate or mimic activation of Piezo1 by mechanical force – acting either directly or via intermediate proteins. The chemicals identified so far have been named Yoda1, Dooku1, Jedi1/2 and OB-1/2 based on the catch-phrase of the Star Wars films: “may the force be with you”. These chemicals are tool compounds that carry significant limitations. Small-molecule modulators for Piezo2 are not yet reported. Any drug discovery efforts towards Piezos will need to consider that these proteins are broadly expressed, so modulation could result in more than changes in blood pressure.



Piezo1
Endothelium
Erythrocytes
Smooth muscle
Epithelium
Fibroblasts

Figure 1 A simple sketch of the major supra-cardiac arteries, showing the location of the pressure-sensing mechanisms referred to by Zeng et al [1]. Listed on the right are additional systems which should be taken into consideration for the overall cardiovascular impact of these special Ca^{2+}-permeable ion channels – the triskelion Piezo1 channels.

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