

TRPCs, GPCRs and the Bayliss effect

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An increase in pressure inside most small arteries unexpectedly results in a vasoconstriction. This phenomenon, known as the Bayliss effect, involves the stretch-induced activation of non-selective cation channels in the vascular smooth muscle cells. Recent work by Mederos y Schnitzler *et al.* now demonstrates that the stretch-induced channel activity originates from a fascinating interplay between a TRP cation channel and the angiotensin receptor.

Intuitively, we all appreciate that increasing the intracellular pressure in an elastic container (e.g. a balloon or the tyre of your bicycle) leads to expansion of that container. However, many blood vessels, in particular small resistance arteries, behave oppositely: increasing intraluminal blood pressure makes them constrict instead of dilate (Figure 1A). This pressure-induced myogenic vasoconstriction is generally known as the Bayliss effect, after the English Physiologist William Maddock Bayliss, who first described it in 1902 (Bayliss, 1902). On account of the Bayliss effect, the blood flow through small arteries and arterioles in brain, kidney and

several other internal organs remains relatively stable even when the perfusion pressure fluctuates, thus establishing autoregulation.

Hence what is the mechanism underlying the Bayliss effect? It was already known for some time that the effect is mediated by the vascular smooth muscle, independent of the endothelial cell layer that lines the vessels (Figure 1B). The increased intraluminal pressure results in the activation of non-selective cation channels in the plasma membrane of the smooth muscle cells, which causes membrane depolarization, Ca^{2+} influx through voltage-gated L-type Ca^{2+} channels and smooth muscle contraction (Davis and Hill, 1999). However, a key unresolved question was the mechanism underlying the stretch-induced activation of the non-selective cation channels.

Several lines of evidence pointed at a possible involvement of cation channels of the TRP superfamily in the Bayliss effect. For example, downregulation of the expression of either TRPC6 or TRPM4 in the smooth muscle rat cerebral arteries using antisense oligonucleotides led to a severe loss of pressure-induced vasoconstriction (Welsh *et al.*, 2002; Earley *et al.*, 2004). Given that several TRP channels have been shown to function as direct sensors of a

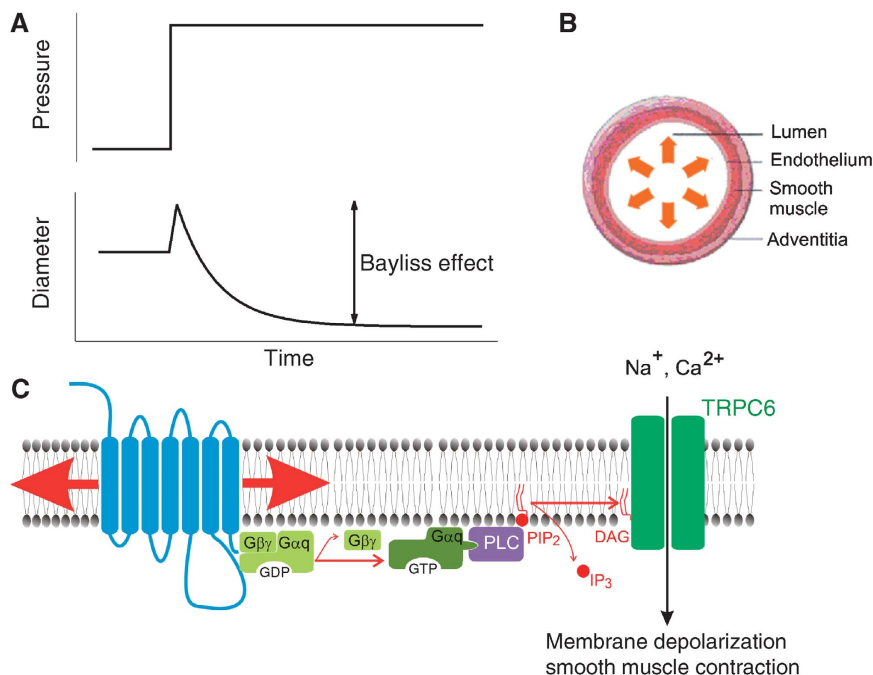



Figure 1 The Bayliss effect. (A) Increasing pressure in certain blood vessels causes vasoconstriction, a phenomenon known as the Bayliss effect. (B) The Bayliss is mediated by the smooth muscle layer, independent of the inner layer of endothelial cells. (C) Proposed mechanism for stretch-induced activation of TRPC6 in vascular smooth muscle membranes.


variety of stimuli, including temperature changes and a variety of endogenous and exogenous chemical stimuli (Voets *et al.*, 2005), it appeared straightforward to propose that some TRP channels could act as mechanosensors in vascular smooth muscle cells. And indeed, it has been reported that heterologously expressed TRPC6 can be directly activated by membrane stretch (Spasova *et al.*, 2006), although later studies have strongly questioned this proposal (Gottlieb *et al.*, 2008). A crucial aspect of the discussion is that proving a (TRP) channel to be an intrinsic sensor of membrane stretch is far from obvious. The most important criterion to establish that a channel is directly mechanosensitive is the latency between stimulus and channel activation, which should be in the order of a few milliseconds (Christensen and Corey, 2007).

In a recent article in *EMBO Journal*, Mederos y Schnitzler *et al.* (2008) report that TRPC6 does not meet the criteria for a *bona fide* mechanosensitive channel. Instead, they show that the TRPC6 (and the related TRPC3 and TRPC7) can be readily gated by membrane stretch in cells that co-express membrane receptors that couple to activation of G_q-type GTP-binding proteins. G-protein-coupled receptors (GPCRs) form a large and well-studied family of transmembrane proteins that sense molecules outside the cell, including neurotransmitters, hormones, odorants, tastants and more. Ligand binding causes a conformational change in the receptors, leading to the activation of trimeric G proteins. The activated G_α and G_{βγ} proteins can initiate various signal transduction pathways. For example, GPCRs that are coupled to G_q lead to activation of phospholipase C, which hydrolyses the membrane phospholipids phosphatidyl inositol 4,5-bisphosphate (PIP₂) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP₃). It was previously shown that TRPC3, TRPC6 and TRPC7 are directly activated by DAG, which clearly explained the activation of these channels upon ligand activation of G_q-coupled GPCRs (Hofmann *et al.*, 1999).

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