protein[12]. Studies in animal models have demonstrated that without vasopressin, transcription of the gene encoding aquaporin-2 is suppressed, aquaporin-2 protein abundance is low and water transport across the renal collecting duct is markedly decreased[12]. The suppression of aquaporin-2 in the kidney takes several days to reverse, a process too slow to cope with sudden demands for renal water conservation.

For normal individuals, the best course may be to avoid deliberate overhydration or water-drinking quotas and instead rely on the thirst mechanism to govern drinking behavior.

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Salt abuse: the path to hypertension

Wilhelm Schoner

Excess salt intake over many years can lead to high blood pressure. An essential signaling mechanism behind this effect is now uncovered (pages 64–68).

Treatment for high blood pressure generally involves numerous types of drugs. β- and AT1-receptor blockers abolish the action of the pressure-increasing hormones epinephrine and angiotensin II, angiotensin-converting enzyme inhibitors inhibit formation of angiotensin II, diuretics treat hypertension-related increases in plasma volume and calcium antagonists aim to treat vasoconstriction. Despite these options, all of these drugs have numerous side effects and the condition is often resistant to therapy.

Because arterial blood pressure ultimately rises owing to increased vasoconstriction, information is needed on how hormone signaling pathways differentiate between the regulation of basal blood pressure and salt-induced hypertension in arterial smooth muscle cells.

The findings of Wirth *et al.*[1] in this issue of *Nature Medicine* could lead to a more refined approach to treating hypertension. The researchers identify a signaling pathway in the vasculature that specifically responds to high salt intake but does not regulate basal blood pressure (which controls the ability of the body to respond to events such as exertion[1]). The findings open the door to developing drugs targeting this pathway. Such an approach has the potential to regulate blood pressure without the hypotensive side effects that occur with drugs that block all blood pressure regulation—including regulation necessary for adaptation to normal physiological stress.

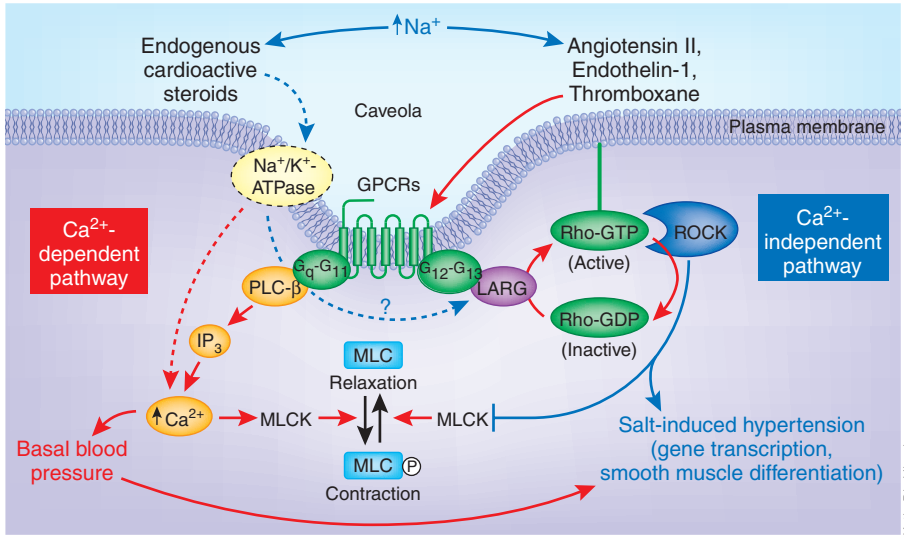

Figure 1 Keeping up the pressure. Intracellular signaling pathways of hormonal regulation of vascular tone in mammalian smooth muscle cells exposed to salt. Hormonal receptors for GPCRs, as well as the Na^+/K^+-ATPase signalosome, reside in the caveolae of arterial smooth muscle cells. Hormone levels increase in response to a high-salt diet. These hormones dock to GPCRs and activate the G_{12}-G_{13}–LARG–mediated signaling pathway, raising blood pressure by inhibiting the dephosphorylation of myosin light chain. PLC-β, phospholipase C-β; IP_3, inositol triphosphate; MLCK, myosin light-chain kinase.

Arterial hypertension affects 25% of the adult population in industrialized societies and is a major cause of stroke. The condition is intimately linked to excessive salt uptake over the years. High salt intake raises blood volume and vasomuscular contraction, increases the workload of the heart, and induces natriuresis—excretion of excess sodium into the urine—which is a counter-regulatory system involving the kidneys that restores normal osmotic pressure[2].

In the kidneys, natriuresis occurs through the inhibition of sodium reabsorption from the tubular lumen in the nephron as well as through changes in the glomerular filtration rate and pressure. Several hormones cooperate to achieve such effects.

The midbrain produces natriuretic sig-

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nals[3] that operate via the adrenal gland (which produces endogenous cardioactive steroids) and the heart (which makes atrial natriuretic factor)[4].

An insufficient blood supply to the kidneys is answered by increased release of the pressure hormone angiotensin II from the kidneys. Furthermore, blood pressure must be regulated to respond to the physiological requirements in healthy individuals. This is accomplished by the release of additional pressure hormones from the adrenal glands (epinephrine, serotonin or endogenous cardioactive steroids) or from vascular endothelial cells (endothelin-1).

Unfortunately, a long-term rise in blood pressure causes the heart, vascular tissue and kidneys to adapt to the situation. This tissue remodeling, which proceeds by altered gene expression, may lead within days or weeks to defective organ function.

Wirth *et al.*[1] asked how blood pressure is increased by pressurizing hormones in arterial smooth muscle cells. They investigated how docking of hormones to G protein–coupled hormone receptors (GPCRs) leads to the phosphorylation of myosin light chain (MLC), a trigger for the contraction of arterial smooth muscle cells.

GPCRs form complexes with GTP-hydrolyzing G proteins in caveolae of smooth muscle cells. There, the complexes transduce the amplified signal to contract through calcium-dependent and calcium-independent pathways[5,6]. The calcium-dependent pathway starts with G_q-G_{11}, induces calcium release from intracellular stores and activates MLC phosphorylation, thereby stimulating contraction.

The calcium-independent pathway blocks the degradation of phospho-MLC and thereby the relaxation of smooth muscle contraction. This pathway uses $G_{\alpha12}$-$G_{\alpha13}$ as a signal amplifier and operates through leukemia-associated guanine nucleotide exchange factor (LARG), Rho and the protein kinase ROCK—ultimately blocking the dephosphorylation of phospho-MLC and preventing relaxation. This pathway also affects gene transcription and induces the remodeling of vascular tissue[7,8] (**Fig. 1**).

The authors asked which G protein is used to regulate vascular tone under normal and salt-induced hypertensive conditions[1]. They generated mice in which the α subunits of G_q-G_{11} or G_{12}-G_{13} could be selectively switched off in smooth muscle cells and found that none of the pressure hormones tested used exclusively G_{12}-G_{13} to activate the GPCR signaling cascade. When the G_{12}-G_{13} signaling pathway was switched off, basal blood pressure remained unchanged. Hence the pathway governed by G_q-G_{11} is responsible for the maintenance of basal blood pressure.

Treatment of mice with DOCA-salt resulted in a rise of arterial blood pressure, but this did not happen in mice in which the signaling cascade starting with G_q-G_{11} or G_{12}-G_{13} had been knocked out. The authors next knocked out the gene encoding LARG, which is part of the G_{12}-G_{13} pathway[1]. They found that mice deficient in LARG were unable to respond to DOCA-salt treatment. The findings suggest that the GPCR–G_{12}-G_{13}–LARG signaling pathway is key for generating salt-induced hypertension—and that the lack of salt-induced hypertension in G_q-G_{11} knockout mice is probably due to the loss of the regulation of basal blood pressure (**Fig. 1**).

The findings not only illuminate how hormones binding GPCRs may regulate blood pressure, but also may provide insight into how the cardiac glycosides may work in vasoconstriction. These hormones spike in response to sodium and bind to a sodium-potassium ATPase to regulate increases in smooth muscle contraction and arterial hypertension[4]. A signal may be sent from the sodium-potassium ATPase via LARG and Rho to block smooth muscle relaxation; this makes sense, as Rho is a member of the Ras superfamily, and Ras is part of the sodium-potassium-ATPase signaling complex[4] (**Fig. 1**).

It is now possible to search for antihypertensive drugs that specifically interrupt the G_{12}-G_{13}-LARG pathway.

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The movers and shakers of deep brain stimulation

Wael Asaad & Emad Eskandar

Deep brain stimulation is increasingly used in the treatment of Parkinson's disease, essential tremor and other disorders, yet its mechanism of action remains unknown. New findings suggest that at least some of its action involves the release of adenosine, dampening tremors (pages 75–80).

Deep brain stimulation (DBS) has been used successfully in the treatment of neurologic illnesses such as Parkinson's disease, tremor and dystonia, and it is currently being explored as a treatment for major depression and obsessive-compulsive disorder. Yet, empirical efficacy aside, little is known of the mechanisms by which the electrical stimulation of deep brain structures alleviates these conditions. In fact, there is not even widespread agreement as to whether such stimulation facilitates, impedes or 'overwrites' information passing through the stimulated nuclei[1].

Nevertheless, the reversible and adjustable nature of DBS has made it an attractive, if rather blunt, tool for treating an increasingly large number of problems—when the only surgical tool available is a hammer, every disorder starts to look like a nail. Hence, it is of immense importance to understand the mechanistic basis of DBS in order to improve, revise or expand its application in a more rational fashion. Toward this end, Bekar *et al.*[2] show that, at least in the case of tremor, adenosine may have a major role in mediating the therapeutic efficacy of DBS.

Adenosine, a neuromodulator found throughout the brain, exerts its postsynaptic effect through G protein–coupled receptors[3,4].

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