

less than the earlier value. This faster rotation rate means that to fit the observed gravitational moments, the internal density distributions computed for Saturn must be revised. The core mass will most probably be reduced, bringing it closer to that of Jupiter (see the figure). The extent of this reduction will depend on the details of the physics.

Saturn's mass is only one-third that of Jupiter's; thus, it is likely that the secondary processes that have been suggested to reduce

the size of Jupiter's core in the core accretion scenario, or to form the core in the disk instability scenario, might be different enough between the two planets to explain the difference in the size of their cores. Perhaps we will even be able to use this information to help decide between the two hypotheses. Like Sherlock Holmes, I hesitate to speculate too much before having the facts. In view of this new data, planet formation theorists should sit up and take notice.

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## CELL BIOLOGY

# The Stress of Relaxation

H. Criss Hartzell

Oxidants and free radicals, according to the vitamin mongers, are the ruination of our existence. They include superoxides ( $O_2^-$ ), hydroxyl radicals ( $OH^\cdot$ ), and peroxides ( $H_2O_2$ ), collectively called "reactive oxygen species" (ROS). These molecular brigands—the by-products of mitochondrial metabolism—corrode molecules by snatching their electrons. They are blamed for causing cancer, heart disease, Alzheimer's disease, and old age (1). Yet in a reversal of the view that has dominated since the 1950s, we have come to appreciate that ROS play essential roles in healthy cell signaling. On page 1393 in this issue, Burgoyne *et al.* (2) show that oxidation activates a key enzyme that causes blood vessels to relax. This finding raises a paradox: Why, if oxidation can relax blood vessels, is oxidative stress associated with hypertension?

Vascular smooth muscle cells contract using filaments of actin and myosin molecules.

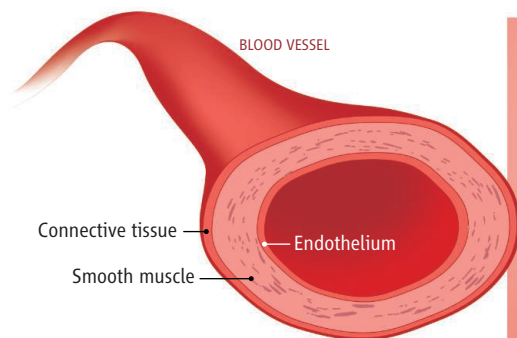
Hormones and neurotransmitters control muscle tone by affecting the phosphorylation state of myosin (see the figure) (3, 4). Vasoconstrictors, such as angiotensin II, increase the concentration of cytosolic calcium ions ( $Ca^{2+}$ ), which activates an enzyme (myosin light chain kinase) that phosphorylates myosin. Also, an enzyme (myosin light chain phosphatase) that dephosphorylates myosin is inhibited. Vasorelaxants, such as acetylcholine, have the opposite effects. Protein kinase G (PKG) is a pivotal enzyme in vasorelaxation (3). The PKGI $\alpha$  isoform studied by Burgoyne *et al.* phosphorylates a panoply of substrates, ultimately decreasing myosin phosphorylation.

How is PKG activated by vasorelaxants? The best-understood pathway involves endothelial nitric oxide synthase (eNOS), which generates nitric oxide (NO). This gaseous molecule diffuses from the endothelium to vascular smooth muscle and activates cytosolic guanylate cyclase, thus triggering the production of guanosine 3',5'-monophosphate (cGMP), which activates PKG. The new mechanism proposed by Burgoyne *et al.* involves oxida-

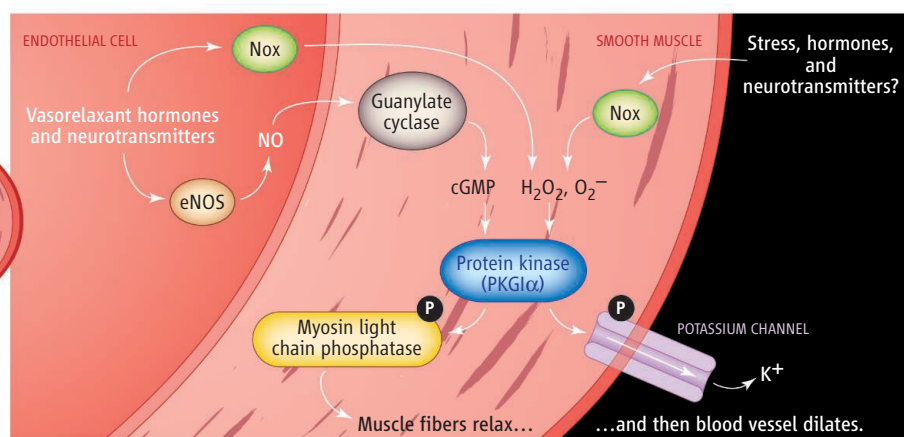
tion-mediated PKGI $\alpha$  dimerization. The authors noted that  $H_2O_2$  relaxes aortic rings and that relaxation correlates with dimerization (and hence, activation) of PKGI $\alpha$ .  $H_2O_2$ -mediated dimerization decreases the affinity of PKGI $\alpha$  for substrate, whereas cGMP-activation of PKGI $\alpha$  increases the maximum velocity of substrate phosphorylation. More importantly, Burgoyne *et al.* noted that  $H_2O_2$  stimulates numerous downstream vasorelaxant events including decreased myosin phosphorylation. Thus,  $H_2O_2$  is worthy of being an important relaxation signal.

Many proteins are affected by their redox states, but the physiological relevance is unclear, partly because high concentrations of oxidant are often used. Although tissue concentrations of  $H_2O_2$  are not known, PKGI $\alpha$  is activated by 100  $\mu$ M  $H_2O_2$  (2), which is probably physiological. The best-documented targets for ROS are protein tyrosine phosphatases (5, 6), whose enzymatic activity is abolished by oxidation of a cysteine residue in their active sites. This oxidation is stimulated by growth factors whose receptors trigger  $H_2O_2$

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**Vascular relaxation.** The enzyme PKGI $\alpha$  phosphorylates multiple targets (two shown here) when activated by cGMP or oxidation. These events result in relaxation of smooth muscle cells in the blood vessel wall.



production via Nox [NADPH (nicotinamide adenine dinucleotide phosphate, reduced) oxidase] enzymes (7, 8). The cysteine is susceptible to reversible oxidation because a nearby arginine lowers the  $pK_a$  (acid dissociation constant) so that the cysteine is in the thiolate form. Interestingly, PKGI $\alpha$  Cys<sup>42</sup> is flanked by basic residues that might also lower its  $pK_a$ .

Endothelium-dependent relaxation involves several molecules besides NO. One of these, endothelium-derived hyperpolarization factor, relaxes muscle cells by opening Ca<sup>2+</sup>-activated K<sup>+</sup>-channels (BK<sub>Ca</sub>). This hyperpolarizes the cell, causing voltage-gated Ca<sup>2+</sup> channels to close. It has been supposed that this relaxing factor may be H<sub>2</sub>O<sub>2</sub> (9). The observation of Burgoyne *et al.* that PKG-mediated phosphorylation of the BK<sub>Ca</sub> channel is stimulated by H<sub>2</sub>O<sub>2</sub> may strengthen the H<sub>2</sub>O<sub>2</sub>-endothelium-derived hyperpolarization factor link.

A major question is which vasorelaxants use H<sub>2</sub>O<sub>2</sub> signaling. Burgoyne *et al.* show that insulin may use this pathway, but the amount of PKGI $\alpha$  dimerization is insufficient to fully explain insulin-induced vasorelaxation. Another question is which enzymes generate

relaxant H<sub>2</sub>O<sub>2</sub>. Although Nox enzymes are the main source of ROS in the vasculature (10), Nox-produced ROS are associated with increased blood pressure, not vasodilation. Evidence points to angiotensin II as the chief culprit: Infusion of mice with angiotensin II stimulates Nox, increases ROS, and produces hypertension (10–12).

If ROS is associated with hypertension, how, then, can we explain the observation that H<sub>2</sub>O<sub>2</sub> can produce vasorelaxation? There is a simple, but plausible answer: All ROS are not equal. Four different Nox isoforms are expressed in different subcellular locations in the vasculature (10), and produce ROS with different properties. Although Nox enzymes generate O<sub>2</sub><sup>-</sup>, O<sub>2</sub><sup>-</sup> dismutates to H<sub>2</sub>O<sub>2</sub>. Compartmentalization is probably the key: Targets must be close to the site of O<sub>2</sub><sup>-</sup> generation, because O<sub>2</sub><sup>-</sup> has a fleeting lifetime and is membrane-impermeant; H<sub>2</sub>O<sub>2</sub> targets are less restricted because H<sub>2</sub>O<sub>2</sub> has a longer lifetime and is membrane-permeant. At least part of the vasoconstriction can be explained by destruction of NO by extracellularly generated O<sub>2</sub><sup>-</sup>. By contrast, H<sub>2</sub>O<sub>2</sub> may be generated within the muscle, conveniently

located near its intracellular target, PKGI $\alpha$ .

There is also another way out of the paradox. Endothelial NOS can generate O<sub>2</sub><sup>-</sup> and H<sub>2</sub>O<sub>2</sub> under certain conditions, resulting in vasorelaxation (13). This could provide a mechanism whereby the diffusible products generated by NOS switch between NO and H<sub>2</sub>O<sub>2</sub>. That, of course, raises the question of how the switch may be regulated.

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## PHYSICS

# Heavy Fermions in the Original Fermi Liquid

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Physicists have long been fascinated by so-called heavy-fermion materials (1, 2), in which the electrons act as though they had put on a lot of extra mass. Some of these compounds are also superconductors, so extracting the secrets of heavy fermions may yield insights into high-temperature superconductivity and other open questions. On page 1356 of this issue, Neumann *et al.* (3) report heavy-fermion behavior in an unexpected setting: two-dimensional layers of <sup>3</sup>He adsorbed on a graphite surface. Their experiments raise the prospect of studying heavy-fermion physics in a quite different context, hopefully shedding new light on an old and fundamental puzzle.

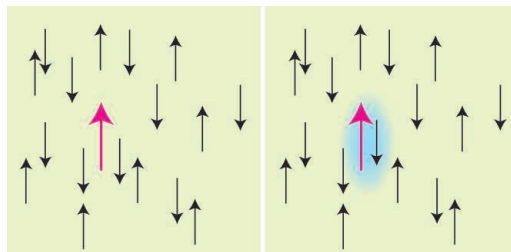
The <sup>3</sup>He atom is a fermion (that is, a quantum particle with half-integer spin, like elec-

trons themselves). When gaseous <sup>3</sup>He is cooled at atmospheric pressure, it liquefies at  $T = 3.2$  K and remains liquid down to  $T \approx 1$  mK, where it undergoes a superfluid transition (4). It is therefore unique in the periodic table: the only fermionic liquid at temperatures where quantum effects become important. Measurements

In some complex materials, the electrons appear to be unexpectedly heavy. Helium atoms show similar behavior in much simpler thin films of helium-3.

of the properties of bulk liquid <sup>3</sup>He in the 1950s revealed that the low-temperature behavior of the liquid was remarkably similar to that predicted theoretically for a gas of weakly interacting fermions. This is surprising, because at the densities of liquid helium, the interatomic interactions ought to be rather strong.

This riddle was resolved by Landau (5–7), who argued that the reason for the similarity was that something was behaving like weakly interacting fermions—it just wasn't the original atoms. The “something” is now called a quasi-particle—a collective excitation that retains some of the properties of the original atom (e.g., it behaves like a spin- $\frac{1}{2}$  fermion) while having others modified (it can have a much different mass). The description of the residual interactions between these quasi-particles—which determine the properties of the liquid—was the vital ingredient of Landau's Fermi liquid theory.



**The Kondo effect.** (Left) When a magnetic impurity (red arrow) is embedded in a Fermi liquid (quasi-particles represented by black arrows), it acts at high temperatures like a strong magnetic scatterer. (Right) At low temperatures, a spin singlet state forms with quasi-particles from the Fermi sea. This reduces scattering and incorporates the magnetic impurity electron into the heavy-fermion liquid.

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