deformation due to viscous flow of rocks induced by large earthquakes in western North America indicate that, at these short timescales, the lower crust is quite strong, whereas the upper mantle below about 50 km is much weaker[3,8]. The effective flow strengths of the lower crust found in the geodetic studies seem too high for the quartz-rich make-up suggested by Lowry and Pérez-Gussinyé. On the other hand, low, long-term static strength, inferred from estimates of effective elastic plate thickness of only 10 km or less (see Fig. 4 on p. 356), is consistent with a weak lower crust in the region. Thus, lower-crustal viscosities at very long (millions of years) timescales may effectively control the stability of continental crust and upper mantle[8].

Is a quartz-rich layer in the crust, only tens of kilometres thick, able to initiate break-up of a continental plate originally dominated by a strong mantle layer up to 200 km thick[9]? Lowry and Pérez-Gussinyé argue that, following initial deformation enabled by the quartz-rich crust, the strong mantle layer can be further softened by high temperatures and/or fluids derived from subducting oceanic plates[10], leading to the eventual loss or sogginess of the bottom slice of the jelly sandwich. Importantly, even where the uppermost mantle remains stable, as indicated by high estimates of elastic-plate thickness, a quartz-weakened lower crust can promote tectonic deformation. This may have been the case during the most recent tectonic period of the northern Rocky Mountains (Fig. 1), the Laramide orogeny[1].

The validity of the model can be tested when similar techniques are applied to different tectonic provinces that have experienced successive cycles of supercontinent formation and mountain-building. In particular, as Lowry and Pérez-Gussinyé suggest, the extension of the Transportable Array across older orogens in eastern North America during the next two years will provide a unique opportunity to test the role of quartz in mountain building. ■

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REPRODUCTIVE BIOLOGY

Progesterone's gateway into sperm

The hormone progesterone rapidly activates intracellular signalling in human sperm, regulating key aspects of their physiology. An ion channel unique to the sperm tail seems to relay progesterone's signal. SEE LETTERS P.382 & P.387

STEVE PUBLICOVER & CHRISTOPHER BARRATT

The ovarian hormone progesterone classically binds to a nuclear receptor, initiating gene transcription. But how does it stimulate the transcriptionally inactive human spermatozoon in preparation for fertilization? This question has long both fascinated and frustrated reproductive biologists. In this issue, Strünker and colleagues[1] and Lishko *et al.*[2] provide an unexpected answer: progesterone activates a sperm-specific calcium ion (Ca^{2+}) channel called CatSper.

For a sperm to reach the egg, it must penetrate the cumulus oophorus, a thick layer around the egg composed of granulosa cells embedded in a gelatinous matrix. These cells actively synthesize progesterone, such that its concentration within the cumulus is in the micromolar range. It was first reported more than 20 years ago[3] that progesterone, even at concentrations well below those present in the cumulus, induces immediate influx into human sperm of Ca^{2+} — a factor central to regulation of sperm function[4,5]. Progesterone is therefore believed to have a crucial role during the events leading to fertilization[6].

Sperm cells respond to progesterone within less than a second, which is characteristic of classical signalling pathways that involve cell-surface receptors[3,6]. Such non-nuclear actions of steroid hormones are quite common. In fact, progesterone and its related hormones are considered to have two distinct modes of action: through intracellular nuclear receptors, which regulate transcription; and through non-genomic receptors, probably at the plasma membrane, which regulate ion channels, G-protein-coupled receptors and signalling pathways mediated by kinase enzymes[7]. However, the mechanism of progesterone-induced Ca^{2+} influx in sperm has resisted all attempts at characterization, with even the type of 'receptor', let alone the nature of the Ca^{2+}-influx pathway, remaining a mystery. This has been particularly frustrating because the phenomenon is probably of considerable clinical significance: in human sperm, failure of progesterone-activated Ca^{2+} influx is correlated with reduced fertility[6].

The solution to this mystery follows directly from two crucial advances in the field. First, in 2001 two groups[8,9] reported the discovery of the Ca^{2+}-permeable cation channel (CatSper), which is expressed only in the plasma membrane of a domain in the sperm tail called the principal piece. Sperm from genetically manipulated mice that cannot express CatSper have impaired motility and, crucially, cannot display hyperactivation — an extravagant, highly asymmetric form of flagellar beating that is regulated by Ca^{2+} and is essential for fertilization. CatSper-deficient male mice are infertile.

The second, more recent, advance was the development of a method for applying to sperm the technique of whole-cell patch clamping, which records ionic currents across the entire plasma membrane of a cell. Using this technique, researchers showed that increased alkalinity of the sperm cytoplasm strongly activates CatSper channels, promoting Ca^{2+} flux into the cell. Strünker *et al.* (page 382) and Lishko and colleagues (page 387) now use this powerful technique to elucidate the mechanism by which progesterone induces rapid Ca^{2+} influx into human sperm.

Progesterone-induced membrane currents have identical characteristics to those carried by CatSper. For instance, the biophysical aspects of the currents are indistinguishable, with both progesterone and increased intracellular pH stimulating CatSper by shifting its voltage sensitivity so that it opens at lower voltages (Fig. 1). What's more, pharmacological manipulation has the same effects both on CatSper currents activated by increasing intracellular pH and on those stimulated by progesterone; applied together, progesterone and increased alkalinity act synergistically[1,2].

The effect of progesterone on CatSper is not simply a nonspecific effect of steroid hormones: another steroid hormone, oestradiol, has no effect on this channel[2]. However, several prostaglandins — non-protein mediators that increase intracellular Ca^{2+} concentration in human sperm — have strikingly similar effects to progesterone. Moreover, Strünker and colleagues' measurements of intracellular Ca^{2+} concentration in progesterone-stimulated sperm showed that compounds that block CatSper currents also reduce the progesterone-induced rise in Ca^{2+} concentration, and that

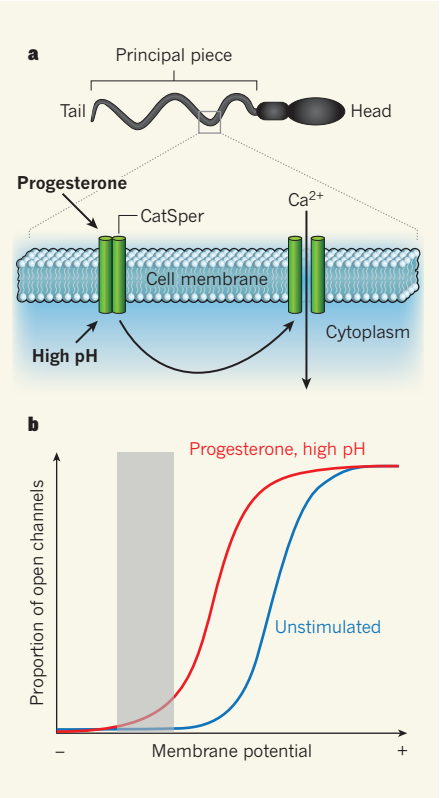

Figure 1 | CatSper and calcium-ion influx. **a**, The CatSper ion channel, which occurs in the plasma membrane of the principal-piece domain of the sperm tail, allows Ca^{2+} influx into these cells. New work[1,2] shows that progesterone leads to the opening of this channel, probably either by binding to it directly or through an associated protein; increased intracellular pH has the same effect. On opening, CatSper channels allow Ca^{2+} entry into the cell, which regulates events vital for fertilization. **b**, Opening of CatSper channels depends on the electrical difference across the cell membrane (the membrane potential) and occurs when the cell becomes electrically more positive inside. The normal membrane potential in sperm (grey bar) is such that nearly all CatSper channels are closed (blue line). Both progesterone and increased intracellular pH 'shift' the electrical sensitivity of CatSper so that the channel can open at more negative membrane potentials (red trace).

stringent buffering of this ion in the external medium abolishes the response to progesterone[1]. Intriguingly, the efficacy of progesterone is increased by *in vitro* manipulations designed to induce sperm capacitation (a crucial maturation process that naturally occurs in the female reproductive tract before fertilization).

The non-genomic action of progesterone is much more potent in human sperm than in mouse sperm[2]. But why? Lishko and colleagues show that, at the intracellular pH of 7.0 (a value within the physiological range), mouse spermatozoa show notable CatSper currents, whereas human sperm show a much smaller current. On applying progesterone to human sperm, the current increases to a level closely resembling that in mouse sperm, but in mouse sperm stimulation with this hormone leads to no further increase in current[2]. It seems, therefore, that in human sperm, progesterone induces a modulation of CatSper function that in mouse sperm is constitutive (at least under the conditions used in these experiments). This is potentially a crucial species difference in sperm regulation within the female reproductive tract.

The two papers also present a much clearer idea of how progesterone exerts its effect by modulating CatSper. Lishko *et al.*[2] could record progesterone-induced currents even in isolated sperm tails, which precludes indirect effects of progesterone exerted through receptors on the sperm head. Furthermore, Strünker *et al.*[1] provide compelling evidence that progesterone does not stimulate synthesis of the signalling molecule cyclic AMP, and they couldn't detect any effects of manipulating cAMP levels on Ca^{2+} influx through the sperm membrane. These observations rule out involvement of the cAMP–protein kinase A signalling cascade in the progesterone–CatSper response.

The new data also suggest that progesterone directly activates CatSper, by binding either to the channel itself or to an associated subunit(s). Whether CatSper activation is the only effect of progesterone on Ca^{2+}-signalling in human sperm remains to be seen. Several previous studies have attempted to identify progesterone receptors[6]. Both novel receptors and truncated versions of the classical (nuclear-type) receptors (some of these apparently localized to the sperm head) were proposed to mediate the effects of this hormone. Although such receptors almost certainly do not contribute to the modulation of CatSper reported here, it is noteworthy that completely blocking CatSper currents inhibits — but does not abolish — the effect of progesterone on intracellular Ca^{2+} levels[1,10].

Mobilization of intracellular Ca^{2+} stores, leading to complex Ca^{2+} signalling, occurs in progesterone-stimulated human sperm[5]. Is this purely a downstream effect of CatSper activation or does progesterone activate a separate pathway? Are store-controlled Ca^{2+} channels involved? These two studies[1,2] provide exciting insights, and there is more to come. ■

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HIGH-TEMPERATURE SUPERCONDUCTIVITY

The secret of the hourglass

The finding that a cobalt oxide insulator's magnetism is similar to that of cuprate superconductors lends support to the popular but contentious idea that stripe-like electronic order is present in the latter materials. SEE LETTER P.341

JAN ZAANEN

One hundred years after its discovery, superconductivity is still an active field of research. On page 341 of this issue, Boothroyd *et al.*[1] describe experimental results on an insulating material that offer insight into the physics of one of the most intriguing families of superconductors — the copper oxides, or cuprates.

Conventional superconductivity — that which occurs in simple metals such as lead and aluminium — was explained back in 1957 by Bardeen, Cooper and Schrieffer, in what is known as the BCS theory[2]. But in 1986, a different, high-temperature form of superconductivity was discovered in complex cuprates[3]. This discovery rumbled like an earthquake through the physics community, because the superconducting transition temperatures (T_c), below which these materials conduct electricity without resistance, were much too high to be explained by BCS theory. What causes superconductivity in the cuprates is still much of a mystery, but intensive research has shown that the ground rules of