NEUROSCIENCE

Controlled capillaries

Brian A. MacVicar and Michael W. Salter

The finest scale of blood flow through the brain occurs in capillaries. Suspicions that capillary flow is regulated by cells that put the squeeze on these vessels are now borne out by detailed experiments.

The control of brain blood flow poses an intriguing 'plumbing' problem. On the one hand, high overall flows are required to maintain healthy brain function, because in humans the brain accounts for 20% of the body's energy consumption even though it forms only 5% of the total weight. On the other hand, there is a need to precisely regulate increases and decreases in flow to match the changing metabolic needs of specific brain regions. It has been known for more than 100 years[1] that the brain regulates its own blood supply. It can increase blood flow specifically to discrete regions to follow increases in neuronal activity. This principle has been exploited in functional magnetic resonance imaging and positron emission tomography, which have been extensively used to map the brain regions that are associated with different tasks[2].

However, the cellular mechanisms by which specific brain regions regulate blood flow, and therefore their own nutrient intake and waste removal, are not fully understood. In their paper on page 700 of this issue[3], Peppiatt *et al.* implicate new players in regulating blood flow at the smallest level in the brain — cells known as pericytes.

The large blood vessels supplying the brain are the carotid and vertebral arteries, which then branch to form the network of pial arteries covering the surface of the brain. In the cerebral cortex, the pial vessels branch into smaller arteries, which enter the brain tissue itself and are called the penetrating arterioles. These arterioles branch into secondary and tertiary arterioles, until they reach the smallest vessel supplying the brain tissue, the capillary, which is only wide enough for one red blood cell to pass through it at a time. The capillaries then feed into the venuoles and veins, which carry the blood away.

By virtue of the smooth muscle that surrounds them, arteries and arterioles can regulate blood flow. Various processes, including the release of mediators from the endothelial cells that line these vessels, cause contraction or relaxation of the smooth muscle cells, thereby decreasing or increasing the diameter of the artery or arteriole — *et voilà*, as we know from Poiseuille's law of fluid dynamics, blood flow can be controlled.

It had been suspected that blood flow through capillaries is also regulated, even though there are no surrounding smooth muscle cells to constrict them. The suspicions were based on the observation that capillaries are enwrapped at intervals by a little-studied cell type with contractile capabilities, the pericyte. Peppiatt *et al.*[3] now show definitively that pericytes in living tissue of the central nervous system can constrict and relax, correspondingly changing capillary diameter, and that they do this in response to changes in neuronal activity. Pericytes were identified by staining with a specific marker. The cells are spaced at intervals along capillaries, and also occur at capillary junctions. Their cell bodies abut the capillaries, with their processes enwrapping them (see Fig. 1a of the paper[3] on page 701).

Peppiatt *et al.* obtained the proof that pericytes modify capillary diameter by stimulating the cells directly with microelectrodes in rat brain slices and in retinal explants. They also found that drugs that activate purinergic receptors, a type of receptor found in the surface membrane of pericytes, stimulated pericyte-induced contractions. The constriction of the capillary occurred only in discrete regions or at capillary branch points. These types of localized change in capillary diameter should be very effective in blocking the entry of red blood cells, and thus slowing blood flow. The branch-point constriction might also divert flow into a capillary supplying an active region of neurons.

Inhibiting pericyte constrictions, by lowering the levels of external calcium (a common agent of cell signalling) or applying the neurotransmitter glutamate, caused dilation of pre-constricted capillaries, indicating that pericytes exert bidirectional control over capillary diameter. Significantly, the pericytes became constricted in response to stimulation by local neurons, showing that pericytes are sensitive to changes in neuronal activity.

DEVELOPMENTAL BIOLOGY

A change of heart

Vertebrate hearts have at least two chambers. But how did these evolve from the single-chambered pumps seen in simpler organisms? While examining the development of the heart of the sea squirt, Brad Davidson and colleagues (*Genes Dev.* **20**, 2728–2738; 2006) may have chanced on the answer.

The adult sea squirt (*Ciona intestinalis*, pictured) is a classic squishy invertebrate, but as a larval tadpole it resembles a fish embryo. This puts it closer to humans on the evolutionary scale than other genetic model organisms such as fruitflies and worms, and makes it a useful system for studying certain developmental processes.

Davidson *et al.* followed the single-chambered sea-squirt heart as it grew from two cells in the early embryo. These cells divide and specialize to form muscle cells in either the heart or the tadpole tail. The authors find that the decision about which muscle type develops centres on a gene-regulatory factor called Ets1/2 — cells in which the factor is active become heart cells.

But Ets1/2 is also present, though inactive, in the cells destined to become tail. So something must activate it to set embryonic cells on the path to becoming heart cells. Davidson *et al.* teased apart the genetics to discover that the activating signal comes from a classic growth factor called FGF. Both Ets1/2 and the FGF signalling pathway have relatives in vertebrates, and these have been linked to heart development. This implies that the developmental pathway in the sea squirt has been conserved through evolution.

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The twist in the tale came from an experiment in which Davidson and colleagues looked at the effect of a permanently active form of Ets1/2 on embryonic cells destined to become tail. Not only did these cells develop into heart cells, confirming the role of Ets1/2, but in some animals the resulting organ had two chambers rather than one.

So the authors speculate that since it separated from the sea-squirt lineage, an ancestral vertebrate recruited additional heart precursor cells to make a two-chambered heart. As their study shows, even a subtle change in signalling in the pool of cells that can form muscle cells might have allowed this transition.

Helen Dell