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PHARMACOLOGY

# New methods to permeabilize the blood–brain barrier

Two studies in animal models have identified novel mechanisms to open the tight vascular endothelial junctions that form the blood–brain barrier (BBB). These methods might eventually be used to enhance drug delivery to the brain for the treatment of patients with neurological disorders.

In one study, researchers used pulses of ultrasound, focused to a specific brain region, to induce expansion and contraction of systemically administered microbubbles. This procedure caused opening of the microvessel walls, thereby increasing the permeability of the BBB. "We previously used very long pulses that could incur more damage and also led to the concentration of the openings in larger vessels," explains lead researcher Elisa Konofagou. "We wanted to determine the shortest ultrasound pulse that would open the BBB because that would incur the lowest risk of damage."

Three short cycles of ultrasound given over several bursts allowed the microbubbles to replenish and distribute evenly along the microvasculature without biased accumulation at large vessels, thus reducing the risk of vascular damage. Fluorescent molecules not only crossed the opened BBB, but also reached the neurons—a finding only evident when the researchers used short ultrasound pulses. Konofagou hopes that this technique will be ready for human trials within the next 5–10 years.

Previous studies by Margaret Bynoe and colleagues have shown that signaling via adenosine receptors controls cell-trafficking between the blood and cerebrospinal fluid in mice. In a study published in *The Journal of Neuroscience*, the researchers used adenosinergic drugs to show that adenosine receptor signalling also controls the BBB. Activation of adenosine receptor signaling increased the permeability of the barrier and enabled both small and large molecules to enter the brain, whereas inhibition of adenosine receptor signaling decreased BBB permeability.

"Our studies are the first to establish a clearly defined role for adenosine in modulating the BBB," states Bynoe. "The next major goal is unraveling the mechanism of adenosine signaling at the BBB."

*Katy Malpass*

**Original articles** Choi, J. *et al.* Noninvasive and localized neuronal delivery using short ultrasonic pulses and microbubles. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1105116108 | Carman, A. J. *et al.* Adenosine receptor signalling modulates permeability of the blood-brain barrier. *J. Neurosci.* **31**, 13272–13280 (2011)