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Commentary

Unsuspected stroke signals: From extravascular blood to vessel lumen

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Subarachnoid hemorrhage, a stroke on the surface of the brain or spinal cord caused by a ruptured blood vessel, would provoke little concern among clinicians as the least brain-destructive of all stroke types if it was not for its late after-effects: vessel re-rupture and additional ischemic stroke due to brain tissue hypoperfusion. Hypoperfusion, the result of progressive narrowing of large and medium blood vessels (vasospasm), starts to overshadow most other complications several days following subarachnoid hemorrhage and is readily detectable, but remains poorly treatable. The late appearance and progressive nature of vasospasm suggest that signaling mechanisms -perhaps triggered by a blood-bound extravascular signal acting on the external surface of the blood vessel wall must be activated. Neurosurgical observations support this contention. It has been known for decades that early operative removal of subarachnoid blood leads to less vasospasm and better outcome and that larger subarachnoid blood collections are associated with more severe hypoperfusion. By analogy reasoning, a counterbalancing vasodilatory mechanism may also exist.

Among the candidate vasodilatory molecules, adiponectin, a circulating protein almost absent from neural tissue, has been intensively studied in relation of obesity, diabetes and the "metabolic syndrome". Circulating adiponectin is reduced in these patients such that it is considered a beneficial molecule. Adiponectin has also been characterized as a neuroprotectant against cerebral ischemia [4]. The neuroprotective mechanisms of adiponectin include the capacity to activate endothelial nitric oxide synthase (eNOS), resulting in an enhanced nitric oxide (NO) production by endothelial cells. NO is an important mediator of protection against cerebral ischemia [1].

In the study by Osuka et al. [5], the authors first set out to quantify human adiponectin levels in the cerebrospinal fluid (CSF) after subarachnoid hemorrhage to identify the potential physiological relevance of such a mediator. Adiponectin is present at low abundance in CSF: Normally, the plasma to CSF adiponectin concentration ratio reaches almost 2000. Having detected a transient, ~200-fold increase in adiponectin concentration in CSF after hemorrhage (perhaps of hematic origin), a key question is whether adiponectin is endowed with signaling capacity when acting on cerebral blood vessels. Using rat brain vessels, the authors illustrate that adiponectin phosphorylates AMPKa, resulting in activation of eNOS in cerebral arteries. In contrast, subarachnoid space blood induces disruption of eNOS-dependent vasodilatation [2], a well-known contributor to cerebral vasospasm. Therefore, increased adiponectin in CSF after subarachnoid hemorrhage is positioned to counteract vasospasm and regulation of adiponectin action may constitute a therapeutic opportunity.

Other unproven adiponectin effects may also be relevant in the pathogenesis of the syndrome. Immediately after the onset of subarachnoid hemorrhage, some patients suffer from neurogenic pulmonary edema (i.e., edema of a previously normal lung) or cardiac dysfunction [3], which are life-threatening complications linked to autonomic nervous system dysfunction. Given the presence of hypothalamic adiponectin receptors, increased adiponectin levels in the vicinity of the hypothalamus might be further involved in the pathogenesis of these disabling complications.

If these contentions hold true, adiponectin would constitute a remarkable ectopic signaling molecule after gaining access to sites normally protected from blood exposure by blood–CSF barriers.

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