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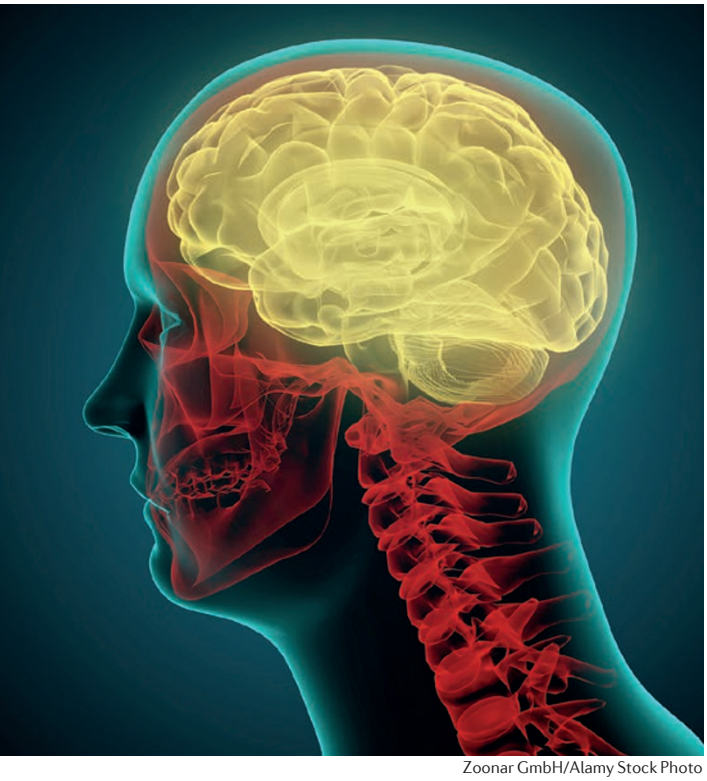
NEURODEGENERATION

# HIF-PHD inhibition ameliorates damage after brain haemorrhage

Secondary brain injury following intracerebral haemorrhage (ICH) has been attributed to blood cell lysis, toxic iron release and subsequent oxidative stress. Although iron chelators have displayed protective effects in some animal models of ICH, a challenge in their therapeutic use is to reduce iron accumulation without disrupting iron-dependent cellular functions. Now, Ratan and colleagues report that specific inhibition of hypoxia-inducible factor prolyl hydroxylase domain enzymes (HIF-PHDs), using the small molecule adaptaquin, promotes motor recovery and reduces neuronal degeneration in rodent ICH models.



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HIF-PHDs are a family of iron-containing, oxygen-sensing enzymes that destabilize the transcriptional activator HIF1α under normoxia. Iron chelators are known to inhibit the HIF-PHDs and have been shown to stabilize HIF1α, leading to activation of a set of adaptive genes that protect neurons from oxidative death. With this in mind, the authors set out to investigate the potential of specific HIF-PHD inhibition in the treatment of ICH.

First, they show that three structurally diverse HIF-PHD inhibitors prevented neuronal death induced by haemin (a blood breakdown product) in primary rat neurons and mouse neuronal cell lines. Only one of the inhibitors, deferoxamine, is also an iron chelator, indicating that PHD inhibition, rather than metal chelation, is the mechanism protecting neurons against haemin-induced toxicity.

Next, the authors conditionally reduced HIF-PHD expression in the mouse striatum (where ICH often occurs) and induced ICH using collagenase. Compared with wild-type mice, mice with reduced HIF-PHD expression exhibited increased HIF-dependent gene expression and improved somatosensory function within 7 days after the injury.

They then set out to identify a brain-penetrant HIF-PHD inhibitor for testing in ICH models. To monitor HIF-PHD activity dynamically, they engineered mice to ubiquitously express the oxygen degradation domain (ODD) of HIF1α (which is degraded by HIF-PHDs) fused to luciferase. They found that a previously identified 8-hydroxyquinoline HIF-PHD inhibitor — named adaptaquin — penetrated the blood–brain barrier and significantly increased ODD–luciferase activity in the cortex, hippocampus, striatum and cerebellum.

The ability of adaptaquin to inhibit brain HIF-PHDs translated into beneficial effects in rodent ICH models. In mice, intraperitoneal administration of adaptaquin once a day for 7 days, starting 2 hours after injection of collagenase into the striatum, resulted in significant behavioural improvements that were associated with a reduction in the number of degenerating neurons. Similar beneficial effects on motor recovery were seen in rats, in which adaptaquin treatment was initiated 2 hours after autologous blood infusion.

Surprisingly, the beneficial effects of adaptaquin following ICH were found to be independent of iron chelation or activation of the HIF prosurvival pathway. Instead, further *in vitro* and *in vivo* studies revealed that adaptaquin-mediated HIF-PHD inhibition protected neurons by reducing transcriptional activity of ATF4, thereby suppressing ATF4-mediated prodeath gene expression.

In summary, these findings support inactivation of HIF-PHD metalloenzymes in the brain as a potential approach for treatment of ICH. Other oxyquinolines have proved to be safe in humans; therefore, further evaluation of adaptaquin is warranted.

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**ORIGINAL ARTICLE** Karuppagounder, S. S. *et al.* Therapeutic targeting of oxygen-sensing prolyl hydroxylases abrogates ATF4-dependent neuronal death and improves outcomes after brain hemorrhage in several rodent models. *Sci. Transl Med.* **8**, 328ra29 (2016)



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