Hypoxic signaling: some organs are more equal than others. Focus on “Differential HIF and NOS responses to acute anemia: defining organ-specific hemoglobin thresholds for tissue hypoxia”

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Submitted 26 November 2013; accepted in final form 18 April 2014

The direction of physiological research is often shaped by the nature of the clinical problems we can potentially solve through advances in our understanding of the underlying biology. Consequently, we can lose sight of the fact that evolution is chiefly driven by the imperative for organisms to adapt to common physiological challenges rather than for us to cope with the ravages of old age in our modern world. So it is with the kidney and the extraordinary paradox that this highly perfused organ is susceptible to the development of hypoxic damage (2). For example, it seems likely that hemodilution during surgery performed in combination with cardiopulmonary bypass promotes renal hypoxia, and thus the development of acute kidney injury. Evidence for this includes the observations that whole body oxygen delivery during cardiopulmonary bypass, which is largely determined by the degree of hemodilution, is a major determinant of the risk of postoperative acute kidney injury (1). Furthermore, the kidney appears to be more sensitive than other organs (e.g., heart and intestines) to the ability of acute anemia to induce tissue hypoxia (7, 10).

Acute blood loss and consequent temporary anemia is no doubt a common physiological challenge for most mammalian species. So what selection pressures might have led to the kidney being so poorly adapted to cope with anemia? The likely answer is that the kidney is the body’s “criterion,” through its role in the synthesis and release of erythropoietin (5). Consequently, in order for the kidney to mount an appropriate response to anemia, through its role in the synthesis and release of erythropoietin, cortical tissue PO2 must fall in response to anemia. Indeed, it seems that the kidney has evolved multiple mechanisms that enhance its susceptibility to tissue hypoxia in anemia. These likely include the relative insensitivity of renal vascular tone to hypoxia and the ability of anemia to enhance the diffusional shunting of oxygen from arteries to veins (2, 6).

Given that the response of tissue PO2 to anemia differs in the kidney relative to other organs, one might also expect to find differences in the cellular signalling cascades mediating the cellular responses to hypoxia. In this issue of American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Tsui and colleagues (9) provide strong evidence that this is the case. In a previous study, they demonstrated a critical role of neuronal nitric oxide (NO) synthase (nNOS) in the adaptive response of the brain to anemia (8). Their observations indicate that NO produced by nNOS, particularly in perivascular regions, S-nitrosylates the Cys162 residue of von Hippel-Lindau protein, thus leading to increased levels of hypoxia-inducible factor (HIF)-1α. Interestingly, their observations also indicate that this mechanism is important in the adaptive response to anemia but not to hypoxemia.

In their paper in the current issue, Tsui and colleagues compare the HIF signalling responses to graded anemia of the kidney and liver with that of the brain. They used a transgenic mouse in which firefly luciferase acts as a reporter for HIF-1α bioavailability (9). They showed that in the kidney, unlike the brain, activation of HIF-1α by anemia is independent of nNOS. This seems to make adaptive sense, in that HIF signalling in the kidney may be more finely tuned to respond to hypoxia than in other tissues, where an ability to respond to additional stimuli might provide some adaptive advantage.

Using their transgenic mouse as a reporter of HIF-1α bioavailability, Tsui et al. also showed that, as in the brain, activation of HIF-1α in the kidney can be detected during severe (hemoglobin = 50 g/l) anemia but not during mild (hemoglobin = 90 g/l) or moderate (70 g/l) anemia (9). Nevertheless, by Western blot they were able to detect increased renal expression of HIF-1α in mild anemia and increased HIF-2α protein in moderate anemia. Importantly, both methods indicated that mild anemia paradoxically reduces HIF-1α activation in the brain, indicating some level of organ specificity of HIF-1α stabilization. The mechanisms underlying this phenomenon remain to be elucidated. One possibility is that tissue PO2 is better maintained in the brain than the kidney during mild acute anemia due to the greater capacity of the resistance vasculature of the brain to vasodilate in response to tissue hypoxia. This hypothesis merits testing.

Expression of a number of hypoxia-sensitive genes, including erythropoietin, was observed in both the brain and the kidney, even during mild anemia (9). Levels of erythropoietin in the plasma were also increased by mild anemia, consistent with their ability to detect increased renal expression of HIF-1α and HIF-2α protein by Western blot. HIF-2α is the predominant regulator of erythropoietin production (4). Nevertheless, HIF-1α likely contributes to the renal response to hypoxia, but in a complex manner that is far from fully elucidated. For example, HIF-1α appears to mediate many of the deleterious effects of hypoxia in the setting of acute kidney injury and chronic kidney disease, as well as some of the mechanisms underlying adaption to hypoxia and the protective effects of hypoxic preconditioning (3). The findings of Tsui and colleagues, presented in the current issue, indicate that these responses are likely mediated independently of nNOS.

The findings of Tsui and colleagues are important because they uncover an additional level of complexity in the already bewilderingly complex field of hypoxic signalling. Considered from a teleological perspective, it would seem important for...
the factors regulating hypoxic signalling to be “tailored” by evolution to the functions of individual organs and tissues. Teasing out how this concept works in practice will provide a rich area for further study.

GRANTS

The author’s work is funded by grants from the National Health and Medical Research Council of Australia (606601 and 1024575) and the Australian Research Council (DP140103045).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

Author contributions: R.G.E. drafted manuscript; R.G.E. edited and revised manuscript; R.G.E. approved final version of manuscript.

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