Structural antioxidant defense mechanisms in the mammalian and nonmammalian kidney: different solutions to the same problem?

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O’Connor PM, Evans RG. Structural antioxidant defense mechanisms in the mammalian and nonmammalian kidney: different solutions to the same problem? Am J Physiol Regul Integr Comp Physiol 299: R723–R727, 2010. First published July 21, 2010; doi:10.1152/ajpregu.00364.2010.—Tissue oxygen levels are tightly regulated in all organs. This poses a challenge for the kidney, as its function requires blood flow, and thus, oxygen delivery to greatly exceed its metabolic requirements. Because superoxide production in the kidney is dependent on oxygen availability, tissue hyperoxia could drive oxidative stress. In the mammalian renal cortex, this problem may have been solved, in part, through a structural antioxidant defense mechanism. That is, arteries and veins are closely associated in a countercurrent arrangement, facilitating diffusional arterial-to-venous (AV) oxygen shunting. Because of this mechanism, a proportion of the oxygen delivered in the renal artery never reaches kidney tissue but instead diffuses to the closely associated renal veins, thus limiting oxygen transport to tissue. In the nonmammalian kidney, arteries and veins are not arranged in an intimate countercurrent fashion as in mammals; thus AV oxygen shunting is likely less important in regulation of kidney oxygenation in these species. Instead, the kidney’s blood supply is predominately of venous origin. This likely has a similar impact on tissue oxygenation as AV oxygen shunting, of limiting delivery of oxygen to renal tissue. Thus, we hypothesize the evolution of structural antioxidant mechanisms that are anatomically divergent but functionally homologous in the mammalian and nonmammalian kidney.

OXYGEN IS THE STAFF OF LIFE. Too little oxygen (hypoxia) reduces the ability of tissues to function and initiates a cascade of events loosely called hypoxic injury. In clinical medicine, we are familiar with the contributions of acute and/or chronic tissue hypoxia in the pathogenesis of myocardial infarction (4), chronic heart failure (12), stroke (38), and peripheral vascular disease (21). There is also now very strong evidence that kidney tissue hypoxia is a major player in the pathogenesis of acute kidney injury (37) and chronic renal disease (29) and likely also contributes to development of kidney damage in hypertension (44) and diabetes (35). But oxygen is the source of reactive oxygen species (ROS), which are highly toxic to living tissue (18). Thus, the level of oxygen in living tissues must be tightly regulated.

It is a functional requirement for the lungs of air-breathing animals to be exposed to a relatively high partial pressure of oxygen (~110 mmHg) (11) to allow uptake of oxygen into the circulation. This results in the production of ROS, but the lungs have a range of highly developed chemical antioxidant defense mechanisms that act to prevent oxidative stress. Thus, inhibition of antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase exacerbates oxygen toxicity in the lungs (23). Nevertheless, the toxicity of oxygen is graphically demonstrated by the consequences of placing experimental animals in an environment of 100% oxygen. These animals rapidly perish as a consequence of ROS-induced lung damage. Ironically, they die of hypoxia (6).

Most other tissues in the body are exposed to oxygen levels considerably lower than those in the lungs (~30 mmHg). But the function of the kidney poses a series of challenges for maintenance of homeostasis of intrarenal oxygenation (16, 30). In particular, a high level of blood flow, well in excess of metabolic demand, is required to facilitate a high glomerular filtration rate (16, 30). Superoxide production in renal tissue is exquisitely sensitive to oxygen availability (5), thus renal tissue hyperoxia would be expected to result in oxidative stress. Indeed, NADPH-dependent superoxide production appears to be, if anything, greater in kidney tissue than in vascular smooth muscle and cardiac tissue, at equivalent levels of oxygen availability (5). As is the case in the lungs, enzymatic antioxidant defense mechanisms, such as superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase are well developed in the kidney (19, 27, 34, 41). We have previously argued that an additional solution to the problem of oxygen-driven oxidative stress in the mammalian kidney has been the evolution of a structural antioxidant defense mechanism: AV oxygen shunting (31). Here, we mount an argument that a very different solution has evolved in the nonmammalian kidney.

The Mammalian Solution: Arterial-to-Venous Oxygen Shunting?

The kidney of humans and other mammalian species filters the entire plasma volume ~60 times each day (30). This is achieved through a unique aspect of the glomerular capillary bed: its high intracapillary hydrostatic pressure (30–70 mmHg) (13). Furthermore, to achieve a high glomerular filtration rate, renal blood flow must greatly exceed that required for the metabolic requirements of the kidney. Indeed, together the kidneys receive ~25% of the cardiac output, yet weigh < 1% of body weight. Consequently, the kidney extracts only ~10% of the oxygen delivered to it via the renal artery (30). One might expect this to result in a relatively high oxygen tension in kidney tissue, particularly in the renal cortex. There is considerable spatial heterogeneity in renal tissue PO₂. PO₂ in microdomains within the renal cortex varies from ~85 mmHg to < 10 mmHg, while medullary tissue PO₂ can be as low as 5 mmHg (2, 24). Nevertheless, spatially averaged tissue PO₂ in

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the kidney is comparable to that in other tissues, such as resting skeletal muscle, ranging from ~20 to 50 mmHg in the cortex and 10–30 mmHg in the medulla (30). The normalization of tissue PO2 in the kidney is achieved largely through the diffusional shunting of oxygen from arteries to veins (31). This mechanism is facilitated by the intimate relationship between arteries and veins in the mammalian kidney (17, 28, 31). Not only are these vessels arranged in a countercurrent fashion, but the veins appear to wrap around much of the axial profile of the arteries, thus providing a direct pathway for oxygen diffusion (Fig. 1). The marsupial kidney appears to have a vascular structure similar to that of the eutherian kidney (36). The critical evidence for the existence of arterial-to-venous (AV) oxygen shunting in the kidney was the finding in rats that the PO2 of renal venous blood is greater than that of blood in the efferent arterioles of the outer cortex, the most well-oxygenated part of the kidney (45). Thus, because of diffusional oxygen shunting, a proportion of the oxygen delivered to the kidney in the renal artery never reaches the renal parenchyma.

We have argued that the adaptive advantage of AV oxygen shunting in the mammalian kidney is that it prevents excess oxygenation of kidney tissue, which would otherwise lead to excessive production of ROS and kidney damage (31). The corollary of this argument, of course, is that the price paid for this structural antioxidant defense mechanism is that the kidney is rendered susceptible to damage from hypoxia when oxygen delivery is limited (e.g., anemia and ischemia) (15, 25, 43).

As we will see below, renal vascular architecture in many nonmammalian species is strikingly different from that in mammals. In particular, the intimate countercurrent arrangement of arteries and veins, which facilitates AV oxygen shunting in the mammalian kidney, is not present in the kidneys of birds, amphibians, reptiles, and fishes. How, then, are they protected from renal tissue hyperoxia and oxidative stress? Before considering this question, we will first remind readers

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**Fig. 1. Arrangement of arteries and veins in the mammalian kidney.** A: artist’s impression of the parallel arrangement of arteries (red) and veins (blue) in the renal cortex, based on the structural analysis of the renal circulation performed by Nordsletten et al. (28). B: diagrammatic representation of the pathways for oxygen diffusion from arteries and veins in the renal cortex relative to skeletal muscle. In the kidney, arteries and veins are intimately associated, allowing a direct pathway for arterial-to-venous (AV) oxygen shunting. The left side of the diagram depicts the typical arrangement of arcuate and interlobular vessels and is based on a photomicrograph of arcuate vessels from O’Connor et al. (31). Arteries (A) and veins (V) in skeletal muscle are also arranged in a countercurrent fashion but are usually separated by tissue, which would be expected to retard AV oxygen shunting, as demonstrated by Honig et al. (22). The right side of the diagram depicts the typical arrangement of arteries and veins within canine and rat gracilis muscle reported by Honig et al. (22). Note differences in scale.
of some critical issues in the developmental biology of the kidney.

**Ontogeny and Phylogeny of the Vertebrate Kidney**

All vertebrates have distinct embryonic and adult kidneys. When the adult kidney develops, the embryonic kidney either degenerates, becomes part of the male reproductive system, or switches to a new role as a lymphoid organ (42). Three different pairs of renal organs develop progressively during the embryological and fetal phases of development in mammals: the pronephros, the mesonephros, and the metanephros (26). The pronephros is essentially a single large nephron. It is nonfunctional in developing mammals, but does act as the embryonic kidney in amphibians and fish. It plays a particularly important role in organisms with aquatic larvae, allowing them to excrete dilute urine to maintain water balance (42). The mesonephros is more complex than the pronephros and is the permanent kidney in fish and amphibians (8). It regresses during development in animals that develop a metanephric kidney, which includes reptiles, birds, and mammals. Yet, despite the similar embryonic origin of the kidney in mammals and many other vertebrates, they are structurally and functionally very different (8).

**The Nonmammalian Solution: Perfusion of the Kidney with Venous Blood?**

There are considerable morphological and functional differences between the kidneys of mammals compared with those of birds, reptiles, and amphibians (10). Nevertheless, the requirement for perfusion, well in excess of metabolic demand, to facilitate a high glomerular filtration rate, appears to be conserved, at least across homeothermic vertebrate species (10). For example, basal renal blood flow in the domestic chicken [~ 6 ml·min⁻¹·g wet kidney weight⁻¹ (20)] is not less than that in the rat or rabbit (32). In contradistinction to mammals, the kidneys of amphibians, reptiles, birds, and some seawater fishes have a portal vascular system (7) (Fig. 2). That is, while the blood supply to glomeruli is chiefly arterial, the blood supply to most peritubular capillaries is venous. For example, in the domestic chicken the renal portal vein arises from the external iliac vein and supplies one-half to two-thirds of total renal blood flow (20, 39). Blood flow in this portal...
system can be regulated by the portal valve, which controls the balance of blood flow to the kidney and common iliac vein. Vascular tone in other segments of the portal system, such as the hepatic portal circulation, likely also contribute to regulation of renal perfusion (33). This arrangement has been considered to be adaptive for water conservation by allowing maintenance of relatively stable renal blood flow but allowing glomerular filtration to be labile (47). There are also a few examples of nonmammalian kidneys that do not have a portal circulation, such as the lamprey kidney, which has a system of venous sinuses intimately associated with tubular elements but not intrarenal arteries (47). Thus, arteries and veins are not arranged in a countercurrent fashion in the nonmammalian kidney (20) and there is little opportunity for AV oxygen shunting (31). Instead, the kidney is perfused with blood predominantly of venous origin. Potentially, renal portal systems could also facilitate physiological regulation of kidney oxygenation by adjusting the proportions of oxygenated and deoxygenated blood delivered to the kidney through fine control of portal blood flow. Importantly, regulation of blood flow in this system can be achieved not just through control of the renal portal valve, but also through adjustments to vascular tone in other parts of the venous network, including the associated hepatic portal system (33). There is evidence that the renal portal system operates as a partial shunt rather than in an all-or-none fashion and that the blood supply to the two kidneys is under independent control (1, 33). The portal system also seems to allow independent control of blood flow to the different lobes of the avian kidney (1), contributes to autoregulation of total renal blood flow (20, 46), and is known to be under autonomic control (3).

Conclusions

Many of the seminal studies in renal physiology were carried out in nonmammalian species. For example, the studies of William Bowman (9, 14), which formed the initial basis of our understanding of glomerular filtration, relied heavily on a comparative approach through the study of both mammalian and nonmammalian species. A large proportion of Homer Smith’s work focused on the function of the fish kidney (40). Furthermore, the art of renal micro puncture arose out of studies of the kidneys of amphibians (14). The study of comparative renal physiology can shed light on the evolution of physiological processes and also allows investigation of specific mechanisms that might be exaggerated or diminished or absent in specific species.

The central message of this article is the hypothesis that structural antioxidant defense mechanisms have evolved to partially deoxygenate blood delivered to the renal microcirculation, and thus reduce the potential for tissue hyperoxia to drive oxidative stress. We propose that these structural antioxidant defense mechanisms are very different in the mammalian and avian kidney. The mammalian solution may be AV oxygen shunting, while the avian solution may be perfusion of the kidney with a mixture of venous and arterial blood. This structural antioxidant defense mechanism could potentially also operate within the kidneys of poikilotherm vertebrates such as reptiles, amphibians, and fish whose kidneys are also perfused with a mixture of venous and arterial blood. However, glomerular filtration rate (and thus presumably renal blood flow) tends to be lower in these species than in mammals and birds (9, 10). Thus, a structural antioxidant defense mechanism may not be an adaptive imperative for these species. Unfortunately, we are aware of no experimental studies of intrarenal oxygenation in nonmammals. Such studies may provide new insights into the physiological and pathophysiological significance of kidney oxygen regulation.

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DISCLOSURES

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Comparative Physiology of Kidney Oxygenation


