Angiotensin II type 1A receptor deficiency and longevity*

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Benigni et al. [1] showed that mice lacking the Agtr1a gene encoding AT1A, the major mouse AT1 isoform and the closest murine homologue to the single human AT1, exhibit marked prolongation of their lifespan. The longevity in AT1A receptor-deficient mice was not related to caloric intake, but was associated with decreased cardiac, vascular, renal and pancreatic injury, reduced oxidative stress in many organs and increased proximal tubular mitochondrial volume or upregulation of the prosurvival genes nicotinamide phosphoribosyltransferase (Nampt) and sirtuin 3 (Sirt3) in the kidney. In vitro experiments showed that angiotensin II (AngII) decreased the mRNA levels of Nampt and Sirt3 in mouse proximal tubular epithelial cells, and these effects were prevented by pretreatment with the AT1 receptor blocker (ARB) candesartan. Based on these data, the authors conclude that the AT1 receptor deficiency-dependent longevity observed in mice is a consequence of reduced mitochondrial damage owing to attenuation of oxidative stress and up-regulation of the Nampt and Sirt3 survival genes. The authors extrapolate their findings in animal experiments to humans and suggest the potential benefit of ARBs for the prolongation of lifespan in humans.

Recent preclinical and clinical studies have indicated that blockade of the renin–angiotensin system (RAS) with ARBs and angiotensin-converting enzyme (ACE) inhibitors attenuates the progression of organ injury, including injury to the heart, vasculature, kidney, liver, pancreas, brain, etc. [2]. These benefits of RAS inhibitors are likely to contribute to the improvement of morbidity and mortality, and eventually lead to the longevity observed in experimental animals. On the other hand, complete inhibition of AngII may be harmful. Firstly, the RAS plays important roles during fetal and perinatal development and growth of the kidney. Indeed, administration of RAS inhibitors to foetuses or infants causes teratogenicity, including structural abnormalities in the kidney [3]. Consequently, treatment with RAS inhibitors is usually prohibited in pregnant patients. Secondly, the majority of, if not all, angiotensinogen knockout mice, ACE knockout mice, Ren1 and Ren2 dual knockout mice and AT1A and AT1B dual knockout mice do not survive until weaning [4–6]. Thirdly, these mutant mice eventually develop severe renal structural abnormalities, including renal vascular hypertrophy [4–6]. Therefore, the degree and timing of AT1 receptor blockade may need to be taken into consideration.

In the study by Benigni et al. [1], the longevity of AT1A knockout mice on F1 (C57BL/6 × 129/SvEv) background mice was associated with decreased cardiac, vascular and pancreatic injury. Nevertheless, the eventual cause of death in their model mice remains elusive. Of interest is the question of which organ injury has a critical impact on longevity in mice. Mice with tissue-specific AT1A receptor gene disruption would be useful for clarifying this point. Another intriguing question is whether the critical injury to a particular organ in mice can be extrapolated to determining longevity in humans. It should also be pointed out that the F1 (C57BL/6 × 129/SvEv) genetic background used in their study carries modifier genes that attenuate the renal structural abnormalities in AT1A knockout mice. Therefore, the longevity of AT1A knockout mice may be specific to this renoprotective genetic background. The irreproducibility of experimental results in ageing research owing to supplier-dependent differences has also been pointed out [7].

The authors provide evidence that the organ protection observed in their animals is a consequence of reduced mitochondrial damage owing to attenuation of oxidative stress. Many studies have indicated that AngII induces NADPH oxidase-dependent oxidative stress [8], leading to mitochondrial damage. Although the detailed mechanisms by which disruption of the AT1A receptor results in the reduction of oxidative stress remain to be determined, Benigni et al. [1] showed that the longevity in AT1A-deficient mice was associated with upregulation of Sir3 (a factor maintaining mitochondrial vitality) and Nampt (a factor promoting cell survival via activation of mitochondrial Sirt3) in the kidney. These findings are particularly interesting because renal cells are exposed to remarkably higher concentrations of AngII than other cells [9]. Recently, Aragonés et al. [10]...
demonstrated that specific disruption of the oxygen sensor Phd1 induces hypoxia tolerance by reprogramming the basal oxygen metabolism and decreasing mitochondrial oxidative stress. ARBs and ACE inhibitors are highly potent radical scavengers, and inhibitors of both advanced glycation end-products and protein carbonyls [11], which are biomarkers of tissue ageing and senescence. The interplays among the RAS, hypoxia/oxidative stress and renal injury have been discussed by Miyata and van Ypersele de Strihou [12].

In conclusion, although the precise mechanisms of the longevity observed in AT1A receptor-deficient mice have not yet been clarified, the experimental results obtained by Benigni et al. [1] support the concept that partial, but not complete, blockade of AT1 receptors with ARBs or ACE inhibitors will improve the mortality and lifespan of humans.

The longevity observed in AT1A receptor-deficient mice is associated with reduced mitochondrial damage to the kidney owing to attenuation of oxidative stress and overexpression of the Nampt and Sirt3 survival genes. Renal protection by partial RAS inhibition with ARBs and ACE inhibitors consequently leads to a long life expectancy through inhibition of AngII-induced oxidative stress. The question then arises as to how renal protection leads to the promotion of longevity during RAS blockade. Further studies are required to ascertain the precise mechanisms by which RAS blockade promotes longevity. Nevertheless, this paper undoubtedly opens a new avenue for future investigations into the intriguing links among the RAS, organ injury, including injury to the kidney, oxidative stress and longevity.

It is possible that improvement of renal injury by RAS inhibitors promotes longevity.

Conflict of interest statement. None.

References

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