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Live Longer Sans the AT_{1A} Receptor

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Abstract

Excessive activation of the AT_{1A} receptor ($AT_{1A}R$) by angiotensin II is implicated in the age-related development of hypertension, diabetes and kidney disease. $AT_{1A}R$-deficient mice live longer and have lower levels of oxidative stress than wild-type mice (Benigni et al., 2009), suggesting a role for $AT_{1A}R$ signaling in the aging process.

Persistent and poorly regulated hypertension is a major risk factor for many of the most prevalent age-related disorders that limit lifespan including cardiovascular disease, stroke, kidney disease and neurodegenerative diseases. Angiotensin II (Ang II), a peptide produced from renin via the proteolytic activity of angiotensin converting enzyme (ACE), is a key component of an endocrine/paracrine signaling system that increases vasoconstriction and blood pressure. Angiotensin II functionally interacts with two forms of G protein-coupled receptor (GPCR), the AT_1 or AT_2 type receptors. The A subtype of the AT1 receptor ($AT_{1A}R$) is located on the surface of vascular smooth muscle cells and its activation by Ang II results in elevated levels of intracellular calcium, generation of reactive oxygen species (ROS), and contraction of the cells. Ang II therefore acts to increase vascular pressure, and accordingly ACE inhibitors and $AT_{1A}R$ antagonists have proven to be highly effective for the treatment of hypertension (Werner et al., 2008). As maintaining cardiovascular health can have a major impact on longevity in humans, Benigni et al. (2009) recently examined the consequences of disruption of the $AT_{1A}R$ gene on aging of the cardiovascular and renal organ systems in mice. Strikingly, both the average and maximum lifespans of $AT_{1A}R$-deficient mice were increased by approximately 20%.

At a gross level the AT1AR -/- mice demonstrated no significant alteration in body weight, fasting blood glucose, heart weight/body weight ratio or activity levels demonstrating an ability of the animal to partly mitigate the loss of $AT_{1A}R$ with respect to overall energy metabolism However, age-related pathologies in the cardiovascular system, including atherosclerotic lesions and cardiac fibrosis were reduced in $AT_{1A}R$-deficient mice compared to wild type control mice (Benigni et al., 2009). While the cellular structure and function of the kidneys and pancreas were unaffected by $AT_{1A}R$ deficiency, age-related changes in the liver (degeneration of hepatocytes, vesicular steatosis and exudation) were reduced in the $AT_{1A}R$-deficient mice. The aging process involves damage to cells by ROS, probably as the result of both increased free radical production and a reduced ability of cells to protect themselves against the ROS (Bokov et al., 2004). To determine whether the increased longevity of $AT_{1A}R$-deficient mice was associated with reduced levels of oxidative stress, levels of nitrotyrosine, a marker of oxidative attack on cellular proteins, were measured in the heart, artery and kidney tissues from young and old wild-type mice and aged $AT_{1A}R$-deficient mice. In all three tissues, levels of oxidative protein damage were increased by aging in wild-type mice, but not in the $AT_{1A}R$-deficient mice. Benigni et al. used only 20 AT_{1A}-deficient and 10

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wild-type male mice of one mixed genetic background for their lifespan studies, an unusually small number of animals for such a study. It will therefore be important to repeat the experiments with larger numbers of mice of more than one genetic background; females should also be evaluated as there may be sex differences in the effects of $AT_{1A}R$ signaling on aging. In addition a comprehensive assessment of how other blood-borne metabolic factors and hormones also change in response to the loss of Ang II signaling may also provide insights into the longevity mechanism.

The low level oxidative damage in old $AT_{1A}R$-deficient mice may not be due to reduced production of ROS because numbers of mitochondria, a major source of free radicals, were increased in cells from the $AT_{1A}R$-deficient mice. Instead, the authors' data suggest that the lack of $AT_{1A}R$-mediated signaling results in increased production of proteins that protect cells against free radical attack. Indeed, the expression of two cytoprotective mitochondrial proteins, Nampt and sirtuin 3, were increased in kidney cells of old $AT_{1A}R$-deficient mice compared to old wild type mice (Benigni et al., 2009). Nampt is a NAD^+ biosynthetic enzyme that protects cells against genotoxic stress (Yang et al., 2007), while sirtuin 3 is a histone deacetylase that protects cells against oxidative stress-induced apoptosis (Sundaresan et al., 2008). Benigni et al. (2009) did not evaluate levels of Nampt and sirtuin 3 in the heart or blood vessels, so it is unclear whether these stress resistance proteins contribute to the reduced cardiovascular pathology in aged $AT_{1A}R$-deficient mice. Interestingly, the effects of $AT_{1A}R$-deficiency on cellular stress resistance are similar to the effects of dietary energy restriction and exercise, two conditions that can improve health and longevity (Martin et al., 2007). An impaired ability to efficiently adapt to stressors is a common feature of the aging process, and it will be of interest to determine the cellular signaling pathway(s) that mediate the apparent adverse effects of angiotensin II on stress responses.

The $AT_{1A}R$ is a member of the rhodopsin-like GPCRs and is primarily associated with $G_{\alpha}q$ and $G_{\alpha}i$ type G proteins. Like many other receptors in this superfamily its activation can impact a variety of signal transduction pathways (Higuchi et al., 2007) (Figure 1). One pathway involving the protein kinases (Rho kinase) ROCK and (c-jun N-terminal kinase) JNK promotes inflammation and cellular hypertrophy and migration, while another can activate NADPH oxidase, resulting in oxidative damage to DNA, proteins and lipids. The insulin/insulin-like growth factor-1 (IGF-1) signaling pathway is strongly implicated in aging as mutations in the genes that encode components of this pathway extend lifespan in organisms ranging from worms and flies to mice (Tatar et al., 2003). Angiotensin II signaling through an epidermal growth factor receptor-mediated ‘transactivation’ pathway activates components of the insulin signaling pathway including the Shc adaptor protein, phosphatidyl inositol-3 kinase (PI3K) and Akt kinases. Two substrates of Akt implicated in aging are forkhead transcription factors (FHTF) and the mammalian target of rapamycin (mTOR). FHTF are inhibited by Akt resulting in reduced cellular production of antioxidant proteins, whereas mTOR is activated Akt resulting in increased protein synthesis and cell hypertrophy. It will be important to establish which of the $AT_{1A}R$ signaling pathways enhances cardiovascular aging, and whether $AT_{1A}R$ deficiency suppresses age-related changes in other tissues. In particular, the activation status of p66Shc and mTOR should be evaluated in tissues of the $AT_{1A}R$-deficient mice in light of the increased longevity of mice lacking p66Shc (Purdom and Chen, 2003).

Is the increased longevity of $AT_{1A}R$-deficient mice simply the result of reduced cardiovascular pathology as suggested by the authors (Benigni et al., 2009)? Mice rarely die from cardiovascular disease; instead in laboratory settings they typically succumb to cancers, infections or renal disease (Brayton, 2007). The observation that $AT_{1A}R$ deficiency extended both average and maximum lifespan suggests that $AT_{1A}R$ signaling may accelerate the aging process in cells throughout the whole body rather than affecting only age-related cardiovascular disease. Although Ang II is best known for its effects on cardiovascular and renal cells,

$AT_{1A}R$ are widely expressed in cells of the nervous system where they may influence neuroendocrine function, autonomic/stress responses and possibly a range of behaviors, some of which may be preferentially preserved during aging in $AT_{1A}R$-deficient mice. Moreover, $AT_{1A}R$ have been shown to play an important role in tumor angiogenesis and growth (Egami et al., 2003) which could contribute to the extended survival of the $AT_{1A}R$-deficient mice. Finally, the findings of Benigni et al. open the possibility that ACE inhibitors and $AT_{1A}R$ antagonists could increase the longevity of healthy humans who may not present significant hypertensive symptomology.

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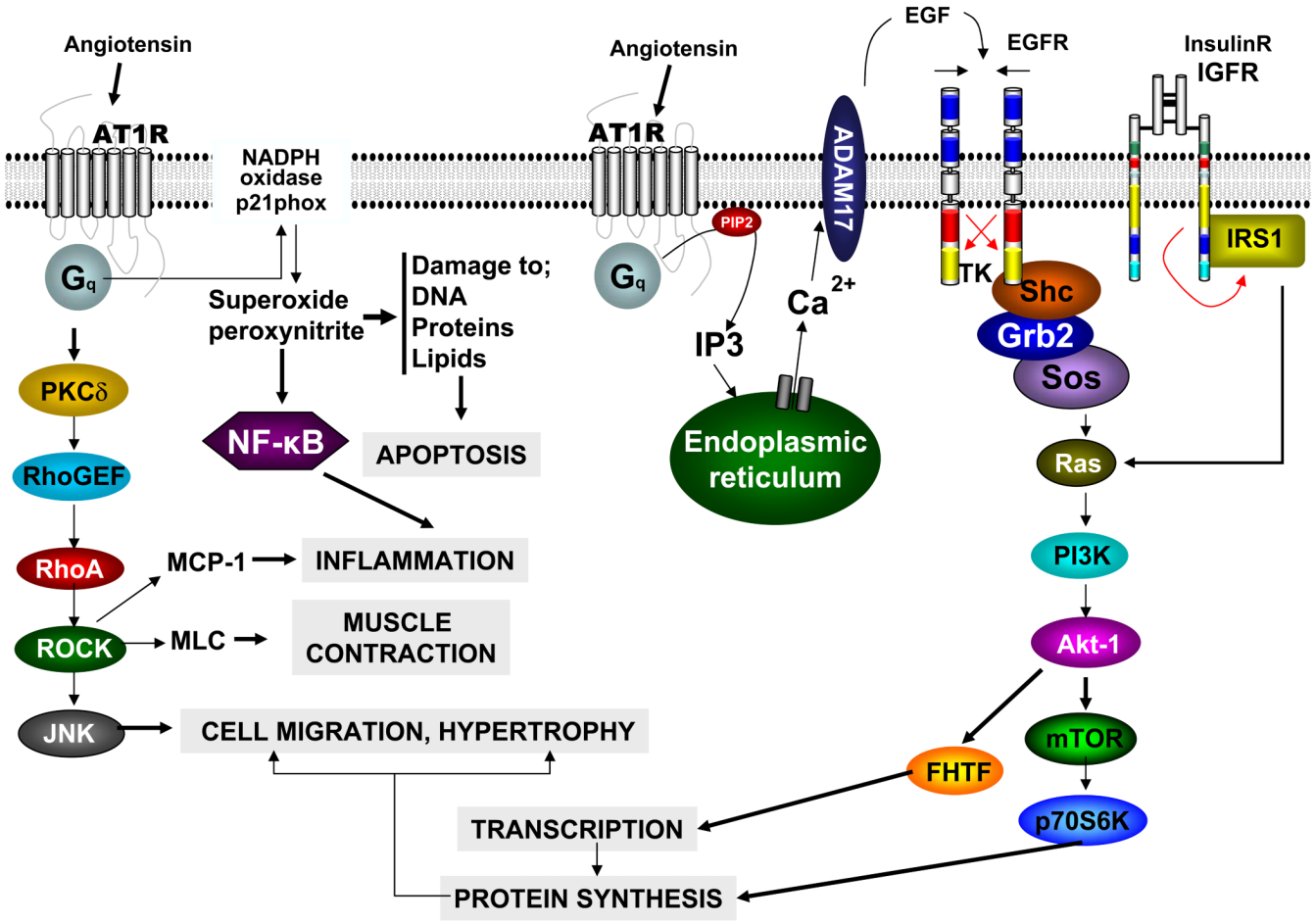

Figure 1. $AT_{1A}R$ signaling pathways that may mediate effects of angiotensin II on age-related disease etiology and eventual longevity

The angiotensin receptor (AT1R) is coupled to the GTP-binding protein G_q. One major downstream pathway involves protein kinase C- δ (PKC δ) Rho-GEF (guanine exchange factor) and RhoA, resulting in the activation of ROCK (Rho-kinase). ROCK can promote inflammation by inducing the expression of the chemokine monocyte chemoattractant protein-1 (MCP-1) and can also stimulate cell hypertrophy and migration by activating JNK (c-jun N-terminal kinase). In addition, ROCK promotes the contraction of vascular smooth muscle cells via a kinase cascade that activates myosin light-chain (MLC) which may contribute to hypertension and vascular pathology. Activation of the $AT_{1A}R$ can also induce free radical (superoxide and peroxynitrite) production by stimulating membrane-associated NADPH oxidase. The resulting ROS can cause oxidative damage to DNA, proteins and lipids and can also activate the transcription factor NF-κB which induces the expression of pro-inflammatory cytokines. Activation of AT1R coupled to $G\alpha_{q11}$ causes membrane inositol phospholipid (PIP2) hydrolysis, generating inositol trisphosphate (IP_3) which triggers Ca^{2+} release from endoplasmic reticulum stores. This Ca^{2+} release then activates matrix metalloproteases such as ADAM17 that cleaves heparin-binding epidermal growth factor (EGF) on the cell surface releasing EGF which binds and then activates EGF receptor tyrosine kinase activity (TK). Receptors for the EGF receptor, and the insulin and insulin-like growth factor (IGF) receptors, are coupled to intracellular adaptor proteins (Shc, Grb2 and Sos in the case of the EGF receptor, and IRS1 in the case of the insulin/IGF receptor) that activate the monomeric G protein Ras. Activation of these growth factor receptors can also lead to

activation of phosphatidylinositol-3 kinase (PI3K) which in turn can activate Akt kinase. Downstream targets of Akt that may mediate effects of $AT_{1A}R$ on cellular aging include forkhead transcription factors (FHTF) and the mammalian target of rapamycin (mTOR). Figure prepared by KC Alexander.