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Review

Angiotensin type 1 and type 2 receptors during ontogeny: cardiovascular and renal effects

Angela Elena Vinturache [a,b,c,*], Francine Gabriel Smith [a,c]

[a] Alberta Children's Hospital Research Institute for Child and Maternal Health Calgary, Alberta,Canada
[b] Department of Paediatrics, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada
[c] Department of Physiology & Pharmacology, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada

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ABSTRACT

The renin–angiotensin system (RAS) is a major component of cardiovascular and renal homeostasis, maintaining blood pressure and water and electrolyte balance in health and disease. Whilst knowledge regarding the RAS in adult organisms has substantially increased over the last three decades, physiological effects and levels of functioning of the system during the perinatal period are poorly understood. It has been shown, however, that the RAS is subject to remarkable developmental changes that involve all system components, including the main active biologic peptide, angiotensin II (Ang II) and the receptors through which these effects are mediated, type 1 receptors (AT1Rs) and type 2 receptors (AT2Rs). The pattern of developmental changes suggests a relevant physiological role for the RAS in the critical cardio-renal adaptations to life after birth. In adulthood, the majority of the physiological functions of Ang II are mediated by activation of AT1Rs, whilst the roles for AT2Rs are less clear. Although the integrity of the AT1R signalling pathway is a pre-requisite for normal renal development, the physiological effects mediated by A1TRs during ontogeny are not well characterized. Much less is known regarding the roles that AT2Rs may play in regulating cardio-renal homeostasis in the newborn, despite the fact that the RAS appears to be a major player in fetal programming of disease. This article reviews current knowledge regarding the temporal and spatial expression pattern of ATRs during ontogeny, the cardiovascular and renal effects mediated by the ATRs early in life, as well as the clinical relevance for ATRs in the newborn period.

Contents

Abbreviations: RAS, renin–angiotensin system; Ang II, angiotensin II; AT1R, angiotensin receptor type 1; AT2R, angiotensin receptor type 2; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; Ang-(1–7), angiotensin-(1–7); ARB, angiotensin receptor blockers; ACEI, angiotensin converting enzyme inhibitors; NO, nitric oxide.

* Corresponding author at: Department of Paediatrics, Cummings School of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada. Tel.: +1 403 955 5975.
E-mail address: aevintur@ucalgary.ca (A.E. Vinturache).

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1. Introduction

The renin–angiotensin system (RAS) is an integral component of cardiovascular, adrenal and renal regulation of blood pressure, endocrine function and water and electrolyte homeostasis in health and disease in adulthood. The importance of the RAS in cardiovascular and renal regulation is illustrated by a multitude of antagonist and agonist drugs that target this system largely used in both clinical and research settings. There have been tremendous advances in our understanding of the complexity of the RAS as a result of discovery of new components as well as descriptions of multiple independent functional levels of RAS in the systemic circulation, as well as tissues and cells. The primary active peptide of the system, angiotensin II (Ang II) activates at least two pharmacologically distinct receptors, type 1 (AT1R) and type 2 (AT2R). Considered to mediate the majority of the biological functions of Ang II, AT1R activation is associated with the regulation of blood pressure, renal function, thirst and drinking behaviour, hormone secretion and sympathetic activity. AT1Rs are also considered to be involved in a variety of pathological conditions in which the RAS activity is altered, such as hypertension, heart failure and diabetic nephropathy [26]. Thus, pharmacotherapy for the cardiovascular and renal systems primarily targets this receptor. On the other hand, the roles for AT2Rs are less well characterized and generally viewed as mediating vasodilation, to counterbalance the vasoconstrictor effects mediated by activation of AT1Rs [15,58]. Nonetheless, these vasodilator and hypotensive actions of AT2Rs are revealed only against a background of RAS up-regulation, such as in conditions of RAS-dependent increase in blood pressure, and pharmacological inhibition of AT1Rs [27,101].

Despite this accumulating evidence for the roles of the RAS in adulthood, the physiological roles for the RAS in the perinatal period – a time when all components of the system are upregulated – have not been thoroughly investigated [81]. Emerging evidence demonstrates an important role for the ATRs in the development of both cardiovascular and renal systems, yet the physiological functions of the RAS components during postnatal development are not well understood. In addition to mediating organogenesis and growth, the RAS may contribute to the adaptation of the newborn kidney and the systemic circulation to extrauterine life. There are temporal and spatial age- and species-dependent differences in the expression and distribution patterns of the ATRs during perinatal development that have so far provided a challenge to the interpretation of varied results. Furthermore, in the immature kidney and vasculature, ATR expression is developmentally regulated, but specific roles for ATRs and their regulation are still unknown. The purpose of this review is to integrate some aspects regarding expression and localization of ATRs during function. To this end, the following paragraphs will focus on the roles for ATRs in regulating the cardiovascular and renal adaptations of the newborn to life after birth.

2. Structure and pathways of activation for ATRs

An impressive number of studies and extensive review articles address the biochemistry, molecular biology, physiological functions and potential pathophysiological implications of ATRs [11,27,113]. Both AT1R and AT2R subtypes are seven transmembrane G protein-coupled receptors that share 32–34% sequence homology [69,72,79] and differ by their pharmacological and biochemical properties as well as signalling pathways utilised. A great deal is known about the signalling events triggered after the stimulation of AT1Rs and AT2Rs, that is reviewed elsewhere [26,56,65] (summarized in Fig. 1).

2.1. AT1Rs

In all mammalian species examined including rabbit, dog, pig, sheep, cow and human only one AT1R type has been observed [26] with the exception occurring in rodents in which two AT1R subtypes exist, AT_{1a} and AT_{1b}. After Ang II binds to the extracellular domain, complex, receptor-specific intracellular signalling pathways are activated [90]. Briefly, AT1Rs mediate the vasoconstrictor effects of Ang II via activation of five classical signal transduction pathways, activation of phospholipase A_2 (PLA_2), phospholipase C (PLC), phospholipase D (PLD), and L-type Ca^{2+} channels and inhibition of adenylate cyclase (AC) (reviewed by [26,29]). See also Fig. 1. Activation of AT1Rs also stimulates cellular growth and proliferation through activation of tyrosine phosphorylation and phospholipase C-γ and downstream proteins, mitogen activated protein kinases (MAPK) [39,40], janus kinases (JAK), and the signal transducers and activators of transcription (STAT) proteins [63,90].

2.2. AT2Rs

Various intracellular signalling pathways, G-protein dependent and independent, have been assigned to AT2Rs [10,49]. Binding of Ang II leads to downstream activation of various phosphatases, such as protein tyrosine phosphatase, SH2-domain-containing phosphatase 1 and serine/threonine phosphatase 2A resulting in opening of delayed rectifier K^+ channels and inhibition of T-type Ca^{2+} channels [72], which may mediate vasodilation [76] (Fig. 1).

Inhibition of MAP kinase enzymes and inactivation of extracellular signal-regulated kinase mediate the pro-apoptotic effects of AT2Rs, signalling activity that opposes AT1R activation [10,29,125]. Furthermore, stimulation of AT2Rs enhances the bradykinin (BK) – nitric oxide (NO) – cGMP vasodilatory cascade [102].

Different levels of molecular and functional interactions between AT1Rs and AT2Rs have also been revealed which may contribute to the regulation of the net physiologic responses to Ang II [115]. For example, in adult mammals, activation of AT2Rs mediates the vasodilatory effects of AT1R inhibition through the aforementioned BK-NO-cGMP autacoids cascade [105], whereas an AT2R-induced natriuresis counteracts the anti-natriuresis initiated by AT1R activation [75]. Other experimental evidence does not support the "*ying-yang*" principle for ATR roles, suggesting instead that AT2Rs may potentiate AT1R-induced physiological effects (for review see Paul et al., 2006 [77]).

3. Distribution and localization of ATRs during ontogeny

An important body of research provides evidence for a developmentally regulated distribution and expression of ATRs within the kidney and other organs and tissues, which support differential functional roles for the ATRs during the transition to life after birth and further during postnatal maturation. As ATR antagonists are used clinically to control blood pressure, it is crucial to identify the tissues that express the ATR genes, determine the level of expression and whether they are involved in cardiovascular homoeostasis. The distribution of AT1Rs and AT2Rs in the human kidney has been mapped and provides the anatomical basis for inferences regarding the physiological role for Ang II in the human renal and cardiovascular systems during postnatal development as described below.

3.1. ATR expression is developmentally regulated

The expression of AT1Rs and AT2Rs in the cardiovascular and renal systems is developmentally regulated in most species: AT2Rs are the dominating subtype in embryonic, fetal and newborn tissues of many species including mouse, rat, pig, sheep and humans [6,7,12,83,96,99,128,129]. AT2R expression gradually declines after birth in these species, thus suggesting that they may play a role in morphogenesis. The observation that AT2R expression is up-regulated later in life in cardiovascular pathologies associated with tissue remodelling and inflammation such as hypertension, atherosclerosis, heart failure, myocardial infarction, and *diabetes mellitus* supports this assumption. See also reviews by Qi et al. [81] and Porrello et al. [79]. Conversely,