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Development of fetal brain renin–angiotensin system and hypertension programmed in fetal origins

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ABSTRACT

Since the concept of fetal origins of adult diseases was introduced in 1980s, the development of the renin–angiotensin system (RAS) in normal and abnormal patterns has attracted attention. Recent studies have shown the importance of the fetal RAS in both prenatal and postnatal development. This review focuses on the functional development of the fetal brain RAS, and ontogeny of local brain RAS components *in utero*. The central RAS plays an important role in the control of fetal cardiovascular responses, body fluid balance, and neuroendocrine regulation. Recent progress has been made in demonstrating that altered fetal RAS development as a consequence of environmental insults may impact on "programming" of hypertension later in life. Given that the central RAS is of equal importance to the peripheral RAS in cardiovascular regulation, studies on the fetal brain RAS development in normal and abnormal patterns could shed light on "programming" mechanisms of adult cardiovascular diseases in fetal origins.

Contents

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Abbreviations: ACE, angiotensin converting enzyme; ACTH, adrenocorticotropic hormone; Ang, angiotensin; AP, area postrema; AT1R, angiotensin II receptor subtype 1; AT2R, angiotensin II receptor subtype 2; ATIP, AT2R-interacting protein; AVP, arginine vasopressin; BBB, blood–brain-barrier; CNS, central nervous system; CRF, corticotropin-releasing factor; CRF-R1, corticotropin releasing factor receptor; CVOs, circumventricular organs; DEX, dexamethasone; ECoG, electrocorticogram; GD, gestation day; GH, growth hormone; GTPγS, GTP gamma S; HAGT, human angiotensinogen; HPA, hypothalamic-pituitary-adrenal axis; HPD, hypothalamic-pituitary disconnection; Icv, intracerebroventricular; IGF-I, insulin-like growth factor 1; LPBN, lateral parabrachial nucleus; MABP, mean arterial blood pressure; MnPO, median preoptic nucleus; NGF, nerve growth factor; NTS, tractus solitarius nuclei; OT, oxytocin; OVLT, organum vasculosum of the lamina terminals; PRL, prolactin; PVN, paraventricular nuclei; RAS, renin–angiotensin system; REN-eGFP, renin-enhanced green fluorescent protein; SFO, subfornical organ; SHP-1, Src homology 2 domain-containing protein-tyrosine phosphatase 1; SON, supraoptic nuclei; TSH, thyroid-stimulating hormone.

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1. Introduction

Since the concept of fetal origins of adult health and disease was first introduced in the late 1980s (Barker and Osmond, 1986), the development of the renin–angiotensin system (RAS) in normal and abnormal patterns before birth has attracted significant attention. The RAS has been studied extensively in adults (Fitzsimons, 1998; Paul et al., 2006), but to a much less degree in fetuses. Recent progress in perinatal studies has been made in demonstration of the importance of fetal RAS in both prenatal and postnatal development.

In the classic definition, the substrate of RAS, angiotensinogen, a glycoprotein, is synthesized and released from the liver, and is cleaved in the circulation by renin secreted from the juxtaglomerular apparatus to generate decapeptide angiotensin (Ang) I. Angiotensin converting enzyme (ACE), a membrane-bound metalloprotease, which is in high density on the surface of pulmonary vascular endothelium, converts Ang I to the octapeptide Ang II. Ang II, the most active peptide of the RAS, binds to Ang II type 1 (AT1R) and type 2 (AT2R) receptors for its physiological or pathophysiological functions (Fitzsimons, 1998; Paul et al., 2006).

Several decades ago, the first evidence of central effects of Ang II was shown with the demonstration that circulating Ang II increased blood pressure *via* a central nervous system (CNS) (Bickerton and Buckley, 1961). The existence of an isolated brain RAS was proposed by the discovery of the renin-like activity in the brain (Fischer-Ferraro et al., 1971; Ganten et al., 1971). Since these initial discoveries, most intrinsic components of the RAS, including angiotensinogen, angiotensins, and converting enzymes, have been well demonstrated in the brain (Saavedra, 1992). More recent developments of molecular biological methods, including transgenic technology and use of infusion gene REN-eGFP (renin-enhanced green fluorescent protein) (Lavoie et al., 2004), have been used to demonstrate the existence of the brain RAS independent of the peripheral RAS.

Studies over the last decades have shown that the central RAS plays an important role in the control of fetal cardiovascular responses, body fluid balance, and neuroendocrine regulation. This review aims at the development of the central RAS during fetal period and examines the ontogeny of the local RAS components in the developing brain *in utero* as well as their functional development before birth. This review also pays attention to alterations of the development of the fetal brain RAS by environmental factors, and its impact on *in utero* "programming" of hypertension in later life. Given that the central RAS and its receptors in the brain are of equal importance to the peripheral RAS in the control of blood pressure, we presumed that studies on the development of the fetal brain RAS in normal and abnormal patterns should shed light on "programming" mechanisms for adult cardiovascular diseases in fetal origins.

2. Components of the fetal brain RAS during development

2.1. Angiotensinogen

Angiotensinogen has been widely studied in both adult and fetus. In adult brain, the angiotensinogen sequence is identical to that in the liver (Campbell et al., 1984) and both angiotensinogen mRNA and protein have been detected (Campbell et al., 1984; Deschepper et al., 1986; Ohkubo et al., 1986; Imboden et al., 1987; Lynch et al., 1987; Thomas and Sernia, 1988). In the fetal brain, angiotensinogen immunoreactivity has been found to be present on day 19 of gestation in rats (Sood et al., 1987a,b). Further studies showed the existence of angiotensinogen in choroid plexus and ependymal cells lining the 3rd ventricle on 18th day of gestation in the rat fetus (Mungall et al., 1995).

Transgenic mice containing the human angiotensinogen (HAGT) gene were utilized to determine the developmental regulation of HAGT expression (Yang and Sigmund, 1998). HAGT expression in rodents was first detected at embryonic day 8.5 and was abundant after day 9.5. Northern blot analysis showed moderate levels of HAGT mRNA in the fetal brain from gestation day (GD) 16.5 onward. In situ hybridization performed on tissue sections revealed that HAGT mRNA became widely distributed in the fetal brain at GD 13.5 (Yang and Sigmund, 1998). Moreover, rat brain angiotensinogen mRNA was shown on day 15 of gestation, and its levels were about 10-fold less than those of days 17–19 of gestation (Lee et al., 1987; Kalinyak et al., 1991; Yang and Sigmund, 1998). From GD 15 to GD 20, angiotensinogen mRNA was more abundant in the brain than in the liver in rat fetuses. Soon after birth, the level in the brain increased to a concentration of 3-fold above fetal levels whereas that in the liver increased 30-fold within 12 h after birth (Kalinyak et al., 1991). Thus, the temporal difference of brain angiotensinogen mRNA and protein, and the ontogenetic and transitional difference between central and peripheral angiotensinogen mRNA levels suggest intrinsic functions of the brain angiotensinogen during fetal life, which is likely to contribute to the differentiation and/or proliferation in the CNS.

Immunocytochemical localization of brain angiotensinogen in the choroid plexus and ependymal cells lining the third ventricle has been observed on GD 18 in rats. This initial angiotensinogen expression was followed by a rapid progression of staining appearing in astrocytes in the paraventricular nucleus, medial preoptic area, ventromedial and arcuate hypothalamic nuclei (Sernia et al., 1997). In general, neuroglial staining was higher in regions proximal to the cerebral ventricles and cerebral aqueduct.