Hypertension Research (2009) 32, 1051–1052

www.nature.com/hr

COMMENTARY

# Epigenetics, essential hypertension and renin–angiotensin system upregulation in the offspring of water-deprived pregnant rats

Richard M Millis

*Hypertension Research* (2009) **32,** 1051–1052; doi:10.1038/hr.2009.168; published online 9 October 2009

Interest in the renin–angiotensin system as a model for studying essential hypertension began in the 1930s with experiments based on the Goldblatt dog model in which renal artery constriction was shown to produce a sustained increase in arterial blood pressure.[1] Since then, numerous studies have confirmed multifarious roles for the renin–angiotensin system in producing adaptations to diverse conditions, such as hyperkalemia,[2] pregnancy,[3] orthostatic hypotension[4] and chronic obstructive pulmonary disease[5] among others. The fact that the renin–angiotensin system is one of the main regulators of blood pressure is now a tenet of medical theory and practice. However, one of the challenges of 21st century medicine is to apply the extensive renin–angiotensin database developed since the 1930s to foresee and prevent the development of the many chronic diseases that are characterized by dysregulation of the renin–angiotensin system, such as essential hypertension.

The article by Guan *et al.*[6] makes an important contribution to this effort. Water deprivation is a stimulus to the renin–angiotensin system, and renin–angiotensin system activators administered to rodent mothers during pregnancy have been shown to affect the development of thirst threshold in their offspring.[7] However, there have been no previous studies questioning whether water deprivation during pregnancy may stimulate the renin–angiotensin system and produce a persistent dysregulation of blood pressure in the offspring.

Dr RM Millis is at the Department of Physiology & Biophysics, Howard University College of Medicine, Washington, DC, USA.
E-mail: rickmillis@aol.com

The study by Guan *et al.*[6] has demonstrated the potential for such a persistent defect in renin–angiotensin regulation of blood pressure resulting from prenatal exposure to maternal water deprivation for 3 days during late gestation. Guan *et al.*[6] have documented increased hepatic angiotensinogen mRNA, plasma angiotensin I and II levels; expression of angiotenisn-2 receptors and exaggerated responsiveness to administration of angiotensin with decreased baroreceptor reflex sensitivity in the offspring. High plasma renin activity has been reported in 10–20% of individuals diagnosed with essential hypertension in the absence of water deprivation.[8] Renin is an angiotensinogenase and, therefore, required for increasing the plasma level of the angiotensins physiologically. Angiotensin I is inactive but angiotensin II, produced by the activity of angiotensin-converting enzyme in various tissues, especially the pulmonary endothelium, induces exaggerated vasoconstriction, increases in arterial resistance, systolic and diastolic blood pressures and cardiac hypertrophy in humans with established and prehypertension,[9] as well as in experimental models for essential hypertension.[10]

Several epigenetic hypotheses have been proposed to explain the higher prevalence of essential hypertension in African Americans compared with other ethnicities.[11] In the 1990s, a number of researchers embraced the hypothesis that the African-American predilection for hypertension may be partly explained by natural selection of individuals exhibiting renin–angiotensin system upregulation, as the founders of the present African-American population, because of water deprivation and dehydration on the slave ships from West Africa.[12] Presumably, greater fitness and survival would have occurred in individuals with renin–angiotensin system upregulation under conditions in which food-borne gastrointestinal diseases and lack of potable water were thought to exist. This 'slave ship' hypothesis has been discredited because of lack of evidence for the fine-tuning of hypertension candidate genes that would be required within a relatively short period of time, namely, a few hundred years. Moreover, the greater genetic diversity observed in African Americans than in Caucasians and other US sub-populations seems to argue against a purely genetic basis for an African-American predilection for hypertension.[13]

The study by Guan *et al.*[6] suggests an epigenetic mechanism. Certain resurrection plants are known to possess gene products that impart an exquisite resistance to desiccation, exhibited by survival after a 96% water loss. The dehydration resistance of such plants is known to be regulated by genes that can be activated by dehydration, as well as by exogenous abscissic acid.[14] Animal evolution is replete with examples of adaptations imparting resistance to dehydration from the amniote egg to mammalian hair, as well as the vasopressin and renin–angiotensin neuroendocrine systems.[15] During mammalian pregnancies, plasma osmolality decreases, lowers the threshold for thirst and decreases the tolerance of pregnant women for water deprivation.[16] This should ensure greater water intake to support the expansion of plasma volume,[17] increase the sensitivity of the renin–angiotensin system and produce higher angiotensin levels at lower plasma osmolality in pregnant women.

Although there are angiotensin receptors for regulating fetal blood vessel caliber and nutrient delivery,[18] angiotensins do not seem to be transported across the placenta, and an explanation for higher fetal than maternal plasma angiotensin concentrations has been lacking. The study by Guan *et al.*[6] seems to provide a plausible mechanism for the higher fetal angiotensin levels by suggesting that maternal water deprivation, with plasma hypertonicity, increased placental osmotic gradient and fetal plasma osmolality, may be a stimulus for the upregulation of the fetal renin–angiotensin system. The effects of administering hypertonic solutions and ethanol, to mothers during pregnancy, on the fetal renin–angiotensin system have not been systematically studied. However, the study by Guan *et al.*[6] may be a good model for confirming that the higher osmolality of maternal, compared with fetal, blood effectively upregulates the renin–angiotensin system of their offspring to protect against fetal dehydration.

If late gestational maternal water deprivation stimulates the fetal renin–angiotensin system in humans, the article by Guan *et al.*[6] also suggests a role of maternal lifestyle in eliciting a persistent defect in baroreflex sensitivity and susceptibility to the evolution of hypertension in their offspring. Gestational vomiting, hyperhydrosis, heat stress and ethanol consumption are similar to water deprivation because of their effect in increasing plasma osmolality. For water and ethanol consumption, substantial variability exists with respect to diet, culture and lifestyle,[19] which could be reflected in ethnicity-related health and disease disparities. The article by Guan *et al.*[6] is a good indicator of the progress made in elucidating the roles of the renin–angiotensin system, from Goldblatt's landmark studies in the 1930s to establishing points of intersection between the renin–angiotensin system, a mother's diet, culture, lifestyle or ethnicity, and the potential for understanding a predilection for her offspring developing hypertension in the future.

1 Van Epps HL. Harry Goldblatt and the discovery of renin. *J Exp Med* 2005; **201**: 1351.
2 Khanna A, White WB. The management of hyperkalemia in patients with cardiovascular disease. *Am J Med* 2009; **122**: 215–221.
3 Anton L, Brosnihan KB. Systemic and uteroplacental renin–angiotensin system in normal and pre-eclamptic pregnancies. *Ther Adv Cardiovasc Dis* 2008; **2**: 349–362.
4 Jarmuzewska EA, Ghidoni A, Mangoni AA. Relative preservation of the renin–angiotensin–aldosterone system response to active orthostatism in type 2 diabetic patients with autonomic neuropathy and postural hypotension. *Scand J Clin Invest* 2003; **63**: 225–232.
5 Andreas S, Herrmann-Lingen C, Raupach T, Lüthje L, Fabricius JA, Hruska N, Körber W, Büchner B, Criée CP, Hasenfuss G, Calverley P. Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial. *Eur Respir J* 2006; **27**: 972–979.
6 Guan J, Mao C, Xu F, Geng C, Zhu L, Wang A, Xu Z. Prenatal dehydration alters renin–angiotensin system associated with angiotensin-increased blood pressure in young offspring. *Hypertens Res* 2009; **32**: 1104–1111.
7 Perillan C, Costales M, Vijande M, Arguelles J. *In utero* extracellular dehydration modifies thirst in neonatal rats. *Appetite* 2008; **51**: 599–603.
8 Corry DB, Tuck ML. Renin–angiotensin system and aldosterone. In: Becker KL, Bilezikian JP, Bremner WJ, *et al.* (eds). *Principles and Practice of Endocrinology and Metabolism*. Lippincott, Williams & Wilkins: Philadelphia, PA, 2001. p 798.
9 Bianchetti MG, Weidmann P, Beretta-Piccoli C, Ferrier C. Potassium and norepinephrine- or angiotensin-mediated pressor control in pre-hypertension. *Kidney Int* 1987; **31**: 956–963.
10 Liu KL. Regulation of renal medullary circulation by the renin–angiotensin system in genetically hypertensive rats. *Clin Exp Pharmacol Physiol* 2009; **36**: 455–461.
11 Kuzawa CW, Sweet E. Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *Am J Hum Biol* 2009; **21**: 2–15.
12 Curtin PD. The slavery hypothesis for hypertension among African Americans. The historical evidence. *Am J Public Health* 1992; **82**: 1681–1686.
13 Reed FA, Tishkoff SA. African human diversity, origins and migrations. *Curr Opin Genet Dev* 2006; **16**: 597–605.
14 Furini A. The stratagem to survive extreme vegetative dehydration. *Plant Signal Behav* 2008; **3**: 1129–1131.
15 Ho M-W. Evolution. In: Greenberg G, Haraway MM, (eds). *Comparative Psychology, a Handbook*. Garland Publishing: London, 1998. pp 107–119.
16 Hines T, Veeh J, Grimes D. The hypo-osmolality of pregnancy does not alter baroreceptor responses to acute changes in osmolality. *Biol Res Nurs* 2006; **7**: 214–221.
17 Lindheimer MD, Barron WM, Davison JM. Osmoregulation of thirst and vasopressin release in pregnancy. *Am J Physiol Renal Physiol* 1989; **257**: F159–F169.
18 Buttar HS. An overview of the influence of ACE inhibitors on fetal–placental circulation and perinatal development. *Mol Cell Biochem* 1997; **176**: 61–71.
19 Cacioppo JT, Berntson GG, Sheridan JF, McClintock MK. Multilevel integrative analyses of human behavior: social neuroscience and the complementing nature of social and biological approaches. In: Cacioppo JT, Berntson GC, Adolphs R, *et al.* (eds). *Foundations in Social Neuroscience*. MIT Press: Cambridge, MA, 2002. p 25.