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Programmed repression of tubular 11β-HSD2—a novel form of AME?

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Exposure to an adverse intrauterine environment during development predisposes offspring towards the development of hypertension in adult life [1]. We and others previously demonstrated a link between maternal undernutrition, offspring nephron complement [2–4] and blood pressure [5], supporting Brenner’s hypothesis that hypertension may be consequent to a nephron deficit [6]. In this issue of Nephrology Dialysis Transplantation, Osttreicher and colleagues [7] show diminished expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in the distal nephron of rats exposed to a maternal dietary protein restriction during gestation, suggesting that the elevated blood pressure observed in these animals may be the result of insufficient protection of the mineralocorticoid receptor (MR) from inappropriate binding by circulating glucocorticoids. The enzyme 11β-HSD2 oxidizes glucocorticoids, cortisol in human and corticosterone in rodents, to form the inactive 11-ketoglucocorticoids cortisone and 11-dehydrocorticoesterone, respectively. The affinity of the MR for aldosterone and glucocorticoids is similar [8]; however, glucocorticoids circulate at concentrations of up to 1000-fold that of aldosterone. In order for the MR to respond exclusively to aldosterone in specific tissues therefore, it is necessary for 11β-HSD2 to also be expressed [9]. In unstimulated tissue, the MR is localized to the endoplasmic reticulum in a complex with several proteins including heat shock proteins 90 (hsp90) and 70 (hsp70) [10] and 11β-HSD2 [11]. Upon binding of aldosterone, the complex dissociates, and the ligand-bound MR dimerizes and is translocated to the nucleus where it exerts its transcriptional effect.

Under conditions of glucocorticoid excess, such as those found in Cushing’s syndrome [12], the amount of renal 11β-HSD2 is insufficient to prevent cortisol from...
binding the MR, resulting in sodium retention, hypokalaemia and hypertension [13]. Conversely, in conditions where the expression of 11β-HSD2 is severely reduced or absent [14], or if an inactive mutant is expressed [15], the syndrome of apparent mineralocorticoid excess (AME) [16] is exhibited despite a potentially normal glucocorticoid profile. The results of Ostreicher et al. [7] suggest that 11β-HSD2 expression, and presumably therefore activity, is more than halved in the distal nephron of offspring of protein-restricted mothers. From the perspective of the renal distal tubular MR, this would be the equivalent of a doubling of circulating glucocorticoids. It is interesting to note that no change in fractional sodium excretion was observed, which raises the question as to what level of circulating glucocorticoid would be required to exceed the capacity of the 11β-HSD2 in the distal nephron.

Plasma corticosterone measurements in rats appear to vary widely within the literature, ranging from 30 to 1300 nmol/L [7,17,18] (and in some cases even higher) depending upon the time of day, mode of measurement and degree of stress. Glucocorticoids in the circulation are predominantly bound to corticosteroid-binding globulin (or transcortin) and albumin. This comprises ~90% of the circulating glucocorticoids, with the remainder (unbound) representing the biologically active fraction (~8–10%) [19]. Incubation of HEK293 cells expressing both 11β-HSD2 and MR, with corticosterone at 200 nmol/L was shown to induce a small degree of nuclear translocation of the MR [11]. In order to achieve this concentration of free glucocorticoids and generate a physiologically significant activation of the MR, circulating levels would need to approach 1000–2000 nmol/L. These levels of glucocorticoids approximate those seen in patients with Cushing’s syndrome [20].

A 50% reduction in the level of expression of 11β-HSD2 would halve the level of circulating glucocorticoids required to activate inappropriately the MR in the distal nephron. Under such circumstances, it is possible to envisage a situation where symptoms of AME might appear either only at certain times of the day, during peak glucocorticoid production, or under conditions of stress. Cortisol secretion, under the control of adrenocorticotropic hormone (ACTH), peaks in the morning between 4 a.m. and 10 a.m. At this point, circulating cortisol may reach 700 nmol/L. While this concentration would not induce activation of the MR under normal circumstances, it may do so in a situation where expression of 11β-HSD2 is halved. Because this is not an excessive level of cortisol unless chronically maintained, no outward signs of glucocorticoid excess would be visible.

The observations of Ostreicher and colleagues suggest the existence of a tissue-specific version of AME. These individuals do not possess any mutant form of 11β-HSD2 and so would not be aided by mutation screening, but may simply have a reduced expression of 11β-HSD2 in the distal nephron (and perhaps in other aldosterone target tissues). This raises a couple of important questions. How is such tissue-specific repression of expression established? And are there any potential methods to enable diagnosis of such a condition?

The control of 11β-HSD2 expression is mediated by the careful interplay of a number of factors which interact within the promoter. Specificity proteins 1 (Sp1) and 3 (Sp3) and the active NF-κB p65/p50 heterodimer bind consensus sites in the proximal promoter and activate transcription [21]. Inhibition of expression is mediated by competitive binding of early growth response factor (Egr-1) and the inhibitory NF-κB p50/p50 homodimer. Animals subject to fetal growth impairment induced by uterine artery ligation show global repression of renal 11β-HSD2 expression, mediated by reduced binding of Sp1 and NF-κB p65 to the promoter alongside an increase in binding of Egr-1 and NF-κB p50 [22,23]. It was suggested that this may be associated with differential methylation of the 11β-HSD2 promoter [22], a phenomenon which has also been observed for the adrenal AT(1b) angiotensin receptor [24] and hepatic PPARα [25]. It will be interesting to see if any of these mechanisms occur in the offspring of low-protein-fed mothers.

Development of appropriate diagnostic tests may prove problematic. However, if the level of expression of 11β-HSD2 is such that it would be overcome by circulating glucocorticoids within the normal range at their daily maximum, then it should be possible to observe a diurnal fluctuation in fractional sodium excretion which tracks the circulating glucocorticoid concentration. A sharp drop in sodium excretion should be triggered by a ‘sub-Cushing’s’ concentration of cortisol. Alternatively, it may be useful to determine the dose of exogenous cortisol required to trigger a rapid decline in sodium excretion in these individuals. It will be interesting to see if this phenomenon is identified in human populations and to what extent it is responsible for the generation or exacerbation of hypertension.

Conflict of interest statement. None declared.

References

In contrast to sea stars, men are not able to repair or regenerate body parts [1], a price we have to pay for high development and for being able to begin an editorial on a rather jealous note. Due to these underdeveloped maintenance and repair mechanisms, our adult life is mostly characterized by a (hopefully slow) deterioration of various body functions. This also includes the kidney, especially the one with an already impaired function. Several studies have looked and do currently look at biomarkers predicting progression of chronic kidney disease (CKD), which include baseline glomerular filtration rate (GFR) as well as traditional cardiovascular risk factors [2].

In the August issue of *Nephrology Dialysis and Transplantation*, Surdacki and co-workers [3] presented a study on novel biomarkers predicting the decline in GFR in 98 non-diabetic men undergoing elective coronary angioplasty. These patients had a decreased GFR (69 mL/min) already at the time they underwent coronary angioplasty. This is a frequent finding in clinical medicine as the prevalence of CKD is ~14% in industrialized countries [4], and it is known that these patients are more likely to die of cardiovascular diseases than to reach CKD stage 5, i.e. become dialysis-dependent. Due to overwhelming and depressing epidemiological data, the American Heart Association not only listed CKD as a risk factor for cardiovascular disease [5] but also recommended estimating GFR in patients with or at increased risk for cardiovascular disease to detect renal impairment [6]. Surdacki et al. [3]