11β-Hydroxysteroid Dehydrogenase Activity in Spontaneously Hypertensive and Dahl Rats

Irena Pohlová, Ivan Mikšík, Jaroslav Kuneš, and Jiří Pácha

The role of the enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) in hypertension remains unknown even if it appears that the inappropriately decreased 11βHSD activity might be involved in a process that leads to high blood pressure. The possible changes of 11βHSD were therefore investigated in rats with spontaneous or salt-induced hypertension. The adult male rats of the following genotypes were used: spontaneously hypertensive rats (SHR), normotensive Wistar-Kyoto rats (WKY), Dahl salt-sensitive rats fed either a high-salt diet containing 8% NaCl (DS-HS) or low-salt diet containing 0.2% NaCl (DS-LS), and Dahl salt-resistant rats fed the same diets (DR-HS, DR-LS). 11βHSD was investigated in colon, aorta, renal cortex, and renal medulla and was assessed as percentage conversion of [³H]corticosterone to [³H]11-dehydrocorticosterone in the presence of NAD or NADP. The results demonstrated that genotype exerts a significant effect on 11βHSD. 11βHSD activity was significantly increased in colon and renal medulla of SHR compared with WKY rats. No significant differences were observed in renal cortex and aorta. In Dahl rats kept on a low-salt diet, 11βHSD activity was significantly higher in colon, renal medulla, and cortex of DS-LS than in DR-LS rats but no difference was observed in aorta. The differences disappeared in age-matched DS and DR rats fed the high-salt diet. Increased dietary sodium intake stimulated the activity of 11βHSD in renal cortex and medulla of DR rats and decreased the activity in colon of DS rats. We conclude that the development of spontaneous and salt-induced hypertension is not associated with decreased activity of 11βHSD. However, the results showed that salt intake is able to modulate the activity of 11βHSD and that 11βHSD in DS and DR rats responds to high dietary salt intake in a different manner. Am J Hypertens 2000;13:927–933 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: **Hypertension, spontaneously hypertensive rats, Dahl rats, 11β-hydroxysteroid dehydrogenase, glucocorticoids, colon, kidney, aorta.**

The enzyme 11β-hydroxysteroid dehydrogenase (11βHSD) catalyses the conversion of C-11 hydroxylated glucocorticoids, including cortisol (the primary glucocorticoid in humans), to the 11-oxo metabolites (cortisone, 11-dehydrocorticosterone). This prereceptor conversion is believed to protect the mineralocorticoid receptors from nonspecific binding of glucocorticoids.[1,2] To date, two distinct forms of 11βHSD have been purified and cDNA cloned. It was demonstrated that the tis-

sues differ in enzyme distribution, cosubstrate dependencies, glucocorticoid affinities, and reaction reversibility.[3–5] The NADP-dependent isoform (11βHSD-1) is a widely expressed enzyme that shows both oxidative and reductive activities and has a relatively low affinity for glucocorticoids. 11βHSD-2, more recently described, is a NAD-dependent isoform that has high affinity for glucocorticoids, operates only in an oxidative direction, and is localized predominantly in mineralocorticoid target tissues (eg, kidney) and placenta. A congenital deficiency of 11βHSD (syndrome of apparent mineralocorticoid excess) or inhibition of 11βHSD by ingestion of licorice or carbenoxolone leads to the activation of mineralocorticoid receptors by glucocorticoids, excessive sodium retention, and hypertension.[6] In addition, it has been shown that many patients with essential hypertension have altered cortisol-to-cortisone conversion.[7]

Several differences in corticosteroid metabolism have also been described between normotensive and hypertensive strains of established rat models of hypertension. Okamoto-Aoki spontaneously hypertensive rats (SHR) possess significantly higher renal corticosterone 6-hydroxylation than their normotensive controls, Wistar-Kyoto rats (WKY).[8] Similarly, alterations of adrenal 11β- and 18-hydroxylation and 18-oxidation have been observed between Dahl salt-sensitive (DS) and salt-resistant (DR) rats.[9,10] On the other hand, studies of 11β-oxidation in peripheral tissues of hypertensive animals, particularly those associated with volume expansion, are scarce and have produced conflicting results.[11–16] Although the kidney plays a major role in sodium homeostasis and has often been implicated in the pathogenesis of hypertension, no differences of renal 11βHSD were observed between Milan hypertensive rats and their normotensive counterparts,[11] whereas 11βHSD activity was found to be increased in mesenteric arteries and decreased in the hearts of SHR.[13,14] Recently, the decrease of renal 11βHSD was reported in hypertensive DS in comparison with the normotensive DR rats.[15] This decreased activity might play a role in salt sensitivity and development of hypertension. However, high salt intake was shown to increase 11βHSD activity in normal dog kidney[17] and low salt intake stimulated 11βHSD in rat colon.[18]

In the present study we performed a systematic comparison of 11βHSD in SHR and WKY and in DS and DR fed a low- or high-salt diet. The purpose of this study was to determine whether the activity of 11βHSD is different in the two hypertensive models. The other goal was to determine whether the increased dietary salt intake can affect the enzyme activity differently in DS and DR rats. This question is particularly interesting, as recent studies demonstrated the effect of salt intake on 11βHSD.[17,18]

MATERIALS AND METHODS

The studies were performed on 100- to 120-day–old male SHR, WKY, and inbred Dahl rats of both phenotypes housed under 12-h light/12-h dark conditions. The animals were supplied by the breeding colonies of the Institute of Physiology (Czech Academy of Science, Prague), where the Dahl colonies were originally established using breeding stock obtained from Dr. J.P. Rapp (Medical College of Ohio, Toledo, OH). SHR and WKY rats were maintained on a standard diet, whereas Dahl rats were fed a low-salt (LS) or a high-salt diet (HS). Rats fed the HS diet received chow containing natural ingredients that were supplemented with 8% NaCl, whereas the LS diet was the same chow without any NaCl supplementation (0.2% NaCl). Dahl rats received LS diet since birth and in some groups this diet was replaced by the HS diet 5 weeks before killing the animals. Blood pressure was measured by a direct puncture of the carotid artery under light ether anaesthesia several days before the measurement of 11βHSD activity.

The rats were killed by cervical dislocation, and the kidney, aorta, and colon were removed and dissected from the surrounding tissue on ice. The tissue was homogenized in ice-cold buffer containing sucrose 0.2 mol/L and TRIS/HCl 10 mmol/L, pH 9.0 (1:9 w/v) by a Polytron homogenizer. The homogenate was centrifuged at $1000 \times g$ for 10 min and the supernatant was assayed for protein concentration using the method of Bradford.[19] Conversion of corticosterone was assayed in tubes containing 0.25 mL of homogenate (0.25 mg of protein for cortex, medulla, or aorta, and 1 mg for colon), 0.75 mL of buffer (100 mmol/L KCl, 50 mmol/L TRIS/HCl, pH 9.0), and 0.04 mL NAD or NADP (final concentration, 0.4 mmol/L). After 10 min preincubation at 37°C, 1.3×10^{-6} Ci of [³H]corticosterone (final concentration, 14.5 nmol/L) was added to assay and incubated for 10 (renal cortex and medulla), 20 (colon), or 90 min (aorta). Preliminary studies established that the amount of protein added was in the linear part of the relationship between protein concentration and percentage of corticosterone conversion and resulted in less than 55% conversion at the time of incubation (mentioned later). In experimental groups where the corticosterone conversion reached higher than 55%, half the amount of protein was used and the final value was considered as a twofold value of the measured conversion. The concentration of corticosterone (14.5 nmol/L) was chosen to approximate the physiologic level of the free steroid[20] and the glucocorticoid receptor binding constant, K_m, in the investigated tissues.[21–23] Some measurements of NADP-dependent activity of 11βHSD were performed, also at 1 μmol/L corticosterone (15 nmol/L labeled and 985 nmol/L unlabeled steroid).

TABLE 1. BODY WEIGHT AND MEAN BLOOD PRESSURE

Group	SHR	WKY	DS-HS	DS-LS	DR-HS	DR-LS
Body weight	320	311	366*	354	321†	342
(g)	±6	±5	±10	±6	±4	±6
Blood pressure	145*	112	152*†	132	112	119
(mm Hg)	±3	±4	±5	±3	±4	±6
No. of animals	7	7	11	7	7	11

SHR = spontaneously hypertensive rats; WKY = Wistar-Kyoto normotensive rats; DS-HS = Dahl salt-sensitive rats fed a high-salt diet; DS-LS = Dahl salt-sensitive rats fed a low-salt diet; DR-HS = and DR-LS = Dahl salt-resistant rats fed a high- or low-salt diet. Values are the mean ± SEM.

* $P < .01$ v respective normotensive control, † $P < .01$ v low-salt diet.

The reaction was terminated by cooling and the samples were centrifuged for 15 min (3000 × g). The supernatant was loaded onto C_{18} reversed-phase Sep-Pak columns (Waters, Milford, MA) and the steroids extracted by methanol, evaporated to dryness under nitrogen, and stored at −20°C. The steroids present in the evaporated samples were separated by high-performance liquid chromatography.[24] To eliminate the possibility that NADP was converted to NAD by pyrophosphatases and thus the transformation of corticosterone was an NAD- but not NADP-dependent process, some experiments were performed in the presence of 50 mmol/L sodium pyrophosphate, an inhibitor of pyrophosphatases.[25] The experiments proved that pyrophosphatases had no significant effect on the NADP-dependent conversion of corticosterone.

Results are shown as the mean ± SEM. The statistical analysis was performed using BMDP programs (University of California, Berkeley, CA). Differences in blood pressure between the hypertensive strain and the corresponding normotensive control were examined with Student's unpaired t test. The two-way (SHR, WKY: genotype v cosubstrate) or three-way analysis of variance (Dahl rats: genotype v strain v cosubstrate) were performed for the multiple comparison of conversion of [³H]corticosterone. The Newman-Keuls multiple-range test was used to determine significant differences among individual means. Statistically significant changes were accepted at the 5% level.

RESULTS

Table 1 summarizes body weight and mean blood pressure in groups of hypertensive and normotensive rats. The blood pressure of SHR rats was significantly higher than that of WKY rats and elevated dietary salt intake increased blood pressure in DS but not in DR rats.

The conversion of corticosterone to 11-dehydrocorticosterone in SHR and WKY rats was compared in homogenates from distal colon, aorta, renal cortex, and medulla (Fig. 1). The NAD-dependent 11β-oxida-

tion was higher than NADP-dependent oxidation in colon and renal cortex but similar in renal medulla of the two strains, whereas aortic enzyme preferentially used NADP ($P < .003$). Comparison of strains demonstrated higher 11βHSD activity in SHR than in WKY rats (Fig. 1). Analysis of variance proved significantly higher conversion in colon ($P < .0001$) and renal medulla ($P < .03$) of SHR when compared to WKY rats; no differences were found in renal cortex and aorta. Nevertheless, this was only true with NAD but not with NADP as the cosubstrate. Considering
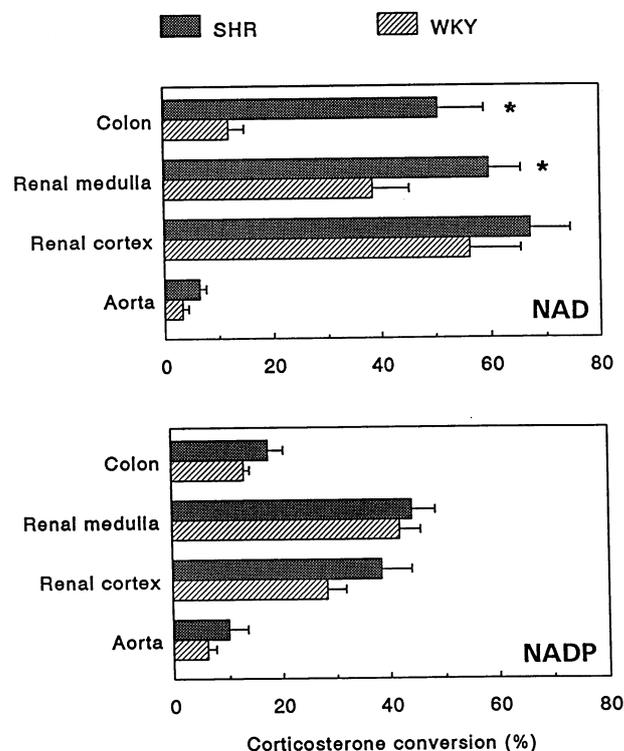

FIG. 1. 11βHSD activity of SHR and WKY rats. 11βHSD activity is expressed as percentage conversion of [³H]corticosterone to [³H] 11-dehydrocorticosterone in the presence of NAD (upper panel) or NADP (lower panel). The values represent mean ± SEM. Asterisks represent significant differences between two genotypes.
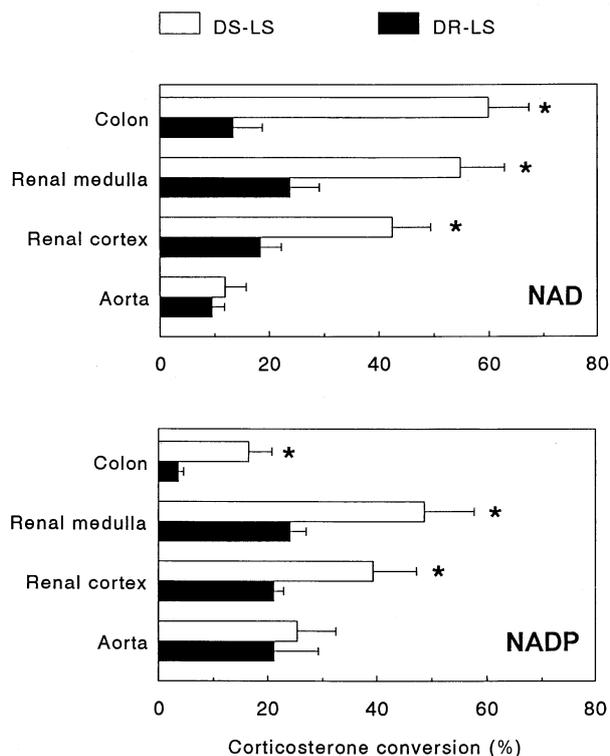
FIG. 2. *11βHSD activity in DS and DR rats fed a low-salt diet. For further details see legend of Fig. 1.*

FIG. 3. *11βHSD activity in DS and DR rats fed a high-salt diet. For further details see legend of Fig. 1.*

the differences of incubation time and protein content in the assay, the hierarchy of 11βHSD activity was cortex > medulla > colon >> aorta.

Similar to findings in SHR and WKY, significant effects were present for genotype and cosubstrate preferences and, in addition, also for salt intake in Dahl rats (Figs. 2, 3). In colon ($P < .001$), renal cortex ($P < .04$), and medulla ($P < .01$) NADP stimulated conversion of corticosterone but the effect was not as great as with NAD, whereas it was the opposite in aorta ($P < .01$). Significantly higher conversion was observed in DS rats fed a low-salt diet in colon ($P < .0001$), renal medulla ($P < .0006$), and cortex ($P < .004$), in comparison with DR rats fed the same diet (Fig. 2). If the Dahl rats were fed a high-salt diet, the differences between 11βHSD activity of DR and DS rats disappeared. Analysis of variance indicated a significant effect of diet on 11βHSD activity in colon ($P < .0001$), renal cortex ($P < .0004$), and medulla ($P < .01$). High-salt diet significantly decreased NAD-dependent 11βHSD activity in colon of DS rats but increased this activity in renal medulla and cortex of DR rats (Figs. 2, 3).

The changes in NADP-dependent activity (11βHSD-1) in Dahl rats induced by dietary salt intake (Figs. 2, 3) were measured under suboptimal conditions because of low substrate concentration. Under these condi-
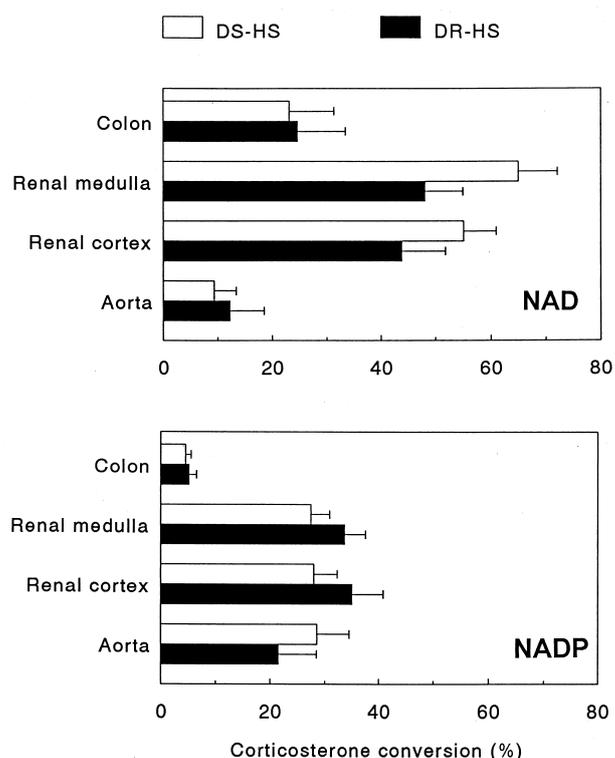
tions, the observed percentage conversion of corticosterone was an underestimate of the real amount of 11βHSD protein activity at the higher velocities of the enzyme reaction. To support the finding that salt intake modulates NADP-dependent 11βHSD-1 activity, the conversion was measured also at 1 μmol/L corticosterone. The conversion of corticosterone was significantly higher ($P < .001$, n = 6) in colon (42 ± 7%), renal cortex (51 ± 6%), and medulla (48 ± 6%) of DS-LS animals in comparison with DR-LS rats (colon: 17 ± 4%, cortex: 33 ± 4%, medulla: 23 ± 4%). NADP-dependent activity of aortic 11βHSD was not significantly different. High salt intake decreased enzyme activity ($P < .001$) in colon (15 ± 2%) and kidney (cortex: 30 ± 5%, medulla: 25 ± 4%) of DS rats but did not modulate the activity of DR rats (not shown).

DISCUSSION

Corticosteroids are known to play an important role in hypertension[10,26] and there is also increasing evidence supporting the role of 11βHSD in hypertension.[6,27] In an attempt to provide insight into the possible role of 11βHSD in the pathogenesis of hypertension we studied 11βHSD activities in two models of hypertension: spontaneous hypertension and hypertension induced by high dietary salt intake.

In the present study we found no evidence for dif-

ferences of aortic 11βHSD activity between hypertensive rats and their normotensive controls (SHR v WKY, DS-HS v DR-HS). Similarly, Smith and Krozowski[13] did not find any differences between cardiac 11βHSD activity in homogenates prepared from male SHR and WKY. However, it has recently been reported that the mesenteric enzyme activity is significantly decreased in both SHR and DS-HS rats compared with their normotensive counterparts.[12,14] It means that there are not uniform changes in enzyme activity in different parts of the cardiovascular systems of normotensive and hypertensive rats or that the differences result from differences in techniques used (homogenate v perfusion of isolated arteries). The reaction direction of 11βHSD (11βHSD-1) depends on the cell context/local environment and therefore the direction of the reaction in homogenate does not always reflect the activity of the intact tissue.[28] The intact vessels showed both unidirectional dehydrogenase activity[14] and bidirectional pattern of both dehydrogenase and reductase activities.[29] In contrast, the intact colonic[1,30] and renal tissue[31] are predominant oxidizers.

Colon and distal parts of nephron are mineralocorticoid target tissues. It is widely accepted that 11βHSD protects mineralocorticoid receptors against glucocorticoid action and thereby facilitates the binding of aldosterone.[1,2] Several studies have also shown that congenital deficiency of 11βHSD[32] or enzyme inhibition[33] causes sodium retention and plasma volume expansion, which can lead to hypertension. In some rat models of hypertension, namely DS and Milan-hypertensive rats, increased renal sodium retention was observed, particularly upon enhanced sodium load.[34,35] Also in the stroke-prone SHR sodium excretion seems to be impaired during the early phase of hypertension.[36] We have, therefore, assumed that if the hypertensive strains had less glucocorticoid metabolizing capacity than their normotensive counterparts, they might be predisposed to greater sodium transport rates. As normal rats have high corticosterone oxidative capacity not only in the proximal tubule, cortical collecting duct, and cortical part of the thick ascending limb, but also in the medullary collecting duct,[37] we have investigated corticosterone oxidation both in the renal cortex and medulla. The kidney contains both isoforms of 11βHSD, the more abundant low-affinity 11βHSD-1 localized predominantly in the proximal tubule and the high-affinity 11βHSD-2 isoform, which has been shown to be present in the distal part of the nephron, mostly in the cortical collecting tubule.[2,38] For comparison, we have also studied the colon, which has similar sodium transport properties and corticosteroid specificity as the cortical collecting duct. However, in contrast to our hypothesis, we have found evidence for increased

corticosterone metabolizing capacity in the kidneys of hypertensive rats (SHR, DS-HS group). It seems that corticosterone metabolizing capacity is not the only factor that might play a significant role in the differences in sodium transport between hypertensive and normotensive rats. This is in agreement with the studies on Milan rats, in which no differences in renal 11βHSD activity and gene expression were found between hypertensive and normotensive strains.[11] In contrast, Franco-Saenz et al[15] reported decreased renal 11βHSD-1 activity in the hypertensive DS rats fed standard 1% NaCl diet, in comparison with DR rats. The reason for these strain differences in 11βHSD-1 activity of Dahl rats remains unclear because these authors did not find any difference in the abundance of 11βHSD-1 mRNA in either strain.[39]

Apart from the interpretation of our data with respect to blood pressure regulation, the data clearly indicate strain differences of 11βHSD activity between SHR and WKY and DS and DR rats fed a low-salt diet. However, the differences between the enzyme activities of the two strains of Dahl rats disappeared after the increase of dietary salt intake, which is able to raise blood pressure in DS rats. The reason for the disappearance of strain differences in Dahl rats fed a high-salt diet reflects the changes in 11βHSD activity after the increase of salt intake. Increased sodium intake was associated in Dahl rats with attenuation of 11βHSD activity in the colon of DS rats by 61% without significant changes of colonic 11βHSD activity in DR rats. On the contrary, a high salt intake stimulated renal medullary and cortical NAD-dependent 11βHSD activity in DR rats by 50% and 57%, respectively. The increase of renal NAD-dependent activity is in good correlation with an increase of renal 11βHSD-2 mRNA level induced by the high-salt diet in Dahl rats.[39] There are also some other data indicating the relationship between dietary salt intake and 11βHSD activity. The increased dietary sodium intake stimulates 11βHSD in proximal tubules of mongrel dogs[17] and decreases 11βHSD activity in the ileum and colon of Wistar rats.[18]

In summary, the absence of decreased renal and colonic 11βHSD activity in hypertensive animals and the absence of changes in aortic 11βHSD indicates that it is unlikely that 11βHSD is involved in the development of hypertension in the animal models studied. However, we cannot eliminate the possibility that endogenous inhibitors modulate 11βHSD activity or that brain 11βHSD is involved in the pathogenesis of hypertension. It has been demonstrated recently that some endogenous steroids are potent inhibitors of 11βHSD,[27,29] and that the infusion of synthetic 11βHSD inhibitors into the brain produces hypertension.[40] This hypothesis is in accordance with the findings that patients with essential hypertension may

have altered glucocorticoid metabolism[41,42] without a clear gene defect in 11βHSD-2.[43] Nevertheless, our study demonstrated an inappropriate decrease of colonic 11βHSD in DS and an increase in renal 11βHSD in DR rats induced by high dietary salt intake. To demonstrate whether the changes of 11βHSD activity by high dietary salt intake play a role in the development of salt-induced hypertension in DS and the protection against the development of hypertension in DR rats will require further studies.

REFERENCES

1. Funder JW, Pearce PT, Smith R, Smith AI: Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. Science 1988;242:583–585.

2. Monder C: Corticosteroids, receptors, and the organ-specific functions of 11β-hydroxysteroid dehydrogenase. FASEB J 1991;5:3047–3054.

3. Lakshmi V, Monder C: Purification and characterization of the corticosteroid 11β-dehydrogenase component of the rat liver 11β-hydroxysteroid dehydrogenase complex. Endocrinology 1988;123:2390–2398.

4. Brown RW, Diaz R, Robson AC, Kotolevtsev Y, Mullins JJ, Kaufman MH, Seckl JR: The ontogeny of 11β-hydroxysteroid dehydrogenase type 2 and mineralocorticoid receptor gene expression reveal intricate control of glucocorticoid action in development. Endocrinology 1996;137:794–797.

5. Agarwal AK, Mune T, Monder C, White PC: NAD$^+$-dependent isoform of 11β-hydroxysteroid dehydrogenase: cloning and characterization of cDNA from sheep kidney. J Biol Chem 1994;269:25959–25962.

6. Seckl JR, Brown RW: 11-beta-hydroxysteroid dehydrogenase: on several roads to hypertension. J Hypertens 1994;12:105–112.

7. Walker BR, Stewart PM, Shackleton CHL, Padfield PL, Edwards CRW: Deficient inactivation of cortisol by 11β-hydroxysteroid dehydrogenase in essential hypertension. Clin Endocrinol 1993;39:221–227.

8. Ghosh S, Grogan WM, Basu A, Watlington C: Renal corticosterone 6β-hydroxylase in the spontaneously hypertensive rat. Biochim Biophys Acta 1993;1182:152–156.

9. Rapp J: Dahl salt-susceptible and salt-resistant rats. A review. Hypertension 1982;4:753–763.

10. Fardella CE, Miller WL: Molecular biology of mineralocorticoid metabolism. Annu Rev Nutr 1996;16:443–470.

11. Stewart PM, Whorwood CB, Valentino R, Burt D, Sheppard MC, Edwards CRW: 11-beta-hydroxysteroid dehydrogenase activity and gene expression in the hypertensive Bianchi-Milan rat. J Hypertens 1993;11:349–354.

12. Takeda Y, Yoneda T, Miyamori I, Gathiram P, Takeda R: 11β-hydroxysteroid dehydrogenase activity in mesenteric arteries of spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 1993;20:627–631.

13. Smith RE, Krozowski ZS: 11β-hydroxysteroid dehydrogenase type I enzyme in the hearts of normotensive and spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 1996;23:642–647.

14. Takeda Y, Miyamori I, Yoneda T, Iki K, Hatakeyama H, Takeda R: Gene expression of 11β-hydroxysteroid dehydrogenase in the mesenteric arteries of genetically hypertensive rats. Hypertension 1994;23:577–580.

15. Franco-Saenz R, Tokita Z, Latif S, Morris DJ: 11β-hydroxysteroid dehydrogenase in the Dahl rat. Am J Hypertens 1997;10:1004–1009.

16. Takeda Y, Inaba S, Furukawa K, Miyamori I: Renal 11β-hydroxysteroid dehydrogenase in genetically salt-sensitive rats. Hypertension 1998;32:1077–1082.

17. Brem AS, Bina RB, King T, Chobanian MC, Morris DJ: Influence of dietary sodium on the renal isoforms of 11β-hydroxysteroid dehydrogenase. Proc Soc Exp Biol Med 1997;214:340–345.

18. Pácha J, Mikšík I: 11β-hydroxysteroid dehydrogenase in developing rat intestine. J Endocrinol 1996;148:561–566.

19. Bradford MM: A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976;72:248–254.

20. Rots NY, Cools AR, Oitzl MS, de Jong J, Sutanto W, de Kloet ER: Divergent prolactin and pituitary-adrenal activity in rats selectively bred for different dopamine responsiveness. Endocrinology 1996;137:1678–1686.

21. Schulman G, Robertson NM, Elfenbein IB, Eneanya D, Litwack G, Bastl CP: Mineralocorticoid and glucocorticoid receptor steroid binding and localization in colonic cells. Am J Physiol 1994;266:C729–C740.

22. Morel F, Doucet A: Hormonal control of kidney functions at the cell level. Physiol Rev 1986;66:377–468.

23. Scott BA, Lawrence B, Nguyen HH, Meyer WJ: Aldosterone and dexamethasone binding in human arterial smooth muscle cells. J Hypertens 1987;5:739–744.

24. Vylitová M, Mikšík I, Pácha J: Metabolism of corticosterone in mammalian and avian intestine. Gen Comp Endocrinol 1998;109:315–324.

25. Gomez-Sanchez EP, Ganjam V, Chen YJ, Cox DL, Zhou M-Y, Thanigaraj S, Gomez-Sanchez CE: The sheep kidney contains a novel unidirectional, high affinity NADP$^+$-dependent 11β-hydroxysteroid dehydrogenase (11β-HSD-3). Steroids 1997;62:444–450.

26. Yagil Y, Levin M, Krakoff LR: Effect of glucocorticoid deficiency on arterial pressure in conscious spontaneously hypertensive rats. Am J Hypertens 1989;2:99–104.

27. Souness GW, Morris DJ: 11α- and 11β-hydroxyprogesterone, potent inhibitors of 11β-hydroxysteroid dehydrogenase, possess hypertensinogenic activity in the rat. Hypertension 1996;27:421–425.

28. Rajan V, Edwards CRW, Seckl JR: 11β-hydroxysteroid dehydrogenase in cultured hippocampal cells reactivates inert 11-dehydrocorticosterone, potentiating neurotoxicity. J Neurosci 1996;16:65–70.

29. Brem AS, Bina RB, King T, Morris DJ: 11βOH-progesterone affects vascular glucocorticoid metabolism and contractile response. Hypertension 1997;30:449–454.

30. Pácha J, Mikšík I: Distribution of 11β-hydroxysteroid dehydrogenase along the rat intestine. Life Sci 1994;54: 745–749.

31. Stahl K, Lichtenstein I, Siebe H, Hierholzer K: Interaction of 11β-hydroxysteroid-oxido reductase in different organs of various mammalian species. Kidney Int 1996; 49(suppl 55):S156–S159.

32. Stewart PM, Corrie JET, Shackleton CHL, Edwards CRW: Syndrome of apparent mineralocorticoid excess: a defect in the cortisol-cortisone shuttle. J Clin Invest 1988;82:340–349.

33. Stewart PM, Wallace AM, Atherden SM, Shearing CH, Edwards CRW: Mineralocorticoid activity of carbenoxolone: contrasting effects of carbenoxolone and liquorice on 11β-hydroxysteroid dehydrogenase activity in man. Clin Sci 1990;78:49–54.

34. Roman RJ: Abnormal renal hemodynamics and pressure-natriuresis relationship in Dahl salt-sensitive rats. Am J Physiol 1986;251:F57–F65.

35. Bianchi G, Baer PG, Fox U, Duzzi L, Pagetti D, Giovanetti AM: Changes in renin, water balance and sodium balance during development of high blood pressure in genetically hypertensive rats. Circ Res 1975; 36(suppl 1):153–161.

36. Dietz R, Schömig A, Haebra H, Pascher W, Lüth JB, Gross F: Studies on the pathogenesis of spontaneous hypertension of rats. Circ Res 1978;43(suppl 1):98–106.

37. Kenouch S, Coutry N, Farman N, Bonvalet JP: Multiple patterns of 11β-hydroxysteroid dehydrogenase catalytic activity along the mammalian nephron. Kidney Int 1992;42:56–60.

38. Rusvai E, Fejes-Toth A: A new isoform of 11β-HSD in aldosterone target cells. J Biol Chem 1993;268:10717–10720.

39. Franco-Saenz R, Shen P, Lee SJ, Cicila GT, Henrich WL: Regulation of the genes for 11β-hydroxysteroid dehydrogenase type 1 and type 2 in the kidney of the Dahl rat. J Hypertens 1999;17:1089–1093.

40. Gomez-Sanchez EP, Gomez-Sanchez CE: Central hypertensinogenic effects of glycyrrhizic acid and carbenoxolone. Am J Physiol 1992;263:E1125–E1130.

41. Soro A, Ingram MC, Tonolo G, Glorioso N, Fraser R: Evidence of coexisting changes in 11β-hydroxysteroid dehydrogenase and 5β-reductase activity in subjects with untreated essential hypertension. Hypertension 1995;25:67–70.

42. Litchtfield WR, Hunt SC, Jeunemaitre X, Fisher NDL, Hopkins PN, Wiliams RR, Corvol P, Williams GH: Increased urinary free cortisol. A potential intermediate phenotype of essential hypertension. Hypertension 1998;31:569–574.

43. Brand E, Kato N, Chatelain N, Krozowski ZS, Jeunemaitre X, Corvol P, Plouin P-F, Cambien F, Pascoe L, Soubrier F: Structural analysis and evaluation of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) gene in human essential hypertension. J Hypertens 1998;16:1627–1633.