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Review

Molecular identity and gene expression of aldosterone synthase cytochrome P450

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Abstract

11β-Hydroxylase (CYP11B1) of bovine adrenal cortex produced corticosterone as well as aldosterone from 11-deoxycorticosterone in the presence of the mitochondrial P450 electron transport system. CYP11B1s of pig, sheep, and bullfrog, when expressed in COS-7 cells, also performed corticosterone and aldosterone production. Since these CYP11B1s are present in the zonae fasciculata and reticularis as well as in the zona glomerulosa, the zonal differentiation of steroid production may occur by the action of still-unidentified factor(s) on the enzyme-catalyzed successive oxygenations at C11- and C18-positions of steroid. In contrast, two cDNAs, one encoding 11β-hydroxylase and the other encoding aldosterone synthase (CYP11B2), were isolated from rat, mouse, hamster, guinea pig, and human adrenals. The expression of CYP11B1 gene was regulated by cyclic AMP (cAMP)-dependent signaling, whereas that of CYP11B2 gene by calcium ion-signaling as well as cAMP-signaling. Salt-inducible protein kinase, a cAMP-induced novel protein kinase, was one of the regulators of CYP11B2 gene expression.

Keywords: Aldosterone synthase; 11β-Hydroxylase; Salt-inducible kinase; CYP11B1; CYP11B2; P450

Having the honor of contributing an article to the issue celebrating the 50th anniversary of the discovery of oxygenases, we offer our congratulations to Professor Osamu Hayaishi and other distinguished scientists who discovered the oxygenases and established this important new concept in the field of biological oxidations. Though our own contribution to this area has been limited, we would like to take this opportunity to briefly review the emergence and development of knowledge concerning the biochemical properties of aldosterone synthase cytochrome P450 (CYP11B2) and describe our recent effort to investigate the regulation of CYP11B2 gene expression.

Molecular properties of aldosterone synthase P450

Corticosterone, the 11β-hydroxylation product of 11-deoxycorticosterone (DOC), and aldosterone, the C18-oxidation product of corticosterone, both secreted from rat adrenal glands, are the natural glucocorticoid and mineralocorticoid, respectively (in humans and bovines cortisol, 17α-hydroxycorticosterone, instead of corticosterone, acts as the natural glucocorticoid). The chemical structures of relevant steroids are illustrated in Fig. 1.

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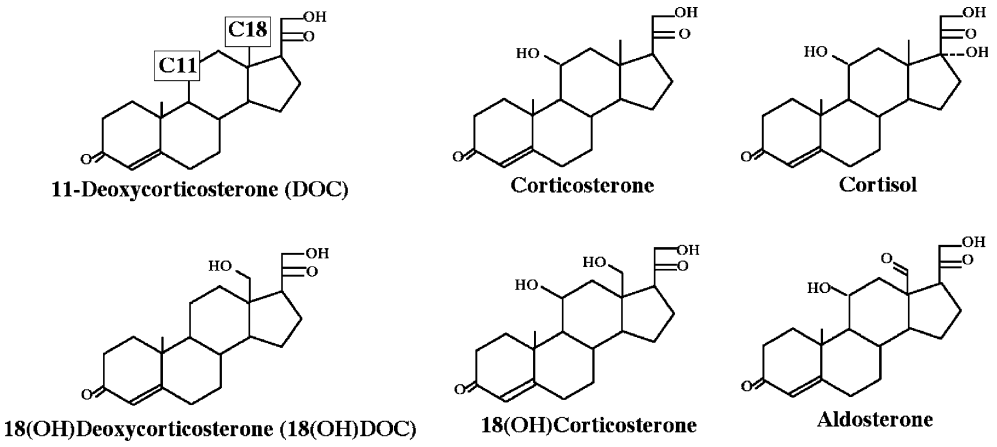

Fig. 1. Structure of steroids relevant to CYP11B reactions. Carbon atoms at 11- and 18-positions are boxed in the structure of DOC.

After the enduring effort to characterize the final step of glucocorticoid production biochemically, Takemori et al. [1] found that 11β-hydroxylase (CYP11B1) activity associated with bovine adrenal cortex mitochondria, when solubilized in detergent-containing buffer, was fairly stable in the presence of the substrate DOC, and by taking advantage of this finding they purified the enzyme to homogeneity for the first time [2]. When the purified enzyme was incubated with DOC in the presence of the mitochondrial P450 electron transport system, it was found to produce not only the 11-hydroxylated product corticosterone but also the 18-hydroxylated products 18-hydroxy-11-deoxycorticosterone and 18-hydroxycorticosterone, showing that the enzyme could catalyze both the 11- and 18-hydroxylation of steroid [3] (Fig. 2). These results suggested a plausible theory that the last step of aldosterone production must be the conversion of 18-hydroxycorticosterone to aldosterone. The nature of the enzyme catalyzing this step, however, was a matter of argument at that time. Two possibilities were considered; one suggested that 18-hydroxycorticosterone could be oxidized by a kind of alcohol dehydrogenase (shown in pathway (a) in Fig. 3), while the other suggested that 18-hydroxycorticosterone could be oxygenated by another cytochrome P450 monooxygenase, to produce 18-dihydroxymethylcorticosterone, which would then undergo nonenzymatic dehydration to produce aldosterone (shown in pathway (b) in Fig. 3). Either one or both of the pathways were described in the standard textbooks in the beginning of the 1980s (see [4–6] for examples).

We were at first interested in the enzymatic properties of purified bovine CYP11B1, which we found catalyzed not only the 11β- and 18-, but also the 19-hydroxylation of steroid [7–9]. Having reported about versatile catalytic properties of the enzyme, we then endeavored to answer the still-unsolved question of the characterization of the enzymatic nature of aldosterone synthase. We found that bovine CYP11B1, purified to homogeneity according to methods essentially similar to those reported by Katagiri and his co-workers [1–3] with some modifications, could produce a small amount of aldosterone from DOC in the presence of the P450 electron transport system [10,11]. The system must contain NADPH-adrenodoxin reductase, adrenodoxin, and the NADPH-generating system. The addition of NAD^+,

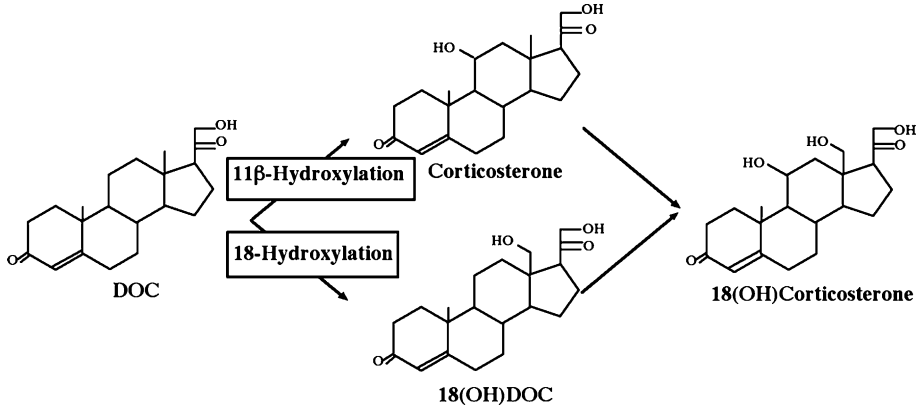

Fig. 2. CYP11B1 catalyzes both 11- and 18-hydroxylation of DOC.

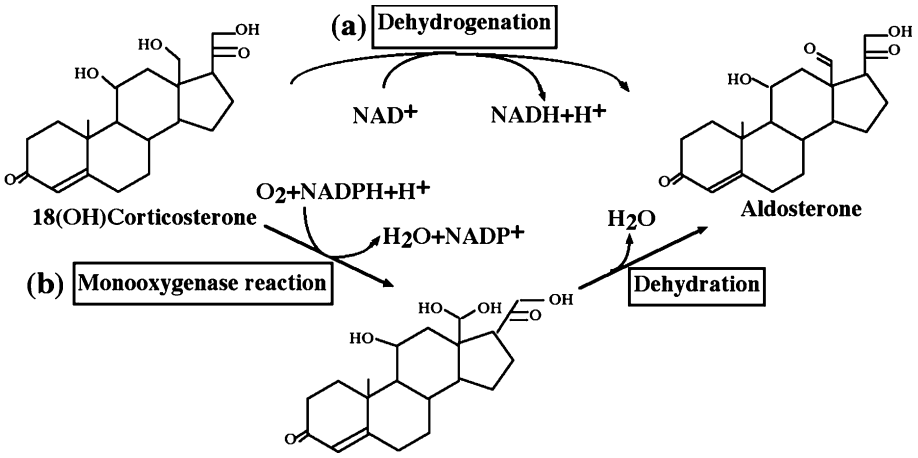

Fig. 3. Two possible pathways of aldosterone production from 18(OH)corticosterone.

$NADP^+$, or FAD, instead of the NADPH-generating system, was ineffective. The aldosterone production was activated by the addition of phospholipids to the reaction mixtures. The purity of the protein was carefully tested to exclude the possibility that the seemingly homogeneous CYP11B1 preparation was contaminated by another protein having aldosterone-producing activity. Our findings indicated that bovine CYP11B1 could produce aldosterone from DOC without the help of another oxidation enzyme. Yanagibashi et al. [12] also reported similar results. Because the immunohistochemical studies using antibodies raised against CYP11B1 showed that the antigen was present in all zones of adrenal cortex, in order to explain the zonal differentiation of corticosteroid production we must consider a possible presence(s) of a zone-specific factor(s) that regulates the process of CYP11B1-mediated oxygenation reactions at C11- and C18-positions of steroid.

In the meantime, Ogishima et al. [13] further examined the purity of the enzyme, and by developing elaborate HPLC systems, succeeded in separating two CYP11B1s from bovine adrenocortical mitochondria. Each of the two, when tested in the presence of P450 electron transport system, produced aldosterone from DOC, confirming that a single CYP11B1 could catalyze 11β-hydroxylation as well as aldosterone production.

By screening a cDNA library constructed from several bovine adrenal glands, Morohashi and his group identified two very similar, but distinct, full-length cDNAs encoding CYP11B1. A collaboration between his and our groups established that when the two CYP11B1s were expressed in COS-7 cells, each produced corticosterone as well as aldosterone from DOC [14]. Then Mathew et al. [15] isolated a bovine CYP11B1 cDNA from their library whose protein product, they reported, also catalyzed 11β-hydroxylation and aldosterone production. These results could be interpreted by the presence of gene polymorphism in the bovine CYP11B1 gene. We concluded, therefore, that in the case of bovine adrenal cortex a single enzyme CYP11B1 is functioning as the 11β-hydroxylase of deoxycortisol to produce cortisol in the zonae fasciculata and reticularis, and as the aldosterone synthase in the zona glomerulosa.

Complementary DNAs encoding CYP11B1 have been isolated from libraries prepared from adrenal glands of sheep [16], pigs [17], and bullfrogs [18]. The cDNAs, when introduced into mammalian cultured cell lines, produced proteins that catalyzed not only 11β-hydroxylation but also aldosterone production.

In the meantime, a report suggesting that aldosterone synthase in rat adrenal glands might be distinct from 11β-hydroxylase was published. Meuli and Muller attempted to purify aldosterone synthase from the adrenal capsular portions (mostly composed of the zona glomerulosa) of rats that had been fed high-potassium diet, and thus had been activated for aldosterone production. They found a protein having MW 49 kDa in SDS–PAGE gel that was distinct from a protein purified from the adrenal decapsular portions (mostly composed of the zonae fasciculata and reticularis), having MW 51 kDa [19]. When subjected to immunoblot analysis using a monoclonal antibody raised against bovine CYP11B1, each of the two proteins reacted with the antibody, indicating that the two were immunochemically related to CYP11B1, though different in molecular weights [20]. We thought that the 49-kDa protein found in the capsular portions might be the rat aldosterone synthase. Since further purification of this protein would be extremely difficult to achieve, we decided to first isolate rat adrenal cDNAs encoding the CYP11B1-like proteins, and then examine the enzymatic nature of the expressed proteins. Nonaka et al. [21] screened a rat adrenal cDNA library using a bovine CYP11B1 cDNA fragment as a probe and isolated a cDNA encoding rat CYP11B1. COS-7 cells, when transformed with

the cDNA, produced corticosterone but not aldosterone from DOC. Next, using this cDNA as a probe, we screened a cDNA library prepared from the adrenal capsular portions of rats fed potassium-enriched diet. In the meantime, Ogishima et al. [22] directed their heroic efforts toward purifying aldosterone synthase from rat adrenal capsular portions and succeeded in obtaining a protein having an N-terminal amino acid sequence distinct from the predicted N-terminus of rat CYP11B1. Then Imai et al. [23] and Matsukawa et al. [24] independently isolated a cDNA encoding this protein. And the latter, by expressing it in COS-7 cells, confirmed that the cDNA indeed encoded rat aldosterone synthase (CYP11B2).

Examining the mouse genome sequence, Domalik et al. [25] identified two genes similar to bovine CYP11B1 gene, one of which encoded mouse CYP11B1 and the other CYP11B2. Human CYP11B2 cDNA was isolated from a cDNA library produced from surgically obtained adrenal glands of primary aldosteronism patients by Kawamoto et al. [26]. Its nucleotide sequence was consistent with the sequence of one of the two human CYP11B1-like genes reported by Mornet et al. [27].

Taken together, our present understanding is that aldosterone is produced from DOC by consecutive oxygenation reactions at C11- and C18-positions catalyzed by a cytochrome P450 enzyme present in the zona glomerulosa of vertebrates, but the nature of P450 is a little different depending on the animal species. In the case of ungulates and amphibians, the enzyme producing aldosterone is CYP11B1, the same enzyme that catalyzes only 11β-hydroxylation of DOC or 11-deoxycortisol in the zonae fasciculata and reticularis. In the case of human and rodents, on the other hand, the aldosterone-producing P450 is CYP11B2, that is distinct from CYP11B1 in the zonae fasciculata and reticularis (Fig. 4). Why this is so would be a difficult question to answer, and even taking into consideration every aspect of animal physiology, we at present cannot reasonably explain what kind of pressure influenced the evolution of CYP11B gene toward differentiation, or undifferentiation, during the phylogeny of the animal species.

Regulation of aldosterone synthase gene expression

Because aldosterone has strong salt-retaining activity, the plasma level of aldosterone in terrestrial animals must be precisely regulated for the animal's survival in the precarious environments. The production of aldosterone, therefore, is subjected to the control of various upstream hormones or plasma ion concentrations. Angiotensin II that is produced by a concerted action of renin and angiotensin-converting enzyme and sodium- and potassium-ions are the major upstream regulators of aldosterone production. Adrenocorticotropic hormone (ACTH), secreted in response to the animal's neurophysiological and metabolic change, is another stimulant of aldosterone production. The elucidation of mechanisms underlying the two regulatory systems under the physiological or pathological conditions of animals is an important issue to address (for a review, see [28]).

The angiotensin II- and potassium-mediated signal transductions in the zona glomerulosa cells have been studied extensively. The two stimulants cause the elevation of intracellular calcium ion that in turn activates lower-stream signaling molecules and eventually activates transcriptional factors such as Nurr1. A nucleotide sequence of −766/−759 bp in the promoter region of human CYP11B2 gene was identified as the region that

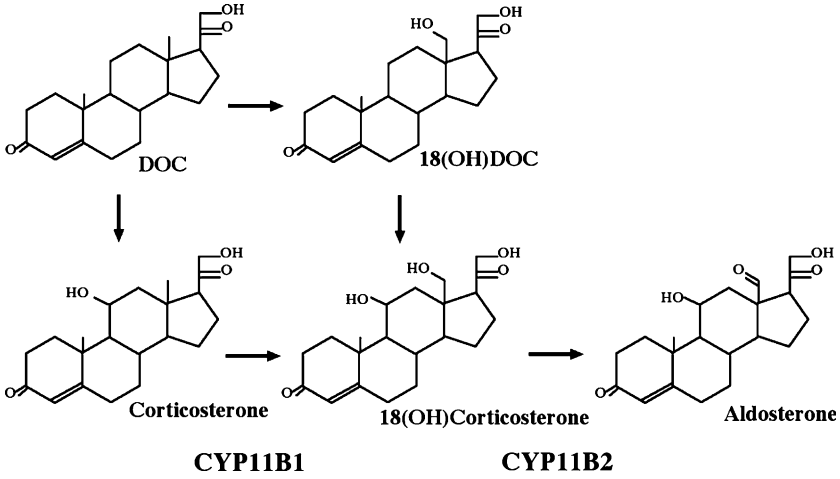

Fig. 4. Differentiation of CYP11B1 and CYP11B2. Ungulates and amphibians have CYP11B1 that catalyzes all the reactions from DOC to aldosterone, whereas rodents and human have two CYP11Bs; CYP11B1 of these animals catalyzes 11β- and 18-hydroxylations, and CYP11B2, the production of aldosterone from DOC.

bound Nurr1, and the mechanisms underlying the Nurr1-dependent transcription activation have been studied in detail [29].

We recently found a serine-specific protein kinase, salt-inducible kinase (SIK), in a cDNA library prepared from rat adrenal glands [30]. Further studies indicated that three SIK isoforms were expressed in various tissues, one of which, SIK2, was abundantly expressed in the zona glomerulosa cells. We have shown that SIK repressed the transcriptional activation mediated by cAMP-responsive element (CRE)-binding protein (CREB) [31–33]. The mechanisms underlying this repression were investigated by collaboration between Montminy's and our groups. SIK in the first place phosphorylated a serine residue(s) in transducer of regulated CREB activity-2 (TORC2), one of the recently found CREB coactivators. The phosphorylated TORC2 then lost its binding capacity to CREB and moved out of the cell nucleus [34,35]. Thus, SIK eventually acted as a repressor of CREB action. We have investigated this general action of SIK on the CYP11B2 gene expression in the H295R cell, a cell line derived from human aldosterone-producing carcinoma. A CRE was found at a region −71/−64 bp of CYP11B2 promoter [36]. When the promoter containing CRE was linked to luciferase reporter gene and the resultant plasmid was introduced into cells and the cells were stimulated with forskolin or overexpression of protein kinase A, the promoter activity was markedly elevated. If an expression vector containing SIK2 was co-introduced, the cAMP-dependent activation of reporter gene was completely repressed. The repression occurred because SIK2 phosphorylated TORC2 and the phospho-TORC2 moved out of the nucleus (J. Doi et al., unpublished observations) (Fig. 5). In addition, we have obtained preliminary results showing that this SIK-involved transcriptional regulation system may crosstalk with the Ca^{2+}-dependent signal transduction system. To sum up, SIK is one of the important regulators of CYP11B2 gene expression.

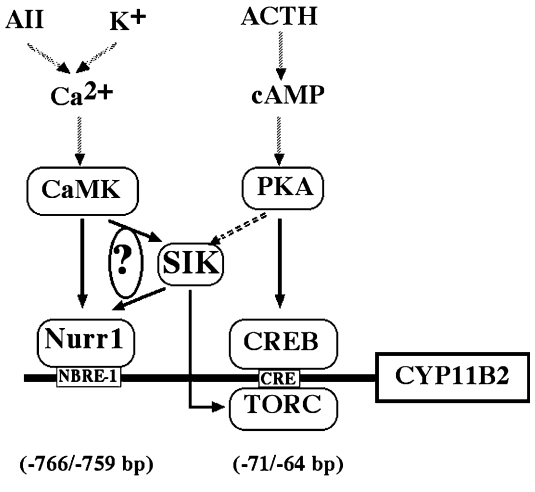

Fig. 5. Signal transduction system of CYP11B2 gene activation: CYP11B2 gene is activated by both Ca^{2+}-mediated signals and cAMP-mediated signals. SIK phosphorylates TORC, a CREB-coactivator, and causes the nuclear export of phospho-TORC, eventually repressing the CYP11B2 gene expression. Whether SIK is involved in the regulation of Ca^{2+}-signaling is currently under investigation. Arrows having straight lines depict the phosphorylation signals, whereas the arrow having dotted-double line depicts the transcriptional activation of SIK gene.

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