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11-β Hydroxysteroid Dehydrogenase-2 and Salt-Sensitive Hypertension

Running title: *Luft; 11-β HSD2*

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Glucocorticoid intracellular metabolism, catalyzed by the two isozymes of 11 β-hydroxysteroid dehydrogenase (11 β-HSD), determines the corticosteroid action on target tissues.[1] 11 β-HSD1 functions as a reductase in most cells and catalyzes the regeneration of active glucocorticoids thereby amplifying their action. This isozyme is wildely expressed in liver, adipose tissue, muscle, pancreatic islets, and adult brain. 11 β-HSD2 is a high-affinity dehydrogenase and inactivates cortisol and corticosterone to the inert product, cortisone. Cortisone in turn can be reactivated through reduction by 11 β-HSD1 (**Figure 1**). The 11 β-HSD2 isozyme is highly expressed in the distal nephron and, as we learn here, in the nucleus tractus solitarius (NTS). 11 β-HSD2 serves to protect the mineralocorticoid receptor (MR) from occupation by cortisol or corticosterone (**Figure 2**).

The development of this complicated arrangement of receptors and steroid ligands has been elucidated by molecular evolutionary biologists. The vertebrate ancestral corticoid receptor has been tracked back to 450 million years ago, its sequence has been "resurrected", and crystallized.[2] Investigators have identified the specific set of historical mutations occuring during evollution that recapitulated the GR's hormone specificity for corisol from an MR-like ancestor, suggesting that back then salt was more important than sugar. Interestingly, the MR is older than the GR.

In mammals, the adrenal cortex synthesizes aldosterone, the major mineralocorticoid, from the zona glomerulosa and the glucocorticoids, cortisol and corticosterone, from the zona fasciculata and zona reticularis.[1] The corticosteroids are bound in the circulation primarily to corticosteroid binding protein. The corticosteroid molecules are highly lipophilic, are believed to readily perimeate biological membranes, and then activate intracellular receptors. The glucocorticoid receptor (GR) has a lower affinity for corticosteroids than the mineralocorticoid

receptor (MR). Both receptors bind 11 β–hydroxycorticosteroids, while the binding of the 11-keto forms is negligible. On binding to GR or MR, the receptors are released from chaperone proteins and can translocate into the nucleus where they bind on target genes. A surprizing 2% of the human genome is said to be regulated by glucocorticosteroids. Membrane receptors also exist. The MR exhibits a more restricted tissue distribution and resides particularly in the kidney, colon, salivary glands, and parts of the central nervous system. The GR is more widely expressed and at higher levels than the MR.

The adrenal cortex secretes nanomolar concentrations of cortisol but only picomolar concentrations of aldosterone. The MR binds cortisol and aldosterone with similar affinity in vitro; however, in the presence of 11 β-HSD2, cortisol is inactivated to cortisone in vivo, enabling the MR in kidney and wherever else 11 β-HSD2 resides, to bind solely with aldosterone. At some sites such as the hippocampus where 11 β-HSD2 is absent, the MR signals primarily by binding to cortisol.

Glucocorticoids have profound effects on brain development and adult CNS function.[3] Elevated hippocampal and neocortical 11β-HSD1 is observed with ageing and causes cognitive decline in humans. Its deficiency prevents the emergence of cognitive defects with age. In contrast, the major central nervous system effects of 11β-HSD2 occur in development, as expression of 11β-HSD2 is high in fetal brain and placenta. Deficient feto-placental 11β-HSD2 results in a life-long phenotype of anxiety and cardiometabolic disorders, consistent with early-life glucocorticoid programming. Geerling et al discovered a novel group of neurons in the NTS that express 11β-HSD2, which makes them selectively responsive to aldosterone.[4] MR activation at this site paralleled salt appetite. In the rat brain, aldosterone-selective areas have also been identified that are important to blood presssure regulation, including the NTS, subfornical organ, and hypothalamic regions. For instance, Janiak et al found that MR central nervous system

binding sites were necessary for the development of deoxycorticosterone acetate (DOCA)-salt hypertension.[5]

Modern molecular technology sheds light on the role of specific MR signaling in the central nervous system. In this issue of *Circulation,* Evans and colleagues report on conditional deletion of the gene encoding 11β-HSD2 (*Hsd11b2*) in the brain. *Hsd11b2* floxed mice were generated on a C57BL6 background and were bred with transgenic mice expressing Cre recombinase under the control of a rat nestin promoter.[6] Nestin is an intermediate filament protein expressed in the central and peripheral nervous system. *Hsd11b2* brain-knockout (*Hsd11b2*BKO) mice had normal basal blood pressures, serum electrolytes, and circulating corticosteroids. However, when offered saline to drink, they drank three times as much fluid as controls and developed salt-sensitive hypertension. The authors measured blood pressure with radiotelemetry and a consistent 10 mm Hg difference in blood pressure was recorded between *Hsd11b2*BKO and control mice. When salt was withdrawn, the blood pressure increase disappeared within one week. When given spironolactone, the salt preference of *Hsd11b2*BKO was reduced by about 30%. The authors gave *Hsd11b2*BKO and control mice exposed to salt dexamethasone to reduce endogenous glucocorticoid production. This maneuver raised blood pressure in contol mice but had little influence on blood pressure of *Hsd11b2*BKO. The authors could detect no volume expansion or failure in salt elimination in *Hsd11b2*BKO subjected to a high-salt intake. However, pressor responses to phenylephrine were enhanced and resultant baroreflex regulation was impaired in the mice.

What are the implications of these findings? The authors suggest that 11β-HSD2 neurons must exist that integrate salt appetite and blood pressure via an MR-dependent pathway. They then suggest that central MR antagonism could increase compliance to a low-salt diet and facilitate management of hypertension. How well does spironolactone cross the blood-brain

barrier? Corticosteroid analogs are highly lipophilic and presumably cross cell membranes; however, there is a role for membrane transporters, such as ABCB1, the multidrug-resistant/p-glycoprotein that is particularly effective at the blood-brain barrier. For instance, the p-glycoprotein minimises the access of dexamethasone into the brain.[7] The spironolactone active metabolite, canrenone, has been studied in detail and crosses the blood-brain barrier fairly well.[8] The authors implanted a 30 mg spironolactone subcutaneously into their mice. Any similarity to doses used in humans is uncertain, although the present findings are suffiently stimulating to warrant studies on salt appetite in humans.[9]

The presence of an enzymatic mechanism protecting the MR and the effects on salt appetite and blood pressure with its absence, underscores the notion that aldosterone regulates salt appetite independent of angiotensin II-related effects. The data also have relevance to salt resistance, since the mice with an intact enzymatic barrier could increase their salt intake five-fold without effects on blood pressure. Aldosterone is believed to activate the same signaling and effector mechanisms in the brain as in the kidney including the MR, the serum and glucocorticoid-induced kinase SGK1, the ubiquitin ligase NEDD4-2, and the epithelial sodium channel ENaC.[10] The latter also mediates the gustatory salt sensing in the tongue, which is required for the manifestation of increased salt intake. Effects of aldosterone on both the brain and kidney synergize with the effects of angiotensin II. Thus, the current findings provide a unifying connection between MR activation in the central nervous system, salt appetite, and blood pressure regulation.

Conflict of Interest Disclosures: None.

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Figure Legends:

Figure 1. 11 β-HSD1 is predominantly a reductase that catalyzes the NADPH-dependent reduction of cortisone to the active glucocorticoid, cortisol. 11 β-HSD2 functions mainly as an NADP-dependent dehydrogenase, inactivating cortisol to cortisone.

Figure 2. 11 β-HSD2 catalyzes the rapid inactivation of cortisol (compound F) to cortisone (compound E) in the kidney and the nucleus tractus solitarius. Cortisol is intended for the

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glucocorticoid receptor (GR). However, 11 β-HSD2 is absent in the hippocampus, which expresses the mineralocorticoid receptor (MR). At this site, the MR can be activated by cortisol. Since the GR has a 10-fold lower affinity for cortisol than the MR, 11 β-HSD1 provides a dynamic range for amlplification to impact signaling events. Figures adapted from Chapman et al.[1]

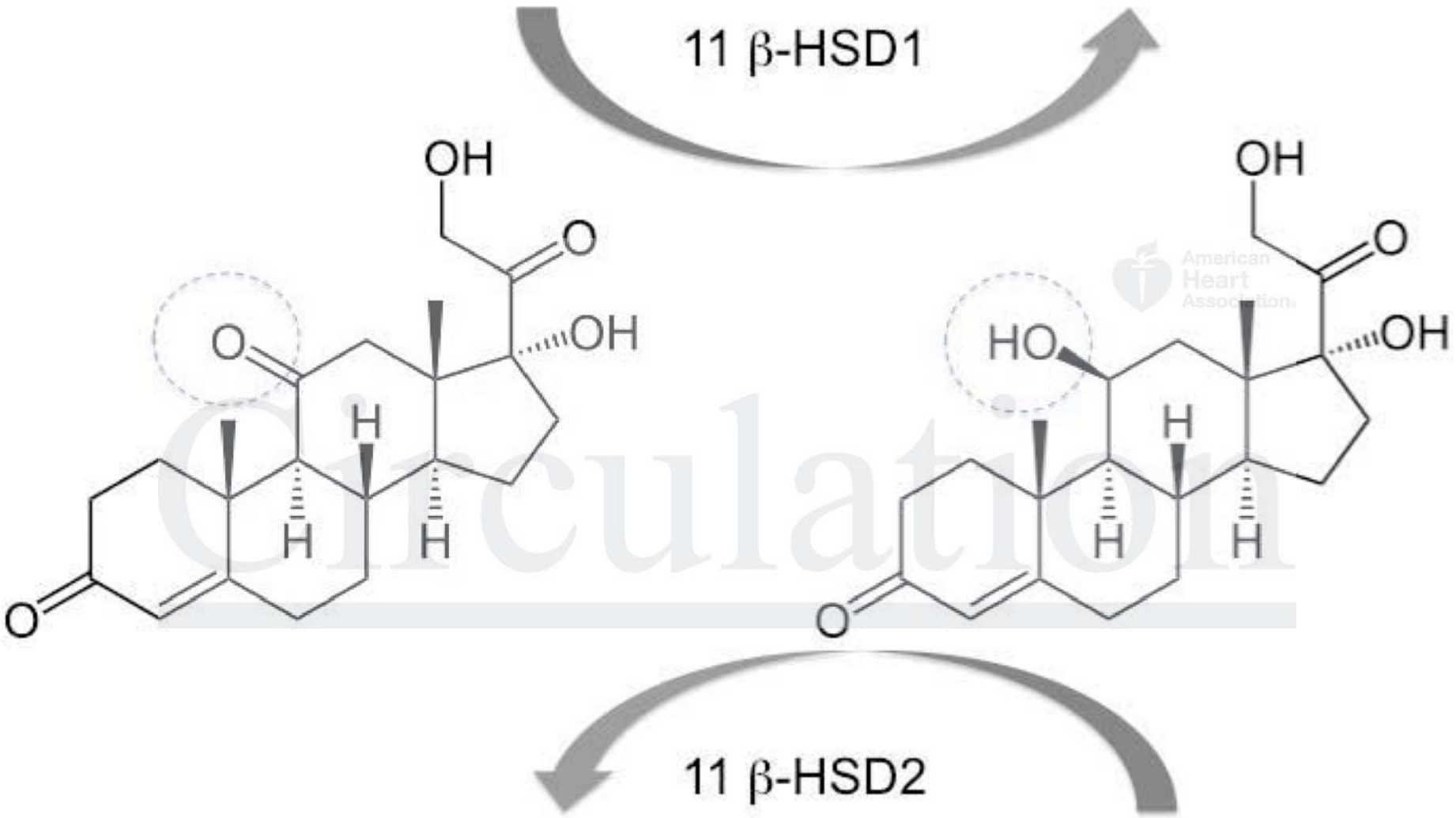
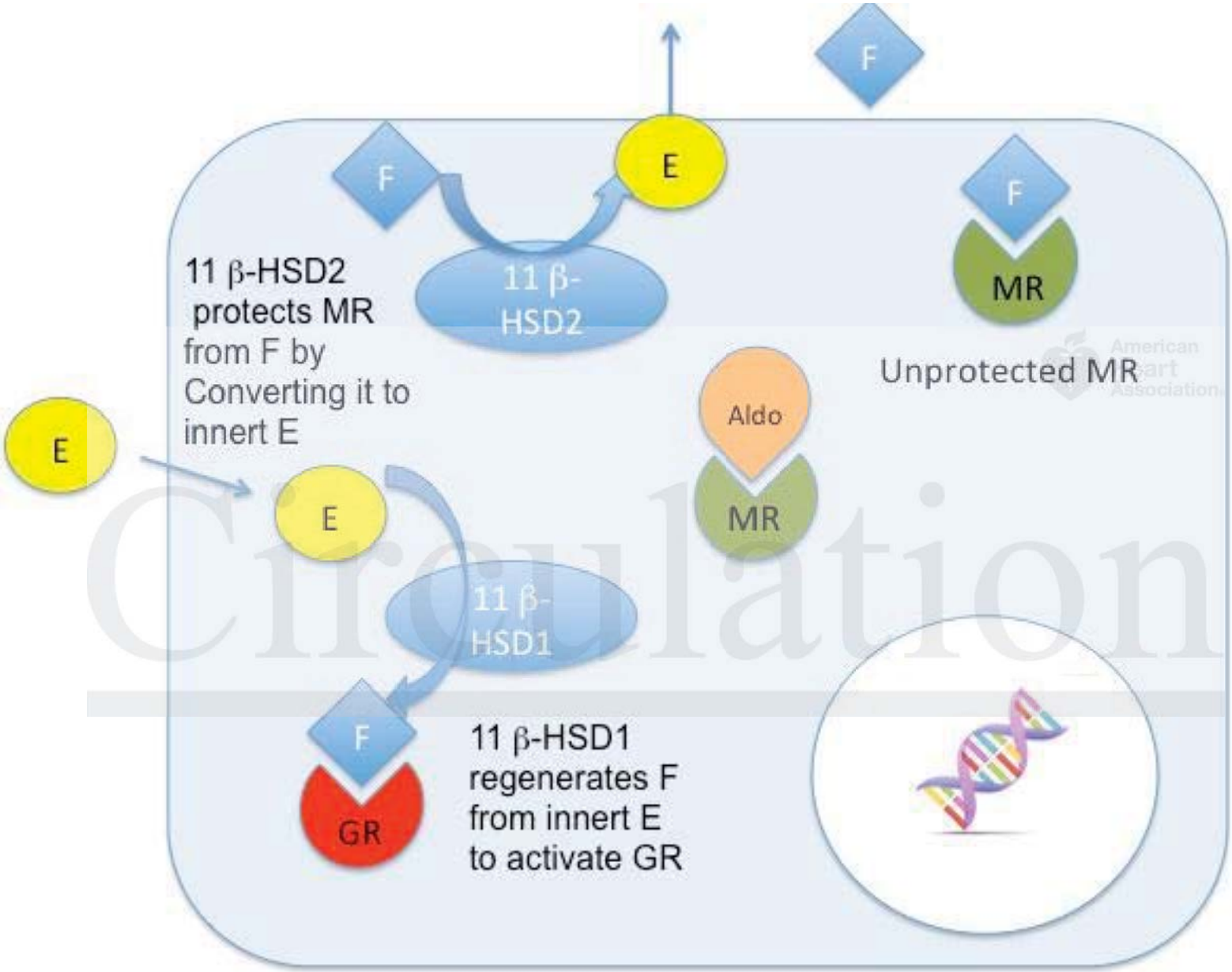


Figure 1


F
E
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protects MR
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innert E
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HSD2
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MR
Unprotected MR
Aldo
MR
E
E
11 β-
HSD1
F
GR
11 β-HSD1
regenerates F
from innert E
to activate GR

Figure 2

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