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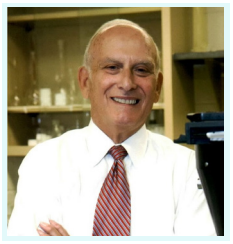
Modulation of Glucocorticoid Bioavailability through 11beta-Hydroxysteroid Dehydrogenase: A Plausible Portal to Reproductive and Developmental Toxicity



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COLUMN ARTICLE

As discussed in a recent review article, stress adversely affects mammalian reproduction and postnatal development of offspring, effects largely attributed to elevated serum levels of endogenous glucocorticoid (cortisol in primates; corticosterone in rodents). Among these effects are suppression of testosterone secretion by Leydig cells of the adult testes, multi-stage inhibition of the hypothalamo-pituitary-ovarian axis, and adverse effects in offspring, such as intrauterine growth retardation (IUGR), postpartum "programmed" effects (e.g., hypertension, insulin resistance), and reproductive abnormalities, most notably demasculinization of male phenotype and behavior [1]. The above effects of stress-induced elevation of glucocorticoids are potential confounders for *in vivo* assays employed to screen for endocrine disruptive chemicals (e.g., adult, pubertal, and one or two generational reproductive toxicity assays). In such assays, an adverse outcome attributed to a direct effect of a chemical on an estrogen or androgen mediated pathway may, in fact, involve an alternative mechanism, activation of the hypothalamic-pituitary adrenocortical (HPA) axis and the effects of elevated glucocorticoid [1]. The potential confounding effects of stress-induced activation of the HPA in reproductive and developmental toxicity studies have also been acknowledged by others [2,3].

In addition to activation of the HPA axis, bioavailability of glucocorticoids can be influenced by another mechanism, the bi-directional oxidation/reduction enzyme pathway, 11β-hydroxysteroid dehydrogenase (11β-HSD). This pathway catalyzes the interconversion between biologically active endogenous glucocorticoids (cortisol and corticosterone) and their oxidized biologically inert metabolites (cortisone and 11-dehydrocorticosterone, respectively). The direction of 11β-HSD is determined largely by two genetically and structurally distinct isozymes, 11β-HSD1 and 11β-HSD2. The first isozyme (11β-HSD1) functions primarily as a reductase, rejuvenating glucocorticoid activity from inactive metabolites (e.g., cortisone to cortisol and 11-dehyrocorticosterone to corticosterone) while 11β-HSD2, an oxidase, catalyzes the reverse reaction and inactivates glucocorticoid biological activity. This bi-directional pathway is widespread throughout the body and can play a pivotal physiological role in determining the availability of biologically active hormoneboth systemically and within specific target tissues. Two major organs exhibiting 11β-HSD activity are the liver and the kidney. In the liver, the reductive pathway (11β-HSD1) is predominant accounting for the fact that the inactive metabolite, cortisone, is biologically active when administered *in vivo*. On the other hand, the oxidative isozyme, 11β-HSD2, predominates in the kidney and is essential for normal renal function. In the distal nephron, 11β-HSD2 is associated with the mineralocorticoid receptor (MR). The MR can interact not only with the mineralocorticoid, aldosterone, but also with glucocorticoids (cortisol and corticosterone). The association between 11β-HSD2 and MR supports the specificity of aldosterone as a mineralocorticoid. This oxidative isozyme

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inactivates cortisol and corticosterone preventing their binding to the MR, while aldosterone, which is resistant to oxidation, remains active. Defects in renal 11β-HSD2 can produce excessive mineralocorticoid effects (such as hypertension and electrolyte imbalances) known clinically as apparent mineralocorticoid excess syndrome. Similar effects can also be produced experimentally by administration of licorice-based inhibitors of 11β-HSD, such as glycyrrhetinic acid and carbenoxolone [1].

The 11β-HSD oxidative/reductive pathways may play physiological roles in male and female reproduction and in utero development. In rat testes, 11β-HSD has been associated with pubertal maturation of Leydig cell function and resistance to glucocorticoid-induced suppression of testosterone secretion in dominant male rats. In human ovary, elevation of cortisol at the expense of cortisone in follicular fluid is postulated to counter the inflammatory effects associated with ovulation and fertilization. Placental 11β-HSD isozymes serve to regulate the bioavailability of glucocorticoids to the fetus providing necessary amounts of biologically active glucocorticoid for normal fetal development while preventing the adverse effects of excess glucocorticoid. Impaired placental 11β-HSD2 function, leading to excessive glucocorticoid exposure of the fetus has been linked to adverse effects in offspring, such as IUGR and programming abnormalities. Such an association has been observed with pre-eclampsia (a pregnancy disorder which manifests hypertension and high urinary protein), maternal protein restriction in rats, and after administration of licorice-derived 11β-HSD inhibitors [1].

In addition to licorice-derived compounds, other xenobiotics affect 11β-HSD activity. Cadmium (Cd) administration to maternal rats during gestation produces pre-eclampsia like symptoms, elevated fetal plasma corticosterone and reduced placental 11β-HSD2 activity. Cd also reduces 11β-HSD2 activity and expression in cultured human placental tissue. In cell free systems, man-made and natural xenobiotics inhibit the 11β-HSD2 isozyme, among these inhibitors are zearalenone, bisphenol A, 4-nonylphenol, endosulfan, perfluorooctanoic acid, and select phthalate esters [1]. Exposure of rats to select phthalate esters in utero produces "phthalate syndrome", demasculinizing effects in male offspring resulting from suppressed testosterone secretion from the fetal testes in late gestation [4]. Elevated glucocorticoid in utero also produces demasculinizing effects in offspring by suppressing fetal testosterone secretion [1]. The structural requirements for phthalate-induced inhibition of microsomal 11β-HSD2 reside in the alcohol moiety esterified to phthalic acid. These structural requirements for phthalate-induced inhibition of 11β-HSD2 activity appear to overlap with those that produce phthalate syndrome *in vivo* [5]. Accordingly, it is plausible that the actions of phthalates in offspring aremediated by exposure in utero to excess glucocorticoidas a result of impairment of 11β-HSD2 activity. In other words, the 11β-HSD pathway may be a portal by which xenobiotics produce glucocorticoid-mediated reproductive and developmental toxicity.

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