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PERSPECTIVES

Identification of scavenger receptor BI as a potential screening candidate for congenital primary adrenal insufficiency in humans

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Hoekstra M. Identification of scavenger receptor BI as a potential screening candidate for congenital primary adrenal insufficiency in humans. *Am J Physiol Endocrinol Metab* 319: E102–E104, 2020. First published May 5, 2020; doi:10.1152/ajpendo.00069.2020.—Glucocorticoids belong to the superfamily of steroid hormones that are synthesized from the common precursor cholesterol. Adrenal gland-derived glucocorticoids, e.g., cortisol in humans and corticosterone in rodents, contribute to various processes essential for normal daily life. Glucocorticoid deficiency, also referred to as primary adrenal insufficiency, therefore, often becomes evident early in life and can be present with hypoglycemia, a failure to thrive, recurrent development of infections, and neurological problems, such as seizures and coma. The majority of congenital primary adrenal insufficiency cases are caused by deleterious mutations in genes involved in the intracellular mobilization of cholesterol and the subsequent conversion of cholesterol into glucocorticoids. A significant number of glucocorticoid deficiency cases, however, cannot be explained by known genetic variations. This perspective highlights existing literature regarding the importance of lipoprotein-derived cholesterol acquisition through scavenger receptor class B, type I (SR-BI/SCARB1) for the maintenance of an optimal adrenal glucocorticoid function in mice and humans. On the basis of the reviewed findings, it is suggested that the SCARB1 gene should be included in the standard glucocorticoid deficiency genetic screening panel to *1*) facilitate knowledge development on the relative contribution of SR-BI-mediated cholesterol acquisition to steroid hormone synthesis in humans and *2*) open up the possibility to reclassify glucocorticoid deficiency patients without a currently known genetic cause for concomitant treatment optimization.

adrenal; cholesterol; glucocorticoid insufficiency; lipoprotein; SR-BI

PRIMARY ADRENAL INSUFFICIENCY DEFICIENCY: PATHOLOGY AND ESTABLISHED GENETIC CAUSES

Glucocorticoids belong to the superfamily of steroid hormones that are synthesized from the common precursor cholesterol. Adrenal gland-derived glucocorticoids, e.g., cortisol in humans and corticosterone in rodents, contribute to various processes essential for normal daily life. Glucocorticoid deficiency, that is, primary adrenal insufficiency, therefore, often becomes evident early in life and can be present with hypoglycemia, a failure to thrive, recurrent development of infections, and neurological problems, such as seizures and coma (7).

Clinically, the majority of the primary adrenal insufficiency cases can be attributed to the presence of an autoimmune reaction against the steroidogenic enzyme 21-hydroxylase (CYP21A2), a condition also referred to as Addison's disease (4, 29). Patients negative for autoantibodies against CYP21A2 are generally subjected to a genetic screen to detect congenital adrenal insufficiency. Characterization of the exact genetic cause is important since different clinical congenital adrenal insufficiency phenotypes require specific treatment strategies. More specifically, a deleterious impact on proteins involved in hormonal activation of the adrenals or the early steps in adrenal cholesterol acquisition and steroidogenesis, that is, melanocortin 2 receptor, steroidogenic acute regulatory protein (STAR/STARD1), and cholesterol side-chain cleavage enzyme (P450scc/CYP11A1) is solely associated with reduced glucocorticoid and mineralocorticoid levels (1, 8, 19, 20, 27), which can be effectively treated with standard hormone replacement therapy. In contrast, human subjects lacking a functional CYP21A2 protein (8, 15, 21, 23) not only suffer from mineralocorticoid and glucocorticoid insufficiency, but also frequently display clinical signs of hyperandrogenism, which requires additional medical attention. Importantly, a significant number of glucocorticoid deficiency cases cannot be explained by known genetic variations (8). Identification of potential novel screening candidates is, thus, of medical interest.

SCAVENGER RECEPTOR CLASS B TYPE I DEFICIENCY AS A POTENTIAL GENETIC CAUSE OF PRIMARY ADRENAL INSUFFICIENCY: INITIAL IN VIVO EVIDENCE FROM STUDIES IN RODENTS

In vitro studies in human adrenocortical cells have indicated that the cholesterol used for the production of glucocorticoids is primarily acquired from circulating spherical lipid-protein complexes, that is, low-density lipoproteins (LDL) and high-density lipoproteins (HDL) (9). In support of this, hypolipidemic drug-mediated depletion of plasma lipoproteins is associated with diminished adrenal lipid accumulation and the induction glucocorticoid insufficiency in rats and mice (3, 13). Cholesteryl ester stores are similarly deprived in adrenals from HDL-deficient apolipoprotein A1 knockout mice (24). Furthermore, isolated HDL deficiency in mice is also associated with a marked impairment in the corticosterone response to ACTH exposure (24). As such, HDL is considered the primary lipoprotein cholesterol donor in rodents.

Scavenger receptor class B type I (SR-BI), encoded by the SCARB1 gene, acts as a functional HDL receptor in mice, as it is able to bind HDL and subsequently transfer cholesteryl esters to cells without parallel whole particle uptake (2). A

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relatively high basal expression of SR-BI is present in steroid-producing tissues, such as the testis, ovary, and adrenals (18). Importantly, within the adrenals, expression of SR-BI appears to be restricted to cortical cells and is highly responsive to ACTH exposure. More specifically, ACTH treatment of wild-type mice increases total adrenal SR-BI expression, leading to clustering of SR-BI proteins in circular or ovular structures within adrenocortical cells (25). Because SR-BI deficiency in murine adrenocortical cells almost completely eliminates the ability of these cells to selectively take up cholesteryl esters from HDL (22), it was hypothesized that SR-BI may be of critical importance to acquire the cholesterol pool needed for glucocorticoid synthesis by the adrenals in mice. To provide experimental proof for this hypothesis, we and others made use of a strain of genetically modified mice lacking a functional SR-BI protein (SR-BI knockout mice), originally generated by the group of Monty Krieger (26). Adrenals from SR-BI knockout mice are largely deprived of cholesteryl esters (11). In accordance with the notion that these lipoprotein-derived cholesterol stores are used for steroidogenesis, SR-BI knockout mice fail to increase their plasma corticosterone levels to a similar extent as wild-type controls upon an ACTH challenge (5). In addition, the corticosterone response to inflammatory (lipopolysaccharide exposure) and metabolic (food deprivation) steroidogenic triggers is largely diminished as a result of total body SR-BI deficiency (5, 11, 12). SR-BI knockout mice are, therefore, more susceptible to inflammation and suffer from fasting hypoglycemia (5, 11, 12). HDL particles in SR-BI knockout mice are enlarged and contain a relatively high amount of unesterified cholesterol (26). To exclude that the change in HDL phenotype is the actual cause of the glucocorticoid insufficiency observed in total body SR-BI knockout mice, the adrenal transplantation technique originally described by Karpac et al. (17) was used. As anticipated, repopulation of bilaterally adrenalectomized wild-type mice with SR-BI knockout adrenals can recapitulate the adrenal lipid depletion and glucocorticoid insufficiency phenotype of total body SR-BI knockout mice (14). In further support, Gilibert et al. (6) have also detected the adrenal insufficiency phenotype in mice with adrenal gland-specific SCARB1 gene targeting.

VALIDATION OF THE PHYSIOLOGICAL RELEVANCE OF SR-BI FOR ADRENAL FUNCTION IN HUMANS

Humans, as opposed to rodents, express the cholesterol ester transfer protein (CETP) that is able to exchange cholesteryl esters from HDL particles with triglycerides from apolipoprotein B-containing very low-density lipoprotein and LDL. Therefore, LDL represents the primary lipoprotein species circulating in humans. Homozygous LDL receptor deficiency in humans, that is, in familial hypercholesterolemia patients, is associated with a decrease in plateau cortisol concentrations during prolonged ACTH stimulation (16). LDL receptor-mediated cholesterol uptake from LDL has, therefore, long been regarded as the driving force in the generation of substrate for adrenal glucocorticoid production in humans.

In accordance with the assumption that the CETP → LDL → LDL receptor pathway is able to effectively shuttle away cholesterol originating from HDL particles, introduction of human CETP in total body SR-BI knockout mice reverses the accumulation of cholesteryl ester-enriched HDL particles (10, 12). Supplying SR-BI knockout mice with the alternative CETP → LDL → LDL receptor cholesterol metabolism pathway does not, however, overcome the glucocorticoid insufficiency (12). This latter observation for the first time highlighted that the HDL/SR-BI-axis is possibly also of importance for adrenal functioning in the human situation. Follow-up studies in human carriers of the functional P297S mutation in the SCARB1 gene that, similarly as SR-BI knockout mice, exhibit elevated plasma HDL-cholesterol levels (28) were, therefore, executed. P297S carriers exhibit a reduced adrenal glucocorticoid function, as evident from the significant decrease in urinary 17-ketogenic steroid and 17-hydroxysteroid excretion (28). In addition, the increase in free cortisol levels upon ACTH exposure is 43% lower in P297S mutants, as compared with wild-type (nonmutated) SR-BI protein-carrying controls (28). Symptoms associated with an impaired adrenal glucocorticoid function, that is, fatigue, dizziness and fainting, are also frequently reported by heterozygous P297 mutation carriers (28). Thus, it can be appreciated that the cholesterol pool used for adrenal glucocorticoid production in humans is also generated by SR-BI-mediated uptake of lipoprotein-associated cholesteryl esters.

CONCLUDING REMARKS

Although the concept highlighted in this perspective, that is, that SR-BI is essential for an optimal adrenal cholesterol acquisition in both rodents and humans, may not be particularly ground-breaking in the eyes of lipidologists, the potential clinical implication appears to be not fully recognized within the endocrinology field. Actual detection of a functional mutation in the SCARB1 gene may possibly help physicians choose the best treatment approach for patients with glucocorticoid insufficiency, since absence of SR-BI is hypothesized to globally reduce the adrenal steroidogenesis rate. However, it should be acknowledged that the overall endocrinological impact of SCARB1 mutations in humans remains largely unknown because the number of thoroughly examined human SR-BI deficiency cases is low. Therefore, it is suggested that the SCARB1 gene should be included in the standard glucocorticoid deficiency genetic screening panel to *1*) facilitate knowledge development on the relative contribution of the SR-BI-mediated cholesterol acquisition to steroid hormone synthesis in humans and *2*) open up the possibility of reclassifying glucocorticoid deficiency patients without a currently known genetic cause for concomitant treatment optimization.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

M.H. drafted manuscript; edited and revised manuscript; approved final version of manuscript.

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