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Intestinal steroidogenesis

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ABSTRACT

Steroids are fundamental hormones that control a wide variety of physiological processes such as metabolism, immune functions, and sexual characteristics. Historically, steroid synthesis was considered a function restricted to the adrenals and the gonads. In the past 20 years, a significant number of studies have demonstrated that steroids could also be synthesized or metabolized by other organs. According to these studies, the intestine appears to be a major source of *de novo* produced glucocorticoids as well as a tissue capable of producing and metabolizing sex steroids. This finding is based on the detection of steroidogenic enzyme expression as well as the presence of bioactive steroids in both the rodent and human gut. Within the intestinal mucosa, the intestinal epithelial cell layer is one of the main cellular sources of steroids. Glucocorticoid synthesis regulation in the intestinal epithelial cells is unique in that it does not involve the classical positive regulator steroidogenic factor-1 (SF-1) but a closely related homolog, namely the liver receptor homolog-1 (LRH-1). This local production of immunoregulatory glucocorticoids contributes to intestinal homeostasis and has been linked to pathophysiology of inflammatory bowel diseases. Intestinal epithelial cells also possess the ability to metabolize sex steroids, notably estrogen; this mechanism may impact colorectal cancer development. In this review, we contextualize and discuss what is known about intestinal steroidogenesis and regulation as well as the key role these functions play both in physiological and pathological conditions.

1. Introduction

In vertebrates, the mucosal surfaces provide a barrier against invading pathogenic microorganisms but represent also an essential interface exchange between the host and its environment [1]. With a surface of broadly 300 m^2 in adults, the intestinal mucosa is the biggest mucosal surface in humans. The gastrointestinal tract is constantly colonized by a huge number of microorganisms (approximately 100 trillion), mostly bacteria, but also viruses and fungi, which are collectively referred to as the microbiota [2]. This colonization leads to a complex mutualistic relationship between the host and the microbiota in which each partner contributes positively to various physiological processes of the other one. For example, the microbiota digests and ferments carbohydrates that provide nutrients to the host cell, produces essential vitamins, contributes to the development of the gut immune system, and protects the host from potential pathogens. In turn, the host regulates microbial ecology by providing nutrients and ecological niches. It also controls microbial density trough the synthesis of antimicrobial peptides and immunoglobulins. This dialog is required to maintain what is commonly called intestinal homeostasis. The disruption of this homeostasis may lead to the development of pathologies such as inflammatory bowel diseases [3,4].

A fundamental actor in the maintenance of the gut immune homeostasis are the intestinal epithelial cells (IECs) [5,6]. IECs, located in the intestinal mucosa, provide a physical and biochemical barrier that separates microbiota and immune cells. In

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addition, interactions of IECs with the microbiota or with pathogens result in anti-microbial and immunoregulatory responses trough the production of numerous molecules [5,7–9]. One immunoregulatory molecule produced locally by IECs is represented by glucocorticoids (GCs; i.e. cortisol in humans and corticosterone in rodents).

Historically, corticosteroid (glucocorticoids and mineralocorticoids) synthesis only occurred in the adrenal cortex. A significant number of studies have now challenged this view by demonstrating that organs such as the thymus [10–12], the skin [13], the brain [14–16], the intestine [17–19], and the lung [20] are capable of producing gluco- or mineralocorticoids.

This review aims to present evidence of local steroid synthesis, particularly that of GCs in the intestine, as well as the key factors involved in the regulation of this production. We discuss the known and potential roles of GCs in the regulation of intestinal homeostasis and then review the data showing that IECs, aside from their ability to produce GCs, are also involved in the metabolism of other steroids (notably sex steroids).

2. Intestinal glucocorticoids

2.1. Evidence of intestinal GC production

The steroidogenic ability of the gut was first suggested in the beginning of the 90's after looking for the expression and activity of the CYP17 (P450c17) enzyme along the gastrointestinal tract of adult rats (see Fig. 1 for a schematic representation of the cortisol and sex steroids synthesis pathway). When Dalla Valle et al. assessed the *ex vivo* metabolism of [4–14C]pregnenolone in various organs, they found that the duodenum and the colon were able to produce high amounts of dehydroepiandrosterone (DHEA), attesting the presence of 17α-hydroxylase and C 17,20-lyase activities in the intestine [21,22]. While rodents are corticosterone-secreting animals, due to the lack of expression of CYP17 in the adrenal, CYP17 expression in peripheral tissues (notably in the intestine) could lead to the synthesis of local cortisol in rats or mice. However, an early study failed to identify GCs (corticosterone or cortisol) in the small intestine of rats by thin layer chromatography [23]. Moreover, the hypothesis of locally produced cortisol in rodents has never been tested and only corticosterone has been investigated.

In the same period of time, the identification of the transcripts encoding both CYP11A1 (cholesterol side-chain cleavage cytochrome P450; P450scc) and 3βHSD (3 beta-hydroxysteroid dehydrogenase) in the primitive gut of the mouse embryo suggested the ability of the gut to synthesize steroids *de novo* [24]. The expression of 11βHSD2 (11 beta-hydroxysteroid dehydrogenase 2), which converts active GCs to inactive metabolites, was also detected in the intestine of rodents and humans [25,26]. Subsequent studies demonstrated steroidogenic enzyme expression as well as intestinal steroid metabolism in various species such as frog [27], fish [28], mouse [17], and human [18,19,29]. Most of the comprehensive studies on intestinal steroidogenesis have been undertaken using mouse models. Cima et al. first measured (by radioimmunoassay) the *de novo* synthesis of corticosterone in murine small intestinal tissue fragments cultured *ex vivo* [17]. This production was highly stimulated in response to immune

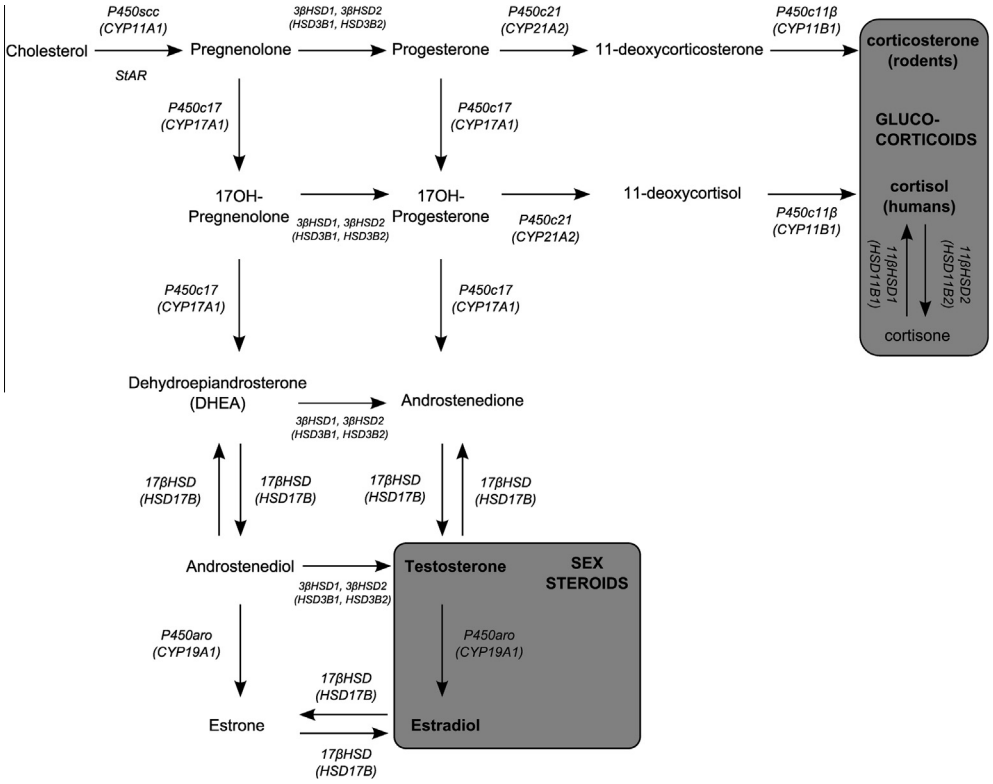

Fig. 1. A simplified overview of the cortisol and sex steroids synthesis pathway. Glucocorticoids and sex steroids result from the conversion of cholesterol by cytochrome P450 enzymes as well as dehydrogenase enzymes (hydroxysteroid dehydrogenases; HSD). StAR protein is a transporter involved in the cholesterol transport to the mitochondria where the first, rate-limiting step catalyzed by P450scc occurs. In humans, cortisol can also result from the conversion of the metabolically inactive prohormone cortisone. In rodents, the first half of the synthesis pathway is conserved, except that rodents do not express the *cyp17a1* gene in adrenals. Progesterone is transformed into 11-deoxycorticosterone (instead of 11-deoxycortisol) and 11-deoxycorticosterone is transformed into corticosterone (instead of cortisol). Corticosterone can also results from the conversion of 11-dehydrocorticosterone (not represented). For each step, both the name of the protein and the corresponding gene are indicated, with the name of the gene in parenthesis.