Molecular Aspects of Medicine 56 (2017) 101–109

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Bile acids and male fertility: From mouse to human?

Lauriane Sèdes [a, b, c, 1], Emmanuelle Martinot [a, b, c, 1], Marine Baptissart [a, b, c], Silvère Baron [a, b, c], Françoise Caira [a, b, c], Claude Beaudoin [a, b, c], David H. Volle [a, b, c, *]

[a] INSERM U 1103, Génétique Reproduction et Développement (GReD), F-63170 Aubière, France
[b] Université Clermont Auvergne, GReD, F-63000 Clermont-Ferrand, F-63170 Aubière, France
[c] CNRS, UMR 6293, GReD, F-63170 Aubière, France

ARTICLE INFO

Article history:
Received 14 December 2016
Received in revised form
9 May 2017
Accepted 12 May 2017
Available online 16 May 2017

Keywords:
Bile acids
Signaling pathways
Testis
Male fertility

ABSTRACT

Next to their involvement in digestion, bile acids have been defined as signaling molecules. They have been demonstrated to control many physiological functions among which lipid homeostasis, glucose and energy metabolisms. Bile acids are ligands of several receptors and multiple studies using transgenic mouse models defined the major roles of their respective nuclear and membrane receptors namely the Farnesoid-X-Receptor (FXRα) and the G-protein-coupled bile acid receptor 1(GPBAR1; TGR5). Here we review the reports highlighting the impacts of bile acids on testicular physiology and on male reproductive functions. The studies on mouse models open perspectives to better understand the deleterious effects of bile acids on testicular pathophysiologies and fertility disorders. Additional studies are needed to corroborate these correlations in humans.

1. Bile acids: from digestion to signaling molecules

Bile acids (BAs) are the main constituent of bile. BAs ensure solubilization and emulsification of fat to help digestion (Poupon et al., 2004). They are produced in the liver from cholesterol. This process of enzymatic modifications results in the production of primary BAs namely cholic acid (CA) and chenodeoxycholic (CDCA) (Ridlon et al., 2006; Russell, 2009). Before being excreted, BAs are, in part, combined with amine residues (glycine or taurine) leading to the production of bile salt, tauro-, or glyco-conjugates in the liver. Primary BAs and their conjugates are stored in the gallbladder and are discharged during the meal into the duodenum to facilitate the digestion of fats and their passage through the enterocyte barrier. In the ileum, BAs are partially deconjugated and are modified by enzymes of the intestinal flora (Ridlon et al., 2006). These transformations lead to the synthesis of secondary BAs with deoxycholic acid (DCA) and lithocholic acid (LCA) generated from CA and CDCA respectively. The complexity of BA pools gives them severals properties and modifies their respective affinity for receptors. Indeed, in the last decade, an increasing number of studies have defined BAs as signaling molecules involved in multiple diseases.

BAs have been described as molecules that signal through two receptors: the nuclear Farnesoid-X-Receptor alpha (FXRα; NR1H4) (Makishima et al., 1999; Parks et al., 1999; Wang et al., 1999) and the membrane receptor TGR5 (GPBAR1, G protein-coupled bile acid receptor) (Maruyama et al., 2006).

Besides their roles in immunity and lipid metabolism, a growing number of studies sustains the idea that alteration of BA homeostasis could impact testicular physiology and male fertility. Here we rapidly present key features of testicular physiology that must be of interest to clearly understand how BAs have been described to be involved in the regulation of testicular physiology.

2. Testis physiology

In male, the differentiation of the gonad leads to the formation of the testis which exerts both endocrine (synthesis of hormones) and exocrine function (production of spermatozoa) (Fig. 1**A**). Testis is divided by invaginations of the tunica albuginea that divide it into small segments called lobules. Each lobule contains several tightly coiled tubes called seminiferous tubules. Seminiferous tubules contain the germ cells, the Sertoli cells and the peritubular cells. Within the testis, Leydig cells are located in the interstitial compartment between seminiferous tubules and produce the male

* Corresponding author. INSERM U 1103, CNRS UMR 6293, Université Clermont Auvergne, Génétique Reproduction et Développement, Faculté de Médecine, 28 place Henri Dunant, F-63000, Clermont-Ferrand, France.
E-mail address: david.volle@inserm.fr (D.H. Volle).
[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.mam.2017.05.004
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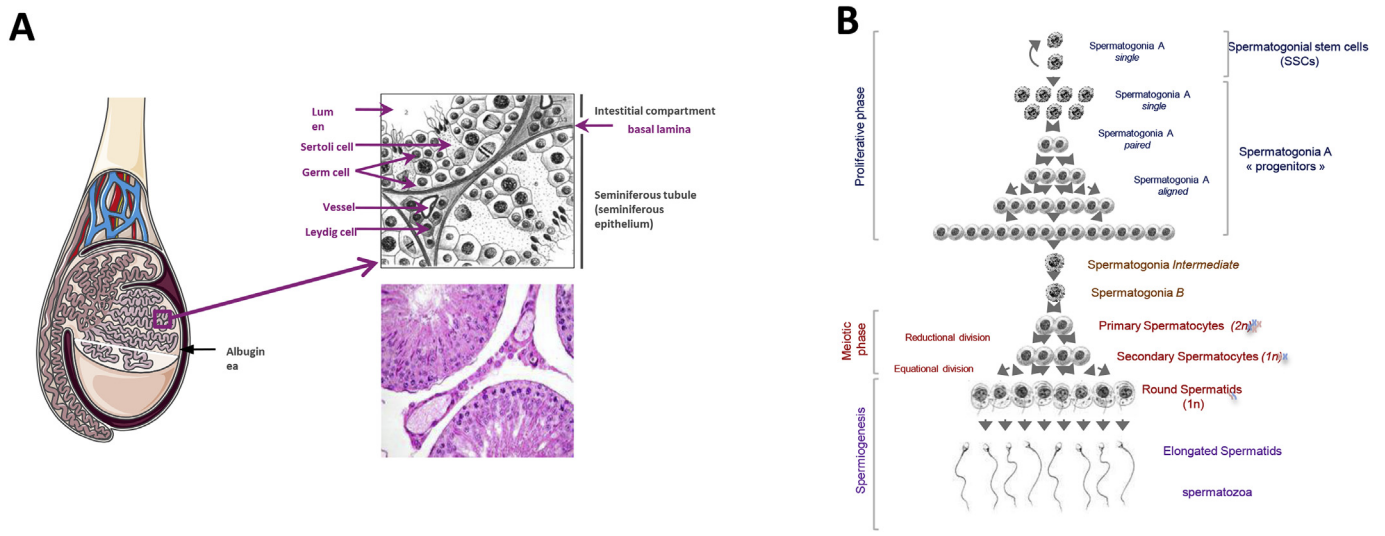

Fig. 1. Testis anatomy and spermatogenesis.
A/Schematic representation and histological view of the structure of the testis. The seminiferous tubules present somatic Sertoli cells and germ cell lineage and within the interstitial space, are located blood vessels, immune cells and Leydig cells.
B/Spermatogenesis begins with a proliferative phase. Type A spermatogonia located in contact with the basement membrane of the seminiferous tubules begins to differentiate. As spermatogonia enter in the spermatogenesis process, they are no longer considered as stem cells but as germ cell "progenitor". Following the amplification step, spermatogonial cells give rised to Type B spermatogonia. These cells undergo one last division by mitosis to produce two primary spermatocytes (Spermatocyte I). At the end of meiosis, the haploid round spermatids undergo several biochemical and morphological changes during spermiogenesis which leads to the formation of spermatozoa.

sexual hormone, e.g. testosterone (Fig. 1**B**, see section 2.2.**)**.

2.1. The endocrine function

Male hormones are essential for the testis development, the attainment of puberty and the maintenance of spermatogenesis (Fig. 2**)**.

In mammals, testosterone is the major source of circulating androgens mainly synthesized by the testis (95%), and to a smaller amounts by other organs such as the adrenal glands in human. This is a difference between species as adrenals in mouse do not produce androgens. The testes also produce estrogen and progesterone. These steroid hormones share a common biosynthesis pathway with cholesterol as precursor. The first enzymatic step of steroidogenesis involves the conversion of cholesterol to pregnenolone within mitochondria. It requires the transport of cholesterol from the outer mitochondrial membrane to the inner membrane. This rate limiting step in steroidogenesis is mainly provided by the Steroidogenic Acute Regulatory protein (*Star*) (Stocco, 2000). Then the cholesterol Side-Chain Cleavage (cytochrome P450scc), encoded by the *Cyp11a1* gene, catalyzes the cleavage of cholesterol side chain resulting in the formation of pregnenolone (Hu et al., 2004). Testosterone is produced *via* complex pathways involving enzymes such as the 3β-hydroxysteroid dehydrogenase/Δ5- Δ4 isomerase (3βHsd), the cytochrome P450 17α-hydroxylase/17,20 lyase (Cyp17a1) and the 17β-hydroxysteroid dehydrogenase enzyme (17βHsd) (Hammar and Petersson, 1986; Rey et al., 1995).

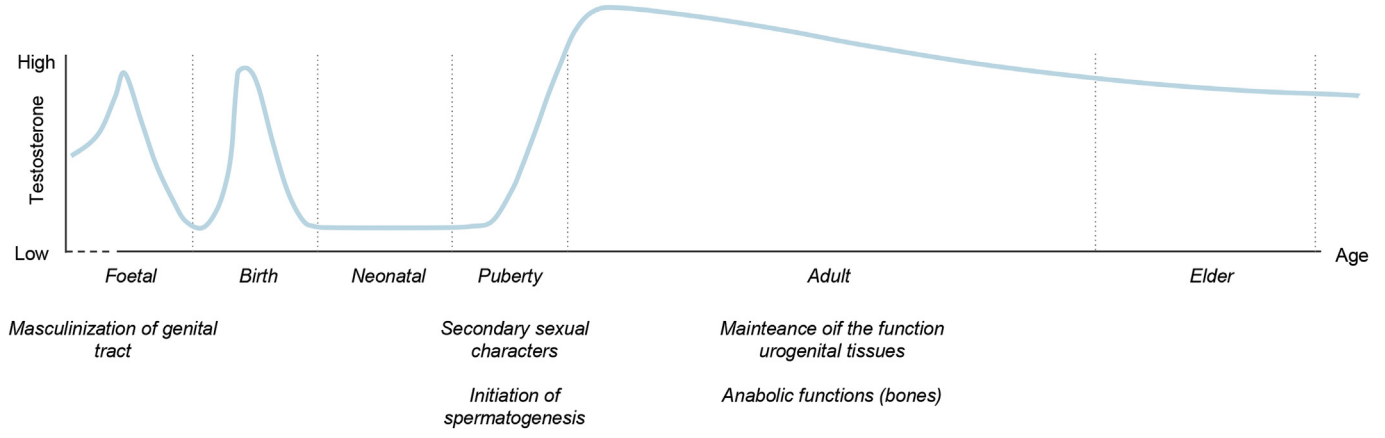

Fig. 2. Multiple roles of testosterone.
Leydig fetal cells are responsible for a first secretory peak of testosterone. This is associated with the masculinization of the urogenital tract (differentiation of the Wolff channels in epididymis, vas deferens and seminal vesicles). At puberty, a new peak of testosterone synthesis by Leydig cells allows the development of secondary sexual characteristics and the initiation of spermatogenesis by acquiring the functional maturity of Sertoli cells. In adults, maintaining testosterone concentrations is necessary for the maintenance of spermatogenesis cycles and for maintaining the function of differentiated organs of the genital tract (prostate, epididymis, seminal vesicle). Testosterone also has an anabolic power promoting the development of muscle or bone.