Molecular and Cellular Endocrinology 368 (2013) 47–58

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Endocrinology

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

Review

Emerging roles for LXRs and LRH-1 in female reproduction

Kevin Mouzat [a,*], Silvère Baron [b,c,d,e], Geoffroy Marceau [f], Françoise Caira [b,c,d,e], Vincent Sapin [f], David H. Volle [b,c,d,e], Serge Lumbroso [a], Jean-Marc Lobaccaro [b,c,d,e,*]

[a] Laboratoire de Biochimie, Centre Hospitalier Universitaire de Nîmes, Hôpital Carémeau, Place du Pr. Robert Debré, F-30029 Nimes, France
[b] Clermont Université, Université Blaise Pascal, Génétique Reproduction et Développement, BP 10448, F-63000 Clermont-Ferrand, France
[c] CNRS, UMR 6293, GReD, F-63171 Aubiere, France
[d] INSERM, UMR 1103, GReD, F-63171 Aubiere, France
[e] Centre de Recherche en Nutrition Humaine d'Auvergne, F-63000 Clermont-Ferrand, France
[f] Laboratoire de Biochimie Médicale, Faculté de Médecine, Université d'Auvergne, Place Henri Dunant, F63000 Clermont-Ferrand, France

ARTICLE INFO

Article history:
Available online 28 June 2012

Keywords:
Female reproduction
Cholesterol controlling nuclear receptors
LXR
LRH1

ABSTRACT

Nutritional status is known to control female reproductive physiology. Many reproductive pathologies such as *anorexia nervosa*, dystocia and preeclampsia, have been linked to body mass index and to metabolic syndrome. Lipid metabolism has also been associated with ovarian, uterine and placental functions. Among the regulators of lipid homeostasis, the Liver X Receptors (LXRs) and the Liver Receptor Homolog-1 (LRH-1), two members of the nuclear receptor superfamily, play a central role. LXRs are sensitive to intracellular cholesterol concentration and decrease plasma cholesterol, allowing to considering them as "cholesterol sensors". LRH-1 shares many target-genes with LXRs and has been considered for a long time as a real orphan nuclear receptor, but recent findings showed that phospholipids are ligands for this nuclear receptor. Acting in concert, LXRs and LRH-1 could thus be sensitive to slight modifications in cellular lipid balance, tightly maintaining their cellular concentrations. These last years, the use of transgenic mice clarified the roles of these nuclear receptors in many physiological functions. This review will be focused on the roles of LXRs and LRH-1 on female reproduction. Their contribution to ovarian endocrine and exocrine functions, as well as uterine and placental physiology will be discussed. The future challenge will thus be to target these nuclear receptors to prevent lipid-associated reproductive diseases in women.

Contents

* Corresponding authors. Address: "Génétique Reproduction et Développement", Unité Mixte de Recherche, CNRS 6293, Clermont Université, INSERM U1103, 24 Avenue des Landais, BP 80026, 63171 Aubière Cedex, France (J.-M. Lobaccaro).
E-mail addresses: kevin.mouzat@chu-nimes.fr (K. Mouzat), j-marc.lobaccaro@univ-bpclermont.fr (J.-M. Lobaccaro).

0303-7207/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mce.2012.06.009

1. Introduction

Nuclear receptors (NRs) belong to a superfamily of transcription factors, widely represented in animal kingdom, which are potentially activated by lipophilic ligands. Interestingly, in the 1950s, biochemists thought a hormone like estrogen entered a cell, where a series of oxidation and reduction reactions with the estrogen provided needed energy for the specific estrogen actions. From the late 1950s, Elwood Jensen entirely overturned that notion by proving that hormones did not provoke chemical change. In 1958, using a radioactive marker, he showed that blood injected estrogens were able to concentrate in female reproductive tract and more precisely bound to proteins, which he called "estrogen receptors" (Jensen, 1968).

From a functional point of view, NRs can schematically be divided in three distinct classes: endocrine receptors activated by high-affinity ligands (including steroid nuclear receptors); "adopted" nuclear receptors (i.e. whose ligand has been identified after the discovery of its receptor) and orphan nuclear receptors, activated by no known ligand (Chawla et al., 2001). Roles of nuclear receptors in female reproductive physiology are known since the discovery of sex steroid receptors. In humans and non-primate mammals, the control of ovarian function by nuclear receptors, particularly progesterone (Conneely, 2010) and estrogen receptors (Drummond and Fuller, 2012), has indeed been widely documented. Steroids act as major actors of female reproductive activity, controlling exocrine (from follicle maturation to ovulation and *corpus luteum* formation and function) as well as endocrine functions (i.e. production of ovarian hormones), both directly and by controlling hypothalamic–pituitary–gonadic axis (for a review, see Neal-Perry et al. (2010)). More recently *in vitro* studies and phenotype analyses of engineered mice have suggested the emerging role of adopted and orphan nuclear receptors. In particular, cholesterol-lowering nuclear receptors have clearly a major role

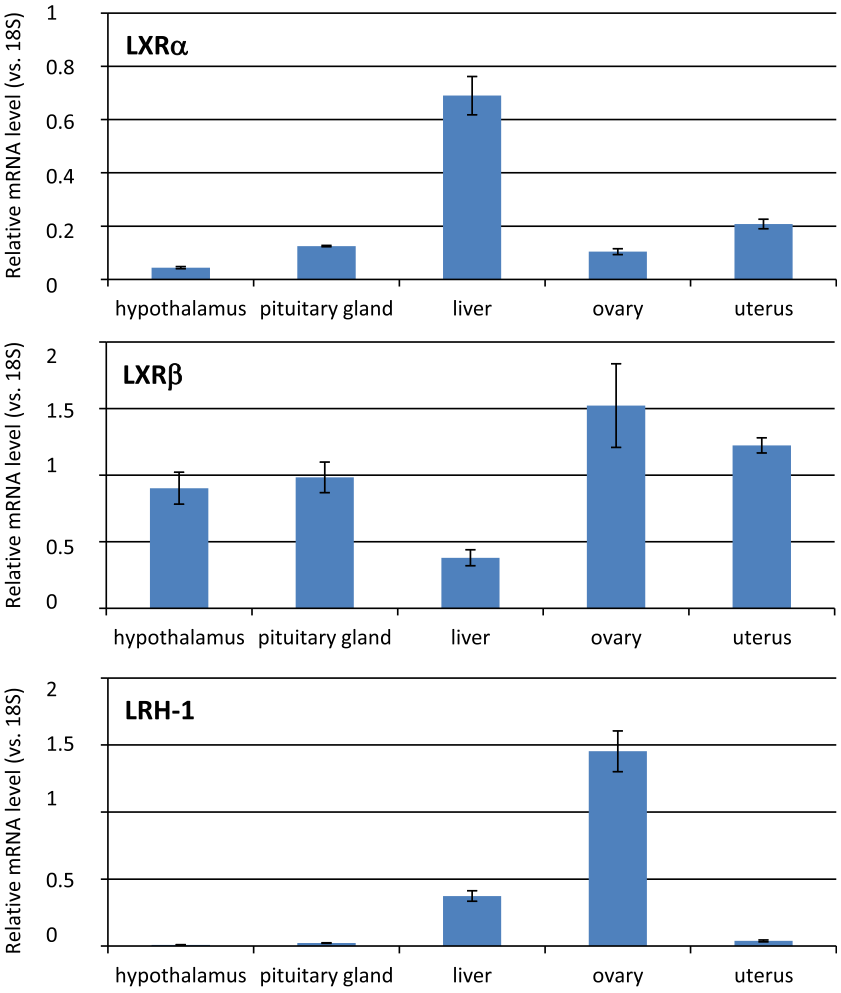

Fig. 1. Accumulation sites of mRNA encoding mouse Lxrα, Lxrβ and Lrh-1. This chart is adapted from NURSA.org data (www.nursa.org/10.1621/datasets.02001). mRNA have been extracted from 129x:SvJ mice and the levels compared to 18S accumulation. For more details regarding the technical aspects see Bookout and Mangelsdorf (2003).