Journal of Steroid Biochemistry & Molecular Biology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

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

Review

Steroids and endocrine disruptors—History, recent state of art and open questions

Q1 Richard Hampl*, Jana Kubátová, Luboslav Stárka

Institute of Endocrinology, Národní 8, 116 94 Praha 1, Czech Republic

ARTICLE INFO

Article history:
Received 24 March 2014
Received in revised form 14 April 2014
Accepted 20 April 2014
Available online xxx

Keywords:
Steroids
Q2 Endocrine disruptors
Sites of action
Overreview

ABSTRACT

This introductory chapter provides an overview of the levels and sites at which endocrine disruptors (EDs) affect steroid actions. In contrast to the special issue of Journal of Steroid Biochemistry and Molecular Biology published three years ago and devoted to EDs as such, this paper focuses on steroids. We tried to point to more recent findings and opened questions.

EDs interfere with steroid biosynthesis and metabolism either as inhibitors of relevant enzymes, or at the level of their expression. Particular attention was paid to enzymes metabolizing steroid hormones to biologically active products in target cells, such as aromatase, 5α-reductase and 3β-, 11β- and 17β-hydroxysteroid dehydrogenases. An important target for EDs is also steroid acute regulatory protein (StAR), responsible for steroid precursor trafficking to mitochondria.

EDs influence receptor-mediated steroid actions at both genomic and non-genomic levels. The remarkable differences in response to various steroid-receptor ligands led to a more detailed investigation of events following steroid/disruptor binding to the receptors and to the mapping of the signaling cascades and nuclear factors involved. A virtual screening of a large array of EDs with steroid receptors, known as in silico methods (=computer simulation), is another promising approach for studying quantitative structure activity relationships and docking.

New data may be expected on the effect of EDs on steroid hormone binding to selective plasma transport proteins, namely transcortin and sex hormone-binding globulin.

Little information is available so far on the effects of EDs on the major hypothalamo–pituitary–adrenal/gonadal axes, of which the kisspeptin/GPR54 system is of particular importance. Kisspeptins act as stimulators for hormone-induced gonadotropin secretion and their expression is regulated by sex steroids via a feed-back mechanism. Kisspeptin is now believed to be one of the key factors triggering puberty in mammals, and various EDs affect its expression and function.

Finally, advances in analytics of EDs, especially those persisting in the environment, in various body fluids (plasma, urine, seminal fluid, and follicular fluid) are mentioned. Surprisingly, relatively scarce information is available on the simultaneous determination of EDs and steroids in the same biological material.

This article is part of a Special Issue entitled 'Endocrine disruptors & steroids'.

Contents

Abbreviations: BPA, bisphenol A; DDE, 2,2′-bis-(4-chlorophenyl)-1,1′-dichloroethene; DDT, dichlorodiphenyltrichloroethane; FSH, folitropin; LH, lutropin; PCB(s), polychlorinated biphenyl(s); PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; SHBG, sex hormone-binding globulin.

* Corresponding author. Tel.: +420 224905289; fax: +420 224905412.
E-mail addresses: rhampl@endo.cz, richardhampl@email.cz (R. Hampl).

http://dx.doi.org/10.1016/j.jsbmb.2014.04.013
0960-0760/

Please cite this article in press as: R. Hampl, et al., Steroids and endocrine disruptors—History, recent state of art and open questions, J. Steroid Biochem. Mol. Biol. (2014), http://dx.doi.org/10.1016/j.jsbmb.2014.04.013

1. Introduction

1.1. History

The term endocrine disruptors (EDs) as substances which can interfere with the endocrine or hormone system in mammals dates back to the early nineties [1], but it was well known much earlier that many chemicals present in the environment may affect, mostly adversely, human and animal life and health. This includes many civilization diseases across the life cycle, such as cancer, genetic modification, metabolic diseases, the malfunction of various organs and, last but not least, reproduction. Concerning their effect on reproduction and, in broader terms the endocrine system, it is not surprising that a great part of this matter deals with steroids. This has been the subject of numerous reviews and monographs, such as that of Gore [2]. Some of these topics were addressed and discussed in this journal two years ago [3].

1.2. Classification

EDs may be divided into natural compounds such as soy phytoestrogens, extracts and formulas from various plants or fungi and a broad spectrum of human and industrial products. The latter comprise chemicals used in fighting undesired wildlife and agricultural threats (pesticides, fungicides, insecticides, and rodenticides) or various synthetic compounds as substances used in the production of plastics and plasticizers, packaging materials, including also non-intentionally added substances (bisphenol(s), phthalates) or a broad spectrum of industrial chemicals used as building materials, paints, isolation materials (PCBs, metals). Endocrine disruptors also include many drugs derived from natural hormones, particularly all contraceptives. Given their duration in the environment, EDs are usually divided into persistent and short-life compounds. The use of many of these chemicals (see e.g. DDT) was banned after their effects on wild life were discovered, but they still persist in the environment.

1.3. Effects

Generally, EDs may intervene in the hormonal function at various sites: they can directly affect hormone biosynthesis, the metabolism, transport, and mechanism of action on both receptor and post-receptor levels. They may act at a genome level by influencing gene expression and even via epigenetic mechanisms, including effects on genomic imprinting. Many EDs are known to affect fetal (prenatal) development. Other characteristic features of some EDs are their transgenerational effects and their often non-linear or non-monotonic dose–response curves. Some EDs act in an additive way with natural hormones and act complexly upon multiple targets. Finally, EDs can interfere with feed-back mechanisms typical for the endocrine system.

In the following text we will not repeat known facts about EDs, but focus on their effect on steroids, namely their biosynthesis, metabolism, mechanism of action, their co-existence with steroids in body fluids as potential biomarkers, and also discuss their participation in feed-back mechanisms in an attempt to point to open questions.

2. EDs and steroid biosynthesis and metabolism

EDs may influence steroid biosynthesis and metabolism either as inhibitors or rarely as activators of key enzymes, or on the level of the respective enzyme expression. Many excellent reviews have appeared since the beginning of this century demonstrating *in vitro* as well as in vivo inhibitory effects of an array of EDs, covering most of their classes – pesticides, plasticizers, dioxins, PCBs and polycyclic aromatic hydrocarbons, and their impact on ovarian or testicular functions [4–9]. The reviews covered all steroidogenic enzyme issues, most of which belong to the cytochrome P450 family [4,5,7]. Some of them dealt preferably with gonadal, ovarian [7,8] or Leydig cell [6,9] steroid biosynthesis.

Particular attention was devoted to aromatase activity [8], not only in humans or rodents, but also in fish regarding the strong impact of EDs pollutants in water on fish reproduction [10]. In rodents, it was shown that bisphenol A from plasticizers may even increase aromatase activity in rat prostate. At the same time, this chemical affects the expression of another important steroid metabolizing enzyme – 5α-reductase – existing in form of three isoenzymes (5α-R1, 5α-R2 and 5α-R3). While the expression of the first two isoenzymes is inhibited by bisphenol A, the third, 5α-R3, known as a biomarker for malignancy, is increased. It is an example of the synergic effect of the disruptor at various sites, each leading to an increased risk of cancer [11]. 5α-Reductase isoenzymes as targets for EDs are important enzymes not only due to metabolizing testosterone and its precursor to peripherally active androgens [12], but also in biosynthesis of 5α-saturated C21 neuroactive steroids as allopregnanolone [13]. So far little is known about EDs action on this enzyme in brain.

3β-Hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) are key enzymes involved in androgen biosynthesis in Leydig cells. Various phthalates were tested as potential inhibitors of these enzymes in human and rat testicular preparations. Their inhibitory activities differed according to the length of carbon chains in the ethanol moieties [14]. Both enzymes were also inhibited by perfluorinated chemicals [15]. For a review of the effect of a broad spectrum of EDs covering industrial materials (perfluoroalkyl compounds, phthalates, bisphenol A and benzophenone) and pesticides/biocides (methoxychlor, organotins, 1,2-dibromo-3-chloropropane and prochloraz) and plant constituents (genistein and gossypol) see e.g. [9].

17β-HSD and 11β-hydroxysteroid dehydrogenase (11β-HSD) are also enzymes regulating the actual concentration of biologically active hormonal steroids in peripheral tissues. While 17β-HSD acts on sex steroids (testosterone and estradiol and its 17-oxo precursors), 11β-HSD isoenzymes convert 11-oxo corticoids into their hormonally active 11β-hydroxy-derivatives and vice versa. While the first type of 11β-HSD acting as reductase is ubiquitous, the especial role of Type 2 11β-HSD acting as oxidase, protects kidney and also testicular Leydig cells from an excess of

Please cite this article in press as: R. Hampl, et al., Steroids and endocrine disruptors—History, recent state of art and open questions, J. Steroid Biochem. Mol. Biol. (2014), http://dx.doi.org/10.1016/j.jsbmb.2014.04.013