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Effects of endocrine disruptors on the human fetal testis

Effets des perturbateurs endocriniens sur le testicule fœtal

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Abstract

The modern societies are exposing us to a huge variety of potentially harmful pollutants. Among these endocrine disruptors (EDs) have been especially scrutinized as several were proven to display reprotoxic effects in rodent models. In the context of high and growing concerns about the reprotoxicity of EDs, it is crucial to carry out studies in order to assess their impact on the human reproductive function. However, such evidence remains scarce. The fetal period is critical for the proper development of the testis and is known as a period of high sensitivity to many EDs. Our team has shown in 2009 that a phthalate, mono-(2-ethylhexyl) phthalate (MEHP), has a potential deleterious effect on the development of human male germ cells. This result was the first direct experimental proof of the toxic effect of an ED in human testis. More recently, we also reported that bisphenol A (BPA) impaired testosterone production in the human fetal testis. Here, we will summarize the known effects of EDs on the various cell types composing the human developing testis and discuss their relevancy to propose future directions.

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Keywords: Endocrine disruptors; Developing gonads; Human health; Reprotoxicity

Résumé

Les différentes activités humaines modernes nous exposent en permanence à une très large variété de perturbateurs endocriniens. Plusieurs de ces substances présentent des effets reprotoxiques avérés chez les rongeurs. De manière inquiétante, une période de vulnérabilité accrue vis-à-vis de certains perturbateurs se situe au cours de la vie fœtale. Ainsi, des études de plus en plus nombreuses rapportent des effets délétères sur la fonction testiculaire du fait de l'exposition in utero. Cependant, il existe peu de preuves expérimentales que ces observations soient transposables à l'homme. Notre équipe fut la première à démontrer les effets néfastes d'un perturbateur endocrinien, le mono-(2-éthylhexyl) phtalate (MEHP) sur le développement testiculaire humain. Récemment, nous avons également observé que le bisphénol A altérait la production de testostérone du testicule fœtal humain. Dans cette revue nous rapportons les effets connus de perturbateurs endocriniens sur les différents types cellulaires du testicule fœtal humain et discuterons leur cohérence vis-à-vis des données issues de modèles rongeurs.

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Mots clés : Perturbateurs endocriniens ; Gonades fœtales ; Santé humaine ; Reprotoxicité

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1. The human developing testis

The testis ensures two main functions, gametogenesis and spermatogenesis. Each relies on specific structures within the testis. Gametogenesis occurs in the seminiferous tubules containing Sertoli and germ cells. A basal membrane and peritubular myoid cells surround those tubules and in-between, the interstitial tissue contains blood vessels and Leydig cells. Leydig cells are the steroid producing cells and secrete large amounts of testosterone.

Both functions are set up early during fetal life in the first stages of testicular organogenesis. In the human, the primordial gonad first appears as a thickening of the coelomic epithelium on the ventral part of the mesonephros. This structure termed gonadal anlage is rapidly colonized by primordial germ cells that migrate from extra-embryonic areas. At this stage, no morphological difference can be observed when comparing XX and XY gonads, and the gonad is termed undifferentiated or bipotential. These events occur between the fourth and the sixth weeks post-fertilization (wpf) [1]. Specifically in the XY gonad, testicular cords, the precursors of the adult tubules, will then differentiate. This and the subsequent differentiation of the testis are due to the differentiation of the Sertoli cells. Testicular cords are clearly visible shortly after 6 wpf in the developing human testis and these contain germ cells surrounded by Sertoli cells. These cords form a niche allowing male germ cell proliferation and progressive differentiation (i.e. orientation toward the spermatogenic pathway) to establish a pool of precursor cells that will provide the spermatogonial stem cells in the adult. In parallel, within the interstitium, fetal Leydig cells differentiate and start producing massively testosterone. At this stage, the Leydig cells also produce another hormone, insulin-like 3 (INSL3), a factor involved in testicular descent. The activity of fetal Leydig cells is largely stimulated by the human chorionic gonadotropin inducing a peak of testosterone secretion at the end of the first trimester of gestation.

Unfortunately, most of the molecular keys regulating the development of the various cell types in the human testis are poorly identified yet and most of the knowledge about this tissue has been gained through comparison with the mouse model due to the numerous genetic models available. However, it is likely that numerous specificities exist, particularly in terms of hormonal sensitivity. As an example, it was recently reported that the human fetal testis is poorly responsive to a synthetic oestrogen (diethylstilbestrol) while the mouse one has been proven to be largely perturbed when exposed to such estrogens [2,3].

2. Related pathologies

Several pathologies are believed to originate from an improper development of the testis. Among these one easily associate oligozoospermia to a defect of proliferation/differentiation of the embryonic germ cells. It is also admitted that an impair differentiation of the male embryonic germ cells may give rise to carcinoma in situ later during post-natal life. This lesion is the precursor of the testicular cancer and shares numerous common markers with undifferentiated

germ cells [4]. Defect of masculinisation may be triggered by alteration of the steroidogenic activity. Those defects encompass hypospadias and cryptorchidism, the later being also susceptible to be due to an impaired production of INSL3.

3. Experimental models

Both epidemiological and experimental approaches can be used to investigate the human response to EDs. However, epidemiological approaches are limited due to the multiple exposures that need to be taken into account and their associative nature. Furthermore relationship between in utero exposures and adult diseases is long and difficult to establish through prospective studies. Thus, experimental work is needed to explore the fetal origin of reproductive defects.

Currently, two main experimental models are used to assess the response of the human fetal testis to various chemicals (Fig. 1). The first one is the organ culture system, which we largely contributed to develop [5]. The second one is a graft model using immunodeficient mice [6,7]. Both have limits and advantages. The main advantages of the organ culture protocol are that:

- it allows a fine control over the concentration of the substance in a defined environment;
- it is rapid and relatively inexpensive;
- it allows following the daily secretions of the gonads (i.e. through changing regularly the media).

On the other hand, such a protocol is poorly adapted for long-term exposure and bypass the metabolism due to other tissues. The grafting protocol allows a vascularisation of the tissue that permits an optimal diffusion through the blood system. Furthermore, it is well adapted for long-term experiments and allows exposure through the oral route.

4. The case of phthalates

Since 1931, phthalates are used in numerous plastics. DEHP (di-(2-ethylhexyl) phthalate) and DBP (di-n-butyl phthalate) are the most abundant phthalates. Once ingested, these are rapidly hydrolysed and form monoesters that are the active metabolites, respectively MEHP and MBP (mono-n-butyl phthalate).

In rodents, the effects of DEHP and DBP exposure in utero have largely been described. Those compounds induce a massive germ cell loss in the developing testis. A hallmark of the effect of phthalates in rodents is also the occurrence of abnormal multinucleated germ cells (MNG). In the developing human testis in organ culture, we evidenced that MEHP also induce germ cell apoptosis with no obvious induction of MNG. Interestingly, this effect was observed after a short exposure (three days) and at mild doses (10^{-5} M), compatible with the human exposure [8]. Human fetal testis xenografts exhibit on the contrary MNG induction after a short exposure to DBP [9] with no decrease in the germ cell density. This discrepancy may be imputable to the difference of stages at which testes were transplanted or cultured. Indeed in the xenografts experiments most tissues were

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