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Endocrine disruptors

Endocrine disruptors: Revisiting concepts and dogma in toxicology

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ABSTRACT

During the last decades, a large number of observations have shown that some exogenous substances could interfere with hormone levels or hormone action and could induce toxic effects. This has led to the identification of endocrine disruptors more than 25 years ago as a new class of toxic agents (Zoeller et al., 2014). Those widely used agents correspond to a variety of chemical classes, are not identified by their chemical structure or by a specific type of usage, but rather by their mechanisms of action; this is not unprecedented in toxicology since genotoxicants have also been identified by their mechanism of action, i.e. their ability to alter DNA structure and function.

During the last decades, a large number of observations have shown that some exogenous substances could interfere with hormone levels or hormone action and could induce toxic effects. This has led to the identification of endocrine disruptors more than 25 years ago as a new class of toxic agents [1]. Those widely used agents correspond to a variety of chemical classes, are not identified by their chemical structure or by a specific type of usage, but rather by their mechanisms of action; this is not unprecedented in toxicology since genotoxicants have also been identified by their mechanism of action, *i.e.* their ability to alter DNA structure and function.

It is not overstated to claim that the discovery of EDCs has opened a new era in the field of toxicology. Studies on EDCs have questioned some of the dogma of traditional toxicology and have changed our ways of viewing toxic actions. In this short report, we will show how those chemicals have triggered both conceptual and practical changes in our approach to toxicity.

1. Back to physiology

One of the most striking consequences of EDC work is that toxicology and physiology have been brought together again. For those interested in the history of toxicology, it is interesting to recall that the initial development of this science in the 19th century has been carried out by physiologists and medical scientists such as Claude Bernard and François Magendie [2]. This was indeed critical to understand the systemic effects of certain toxicants such as curare. However, other disciplines have considerably influenced toxicological studies. Indeed, toxicology has been intimately associated with analytical sciences, which allowed basic and regulatory scientists to detect and quantify toxicants and to answer critical questions such as the type of exposure to chemicals and its level. Later, toxicologists started using chemical, molecular and cellular concepts and tools, and were able to develop mechanistic approaches. To a certain extent,

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this has shifted the focus away from physiological approaches. However, with the advent of EDCs, toxicologists started to address such questions as the consequences of subtle changes in sex hormone levels during the menstrual cycle or the effect of exposure to contaminant during the critical phases of organ development. Clearly, a more integrated approach was required and therefore, toxicologists had to go back to their physiology textbooks. This is not all. In fact, disruption of the endocrine system is only one aspect of what exogenous substances can do to alter a physiological system. There are clearly substances that interfere with the nervous system and not necessarily by disrupting hormone action. Other substances could change developmental programming through mechanisms that are not necessarily related to endocrine action. Those substances share with EDCs a number of properties and consequently we tend to call them EDCs too, although this is not strictly correct. What we are actually talking about are Physiological Homeostasis Disrupting Compounds (PHDCs). Now, the "EDC" brand name is well established and it is probably too late to change, but we have to acknowledge that we deal with EDCs and EDC-like compounds. This has regulatory implications since the EU definition is strictly related to endocrine disrupting compounds and would not cover compounds that may interfere with the nervous system or the immune system.

2. The dose

The discovery of the EDCs has added another chapter to the "low dose" issue in toxicology. This is not a new issue. The 1950s and the 1960s have witnessed some strong controversies between different groups of toxicologists. Some claimed that for most compounds there was no safe dose, even at low concentrations, while other claimed that, below a certain threshold that should be determined, most compounds were safe. The latter view prevailed but with the important exception of genotoxicant carcinogens for which it was considered that even very low doses could lead to irreversible effects (*i.e.* mutagenesis and long-term effects). This Yalta-like conclusion was the dawn of regulatory toxicology and of regulatory reference values below which compounds were considered essentially harmless. It should be noted that scientific foundations for the calculation of those reference values are at best controversial. EDCs have brought the dose issue to light again. First, it was observed that low doses, *i.e.* doses similar to a usual environmental contamination, can have significant effects in some experimental models, notably during developmental windows of vulnerability [3]. This means that some reference values that are determined based on regulatory and often non-comprehensive tests may not be protective enough. One has to keep in mind that most toxic effects related to EDCs have not been discovered through traditional regulatory tests, but rather by academic scientists exploring new mechanisms of toxicity. The second important point is that, in some cases, the dose response curve describing one toxic effect of a chemical as a function of its dose may not be monotonous. Intuitively, most of us would think that a toxic effect should increase with the dose. In reality, there are cases where effects are more potent at lower doses than at higher ones. This has been discussed at length in several conferences and papers [3,4]. The mechanisms are diverse and could be related to multiple mechanisms of action triggered at different doses or to the intrinsic properties of the endocrine system. Recently, Anses and other EU agencies have critically analyzed the literature for dose effects and concluded that, while some of the claims for non-monotonous dose response curves are overstated, there are indeed a few cases where dose response curves could confidently be considered as non-monotonous in humans [5]. One important consequence of non-monotonous curves is that regulatory tests should now encompass a much larger dose range than previously in order not to miss a specific low dose effect and that identification of reference doses may become even more difficult than in the past [6]. A reevaluation of the regulatory approaches to reference value determination appears to be required.

3. Time

One of the most challenging tasks in toxicology is to understand the mechanisms of long-term effects leading to chronic diseases and to find the right models to study them. Long-term means years, decades and possibly generations! With the exception of mutagens, long-term effects were traditionally thought to be related to continuous exposure as in the case of air pollution and smoking. Toxicity related to long-term continuous exposure has some paradoxical features. Indeed, in many cases such a long-term toxicity is unexpectedly related to the adaptive metabolic pathways that are triggered by exposure to chemicals; those pathways, by allowing the elimination of chemicals are protective in the short term, but they also entail the transient production of very reactive intermediate compounds that may lead to toxicity in the long run [7]. What this is telling us is that the same pathway could be adaptive or toxic depending on the time scale that is considered. Long-term effects could also be due to the internal persistence of chemicals as in the case of Persistent Organic Pollutants (POPs) which are poorly metabolized and eliminated and which are stored in adipose tissue; the latter, in turn, becomes an internal source of continuous exposure [8]. Again, this tissue has a paradoxical effect toward POP handling; by storing those pollutants, the adipose tissue protects other sensitive organs such as the brain or gonads, but in the long run, it does constitute an internal source of chronic exposure.

With EDCs, a third mechanism was unraveled. Indeed, both experimental and epidemiological studies indicated that exposure to several EDCs at specific developmental stages was associated with an increase in the risk of disease later in life [9]. In that case, exposure can be either continuous or limited in time, but the targeted organism is in a state of high vulnerability. It is thought that vulnerability is due to the remodeling of tissues and organs during development and to limited defense mechanisms. The most likely mechanism is through the alteration of epigenetic marks that are somatically heritable and that therefore may persist for a long time [10]. Such alterations