Medical Xpress

Genetic inequity towards endocrine disruptors

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Phthalates, one of the most common endocrine disruptors, are commonly used by industry in many plastic products—toys, clothing, baby bottles or even medical equipment—as well as in cosmetics. If guidelines are beginning to be imposed to limit their use, their toxic effect on the endocrine system is worrying. Indeed, the exposure of male fetuses to phthalates can have devastating consequences for the fertility

of future individuals by modifying the regulatory elements of the expression of genes responsible for spermatogenesis. However, we are not all equal: researchers at the University of Geneva (UNIGE) and the University Hospitals of Geneva (HUG), Switzerland, show that phthalate susceptibility depends largely on the genetic heritage of each individual. These results, to be discovered in PLOS One magazine, raise the question of individual vulnerability as well as that of the possible transmission to future generations of epigenetic changes that should normally be erased during fetal development.

Ariane Giacobino, a researcher in the Department of Genetic Medicine and Development at UNIGE Faculty of Medicine and Associate Assistant Physician at HUG Division of Genetic Medicine, is a specialist in epigenetics (the study of the elements that modify gene expression). In 2015, she observed, by comparing two groups of mice, a very different sensitivity to phthalates, one of the most common endocrine disruptors. "We exposed pregnant females to phthalate doses and studied sperm concentration and quality in their male offspring. If one group had very poor sperm quality, the other group, even though they were exposed to the same doses, would get away with it," explains Ariane Giacobino. Why such a difference?

The researchers reviewed possible epigenetic and genetic causes to determine where the difference between the two groups lays. To do so, they studied all variations of the epigenome and genome of these two groups of mice.

Epigenetic changes that goes down to the next generation

Scientists administered a dose of phthalate to both groups of mice for 8 days between 8 and 18 days gestation. Ludwig Stenz, Junior Lecturer in

the Department of Genetic Medicine and Development at UNIGE Faculty of Medicine and first author of this work summarizes their results: "We studied epigenetic and genetic variations in specific portions of the genome, located in the vicinity of genes related to spermatogenesis. This allowed us to identify the exact epigenetic mechanism at work that modulates gene expression upwards or downwards, and thus influences sperm quality and mobility."

The researchers identified hormone-binding sites in the genome of mice vulnerable to phthalates that are not present in the resistant group. This is probably where the endocrine disruptors bind and inactivate these genes. Conversely, the other group presents a protein-binding site in its genome that increases the production of protective elements.

In addition, the researchers observed a worrying phenomenon: not only does the epigenetic effect of phthalates prevent spermatogenesis genes from expressing themselves correctly, but in addition the epigenetic wipe out that usually takes place between generations seems to be no longer completely achieved over the two generations following the individual's exposure.

What about human beings?

This study, funded by the Swiss Centre for Human Toxicology (SCAHT), will now extend to cohorts of men in Switzerland exposed to phthalates. "We currently have no way of knowing to what extent we are –individually or in terms of population—genetically susceptible or not to these epigenetic disruptions, says Ariane Giacobino. We want to have an idea of the proportion of people who are vulnerable to each product. In normative terms, the epidemiological dimension should also be taken into account, as well as possible transgenerational effects. Indeed, if 95 percent of the population is vulnerable or if only 5 percent are, the question could be examined differently. In addition, the regional and

ethnic dimension should perhaps be taken into account."

More information: Ludwig Stenz et al. Genetic resistance to DEHP-induced transgenerational endocrine disruption, (2018). DOI: 10.1101/474155

Ludwig Stenz et al, Genetic resistance to DEHP-induced transgenerational endocrine disruption, *PLOS ONE* (2019). dx.doi.org/10.1371/journal.pone.0208371

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