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Press information

Does *in utero* exposure to endocrine disruptors have an impact on neurodevelopment and the emergence of psychiatric disorders? Learning from diethylstilbestrol.

A research team from Université Paris Descartes, Inserm and Centre Hospitalier Sainte-Anne, led by Prof. Marie-Odile Krebs, has shown that patients suffering from psychotic disorders, and exposed *in utero* to diethylstilbestrol, presented specific epigenetic changes.

These changes correspond to genomic regions notably comprising gene ZFP57, known to play a role in neurodevelopment.

Owing to this new project, the researchers examine the broader issue regarding the impact of *in utero* exposure to endocrine disruptors (including diethylstilbestrol) on neurodevelopment and the emergence of psychiatric disorders.

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Diethylstilbestrol (DES), a synthetic estrogen and endocrine disruptor, was prescribed for dozens of years to pregnant women worldwide, to reduce the risk of miscarriage. Use of this substance, limited over time, at high doses and during a particularly vulnerable period, may be thought to represent the typical pattern of exposure to endocrine disruptors in humans. It is associated with numerous medical conditions, particularly gynecological cancers and urogenital malformations among individuals exposed *in utero*. It has also been suggested to affect several generations.

The precise mechanism explaining these various syndromes has not been fully elucidated. Altered epigenetic homeostasis[1] has been put forward as one hypothesis. Animal studies identified epigenetic changes (notably DNA methylation) after exposure to diethylstilbestrol. **The study investigators examined the possibility of a correlation between prenatal exposure to diethylstilbestrol, associated with DNA methylation, and a possible increase in the risk of onset of psychotic disorders.**

The consumer group *Hhorages (Halte aux HORmones Artificielles pour les GrossessES)* [which means "stop artificial hormones in pregnancy"] helped the team to recruit 247 individuals whose mothers were prescribed diethylstilbestrol during pregnancy, with the aim of creating a cohort. The analyses focused on 69 participants attending face-to-face interviews, which enabled

psychiatric diagnoses to be made via standard questionnaires. A blood sample was then taken with a view to performing the molecular analyses.
Exposed subjects were compared to their non-exposed siblings. This within-family comparison allowed shared genetic and environmental inheritance to be taken into consideration.
Researchers did not observe any significant difference between exposed and non-exposed individuals in terms of DNA methylation.

However, they identified a differentially methylated region comprising gene ZPF57 in a sample of individuals exposed to diethylstilbestrol and suffering from a psychotic disorder (*versus* exposed subjects not presenting such disorders). This result suggests that altered expression of this gene, which is moreover known to play a role in neurodevelopment, could be linked to the emergence of psychiatric disorders in subjects exposed to diethylstilbestrol.

In conclusion, this study encourages further research efforts on *in utero* exposure to endocrine disruptors and the possible effects on neurodevelopment.

[1] *Epigenetic mechanisms are a group of mechanisms, which modulate gene expression without changing the underlying DNA sequence.*

Source: Methylomic Changes in Individuals with Psychosis, Prenatally Exposed to Endocrine Disrupting Compounds: Lessons from Diethylstilbestrol
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