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An epigenetic basis for autism spectrum disorder risk and oral contraceptive use

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ABSTRACT

In the United States 1 in 68 children are diagnosed with autism spectrum disorder (ASD). Although the etiology is unknown, many scientists believe ASD is caused by a combination of genetic and environmental factors and/or epigenetic factors. The widespread use of oral contraceptives is one environmental risk factor that has been greatly overlooked in the biomedical literature. Oral contraceptives, synthetic hormones created to imitate natural human hormones and disrupt endogenous endocrine function to inhibit pregnancy, may be causing the harmful neurodevelopmental effects that result in the increased prevalence of ASD. It is conceivable that the synthetic hormones repeatedly assault the oocyte causing persistent changes in expression of the estrogen receptor beta gene. Ethinylestradiol, a known endocrine disruptor, may trigger DNA methylation of the estrogen receptor beta gene causing decreased mRNA resulting in impaired brain estrogen signaling in progeny. In addition, it is possible the deleterious effects are transgenerational as the estrogen receptor gene and many of its targets may be imprinted and the methylation marks protected from global demethylation and preserved through fertilization and beyond to progeny generations. This article will delineate the hypothesis that ethinylestradiol activates DNA methylation of the estrogen receptor beta gene causing decreased mRNA resulting in diminished brain estrogen signaling in offspring of mothers exposed to oral contraceptives. Considering the detrimental epigenetic and transgenerational effects proposed, it calls for further study.

Introduction

The increase in prevalence of autism spectrum disorder (ASD) has caused alarm and compelled scientists to look for clues about the causes and contributing factors of ASDs. Recently, Pisula and Pisula published extensive work on autism prevalence [1]. The authors provide data on ASD prevalence per 10,000 people across countries and offer detailed analysis of the time frame of the increased prevalence. The numbers differ across countries from 13.1 per 10,000 (Argentina) to 57.2 per 10,000 (USA) [1]. Many explanations for the rise in prevalence of ASD have been offered and yet, causal factors for ASD are still baffling. Many scientists believe that both genetic and environmental factors contribute to the development of ASDs. The use of oral contraceptives is one environmental factor that has been largely ignored by the biomedical community.

Recently, I hypothesized that a link exists between oral contraceptive (OC) use and the prevalence of autism spectrum disorders (ASD) [2]. In the OC hypothesis article, I point out that ubiquitous OC use is a possible risk factor that has been profoundly overlooked in the biomedical literature. Because OCs were designed to imitate natural human hormones, disrupting endogenous endocrine function to prevent pregnancy, there is sufficient reason for concern that the synthetic hormones may be initiating the detrimental neurodevelopmental effects that lead to ASDs.

According to this hypothesis, I proposed ethinylestradiol (EE2) as the likely culprit [2]. EE2 is one of the synthetic compounds found in oral contraceptives. EE2 is known to be an endocrine disrupting compound (EDC) that is able to impair the endocrine system and offspring [3–7]. EDCs have the potential to do damage by adversely affecting sensitive hormonal pathways in animals and humans [8–11]. And, recent studies have proposed that EDCs can influence human physiological processes within cells, tissues and organs by changes in gene regulation [12]. The EDC category includes chemicals that affect endocrine glands, their function, hormone receptors and signaling pathways. The environmental scientific community has been worried about the exposure to EDCs in the womb or early in life for quite some time. They have strongly advised that exposure to EDCs is likely to be associated with neurodevelopmental disorders including reduced IQ, ADHD, and autism [11].

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Their concern is germane. Hormones and their signaling pathways are fundamental to regular functioning of all tissues and organs in invertebrates and vertebrates. Exogenous substances like EDCs, which have the same characteristics as endogenous hormones, are able to disrupt normal endocrine system communication [11]. EDCs can be active at low concentrations and similar to endogenous hormones, they can bind to receptors at very low concentrations [11]. Thus, endocrine disruption can occur from low-dose exogenous hormone exposure or from hormonally active substances that interfere with receptors.

In the domain of environmental risk factors the OC hypothesis first proposed is compelling. As a category of agents there are specific documented mechanisms through which OCs can affect the oocyte and/or the developing embryo. In addition, the exposure concentration is administered directly and pharmacologically effective. And, it may be of greater magnitude than other environmental exposures that mostly happen through passive secondary mechanisms. Also, a temporal correlation exists. The prevalence of OC use has increased as has the prevalence of ASDs over the last fifty years.

The only recent and significant study of oral contraceptive use and the development of ASD in children was conducted by Lyall and published in 2011, *Maternal early life factors associated with hormone levels and the risk of having a child with an autism spectrum disorder in the nurses' health study II* [13]. In this important study of various early life factors, Lyall reported that, "Overall, distributions of the factors under study were similar between the cases and non-cases. In crude comparisons in the full study (66,445 women), cases were more likely to have had an early age at menarche, a longer time until cycle regularity, a longer duration of pregravid OC use in years, and a higher BMI at age 18, though only the OC duration association was significant ($p < 0.05$)". A central finding of Lyall's paper is that OC exposure presented a statistically significant risk factor for children subsequently developing ASD [13]. This provides epidemiologic evidence of the association between OC use and ASD and this evidence calls for further scientific exploration.

The first aim of this article is to propose that epigenetic mechanisms are causing persistent changes in gene expression of estrogen receptor beta (ERβ) that result in autism in offspring of OC exposed mothers. ERβ is the main estrogen receptor expressed in the cerebral cortex, hippocampus, and cerebellum [14]. Interestingly, a recent study discovered a significant association of the lowered levels of the ERβ gene with scores on the Autism Spectrum Quotient and the Empathy Quotient in people with ASD [15,16]. Additionally, ERβ facilitates some of the effects of estrogens on anxiety, fear responses, learning behavior, and locomotion [15,17]. Moreover, there is evidence that impaired estrogen receptor function is involved with other emotional, cognitive and endocrine-related disorders and diseases [18–23].

Impaired estrogen receptor expression has have been associated with altered emotional responses, depression, mood disorders, cognitive dysfunction, brain degeneration, and many other endocrine-related diseases [18–23]. In addition to confirmation that estrogen receptors are a factor in emotional responses [18], there is compelling evidence for estrogen's involvement in the regulation of mood and cognitive functions [19–21]. Because the hippocampus, entorhinal cortex, and thalamus seem to be ERβ-dominant areas, this suggests a function for ERβ in cognition, non-emotional memory, and motor functions [20,21]. Research also shows that estradiol is able to regulate the serotonin (5-HT) system, which has been associated with affective disorders [20,21]. Furthermore, recent studies using estrogen receptor knockout mice have assisted in defining the function of estrogen receptors in brain degeneration [22]. In vivo and in vitro studies also show that estrogen receptors are mechanistically involved in endocrine-related diseases [23]. Given this information, it is not difficult to imagine that epigenetic mechanisms cause persistent changes in gene expression of estrogen receptor beta (ERβ) that result in neurodevelopmental disorders like ASDs. This article proposes a hypothetical model to demonstrate how this can occur.

The second aim of this article is to propose that the adverse effects are potentially passed on not only to the first offspring but to future generations. If the ER gene is imprinted, as it appears to be, the methylation marks are protected from global demethylation and preserved through fertilization and beyond [24]. Moreover, it is well established that many targets of the estrogen receptor are methylated and imprinted in the mammalian central nervous system [25–27]. Thus, I propose that the OC-dependent ER activation causes durable changes to the function of cells that are passed on by aberrant methylation piggybacking on the normal imprinting mechanism that protects these methylation marks from reversal or demethylation. This means that deleterious effects of OC exposure could perpetuate or even increase over generations as a result of both transgenerational transmission of the altered epigenetic programming, and the continued exposure across generations potentially imparting disease sensitivity at a later point in time [28–30]. An additional consideration is that the capacity of familial OC exposure to foster subsequent disease susceptibility in later generations significantly complicates and magnifies the potential health threat caused by exposure to endocrine disruptors such as EE2 [28].

Published results supporting the model

This section will delineate the hypothesis that EE2 triggers altered methylation of the ERβ gene, causing decreased ERβ mRNA transcription and subsequently impaired brain estrogen signaling, that leads to ASDs in progeny. Below I describe key findings in the literature that motivate and support this hypothesis.

Epigenetic mechanisms and estrogen receptors

The epigenome relates to the whole epigenetic state of a cell, and functions as an interface between the environment and the genome [31]. It is dynamic and responsive to environmental signals during development and throughout the entire lifespan of an individual [31]. It has become clear to scientists that chemicals can cause changes in gene expression that persist long after exposure has stopped [31]. Csoka and Zsyf propose the hypothesis that "commonly-used pharmaceutical drugs can cause persistent epigenetic changes. Drugs may alter epigenetic homeostasis by direct or indirect mechanisms. Direct effects may be caused by drugs which affect chromatin architecture or DNA methylation" [31]. Estrogen receptors have been extensively linked to triggering epigenetic alterations, including the central nervous system [25,27]. Thus, estrogen receptors are both epigenetically regulated and are themselves epigenetic regulators as well. So, in the following section I propose a hypothesis to explain the kind of dynamic changes in the transcriptional potential of a cell, which result in ASD.

In a normal cell, estrogen receptors are a collection of proteins located inside the cell. They are a gene product with a specific function and they are activated by the endogenous hormone estrogen (17β-estradiol). After estrogen activates the receptor, it is able to translocate into the nucleus where it binds to DNA to regulate the activity of various genes on the DNA strand.

An estrogen receptor is a DNA-binding transcription factor, that it is a protein that binds to specific DNA sequences and thus controls the rate of transcription of genetic information from DNA to messenger RNA. Messenger RNA is, of course, a molecule that con-