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Environmental contributors to modulation of brain estrogen signaling and male gender bias in autism: A reply to the oral contraceptive use hypothesis by Strifert (2015)

Keith Fluegge *

Institute of Health and Environmental Research, Cleveland, OH 44118, USA

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ABSTRACT

Strifert has recently put forward an interesting hypothesis regarding the role of oral contraceptive (OC) use in mothers and risk of offspring autism spectrum disorder (ASD). First, the author reports that combined oral contraceptives (COCs), containing both estrogen and progesterone, were developed in the late 1950s and early 60s, which is a time-frame distinct from Leo Kanner's documentation of infantile ASD in 1943 that Strifert just briefly mentions. While this important temporal inconsistency of ASD origin does not invalidate the potential role of OC use in contributing to the rise of ASD, it does support the likely possibility of other environmental exposures at play. Second, the epigenetic basis of the hypothesis is that the endocrine-disrupting components (i.e., ethinylestradiol) of OC perturb estrogenic signaling in the fetal brain by triggering aberrant DNA methylation of the estrogen receptor β (ERβ) gene, and such methylation patterns may be imprinted to future generations and could theoretically increase subsequent ASD offspring risk. The premise of the hypothesis is challenged, however, with the recognition that MeCP2, a "reader" of DNA methylation sites, is not only associated with age-dependent alteration in ERβ in females but is also significantly reduced in ASD brain. Furthermore, Strifert does not clearly address how the OC hypothesis accounts for the male bias in ASD. Therefore, the purpose of this correspondence is to address these inconsistencies by proposing a hypothesis that challenges these points. That is, gestational exposure to the agricultural and combustion air pollutant, nitrous oxide (N_2O), may be a leading contributor to the development of an ASD phenotype. The mechanism undergirding this hypothesis suggests that compensatory estrogenic activity may mitigate the effects of fetal N_2O exposure and thereby confer a protective effect against ASD development in a sex-dependent manner (i.e., male bias in ASD).

To the editor:

Strifert [1,2] has recently put forward a hypothesis regarding the role of oral contraceptive (OC) use in mothers and risk of offspring autism spectrum disorder (ASD). First, the author reports that combined oral contraceptives (COCs), containing both estrogen and progesterone, were developed in the late 1950s and early 60s [1], which is a time-frame distinct from Leo Kanner's first documentation of infantile ASD in 1943 [3] that Strifert just briefly mentions. While this important temporal inconsistency of ASD origin does not invalidate the potential role of OC use in contributing to the rise of ASD, it does support the likely possibility of other environmental exposures at play. Second, the epigenetic basis of the hypothesis is that the endocrine-disrupting components (i.e., ethinylestradiol) of OC perturb estrogenic signaling in the fetal brain by triggering aberrant DNA methylation of the estrogen receptor β gene, and such methylation patterns may be imprinted to future generations and could theoretically increase subsequent ASD offspring risk [2]. The premise of the hypothesis is challenged, however, with the recognition that methyl CpG binding protein 2 (MeCP2), a "reader" of DNA methylation sites [4], is not only associated with age-dependent alteration in ERβ in middle-aged females [5] but is also significantly reduced in ASD brain [6]. Furthermore, Strifert [1,2] does not clearly address how the OC hypothesis accounts for the male bias in ASD. Therefore, the purpose of this correspondence is to address these inconsistencies by proposing a hypothesis that could generally account for these variables.

It has recently been proposed for the first time in this journal and elsewhere, in concordance with the budding literature reporting an association between air pollution exposures and risk for offspring ASD, that exposure to trace levels of environmental nitrous oxide (N_2O) may be an etiological factor in the development of ASD and related neuropathologies, including attention-deficit hyperac-

* Corresponding author.
E-mail address: keithfluegge@gmail.com

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tivity disorder (ADHD) and schizophrenia [7–10]. Studies have documented that emissions of the compound have been increasing since 1940, in step with the increasing use of anthropogenic nitrogen amendments in agriculture [11,12], although continental differences in the use of nitrogen fertilizers have emerged since 1981 [13]. Moreover, the CHARGE study, a population-based case–control study on neurodevelopmental disorders, has suggested that prenatal residential proximity to agricultural areas and pesticide applications may increase risk for ASD [14], but these environmental assessment studies fail to consider the confounding use of nitrogen fertilizer use in agriculture and emissions of associated pollutants, like N_2O, which have been clinically demonstrated to affect cognitive capacity at trace levels of exposure, as we have reviewed [7–10,15,16].

Given the popular use of the compound in medicine as a mild anesthetic and analgesic, the neurological effects from exposure to N_2O have been comprehensively discussed [17]. A review of our novel hypothesis highlighted many clinical reports and chronic toxicity studies in animals showing adverse effects on cognition and significant effects on central neurotransmission even at trace levels of exposure to the compound (i.e., $\geq$50 ppm) [8]. We also discussed the N_2O-mediated effects on glutamatergic and opioidergic activity, including its putative role as a N-methyl-D-aspartate receptor antagonist and its induction of central release of opioid peptides, specifically dynorphin, that have been implicated in the behavioral domains of autistic pathology (i.e., stereotypy and social/communicative impairments) [8]. Therefore, the role of this correspondence is to briefly highlight another toxicological mechanism of low dose N_2O exposure, with a specific focus on the compensatory role that estrogenic signaling may have in not only mitigating many of the neural disruptions mediated by low dose N_2O exposure but also facilitating certain neuroanatomical and neurobehavioral attributes of a less severe ASD phenotype. The sex-dependent magnitude of estrogenic influence may contribute to the male bias seen in ASD and related neurodevelopmental disorders.

Subanesthetic doses of N_2O have been shown to reversibly inhibit activation of the alpha 7 nicotinic acetylcholine receptor (α7 nAChR) [18], a ligand-gated ion channel highly permeable to Ca2 + ions that governs synaptic release of neurotransmitters and gene expression in the central nervous system and immune cells [19]. The α7 nAChR receptor is coupled to nitric oxide synthase (NOS) activity in central nervous system [20]. Nitric oxide (NO) is a critical biological messenger with numerous molecular targets that is synthesized from L-arginine by a family of NOS enzymes with distinct functional and regional specification, including neuronal (nNOS), endothelial (eNOS), and inducible isoforms [21]. NOS enzyme activity is governed by Ca2+ influx and calmodulin expression, a protein that binds Ca2+ [21]. Chronic inhibition of the nicotinic acetylcholine receptor α7 may uncouple the neuronal NOS reaction and lead to formation of oxidative stress markers, including H_2O_2. Uncoupled eNOS due to oxidation of tetrahydrobiopterin (BH4), a necessary co-factor for the production of NO by the NOS enzymes, in an animal model of deoxycorticosterone acetate-salt-induced hypertension facilitated H_2O_2 production [22]. An increase in cellular oxidative stress markers, including H_2O_2, has been reported in ASD [23]. With reduced catalase expression in ASD [24], elevated H_2O_2 production may increase NO metabolism in the vasculature through induction of BH4 [25]. This hypothesis is consistent with both the crucial role of NO in N_2O-mediated antinociception [26], as well as recent animal study showing increased oxidative stress from a prolonged exposure to low dose N_2O [27].

Aligned with this hypothesized physiological cascade, ASD symptom severity has been positively correlated with levels of oxidative stress [28], and significantly higher serum NO metabolite levels have been reported in ASD [29]. Snyder et al. [30] demonstrated through in vitro methods that NO potently inhibits microsomal aromatase activity by as much as 80%. Aromatase inhibition in the periphery from excess NO could be expected to promote increased levels of androgen exposure, and excess fetal androgens have been linked to subsequent autistic traits in children [31]. Excess serum NO in ASD may damage the blood-brain barrier [32] and contribute to intestinal permeability [33], both of which have been implicated in ASD [34,35]. These neuroadaptations may facilitate a more severe ASD profile, as others have positively correlated both elevated oxidative stress and hormonal indices with autistic symptom severity [28,31].

However, in another mode of neuroadaptation to chronic environmental N_2O exposure, elevated estrogenic signaling in the brain could compensate for the N_2O-mediated inhibition of α7 nAChR [36]. Animal studies in primates [37] and rodents [38] indicate that estrogens may stimulate the expression of α7 receptor. Fetal cord blood dehydroepiandrosterone (DHEA) concentrations, the necessary estrogen prohormone for placental estrogen production [39], are elevated in female neonates compared to males [40], which may contribute to the male gender bias in neurodevelopmental disorder. Wu et al. [41] pointed out that estrogen may have a key role in masculinizing neural circuitry and thus promoting male-specific territorial behaviors, like aggression. Interestingly, aggressive behavior problems have been found to be associated with a less severe overall autistic phenotype [42], suggesting that the level of estrogenic activity during early development may help to mitigate manifestation of severe autistic pathology. In addition to influences on behavioral development, compensatory estrogen signaling in response to environmental N_2O exposure may heighten abnormal corpus callosum morphology in both ASD [43] and ADHD [44], which is consistent with animal studies reporting a negative correlation between duration of cryoanesthesia exposure and male splenial area [45] as well as the possible effect of estrogenic compounds on callosal development [46]. These studies suggest a role for estrogen signaling in contributing to a neuroanatomical and neurobehavioral profile resembling a less severe ASD phenotype. It is critical to recognize that reports demonstrating reduced aromatase and estrogen signaling in ASD brains (mostly male subjects) [47,48] may reflect the effects of the aforementioned redox-mediated neuroadaptations. Similarly, sex-dependent hormone differences may facilitate a unique gender profile in related neurodevelopmental disorders, like ADHD.

An investigation using a nationally representative sample of women from the Canadian Community Health Survey – Mental Health reported on the health status and sociodemographic profiles of women with self-reported ADHD versus women without the disorder [49]. The authors reported a significantly higher prevalence of a multitude of adverse mental and physical health outcomes (i.e., impaired quality of life, personality traits indicative of suicidality, increased pain perception, elevated anxiety, and smoking, etc.) that remained even after controlling for demographic information of the participants, leaving the authors to conclude that women with self-reported ADHD are at risk for a wide array of health and psychosocial vulnerabilities. However, these adverse psychosocial outcomes are consistent with a premenstrual syndrome phenotype, characterized by higher luteal phase estradiol [50,51], that may be a compensatory response to certain environmental exposures, like N_2O, that have previously been implicated in the etiology of neurodevelopmental disorders like ADHD [7–10,15,16]. Animal studies have provided evidence suggesting that low dose N_2O exposure may induce a constant and prolonged proestrus phase for up to three weeks [52], which is characterized by peak estradiol levels [53].

Therefore, relevant to the characterization of ADHD in females as a compensatory premenstrual-type syndrome to certain