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LETTERS TO THE EDITOR

Autism in 2016: additional discovery☆

Autismo em 2016: descoberta adicional

To the Editor,

Posar and Visconti[1] have recently published their narrative biomedical review on the developments in the field of autism research in 2016, with a particular focus on the hypothetical role of environmental factors, like air pollution. The authors searched the available recent literature using PubMed (United States National Library of Medicine) for interesting hypotheses published between January 1, 2013 and August 20, 2016 and relevant literature (case–control studies involving human participants were preferred) using a variety of selected keywords. Although the authors identified a search strategy, their review did not consider a recently published mini-review identifying the role of the specific agricultural air pollutant, nitrous oxide (N_2O), in autism etiopathogenesis and neurodevelopmental disorders more broadly.

Fluegge[2] has suggested repeatedly that exposure to environmental N_2O may increase susceptibility to a range of neurodevelopmental disorders, including autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD). An initial epidemiological analysis revealed an association between the use of the pesticide glyphosate and ADHD, but subsequent sensitivity analyses found that the association was likely dependent upon the level of land urbanization and glyphosate's strong county-specific association with nitrogen-based fertilizers and presumable emissions of N_2O.[2] These findings were replicated in an analysis of ASD hospitalizations (personal communication). Hypothesized mechanisms of interest underlying these associations included known pharmacological targets of low level N_2O exposure, including NMDA receptor antagonism (N-methyl-D-aspartate receptor), stimulation of central opioid peptide release, and suppression of cholinergic activity.[3] The review is particularly notable since environmental N_2O has not been considered by either Posar and Visconti[1] or the studies that comprise their narrative review as an air pollutant capable of inducing adverse human health consequences and autism, in particular. It is, therefore, interesting to read the authors' suggestion to investigate whether there is a difference in autism prevalence among nations exposed to low *vs.* high levels of pollution.

Tian et al.[4] recently reported on the annual rates of change for a multitude of environmental factors for different continents, having found significant increases in nitrogen fertilizer use in North America from 1981 to 2010 and significant decreases in nitrogen fertilizer use in Europe during the same period. As the use of anthropogenic nitrogen sources is the most directly tied environmental contributor to N_2O emissions,[5] this continental difference in nitrogen fertilizer use going back decades is particularly revealing and suggests higher U.S. emissions of N_2O derived from nitrogen fertilizers compared to Europe, a fact confirmed by the Intergovernmental Panel on Climate Change (IPCC, 2015).[6] This geographical distinction could explain the differential dynamics in ASD prevalence.

Epidemiologic, population-based studies from Europe indicate that much of the increase in ASD prevalence between 1980 and 2003 can be accounted for by changes in administrative and reporting practices,[7,8] while ASD prevalence in the subsequent years in the UK may have plateaued.[9] These data argue for the possibility that the increase in the registered prevalence of ASD may be driven more by administrative changes. However, the marked increase in ASD prevalence in the United States between 2000 and 2012, in particular, could not be readily accounted for by any evolution in diagnostic criteria since no formal changes were introduced or adopted during this time, although it cannot be discounted that the increasing prevalence of ASD during this time might be attributable to lingering diagnostic substitution or the accrual of practices started in the prior decades.[10] This, therefore, leaves open the possibility that secular environmental contributors, like environmental N_2O, may play a role in ASD etiopathogenesis in a continentally distinct way. In light of this research, Posar and Visconti[1] may wish to expand their view on the role of air pollution as a risk factor in ASD. Considering that N_2O is not regarded as a human health pollutant in the literature or by government officials, a call for a re-evaluation of this particular environmental pollutant seems necessary.

Conflicts of interest

The author declares no conflicts of interest.

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Authors' reply: ''Autism in 2016: additional discovery''☆

Resposta do autor: ''Autismo em 2016: descoberta adicional''

Dear Editor,

Fluegge in his letter[1] commented on our review about autism spectrum disorder (ASD) etiopathogenesis, underscoring the possible role of one air pollutant and greenhouse gas, nitrous oxide (N_2O), well known as the laughing gas used in surgery for its analgesic and anesthetic properties.[2] In 2006 Cohen considered the hypothesis of an involvement of N_2O in ASD etiopathogenesis, observing that high amounts of N_2O in the blood could explain the uncontrollable laughter and high pain threshold detected in some subjects with ASD.[2] For some years this hypothesis was passed over in silence, while, especially in the United States (USA), many studies have been performed to investigate the possible association between various air pollutants and an increased risk of ASD. Data from these studies suggest the involvement of early exposure to several air pollutants (including ozone, nitric oxide, nitrogen dioxide, carbon monoxide, sulfur dioxide, diesel particulates, some heavy metals, aromatic solvents) in ASD etiopathogenesis. Recently, Fluegge has frequently mentioned the theory that the early exposure to N_2O may increase the risk for neurodevelopmental disorders, including ASDs, and in one review he described in detail several possible etiopathogenetic mechanisms through which N_2O may lead to neurodevelopmental disorders, including: dopaminergic dysregulation; N-methyl-D-aspartate (NMDA) receptor antagonism; kappa-opioid receptor (KOR) activation; and α7 cholinergic inhibition.[3]

We believe that any effort to better understand the etiopathogenesis of ASDs, and in particular the causes of their dramatically increasing prevalence observed in recent decades at least in the USA,[4] is commendable. However, at present there is no study, neither retrospective nor prospective, involving human individuals to suggest an association between early exposure to N_2O pollution and increased ASD risk. For this reason, in our review we have not mentioned N_2O among the pollutants implicated in the ASD etiopathogenesis based on currently available data. Apart from that, we think that focusing on a single hypothetical pollutant in the research concerning ASD etiopathogenesis may be misleading. Considering the myriad of potential pollutants to which an individual is exposed from the early stages of intrauterine life, we believe it likely that not only one pollutant but rather a complex interaction between various pollutants may be the determining factor in increasing ASD risk through, for example, epigenetic mechanisms. In fact, in agreement with von Ehrenstein et al., we suggest considering the possibility that not single pollutants, but

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