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Subcutaneous injections of aluminum at vaccine adjuvant levels activate innate immune genes in mouse brain that are homologous with biomarkers of autism

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ABSTRACT

Autism is a neurobehavioral disorder characterized by immune dysfunction. It is manifested in early childhood, during a window of early developmental vulnerability where the normal developmental trajectory is most susceptible to xenobiotic insults. Aluminum (Al) vaccine adjuvants are xenobiotics with immunostimulating and neurotoxic properties to which infants worldwide are routinely exposed. To investigate Al's immune and neurotoxic impact in vivo, we tested the expression of 17 genes which are implicated in both autism and innate immune response in brain samples of Al-injected mice in comparison to control mice. Several key players of innate immunity, such as cytokines *CCL2*, *IFNG* and *TNFA*, were significantly upregulated, while the nuclear factor-kappa beta (NF-κB) inhibitor *NFKBIB*, and the enzyme controlling the degradation of the neurotransmitter acetylcholine (*ACHE)*, were downregulated in Al-injected male mice. Further, the decrease of the NF-κB inhibitor and the consequent increase in inflammatory signals, led to the activation of the NF-κB signaling pathway resulting in the release of chemokine *MIP-1A* and cytokines *IL-4* and *IL-6*. It thus appears that Al triggered innate immune system activation and altered cholinergic activity in male mice, observations which are consistent with those in autism. Female mice were less susceptible to Al exposure as only the expression levels of NF-κB inhibitor and *TNFA* were altered. Regional patterns of gene expression alterations also exhibited gender differences, as frontal cortex was the most affected area in males and cerebellum in females. Thus, Al adjuvant promotes brain inflammation and males appear to be more susceptible to Al's toxic effects.

1. Introduction

Autism spectrum disorders (ASD) is a heterogeneous group of neurodevelopmental disorders characterized by impairment in social interaction, verbal communication and repetitive/stereotypic behaviors [1,2]. A growing body of scientific literature shows that general immune dysfunction including various neuroimmune abnormalities (i.e., abnormal cytokine profiles, neuroinflammation and presence of autoantibodies against brain proteins) are key pathological biomarkers in ASD patients [3–15]. Other key characteristics of autistic brains include abnormal neural connectivity [16–19], decreased number of cerebellar Purkinje cells [20–22], small cell size and increased cell packing density at all ages in the limbic system (the hippocampus, amygdala and entorhinal cortex) suggesting a curtailment in normal neuronal development [20].

It is also generally acknowledged that ASDs are complex disorders resulting from the combination of genetic and environmental factors with multiple gene–gene and gene–environmental interactions, although there is still uncertainty about the exact proportions of each component [23]. Moreover, the molecular mechanisms of these gene-environmental interactions which result in autistic pathology remain to be discovered. Aluminum (Al) is an environmental toxin with demonstrated negative impact on human health, especially the nervous system, to which humans are regularly exposed. In particular, Al can enter the human body through various sources including food, drinking water, cosmetic products, cooking utensils and pharmaceutical products including antacids and vaccines [24–33]. In addition, Al is also present in many infant formulas [34]. However, compared to dietary Al of which only ~0.25% is absorbed into systemic circulation, Al from vaccines may be absorbed at over 50% efficiency in the short term [35] and at nearly 100% efficiency long-term [36]. Thus, vaccine-derived Al has a much greater potential to produce toxic effects in the body than

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