Vagal nerve stimulation for the treatment of autism

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Autism is a severe neurodevelopmental disorder characterized by several behavioral presentations, such as impaired social interactions, stereotypic behaviors, limited social communications and restricted social interests. There is no curative therapeutic intervention for autism as there is no consensus regarding its pathogenesis. However emerging data suggests that oxidative stress and neuroinflammation plays a key role in the pathogenesis of autism,[1] and novel pharmacologic targets are introduced which augments our therapeutic armamentarium against autistic spectrum disorders. Central nervous system and immune system are closely interconnected in several ways. Both arms of innate and adaptive immunity are postulated to be involved in the pathophysiology of autism. Helper T cells and particularly T-helper 1 regulate the function of both adaptive and innate immune responses, by producing cytokines. Considering psychoneuroimmunologic discipline, cytokines provide necessary support for the functional integrity of neurons through their neurotrophic effects. However their excessive production leads to immunocytotoxicity which accounts for impairments of neuroanatomical structures and neuronal plasticity Pro-inflammatory cytokines and TNF- (tumor necrosis factor) in particular, are shown to be increased in serum of autistic subjects.[2] Several studies on serum levels of interleukins (IL-1, IL-6, IL-12, IL-23), brain-derived neurotrophic factor and TNF-α in children with autistic spectrum disorder revealed higher levels of these cytokines compared to normal children, and hypothesized that this finding could be related to impairment of sleep, eating and social interactions among affected children.[3-6] Recent findings by Tracey, supports the idea that a neural circuit modulates immune response called the inflammatory reflex. This cholinergic anti-inflammatory pathway exerts its effects through efferent fibers from vagus nerve. Inhibition of TNF- production in spleen following vagal nerve stimulation seems to be through acetylcholine signaling via the 7 nicotinic acetylcholine receptor expressed on cytokine-producing macrophages.[7,8] This signal is relayed through an acetylcholine-producing, memory phenotype T cell population identified in mice that is necessary for inhibition of cytokine production by vagus nerve stimulation.[9]

Immunomodulation via VNS has been implicated in the treatment of other immune disorders involving the TNF- pathway such as inflammatory bowel disease.[10] Here in, we support the hypothesis that VNS may prove useful in the treatment of autism through its cholinergic anti-inflammatory effects by modulating production of TNF-α and IL-6. This hypothesis is congruent with findings by Levy *et al*. that found clinical improvement in autistic subjects who underwent VNS for seizure control.[11] This novel idea encourages conducting a double blind case control study to investigate the possible role of vagal nerve stimulation in treatment of autism.

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