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# Could fever and neuroinflammation play a role in the neurobiology of autism? A subject worthy of more research

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**Abstract**
Autism is neuropsychiatric disorder in which a hyperglutamate state may play a role. It is suggested here that fever or hyperthermia may be able to alter glutamate levels in the brain and may therefore be able to impact on the symptoms of autism. More study on this possibility is clearly warranted.

**Keywords:** *Clinical, hyperthermia, neurotransmitter, treatment*

Autism is a complex, heterogeneous, neuro-developmental disorder. Its characteristic symptoms are: limited and impaired social relationships, impaired communications, restricted interests and repetitive behaviors. Oxidative stress and excitotoxicity is reported in autism [1, 2]. Immunoexcitotoxicity (chronic microglial activation via immune stimulation) is a possible central mechanism associated with autism [3]. Targeting excitotoxicity and brain inflammation have been suggested as treatments for autism [4]. It has been suggested that autism is associated with increased glutamate level in brain [5]. Serum glutamate level is also increased in individuals with autism [6]. The impairment of glutamatergic neurotransmission and the increased function of excitatory receptor by pro-inflammatory immune cytokines play a significant role in the neurobiology of autism [4]. The level of glutamate is increased in Rett syndrome in brain [7, 8]. Of course, dysregulation of other neurotransmitters such as GABA and their interplay with glutamate is also reported. In addition, Memantine, the antagonist of the N-methylD-aspartic acid (NMDA) glutamate receptor, decreases excessive glutamate effects. Memantine has also anti-inflammatory effects and reduces some symptoms of autism [9].

It has been suggested that fever may decrease autism symptoms by improving brain blood flow [10, 11] although this idea is still being debated. In addition to altering vascular parameters, fever is associated with an elevation in body temperature. It is possible that hyperthermia or fever may reduce some symptoms of autism for the following reasons: Hyperthermia alone has been shown to reduce blood glutamate levels [12], and reduce glutamate uptake in hippocampal slices [13] in rats. Although, others reported contradictory findings that elevated extracellular glutamate levels following hyperthermia can reach neurotoxic levels [14]. The antipyretic effect of acetaminophen is through reduction of glutamate release [15]. Blood glutamate levels can partially affect the brain extracellular glutamate level [14]. One of the mechanisms for the removing of excitatory amino acids of glutamate from brain is

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through transportation into blood. A concentration gradient facilitates this transportation [16]. Reduced blood glutamate level increases the brain-to-blood glutamate efflux [17]. In fact, blood glutamate scavenging has neuroprotective effects [18]. The neuroprotective effects of oxaloacetate and pyruvate in the animal models of head injury is through the scavenging of blood glutamate [19]

Because of the evidence linking hyperthermia with an effect on brain glutamate, and gluatamate's relationship to the symptoms of Autism, it is proposed here that it may be worthwhile to conduct more studies to investigate the possible direct or indirect association of fever, blood glutamate level, excitotoxicity, and neuro-inflammation in autism. Of course, this possible association will likely be complex. While acetaminophen may decrease fever through glutamate release inhibition, there is no evidence supporting the possibility that acetaminophen decreases autism symptoms. In addition, it is not clear whether the changes in the serum level of glutamate can affect the brain leading to the rapid improvement of autistic symptoms in hyperthermia. Moreover, fever is part of an inflammatory response and thus more than just temperature elevation (hyperthermia). However, the intriguing evidence presented here suggests a need for more study on the possibility that hyperthermia alone could be a beneficial treatment in autism. Studying this possible association in animal models of autism [20] may increase our understanding and insight into the association of autism, fever and hyperthermia.

***Declaration of interest:*** There is no conflict of interest to be declared.

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