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Modification of the Intracellular Cl^- Concentration as a Putative Tool for the Prevention and/or Treatment of Autism

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COLUMN ARTICLE

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Autism or more widely autism spectrum disorder (ASD), including Asperger syndrome and others, is the most common neurological disorder in children with social communication deficits and uncontrolled repetitive behaviour, usually congenital and a possible cause of lifelong social disability. Although the aetiology of ASD is heterogeneous, including hereditary (Rett, fragile X, oxytocin receptor polymorphism), toxic (valproate) or idiopathic [1], recent studies have indicated that the excitatory/inhibitory (E/I) imbalance in the brain neural network exists as a common background [2]. Excitatory and inhibitory neurons constitute the neural network circuit in the brain, with the former charrying and summing the received and commanding information through the action potentials and synaptic release of excitatory neurotransmitters and the latter modifying the information by suppressing the activity of the excitatory neurons through the release of the inhibitory neurotransmitters. The accumulated evidence has indicated a reduction in GABAergic signalling in patients with ASD [3]. Comparison of EEG coherence between ASD patients and controls also showed a significant difference in mutual connectivity in the brain, suggesting an E/I imbalance of in the neural network [4].

The neural network is, in a sense, automatically completed during the perinatal period even without input from the external world. Neurons in the developing brain appear to ensure mutual connectivity through spontaneous network activity [5], such as the connectivity of circuits with a tester. How can inhibitory neurons be involved in this automatic network formation? Curiously, inhibitory neurons which are, naturally, inhibitory in the matured brain neural network behave like excitatory neurons in the premature developing brain and thought to be the main generator of spontaneous neural network activity [6-8]. Although it seems quite paradoxical, the mechanism of this opposite action is quite simple. Most inhibitory neurons in the brain are GABAergic and act on $GABA_A$ receptors causing an inhibitory postsynaptic potential when the intracellular Cl^- concentration of the target neuron is sufficiently low. The intracellular Cl^- concentration is controlled by NKCC1 (Na-K-Cl cotransporter 1, which imports Cl^- from extracellular to intracellular) and KCC2 (K-Cl cotransporter, which exports Cl^- from intracellular to extracellular). In the matured brain, the intracellular Cl^- concentration is kept low by the relative dominance of KCC2. However, in the immature brain KCC2 activity is relatively weak, allowing the intracellular Cl^- concentration remains sufficiently high to induce an excitatory GABA response [9,10]. This mechanism is thought to ensure the incorporation of GABAergic neurons into the neural network during development. Completion of the development of a well-functioning neural network for post-

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natal life appeares to require a gradual shift of the intracellular Cl^- concentration from high to low at a well-controlled timing, and failure of this process is thought to cause an E/I imbalance in the neural network of ADS. Therefore, any factor that affects these transporters is a potential cause of ASD; conversely, it is also a possible candidate for the develpment of a therapeutic tool or target for ASD.

Tyzio *et al.* [11] reported quite interesting phenomenon wherein, the immature rat brain neurons temporary shift their intracellular Cl^- concentration from high to low, at around the time of delivery, through the effect of oxytocin, presumably to protect the neural network from unnecessary hyperactivity by increasing the inhibitory efficiency of GABAergic neurons. This effect of oxytocin may partly explain the significantly higher incidence of ASD in infants delivered by caesarean section. It has also been suggested that oxytocin regulates the gradual shift of GABAergic neurons from excitatory to inhibitory in the early postnatal life [12], which may explain the therapeutic effect of the intranasal application of oxytocin [13,14]. Based on these findings, Ben-Ari *et al*.[15,16] trialed the use of bumetanide, instead of oxytocin, because it is orally applicable and decreases the intracellular Cl^- concentration by suppressing NKCC1, which yielded significantly positive results.

The use of valproate during pregnancy has been shown to significantly increase the incidence of ASD in children. Valproate has been shown to block the oxytocin-dependent shift in the intracellular Cl^- concentration [17]. Interestingly, it has been shown that the effect of valproate on NKCC1 is gender dependent [18,19], which together with the oxytocin effect, may help explain the male dominance among ASD patients.

Metabolic factors have also been thought to cause ASD by deteriorating the E/I balance in the brain. Beaudet [20] discussed preventable autism and emphasized the possible therapeutic value of the amino acid ornithine in some form of ASD. In addition, a recent report [21] showed that the transplantation of the gut microbiota of late onset ASD patients into germ-free mice has caused the development of ASD-like symptom in the mice; moreover, the GABA agonists 5-aminovaleric acid (5AV) and taurine improved ASD-related behavioral changes of BTBR mice, indicating their possible beneficial therapeutic effects.

To prevent ASD, early diagnosis and intervention, as well as avoidance of risk factors (caesarean section, valproate, etc.) and pre-treatment (carnitine, oxytocin, etc.) of high risks are esssential because the plasticity of the neural circuit of the developing brain is known to have a critical period. Therefore, on-going treatments, which have at least significant beneficial effects, need to be initiated early to obtain a complete cure of ASD. Recent advances in EEG connectivity analysis make this a promising method for the early detection of potential ASD candidates among infants as young as three months [22].

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