THE SEROTONIN SYSTEM INFLUENCE ON AUTISM SPECTRUM DISORDER

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Relevance. Serotonin is an organic compound that acts as a monoamine neurotransmitter and hormone. Biochemically, the amino acid Trp is a key source for production. Indolamines are formed from essential amino acids by hydroxylation by the enzyme tryptophan hydroxylase (TPH). There are two types of isoforms of this enzyme: TPH1 and TPH2. TPH1 is essential for peripheral serotonin synthesis and TPH2 is essential for central serotonin synthesis. It is then decarboxylated by aromatic decarboxylase to form serotonin. It includes in regulation of numerous physiological processes such as mood, cognition, sleep, appetite, social behaviour, reward learning, memory and vomiting.
However, although serotonin is widely accepted as a neurotransmitter, most serotonin is produced in the peripheral system by enterochromaffin cells and subsequently taken up by platelets. Serotonin is found in almost all forms of whole blood as part of platelets. Only 1% of blood serotonin in plasma. Most importantly peripheral serotonin can't cross the blood brain barrier therefore the amount of serotonin in the blood doesn't count on the central level of serotonin. Thereby neurons must synthesis their own serotonin by themselves. In terms of neurotransmitter studies, serotonin signalling promotes many neural processes including neurogenesis, cell migration, survival, synaptogenesis and synaptic plasticity [1].

Object. Analysis of how serotonin system influence on autism spectrum disorder with seasonal changes, vitamin D levels, ethnicity and genetic predisposition.

Research methods. Reviewing researches and articles which have analyse serotonin system and its influence on autism spectrum disorder.

Results and discussion. Recently, autism has been viewed as a spectrum disorder because of the heterogeneity and blurring of boundaries between these core behavioural symptoms like repetitive behaviours, social impairments, impairment of communication skills. Elevated serotonin was the first biomarker identified in ASD. About 25% of people with autism have hyperserotoninemia. An estimated 1 in 160 people worldwide has autism. However, these increase in relation to social requirements, e.g. schooling. There is no exact test for autism. Therefore, it is more likely to be diagnosed on the basis of developmental assessment and behavioural observation. We focus on whether hyperserotoninemia is unique to autism, but we find that higher levels of serotonin are found in non-verbal populations, people with cognitive deficits such as attention deficit and memory loss. In contrast, conflicting

views have been reported from more ethnically homogeneous populations, evaluating two forms of whole blood serotonin distribution in ASD with one group similar to the normal distribution of controls, while the second form group is higher than the levels of controls. Probands of ASD patients from families with two or more autistic children have higher levels of serotonin than those from single families. Although serotonin is strongly associated with ASD, no studies have yet proven that elevated serotonin levels predict ASD risk in young children, including siblings of children with ASD. Mechanisms to be emphasized for elevated serotonin levels are elevated serotonin levels in platelets, prolonged formation of serotonin in enterochromaffin cells in the gut, increased uptake of serotonin into platelets, altered metabolism of the serotonin pathway [2]. Animal models suggest that hyperserotoninemia and hyposerotonin in the brains of people with autism reduce the motivation for social interest, which may be associated with repetitive behaviours in patients with ASD. This is more significantly evident when autistic people adopt a diet low in the amino acid tryptophan. Their repetitive behaviour worsens and their irritability increases. Low serotonin levels elicited in early developmental rat brains have been associated with dendrite numbers, abnormally shaped dendrites, decreased synaptic density, abnormal cortical brain growth, and more or fewer behavioural traits in autistic patients. Reveal neuroanatomical defects such as behavioural traits resembling People with autism have lower levels of serotonin in their brains and higher concentrations of serotonin in their blood compared to people without autism. It has a polymorphism in the TPH2 gene that may be a known cause. Animal models lacking the TPH2 gene are known to cause defects in serotonin synthesis in the brain and exhibit behavioural symptoms of autism.

Not only serotonin but also vitamin D(calcitriol) have been suggested to play a role in autism. Vitamin D has been proposed to have an inverse relationship with autism incidence. Calcitriol regulates many genetic expressions which have a large impact on brain development and its function. The principal source of vitamin D is UVB radiation. The above mentioned symptoms of an autistic population are mostly expected in countries with a high rainy climate, high air pollution, and urban cities which lead to low UV rays. An inverse relationship between a rapid rise in autism incidence in regions with lower sun exposure and vitamin D plasma concentration. This is widely seen among migrants from tropical areas like African countries to European and American countries, which have lower sunlight and an increased prevalence of autism. Autism incidence has been linked with maternal vitamin D levels. Migrants from equatorial/tropical regions have an increased incidence of autism since they require 6-10 times more UVB exposure or an alternative vitamin D source such as diet (salmon, egg yolks, cod liver oil, canned fish) and any other supplementation. It was confirmed that when examining VDRE-specific sequences of TPH1 and TPH2, TPH2 has 2 distal activating VDRE sequences and TPH1 has distal repressor VDRE. It is correlated that vitamin D transcriptionally activates TPH2 unlike vitamin D transcriptionally inhibits TPH1.TPH1-mediated serotonin synthesis also induces osteoclast formation and impairs osteogenesis. In contrast, TPH1-deficient animal models showed decreased

osteoclast production and increased osteogenesis. If we therapeutically reduce TPH1, it increases osteoblast formation and increases bone mass in animal models. This exact mechanism was shown in autistic boys with reduced bone mineral density compared with boys without autism, suggesting that TPH1 induces low serotonin levels in non-autistic boys and vice versa in boys with autism. Vitamin D levels change with the seasons. TPH1-regulated serotonin is highest in winter and lowest in summer, while TPH2-regulated serotonin is highest in summer and lowest in winter. TPH1 mRNA expression is minimal during the day and maximal at night. Expression of TPH2 mRNA is reversed. In summary, all of these validation points point to a novel vitamin D transcriptional mechanism that downregulates TPH1 and upregulates TPH2, thereby oppositely affecting central and peripheral serotonin levels. The main unifying hypothesis which links vitamin D and serotonin concentration levels is that genes encoding TPH2 are induced by vitamin D while TPH1 is repressed by vitamin D. This induction and repression directly influence on the level of serotonin in blood and brain. A low concentration of vitamin D depicts having a high risk of children with behavioural problems, like language difficulties and attention impairments. A lower economic status population is underdiagnosed with ASD likely to significant fewer visits to mental health. Recent suggestions by many scientists are maternal autoimmunity for the development of autism during pregnancy, but still no exact mechanism has been published. The suggestion of lower maternal vitamin D resulting in autoimmunity which attacks the foetal brain is four times more likely to occur in pregnant women with autistic children.

Conclusions. We propose an underlying mechanism to elucidate how vitamin D hormone is a key regulator of brain serotonin synthesis by TPH2, including VDRE, which coincides with its activation. It explains that low levels of the vitamin D hormone lead to abnormal serotonin synthesis, leading to abnormal development of brain. If so, do the treatments for increasing serotonin levels ease autistic patients? Selective serotonin reuptake inhibitors, which allow serotonin to be in the synapses much longer, seem to ease the repetitive behaviour of some autistic children, while many clinical trials are hampered due to their placebo effect. But recent studies suggest that SSRIs don't change the core characteristics of autistic children, although it is possible to help some autistic children with anxiety and depression.

ЛИТЕРАТУРА

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