Extended Abstract

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Joint Event on 19th Global Neuroscience and Neurology Conference and 13th Global Neurologists Meeting on Neurology and Neurosurgery November 07-08, 2019, Frankfurt, Germany - The role of serotonin overexposure in the etiology of autism

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Statement of the Problem: Autism spectrum disorder (ASD) may be a highly prevalent developmental disorder. One out of 68 children of but 8 years old is affected; however, the etiology of its pathophysiology remains unknown. Elevated blood levels of serotonin (5HT) were identified in 25-35% of autistic patients. Serotonin may be a major player in multiple brain developmental processes. Previous studies showed that 5HT dysregulation had an influence on the etiology of ASD; however, the precise mechanism of 5HT effect remains unclear. Recent studies demonstrated that dysregulated 5HT levels may cause changes within the transcriptional levels of the many genes. Our focus during this study was to research the expression levels of previously documented ASD candidate genes in cultured neuronal tissue when 5HT levels are upregulated.

Methodology & Theoretical Orientation: We differentiated mouse embryonic stem cells to neuronal tissue and exposed them to different concentrations of serotonin. then, we measured organic phenomenon levels by PCR arrays that were costumed to contain the foremost common genes related to autism.

Findings: When applying several concentrations of serotonin during neuronal differentiation, the expression levels of apolipoprotein E (apoe), catenin delta 2 (Ctnnd2), amyloid beta precursor protein binding (Apbb1), glial fibrillary acidic protein (Gfap), Neuroligin 1 (Nlgn 1), notch 2 (Notch gene homolog 2), pleiotrophin (Ptn), solute carrier family 38, member 1 (Slc38a1), tenascin R (Tnr), and NIMA (never in mitosis gene-a, Nek3) decreased while the expression of ATPase type 10 A (Atp10a) and neurofilament heavy peptide (Nefh) increased. It is produced from the essential aminoalkanoic acid, tryptophan, via a two-step synthetic pathway. within the initiative, tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase. There are two isoforms of tryptophan hydroxylase, TPH1 and TPH2, which are primarily liable for 5-HT synthesis within the periphery and central systema nervosum (CNS), respectively (Lovenberg et al., 1967, Walther et al., 2003). within the final step, the intermediate product, 5-HTP, is converted to 5-HT by aromatic acid decarboxylase (AADC). Degradation of 5-HT primarily occurs by the mitochondrial bound protein MAO A (MAOA), resulting in the assembly of the metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Importantly, serotonin also is an intermediate substrate for melatonin synthesis. Elevated blood serotonin, or hyperserotonemia, was the primary biomarker identified in autism spectrum disorder (ASD) and is present in additional than 25% of affected children. Emerging data from both neuroimaging and postmortem samples also indicate changes within the brain serotonin system in ASD. In ASD families with evidence of linkage to the present region, multiple rare SERT aminoalkanoic acid variants cause a convergent increase in serotonin uptake in cell models. A knock-in mouse model of 1 of those variants, SERT Gly56Ala, recapitulates the hyperserotonemia biomarker and shows increased brain serotonin clearance, increased serotonin receptor sensitivity, and altered social, communication, and repetitive behaviors. Data from other rodent models also suggest a crucial role for the serotonin system in social behavior, in cognitive flexibility, and in sensory development. Recent work indicates that reciprocal interactions between serotonin and other systems,

Note: This work is partly presented at Joint Event on Down Syndrome, Autism, Brain Disorders & Therapeutics, October on 21-22, 2019 held at Tokyo, Japan

like oxytocin, could also be particularly important for social behavior. Collectively, these datum to the serotonin system as a major candidate for treatment development during a subgroup of youngsters defined by a strong, heritable biomarker.

Although gut-derived 5-HT influences numerous aspects of peripheral physiology, it's unable to cross the mature blood brain barrier and interact with neural tissue (Hardebo and Owman, 1980). Consequently, 5-HT found within the brain is produced by TPH2-expressing serotonergic neurons within the midbrain and hindbrain. Serotonergic neurons are organized into nine discrete clusters (B1–B9), collectively referred to as the raphe nuclei While the more caudal raphe nuclei (B1–B5) project to the peripheral systema nervosum (PNS), the rostral groups (B6–B9), the dorsal and median raphe nuclei, primarily send their projections to forebrain structures (Conrad et al., 1974, Despite their relatively small number, serotonergic neurons innervate a broad collection of brain regions (Jacobs and Azmitia, 1992), allowing 5-HT to influence neural circuitry underlying a myriad of behaviors. Reflective of its seemingly ubiquitous presence within the brain and periphery, 5-HT exerts its effects through 14 genetically distinct receptor subtypes (Hannon and Hoyer, 2008, Millan et al., 2008). Moreover, mRNA editing and alternative splicing adds another layer of complexity to an already diverse signaling systemWhile a radical description of 5-HT receptor function within the brain and periphery is beyond the scope of this review, it should be clearly noted that the unique temporal and spatial patterns of 5-HT receptor expression implicate 5-HT as a key developmental molecule

Conclusion & Significance: Serotonin treatment influenced neuronal differentiation. The detected changes in organic phenomenon may provide an insight into the pathophysiological role of hyperserotonemia in ASD. Serotonin treatment at other time points during differentiation are going to be performed to work out the developmental aspect suffering from these genes