Lack of Parvalbumin leading to autism behaviors in mice

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Abstract. This literature review examines the role of parvalbumin (PV)-expressing interneurons in the development of autism spectrum disorder (ASD), emphasizing the critical impact of PV deficits on the balance between excitatory and inhibitory (E/I) neural transmissions. PV neurons play a key role in maintaining this balance, and their deficit leads to increased inhibitory synaptic transmission and disrupts the E/I equilibrium. This disruption is linked to core ASD-like behaviors in mouse models, including social interaction deficits, communication impairments, and altered sensory processing. These findings suggest that targeting PV expression may offer a potential therapeutic approach for mitigating ASD symptoms.

Keywords: Autism Spectrum Disorder; Parvalbumin; Inhibitory Interneurons.

1. Introduction:

Autism, also called autism spectrum disorder (ASD), is a neurodevelopmental disorder characterized by deficits in social interaction, reduced/impaired communication and restricted and stereotyped behavior that are considered socioculturally inappropriate. With a focus on genetic mutations that may contribute to the disorder, mouse models have been developed to study ASD because firstly, overall patterns of brain organization, including the general pattern of neocortical organization, are similar across all mammals (Lullo& Kriegstein, 2017); secondly, through gene editing technologies such as CRISPR-Cas9（Shao-Shuai Wu et al, 2020）, specific gene mutations can be introduced into mice which will exhibit similar pathological and behavioral characteristics as those of human diseases, thereby modeling human genetic diseases. Advances have included the evaluation of mouse models with behavioral assays designed to reflect disease symptoms, including impaired social interaction, communication deficits and repetitive behaviors, and symptom onset during the neonatal period.[1] One significant area of research focuses on the role of parvalbumin (PV)-expressing interneurons in maintaining the balance between excitatory and inhibitory signals in the brain (Nahar et al, 2021). For effective and individualized treatment of autism, it is important to identify the mechanisms that govern the associated cognitive and behavioral processes. This literature review aims to discuss the lack of PV leading to autism behaviors in mice and further research into the effects of different amounts of PV deficit.

2. Behaviors of mice with PV deficit:

Currently, the studies of inhibitory control and the role of PV+ interneurons examine and compare the behaviors of mice with PV deficit and that of normal mice by conducting several experiments. Three core symptoms are observed with deficits in social behavior, communication impairments, and sensory information processing in mice with altered parvalbumin (PV) levels. Mice with either reduced PV levels (PV+/−) or a complete absence of PV (PV−/−) exhibited a significant reduction in time spent engaging in reciprocal social interactions during their juvenile stage. In terms of communication, both PV+/− and PV−/− mice demonstrated a notable decrease in ultrasonic vocalization (USV) emissions: a primary communication method among rodents; but the frequency and modulation of these vocalizations were unaffected.[2] Interestingly, the impairment in social interaction and USV was of similar magnitude in PV+/− and PV−/− mice, suggesting that even a minor reduction in PV expression is sufficient to elicit social and communication deficits with relevance to ASD. The research conducted by M Wöhr et al in 2015 showed that a reduction of PV to ~30–40% of PV+/+ is sufficient for inducing communication deficits with relevance to ASD.

Furthermore, their sensory information processing was altered, evidenced by a diminished startle response to strong stimuli. For instance, PV−/− mice showed reduced nociception in response to heat stimuli. This symptom is commonly observed in ASD patients, particularly in the auditory domain and in response to pain.[3]

3. Impact of PV deficit

PV deficiency leads to an increase in inhibitory synaptic transmission, thereby altering the E/I balance toward increased inhibition. This change not only affects inhibitory transmission but also impacts excitatory transmission on PV+ interneurons, leading to an alteration in the E/I balance.[4] To further investigate the impact of PV deficiency on autism, additional markers such as Vicia Villosa Agglutinin (VVA) have been used to identify Pvalb neurons. The number of PV+ or VVA+ neurons was counted in three brain regions associated with ASD, and the results showed that while the number of Pvalb neurons remained unchanged, there was a lower number of PV+ neurons or even absence of PV+ cells due to diminished/absent expression of PV in these interneurons.[5]

4. Factors influencing the expression of PV

Findings suggest that both genetic and environmental factors can lead to a down-regulation of PV expression in Pvalb neurons, which will contribute to these core symptoms of ASD.

4.1 Genetic Factors:

4.1.1 Shank1 and Shank3 Knockout Mice

Mutations in the SHANK genes, which are considered highly relevant for ASD, have been shown to decrease PV expression in Shank1-/- and Shank3B-/- mice. These mice exhibit a reduction in PV+ neurons in specific brain regions due to decreased Pvalb mRNA and PV protein levels, without any significant changes in the number of Pvalb neurons.

4.1.2 PV+/-, PV-/- Mice

The lower number of PV+ neurons in these mice is attributed to diminished or absent expression of PV in the Pvalb neurons, indicating that the reduction in PV+ neurons is not due to loss of Pvalb neurons but rather a decrease in PV expression.

4.2 Environmental Factors:

4.2.1 Valproic Acid (VPA) Exposure

In a widely recognized environmental ASD mouse model, prenatal exposure to valproic acid (VPA) results in unaltered numbers of Pvalb neurons but a decrease in PV+ neurons in the striatum. This decrease is due to a reduction in Pvalb mRNA and PV protein levels. Specifically, there is a 50% decrease in Pvalb mRNA and a 30% decrease in PV protein (Federica Filice et al, 2016).

5. Future studies

The validation of a hub consisting of PV-expressing neurons in ASD is expected to facilitate the development of therapeutic strategies that restore brain functions in ASD. Additionally, the properties and functions of PV-FSI are multi-faceted, which means there are many opportunities to manipulate different aspects of PV-FSI activity to resolve gaps in the current understanding of these interneurons and the context of health and disease. [7]

References

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