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## **PARVALBUMIN DEFICIENCY – A COMMON ENDPOINT MOUSE MODEL FOR AUTISM SPECTRUM DISORDER?**

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The core symptoms of autism spectrum disorder (ASD) are impaired sociability/communication and restricted or repetitive behaviors. Due to the divergence and complexity behind ASD development, current research seeks for identification of convergent pathways or common endpoints in ASD pathophysiology in order to develop new and efficient treatment approaches targeted at the core symptoms. A promising point of convergence in ASD appears to be the calcium-binding protein parvalbumin (PV). A decrease in the number of PV+ neurons was observed in the brain of different ASD mouse models, including mice prenatally exposed to valproic acid (VPA) and mice lacking the synaptic cell adhesion molecule contactin-associated protein-like 2 (Cntnap2). Moreover, transgenic mice with reduced (PV+/-) or absent (PV-/-) PV levels show the ASD-associated core symptoms as well as ASD-related morphofunctional abnormalities. Of note, reports about reduced numbers of Pvalb neurons are often based on immunohistochemical analysis using antibodies directed against PV. However, the absence of a signal (i.e. the absence of PV+ neurons) under these conditions does not necessarily correspond to a loss of Pvalb neurons. It might be that only the protein PV is decreased/missing, whilst the Pvalb neurons are still present in normal numbers.

In the first two projects of my PhD thesis, we re-evaluated the previously characterized VPA and Cntnap2-/- mouse models of ASD. We made use of an additional marker for Pvalb neurons, namely Vicia Villosa Agglutinin-positive (VVA+) perineuronal nets (PNNs), previously shown to specifically surround Pvalb neurons. We found that the number of VVA+ cells was unchanged in both ASD mouse models when compared to control mice. Yet the number of PV+ neurons and PV protein levels were significantly decreased in the striatum of VPA and Cntnap2-/- mice compared to control mice. These findings question previous reports about a Pvalb neuron loss in the brain of the two ASD mouse models. In the third project of my PhD thesis, we investigated whether the 17 $\beta$ -estradiol (E2)-mediated restoration of PV levels in PV+/- mice leads to a rescue of the ASD-like behavioral phenotype observed in untreated PV+/- mice. We found that sociability impairments and repetitive behaviors were attenuated in PV+/- mice after E2-mediated upregulation of PV levels. Importantly, E2-treated PV-/- mice, which were still completely lacking PV expression, did not show any changes in behavior compared to untreated PV-/- mice. These results suggest that the behavioral improvement observed in E2-treated PV+/- mice was indeed attributable to the upregulation of PV levels.

In summary, we made progress in our understanding of the involvement of Pvalb neurons in the context of ASD. Restoration of PV levels during early development might represent a novel and seminal treatment approach possibly ameliorating the core symptoms of a broad selection of ASD patients.

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