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Structural and functional remodeling of neuronal input/output properties in mouse models of autism

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The axon initial segment (AIS) constitutes the site of action potential generation in neurons and thus plays an important role in the regulation of cellular excitability and neuronal circuit function. Recent studies have shown that the AIS can undergo structural and functional plasticity both during development and in the adult. Changes can include the remodeling of length and position, both dependent on the network state. It has been hypothesized, that an imbalance of excitation and inhibition in the fronto-striatal circuitry is involved in the development of ASD phenotypes. Therefore, the AIS, as a dynamic regulator of intrinsic excitability and neuronal circuit function might contribute to this imbalance.

VPA is an antiepileptic drug that is known to be highly teratogenic and has severe effects on the unborn child when taken during pregnancy. Effects include the development of autistic features. Similar effects after *in utero* exposure could be found in rodent models. Analogies in brain structure and similarities of behavioral patterns between VPA exposed rodents and patients with ASD lead to the conclusion that the VPA-model of autism is suitable to investigate changes to neuronal circuits in the autistic brain. The transcription factor forkhead box protein 1 (FOXP1) has been shown to regulate neuronal excitability in striatal spiny projection neurons (SPN) and has been identified as a risk factor in the development of ASD. FOXP1 knockout ($FOXP1^{-/-}$) mice show typical ASD features such as restrictive and repetitive patterns of behavioral output, deficits in learning, memory and social interaction.

The question, if AIS-typical neurodevelopmental changes and behavioral pattern could be traced back to alterations in AIS morphology have not been addressed so far. Thus, this present study was carried out to analyze possible alterations to AIS plasticity and intrinsic excitability and find possible anatomical correlations of the ASD phenotype. By using several methodological approaches, as immunofluorescent staining, confocal microscopy and 3D reconstruction, western blot analysis and electrophysiological recording, it was aimed to detect a broad spectrum of various changes on anatomical and single-cell levels. The VPA-model and $FOXP1^{+/-}$ model were chosen to evaluate commonalities and differences between two different mouse models of ASD.

AIS plasticity was analyzed in different areas along the pathway of the fronto-striatal circuit in the VPA-model. Firstly, in layer II/III of S1BF no changes to AIS length or number of inhibitory synapses were detected, indicating that the sensory input to cortical regions might not be affected by VPA exposure. However, several mechanisms could contribute to the shortening of AIS length that was observed in layer V throughout development. Alterations of synaptic transmission and ion channel constitution could result in higher neuronal activity and lead to shortening of AIS length in layer V, accompanied with changes in intrinsic firing properties of the neurons, that were detected via electrophysiological recordings. Decreased excitability in layer V is passed on to the DLS, resulting in a homeostatic upregulation of AIS length.

Interestingly, in adult $FOXP1^{+/-}$ mice, AIS were elongated in the DLS compared to the control group. This morphological change was accompanied in downregulation of ion channel protein expression. Any implications of functional levels remain unclear up to this point and have to be evaluated by further electrophysiological studies.

Possible commonalities could be morphological changes in the DLS of rodents, that could lead to the presentation of ASD-typical behavioral pattern such as repetitive movements. A reduction in the expression of FOXP1, that has been implicated in the development of ASD, could contribute to the pathogenesis of the phenotype.

Taken together, the presented data show, that neurons respond to altered network activity by remodeling of their AIS, either by adapting the length of the AIS or by changing the ion channel constitution. All these observed changes could be subtle hints to a circuit, depending on the sensitive adjustment of excitation and inhibition, being out of balance.