Abstracts poster session III

The putative role of Parvalbumin in Autism Spectrum Disorders

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Autism spectrum disorders are largely neurodevelopmental disorders with a strong genetic component and are characterized by impairments in social interaction, communication and stereotyped patterns of behavior, interests, and activities. Genes associated with autism (NLGN3, 4, Shank1,2,3) encode proteins subjected to activity-dependent changes in neuronal function and participate in processes such as synaptic formation, maturation elimination and plasticity[1]. The dysregulation of this activity - dependent signaling networks controlling synapse development and function may be an important component of the molecular basis of ASD, but alternative explanations must be considered, such as an impairment of neurotransmission, i.e. excitation/inhibition (E/I) balance[2] or defects in earlier steps in nervous-system development[3]. In this scenario, interneurons play a key role in the maintenance of the global balance of activity in cortical networks; evidences have been provided that interneuron dysfunctions are linked with cognitive impairment in neuropsychiatric disorders[4].

In particular, the number of fast-spiking interneurons (FSI) expressing the calcium-binding protein parvalbumin (PV) has been reported to be decreased in different well-assessed mouse models of ASD[5-7]. Of interest, PV-deficient mice (PV-/- and PV+/- respectively) show ASD-like symptoms as reported in other “canonical” ASD mouse models (Whör et al., submitted).

Accordin to the current view, this decrease in PV-immunoreactive (PV-ir) cells is due to a “loss” of PV-expressing FSI, that eventually lead to a change in the E/I balance. In our opinion this “loss” of PV-ir neurons is rather a reduction in PV expression levels or synthesis, possibly as a result of an adaptive/homeostatic mechanism aiming “to restore the impaired FSI function”. To test our hypothesis, we set out to determine whether the number of “PV-FSI” is altered in PV-/- and PV+/- mice using stereological methods[8]. For this we made use of the fact that a large majority of cortical PV-FSI is surrounded by a particular extracellular matrix, termed as perineuronal nets[9].

Initial results indicate the number of “PV-interneurons”, is not altered in PV-deficient mice. Thus, a mere down-regulation of PV affecting the intracellular Ca^{2+} signals appears to be sufficient to precipitate in an ASD-like behavioral phenotype. Future perspective aim to use the same strategy in canonical mouse models of ASDs, to demonstrate that PV-downregulation may be a common/convergent pathway for ASDs with different etiologies.

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Investigating Notch1 contribution to sporadic Alzheimer's disease

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Abstract

Beside the established role of Notch1 in brain development, there is increasing evidence for an involvement of this signaling pathway in sensory processing and neurodegeneration. Previous studies have indicated alterations in Notch1 expression in several neurodegenerative diseases, including Alzheimer's disease (AD). AD is the most common neurological disorder related to aging. There are two forms of AD: the early onset form (familial AD) and the late onset form (sporadic AD) .The latter accounts for the majority of the cases (95%). It remains unclear whether and to what extent, Notch1 contributes to the pathogenesis of AD. In our work, we address how Notch signaling is affected in the sporadic form of this pathology. By using a mouse model of neuroinflammation and late onset dementia (PolyI:C), we observe aberrant Notch1 depositions in the parenchyma of the olfactory bulb, limbic regions, hippocampus and cortex. Notch1 positive plaques are surrounded or engulfed in activated microglia, suggesting a contribution of Notch1 in neuroinflammation. This rosette-like distribution of Notch1 was confirmed in 2 out of 4 definite sporadic AD patients. Notch1 positive clumps stained for some of the hallmarks of AD, such as APP and Thioflavin T, which detects beta-amyloid oligomers. In addition, in all patients examined, Notch1 receptor is mainly localized to the nuclei of the neurons, whereas in the healthy controls Notch1 is expressed in the soma and processes of neuronal cells. The loss of Notch1 in neuronal processes implies that a dysfunction in Notch-mediated plasticity may underlie the memory defects in AD. With this study, we aim to develop further insights into the role of Notch1 in sporadic AD and explore its potential as a therapeutic target.

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Corticobulbar projections from the premotor cortex in the macaque monkey

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Corticospinal and corticobulbar projections act, in parallel with brainstem systems (reticulospinal, tectospinal, vestibulospinal, rubrospinal), to ensure direct or indirect motor control on spinal motoneurons. The aim of the present study was to establish the pattern of projections of the premotor cortex (PM) on the reticular formation in the brainstem, potentially influencing the reticulospinal neurons. The high resolution tract-tracer BDA was injected in PM of 2 intact monkeys and the anterogradelly labeled corticobulbar axonal terminal fields, including *boutons*, were chartered in the brainstem across 12 consecutive frontal histological sections. In one animal, the BDA injection was located in both PMd and PMv (Mk-R13) whereas, in the second animal, the BDA injection was restricted to PMd (Mk-R12).

In both animals, the corticobulbar axons formed bilaterally terminal fields with *boutons terminaux* and *boutons en passant*, in nuclei belonging to the PontoMedullary Reticular Formation (PMRF), mainly rostrally in the Pontine Reticular nucleus Oral (PnO), the Pontine Reticular nucleus Caudatus (PnC) and in the Raphe nuclei, as well as more caudally, but less densely, in the Gigantocellular nucleus (Gi) and the Intermediate Reticular nucleus (IRt). In Mk-R12, caudally, labelled *boutons* were also found in the Lateral Reticular nucleus (LRt). Quantitatively, in Mk-R12, the number of *boutons* were significantly more numerous on the ipsilateral side than on the contralateral side in the rostral half of PMRF (paired t-test, $p=0.05$), but not in the caudal half of PMRF (no systematic side difference). In Mk-R13, the number of *boutons* was not systematically different on the ipsilateral versus the contralateral side of PMRF, both in the rostral and caudal halves. The present pattern of projection from PM to PMRF represent a basis for further comparison with monkeys subjected to a unilateral lesion of the primary motor cortex, in which the intact PM was shown to play a significant role in the functional recovery, possibly via a re-arrangement of the corticobulbar projection from PM.