in CD44 null mice. These results suggest that CD44 is required for the normal development of the hippocampus.

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[P2.09]

Developmental changes in GABAergic inhibitory mechanisms in human primary visual cortex throughout the lifespan

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Keywords: GABA; Inhibition; Development; Human visual cortex

Inhibitory systems play key roles in cortical circuit function and synaptic plasticity during both early neural development and the changes that accompany aging. GABA is the most widespread and abundant inhibitory neurotransmitter in cortex. While previous studies have examined GABAergic mechanisms in animal models, few have looked in human cortex at how these mechanisms change across the lifespan. We completed a comprehensive study of both presynaptic and postsynaptic GABAergic mechanisms in human primary visual cortex (n = 30, age range: 20 days to 80 years). Using Western blot analysis of human postmortem tissue, we looked at the developmental profiles of the GABA synthesizing enzymes (GAD65/67), the GABA vesicular transporter (VGAT), $GABA_A$ receptor subunits ($GABA_A\alpha1$, $\alpha2$, $\alpha3$), the inhibitory modulating cannabinoid receptor (CB1), and the inhibitory receptor anchoring protein (Gephyrin). On the pre-synaptic side, GAD67 was constant across the lifespan, and GAD65 showed a modest developmental increase peaking during the teenage years. In contrast, VGAT expression was high before 1 year of age and then constant across the lifespan. On the post-synaptic side, $GABA_A\alpha1$ expression increased until the teen to young adult years, $GABA_A\alpha2$ expression decreased across the lifespan, and $GABA_A\alpha3$ expression stayed constant throughout life. These receptor changes reflect the developmental shift in relative subunit composition from immature ($GABA_A\alpha2/\alpha3$) to mature ($GABA_A\alpha1$). Gephyrin expression increased gradually into the teen and young adult years then decreased with aging, suggesting a slow development of total $GABA_AR$ expression and age-related loss of these receptors. The inhibitory modulator CB1 was high until 1 year of age, then decreased into the teenage years, then remained relatively constant. Together, these results show modest presynaptic changes in GABAergic mechanisms across the lifespan and large postsynaptic changes in subunit composition during early development and age-related losses in total GABA receptor expression.

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[P2.10]

Postnatal maturation of cortical parvalbumin inhibitory neurons is impaired in FGF receptor mutant mice

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Keywords: GABA; Interneuron; Fibroblast growth factor; Knockout

Mutant mice carrying a deletion of the fibroblast growth factor receptor 1 ($Fgfr1^{f/f;hGfapCre}$) in radial glial cells or in neuroepithelial cells ($Fgfr1^{f/f;NesCre}$) exhibit a deficit in cortical inhibitory interneurons throughout life. Parvalbumin (PV)- and somatostatin (ST)-containing cortical interneurons are selectively decreased in the neocortex of $Fgfr1^{f/f;hGfapCre}$ mice (37%, p = 0.002, and 47%, p = 0.03, respectively), and their decrease correlates with locomotor hyperactivity. A greater loss of PV+ interneurons occurs in $Fgfr1^{f/f;NesCre}$ mice, when the Fgfr1 deletion is more widespread (48% decrease; p = 0.01). Using Gad1-GFP mice to visualize all inhibitory neurons as soon as they are formed in the embryo, we find that the specification of inhibitory neurons in the basal ganglia, their generation and their migration to the cerebral cortical primordium are not altered in Fgfr1 mutant mice. In BrdU birthdating studies at E13.5, Fgfr1 mutants showed no significant differences in Brdu/GFP co-labeled cells in the MGE at E14.5, or at P0 in the cortex. Furthermore, Fgfr1 mutants have equal numbers of GFP + GABAergic neurons in the cortex. In addition, neither the patterning of the ganglionic eminence, as assessed by Dlx2, Mash1 and Nkx21.1 gene expression, nor the density of mitotic cells in the basal telencephalon, are affected in $Fgfr1^{f/f;hGfapCre}$ or $Fgfr1^{f/f;NesCre}$ mutant mice as compared to their littermate controls. Thus, the disruption in Fgfr signaling pathways in postnatal cortical cells – likely glia – is responsible for engendering a decrease in PV inhibitory neurons, which in turn causes locomotor hyperactivity.

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[P2.11]

Retrograde axonal transport of neurotrophic factors in vivo: Saltatory transport and lack of involvement of multivesicular bodies

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Keywords: Trophic factor; Axonal transport; Signaling endosome; Neurotrophic hypothesis

Developing neurons require trophic feedback from their targets. There is a general consensus that neurotrophic factors are transported retrogradely along axons in signaling organelles (signaling endosome hypothesis), but the controversy continues whether these endosome carriers of trophic signals are small vesicles [Cui et al., 2007, PNAS 104: 13666–13671] or larger multivesicular bodies, MVBs [Weible, Hendry, 2004, J. Neurobiol. 58: 230–243; Bronfman et al., 2007, Dev. Neurobiol. 67: 1183–1203]. The arguments for MVBs are based on studies that manipulate transport in vivo or in vitro, but such MVBs may be artifacts of the experimental design.

To settle this long-standing dispute, we traced the fate of retrogradely transported radiolabeled BDNF and GDNF in the hypoglossal nerve of postnatal rats, using quantitative autoradiography at the ultrastructural level to identify and quantify the transporting organelles. MVBs were rare in axons in vivo, and their frequency did not increase by injections of trophic factors in the target. Neurotrophic factors accumulated with a significant labeling density at the distal side of nodes of Ranvier (Fig. 1), while the labeling density along the axon shaft was significantly lower. Silver grains did not accumulate over MVBs. These data indicate that trophic factor transport speed increases along the axon shaft, but slows down considerably in the "bottleneck" paranodal region with constricted axon diameters ("saltatory transport").

Why did previous reports (often in-vitro studies) implicate MVBs as the trophic signal carrier? We tested whether abnormal