W155. Fibroblast Growth Factor 14 is an Essential Element of the Inhibitory Circuit that Controls Cognitive Function Associated with Schizophrenia

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Background: Cognitive processes require gamma-amino-butyric acid (GABA) interneurons. Via complex synaptic connections, these cells regulate cellular excitability and synaptic plasticity of principal neurons, balancing the excitatory/inhibitory (E/I) tone in cortical networks. Loss of and impairment in function of parvalbumin (PV)

interneurons and GABAergic synapses is associated with cognitive impairment in schizophrenia and other psychiatric disorders. Despite efforts to identify the molecular factors leading to E/I imbalance and impaired PV interneuron functioning, much remains to be learned. Additional knowledge of key regulatory nodes that control PV neuronal integrity and function, and GABAergic synapses is essential, especially to develop effective treatments for cognitive impairment. With a combination of animal model studies and post-mortem transcriptomics analysis, we provide what we believe are breakthrough results demonstrating a novel potential link between cognitive decline in schizophrenia and expression of fibroblast growth factor 14 (FGF14), a regulator of intrinsic excitability, synaptic transmission and plasticity. We show that Fgf14-/- mice have significantly reduced number of PV interneurons, decreased expression of the presynaptic GABAergic markers, GAD67 and VGAT, reduced inhibitory connections, decreased gamma frequency oscillations in cortical areas, and impaired working memory. Bioinformatics analysis of schizophrenia transcriptomics from human post-mortem tissue revealed functional co-clustering and correlative decreased expression of FGF14, PVALB, GAD67 and VGAT. Together these results provide evidence that FGF14 is a new risk-factor associated with schizophrenia and perhaps related disorders.

Methods: We employed confocal microscopy and image analysis to quantify changes in the PV interneuron population and GABAergic markers, single-cell patch clamp electrophysiology to assess inhibitory synaptic transmission in an ex-vivo brain slice preparation, in vivo local field potential recordings to analyze EEG spectra, and behavioral studies to evaluate working memory deficits in Fgf14-/- mice. Computational network analysis of FGF14 co-expression genes was conducted using the SEEK, a computational gene co-expression search engine. Functional annotation and pathway enrichment was obtained using GO and KEGG terms. We also evaluated the gene expression of FGF14 and other genes in two independent data sets, which derived from post-mortem DLPFC(BA46) of schizophrenic and controls subjects; the differential gene expression was analyzed by R Limma package.

Results: We show that genetic deletion of Fgf14 leads to loss of PV interneurons in the CA1 hippocampal region (74.21% ± 5.02 in Fgf14-/- mice versus 100% ± 4.89 in Fgf14+/+ littermates; $p<0.001$, $n=4$ littermates per group). These changes were associated with a statistically significant reduction in both GAD67 and VGAT expression in PV somas and in synaptic puncta on CA1 pyramidal neurons (p values were from <0.01 to <0.0001 for each phenotype, $n=3$ littermates per group). Whole-cell patch clamp recordings from CA1 pyramidal neurons revealed a shift in the frequency and amplitude distribution of spontaneous and miniature inhibitory synaptic events consistent with a loss in a subset of synaptic events ($n=8$-10 and $n=6$-7 respectively, $p<0.001$, Kolmogorov-Smirnov test). In vivo local field potential recordings showed a significant ($p<0.05$) reduction in gamma frequency oscillations in Fgf14-/- mice (2.94 ± 0.11 μV2 n = 7) compared to wild type controls (7.92 ± 0.17 μV2 $n=7$), while behavioral tests revealed impaired working memory in Fgf14-/- mice compared to wild type animals ($n=19$-20 per group, $p<0.001$). Through the SEEK-based gene co-expression search engine with pathway enrichment by Gene Ontology (GO) terms, and KEGG orthologue analysis, we found that FGF14 was enriched within the 'GABAergic synapse' pathway and its expression profile correlated with that of PVALB ($p=0.004$ in hippocampus; $p=0.0059$ in prefrontal cortex), GAD67 ($p=0.0009$ in hippocampus; $p=0.0003$ in prefrontal cortex) and VGAT ($p=0.04$ in hippocampus; $p=0.069$ in prefrontal cortex). Furthermore, analysis of transcriptomics data from post-mortem tissue data sets showed significantly decreased expression of and correlation between FGF14, PVALB, GAD67 and VGAT in two independent schizophrenia data sets and matched controls.

Conclusions: The array of phenotypes associated with loss of Fgf14 in mice along with the complementary human studies provide knowledge to generate new hypotheses on the biology and the risk factors associated with disrupted GABAergic signaling in schizophrenia and other complex brain disorders.

Keywords: GABAergic circuitry, parvalbumin interneurons, synaptic connctions, Cognition

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