WTH03-13 | Restoring heart failure-induced long-term memory impairment by targeting the cystic fibrosis transmembrane regulator

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Over 64 million people worldwide live with heart failure (HF). Despite improved acute phase management, long-term consequences that include HF-associated cognitive impairment increasingly impact patients' well-being. The shortage of effective therapies for HF-associated cognitive decline can largely be explained by the lack of mechanistic insight. We previously identified impaired cystic fibrosis transmembrane regulator (CFTR) expression as critical contributor to cerebral perfusion deficits associated with structural and functional alterations in HF brains.

In a murine model of HF, reduced hippocampal neuronal dendrite length and spine density coincide with an apparent reduction of neuronal CFTR expression. Co-occurrence of hippocampal microglia activation and elevated interleukin (IL)-1 beta and IL-18 transcripts led us to investigate the link between inflammation and neuron-specific CFTR expression. Conditioned media from lipopolysaccharide-stimulated microglia (LCM) profoundly reduces neuronal cell CFTR protein and PSD-95 mRNA expression, as measured by western blot and qPCR. Acutely inhibiting CFTR channel activity (10 µM CFTR(inh)-172) mediates a significant downregulation of PSD-95 also in the absence of LCM. CFTR corrector treatment (13 µM Lumacaftor) increases CFTR expression on the cell surface of $CFTR^{+}$ neuronal cells, and corrects both, the LCM-mediated overall CFTR protein reduction and PSD-95 mRNA down-regulation.

Collectively, these results suggest that cytokines released from activated microglia can mediate CFTR downregulation in neurons and that the loss of CFTR in neurons is detrimental to their health. *In vivo*, pharmacological CFTR correction in HF mice normalizes hippocampal neuron CFTR expression associating with improved memory function and alleviation of HF-induced reduction in hippocampal neuron dendrite length and dendritic spine density.

In conclusion, these results suggest that adequate neuronal CFTR expression is critical for maintaining neuronal integrity and that pharmacological correction of CFTR protects neuronal structure and preserves memory function during HF.