Cholinergic Regulation of hnRNPA2/B1 Translation by M1 Muscarinic Receptors

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Abstract:

Cholinergic vulnerability, characterized by loss of acetylcholine (ACh), is one of the hallmarks of Alzheimer's disease (AD). Previous work has suggested that decreased ACh activity in AD may contribute to pathological changes through global alterations in alternative splicing. This occurs, at least partially, via the regulation of the expression of a critical protein family in RNA processing, heterogeneous nuclear ribonucleoprotein (hnRNP) A/B proteins. These proteins regulate several steps of RNA metabolism, including alternative splicing, RNA trafficking, miRNA export, and gene expression, providing multilevel surveillance in RNA functions. To investigate the mechanism by which cholinergic tone regulates hnRNPA2/B1 expression, we used a combination of genetic mouse models and in vivo and in vitro techniques. Decreasing cholinergic tone reduced levels of hnRNPA2/B1, whereas increasing cholinergic signaling in vivo increased expression of hnRNPA2/B1. This effect was not due to decreased hnRNPA2/B1 mRNA expression, increased aggregation, or degradation of the protein, but rather to decreased mRNA translation by nonsense-mediated decay regulation of translation. Cell culture and knock-out mice experiments demonstrated that M1 muscarinic signaling is critical for cholinergic control of hnRNPA2/B1 protein levels. Our experiments suggest an intricate regulation of hnRNPA2/B1 levels by cholinergic activity that interferes with alternative splicing in targeted neurons mimicking deficits found in AD.

SIGNIFICANCE STATEMENT: In Alzheimer’s disease, degeneration of basal forebrain cholinergic neurons is an early event. These neurons communicate with target cells and regulate their long-term activity by poorly understood mechanisms. Recently, the splicing factor hnRNPA2/B, which is decreased in Alzheimer's disease, was implicated as a potential mediator of long-term cholinergic regulation. Here, we demonstrate a mechanism by which cholinergic signaling controls the translation of hnRNPA2/B1 mRNA by activation of M1 muscarinic type receptors. Loss of cholinergic activity can have profound effects in target cells by modulating hnRNPA2/B1 levels.

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