Increasing protein synthesis in the hippocampus prevents cognitive impairments caused by sleep deprivation

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Sleep loss produces deficits in hippocampus-dependent memory storage, but the molecular and cellular mechanisms that underlie these effects of sleep deprivation remain unclear. Several studies have suggested that signaling pathways associated with translation are altered during sleep and after periods of sleep deprivation. Here, we demonstrate that five hours of total sleep deprivation increases phosphorylated AMP-activated protein kinase (AMPK) alpha, reduces mTOR complex 1 (mTORC1) and reduces phosphorylated eukaryotic translation initiation factor 4E binding protein 2 (4EBP2), which subsequently leads to impaired protein synthesis in the hippocampus. However it is yet to be determined whether restoring protein synthesis in the hippocampus is sufficient to prevent the cognitive deficits associated with sleep deprivation. Viral expression of 4EBP2 selectively in hippocampal excitatory neurons in mice that were sleep deprived for five hours increased phosphorylated 4EBP2 levels, which was sufficient to restore hippocampal protein synthesis to non-sleep deprivation levels. Furthermore, viral expression of 4EBP2 prevents the memory deficits associated with sleep deprivation in the object place recognition task. These findings indicate that AMPK-mTORC1-4EBP2 signaling and subsequent impaired protein synthesis is the critical component underlying the memory deficits associated with sleep deprivation in hippocampus-dependent learning tasks. Furthermore, this study defines the molecular mechanism by which loss of sleep impairs cognitive processes and highlights a vital role for protein synthesis and mTOR signaling on long-term memory formation.