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Abstract (appr 300 w)	Although epidemiological studies indicate that sleep-disordered breathing (SDB) such as obstructive sleep apnea is a strong risk factor for the development of Alzheimer's disease (AD), the mechanisms of the risk remain unclear. We developed a method of modeling SDB in mice that replicates key features of the human condition: altered breathing during sleep, sleep disruption, moderate hypoxemia, and cognitive impairment due to the selective degeneration of cholinergic basal forebrain neurons, which are characteristically lost in AD (Qian et al Nature Communications, 2022). These neurons are also known to express the p75 neurotrophin receptor, a regulator of neuronal death that can undergo regulated intramembrane cleavage in response to low oxygen to regulate hypoxia-inducible factor-1α (HIF-1α). Previously, the fate of neurons in which such signalling has been induced was unknown. Here, using neuronal cell culture, we found that hypoxia promoted cleavage of $p75^{NTR}$, HIF-1α activity, and apoptosis. In contrast, inhibiting $p75^{NTR}$ cleavage, its activation, or signalling with candidate drugs, or preventing HIF-1α nuclear translocation decreased neuronal cell death in vitro. Moreover these same treatments prevented hypoxia-induced cell death of basal forebrain cholinergic neurons in the SDB mouse model. These results demonstrate that hypoxia-induced apoptosis requiring HIF-1α nuclear translocation depends on $p75^{NTR}$ expression and cleavage, and can be prevented with systemic application of anti-$p75^{NTR}$ drug candidates.

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