20230810 Ambroxol – a unique disease-modifying compound in neurodegenerative disorders

Studies conducted both in preclinical and clinical settings, focusing on various disorders characterized by neuronal degeneration, have demonstrated that ambroxol aids in promoting the survival of neurons through a range of interconnected mechanisms. Broadly, these studies indicate that ambroxol assists neurons in effectively clearing waste within their structures, improving their metabolic functions, and reducing inflammatory response.

From a clinical perspective, ambroxol has a well-established history of safe usage, even during prolonged periods and at elevated doses. Moreover, it exhibits strong bioavailability within brain tissue. Based on these favorable attributes and the robust outcomes observed in model systems, ambroxol is currently undergoing clinical trials for several neurodegenerative conditions, including Parkinson's disease (phase III (University College, London, 2023), phase II (Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta, 2022)), Lewy body dementia (phase I/II (Pasternak, 2022), phase II (Helse Fonna, 2021)), Amyotrophic lateral sclerosis (phase II (Turner, 2022)), and Gaucher's disease (multiple open label trials (Shaare Zedek Medical Center, 2023; Zhan et al., 2023). Collectively, these results indicate ambroxol's potential for treatment of neurodegenerative disorders including Alzheimer's disease (AD).

In terms of its underlying mechanisms, the initial evidence revealing ambroxol's unexpected impact on the cellular waste elimination process, known as autophagy, emerged from screenings that demonstrated its ability to regulate enzymes responsible for processing sphingolipids. Sphingolipids are molecules that are predominantly processed by enzymes localized within lysosomes. These enzymes experience significant dysregulation in patients with Alzheimer's disease (AD) and even in individuals at the early stages of AD progression (Byeon et al., 2021; Baloni et al., 2022). Through an extensive library screening, ambroxol was identified as the primary candidate capable of acting as a molecular chaperone for glucocerebrosidase (GCase) (Maegawa et al., 2009). Elevated GCase activity has been demonstrated to enhance the lysosomes' ability to break down protein aggregates, such as those formed by alpha-synuclein (Mazzulli et al., 2016). Notably, ambroxol has been shown to boost GCase activity in human patients with Gaucher's disease (Narita et al., 2016) as well as in cases of idiopathic Parkinson's disease (PD) (Mullin et al., 2020), with positive impacts on the overall reported quality of life in both instances. Ambroxol's effects also extend to inhibiting sphingomyelinase (Carpinteiro et al., 2021), an enzyme that tends to become overly active in AD patients (Baloni et al., 2022). Heightened sphingomyelinase activity is linked to the increased amyloidogenic processing of the amyloid precursor protein by gamma secretases (Grimm et al., 2005). Conversely, inhibiting sphingomyelinase has been demonstrated to rescue synaptic deficits in mouse models of AD (Baloni et al., 2022).

Another aspect of AD's underlying mechanisms that ambroxol addresses is the unfolded protein response. In AD and other neurodegenerative disorders, the accumulation of neurotoxic protein waste contributes to the emergence of endoplasmic reticular stress. This stress triggers the production of additional intracellular protein aggregations (Ajoolabady et al., 2022). Ambroxol plays a role in enhancing the removal of protein aggregates by promoting autophagy through the upregulation of transcription factor EB (McNeill et al., 2014; Choi et al., 2018; Magalhaes et al., 2018). Transcription factor EB is a key controller of cellular autophagy processes (Medina et al., 2015). It's worth noting that many substances that amplify TFEB signaling also disrupt cellular metabolism by generating free radicals as by-products

(Lu et al., 2017; Redmann et al., 2017). In contrast, ambroxol acts as a potent antioxidant (Ledwozyw et al., 1991; Stetinová et al., 2004). Its application has demonstrated an association with heightened functionality of lysosomes and mitochondria both in cell cultures and in murine models (Magalhaes et al., 2018; Mishra and Krishnamurthy, 2020). Additionally, ambroxol has been shown to alleviate endoplasmic reticular stress and protect neural function in mouse models of ischemic stroke when administered after reperfusion (Ge et al., 2020; Jiang et al., 2020).

Lastly, ambroxol assumes a powerful role in governing the immune response, which increases during the prodromal phase of AD. Elevated levels of pro-inflammatory cytokines, such as interleukin 1β, 6, 8, and tissue necrosis factor alpha, in longitudinally sampled AD patient sera have been identified as predictive of unfavorable clinical trajectories (Heneka et al., 2015). In contrast, heightened levels of anti-inflammatory cytokines like interleukin 10 and interferon-γ associated with adaptive immunity have been linked to slower cognitive decline in individuals with AD (Yang et al., 2022). Diverse studies across various organ systems (Takeda et al., 2016; Zhang et al., 2016; Jiang et al., 2020; Kókai et al., 2021; Schneider et al., 2021; Cavalu et al., 2022) have collectively affirmed that ambroxol exerts a transformative influence on inflammation and immune response. For instance, in lung tissue, ambroxol has demonstrated the ability to reduce the expression of pro-inflammatory cytokines like interleukins 1β, 6, 8, and tissue necrosis factor-α (Bianchi et al., 1990; Jang et al., 2003; Wang et al., 2011). It has also been shown to reduce activation of pathways leading to inflammasome activation, such as NF-κB, in the gut (Cavalu et al., 2022).

This dampening of inflammation is partially attributed to ambroxol's capacity to scavenge free radicals (Peroni et al., 2013). Moreover, its effects on autophagy, particularly TFEB activation, could play a role in mitigating inflammation by degrading pivotal mediators of inflammation, including components of the inflammasome (Shi et al., 2012; Deretic, 2021). Alongside its inhibitory effects on pro-inflammatory signaling pathways, ambroxol has been found to elevate the expression of interleukin 10, 12, and interferon-γ in lung tissue following challenges with pathogens and ovalbumin (Takeda et al., 2016; Kókai et al., 2021), indicating a reinforced anti-inflammatory and adaptive immune response. Collectively, these immune response effects may contribute to preclinical observations of diminished inflammation in ulcerative colitis models (Schneider et al., 2021) and a reduction in pro-inflammatory M1-type microglial activation in models of intracerebral hemorrhage (Jiang et al., 2020).

Due to its demonstrated capacity to safeguard neuronal integrity in the face of challenges, ambroxol stands out as a promising contender for repurposing in the context of various neurodegenerative conditions. Notably, the International Linked Clinical Trials program has singled out ambroxol as one of the select few FDA-approved drug candidates for repurposing in the treatment of Parkinson’s disease (Stott et al., 2021). Following encouraging outcomes in phase 2 trials (Mullin et al., 2020), this initiative joined forces with the Van Andel Institute and the John Black Charitable Foundation to finance a phase 3 trial investigating ambroxol's potential in treating PD. This milestone marks ambroxol as one of only five candidate drugs to ever attain such a stage of clinical investigation for PD.

In addition, ambroxol earned a place of prominence in the RENEWAL program through expert consensus, positioning it as the most promising candidate for clinical trials targeting Lewy Body Dementia (O’Brien

et al., 2022). Furthermore, strong preclinical study results (Bouscary et al., 2019) have propelled ambroxol into the sphere of evaluation as a prospective therapy for amyotrophic lateral sclerosis.

Thus, ambroxol boasts a robust clinical history and has garnered support from both preclinical and clinical realms as a potential remedy for neuronal loss in degenerative disorders. Its distinctive mechanisms of action at the cellular level align effectively with alleviating the intracellular deficits characteristic of such disorders. Coupled with its favorable safety profile and ability to cross the blood-brain barrier, Ambroxol holds promise for deployment as a flexible solution in the treatment of Alzheimer's disease. It could serve either as a standalone therapy or in synergy with newly approved monoclonal antibodies, which are on the brink of becoming the standard of care.

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