COMMENTARY

# Antipsychotics, versatility in action

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In PNAS Patergnani et al. elucidate tantalizing mechanisms by which neurodegeneration occurs in the context of multiple sclerosis (MS) in their paper entitled "Antipsychotic drugs counteract autophagy and mitophagy in multiple sclerosis" (1). The authors take a deep dive into the significant contributions of autophagy and mitophagy, both of which are catabolic pathways that maintain homeostasis by recycling cellular proteins from damaged or excessive organelles (2). In autophagy, dysfunctional organelles are recycled via formation of the autophagosome, a dynamic process regulated by autophagy-related genes (ATG) (3); mitophagy represents a specific form of autophagy targeting damaged mitochondria (4). By providing the cell with essential amino acids, these evolutionarily conserved processes not only play a physiological role in embryonal development and aging but can also augment survival under stressful conditions like starvation (3). That said, deregulated autophagy has become a hotly investigated mechanism contributing to diseases such as cancer, diabetes, and neurodegenerative conditions like Alzheimer's disease and Parkinson's disease (5, 6), but its contribution to MS pathophysiology has only been cursorily studied thus far.

Starting with a first reveal of the significant degree of both autophagy and mitophagy in patients with active MS, via high levels of ATG5, ATG7, ULK1, WIPI2, Beclin-1, Parkin, and lactate in cerebrospinal fluid and serum, the authors use a slew of well-designed in vitro investigations to arrive at a link between automitophagy and MS pathophysiology. They first show an elevation in LC3-II, Beclin-1, ATG5, ATG7, and WIPI2 after exposure to tumor necrosis factor α and interleukin 1β, inflammatory cytokines that trigger demyelination. Under similar conditions, they reveal colocalization of Parkin and PINK1, primary activators of mitophagy, with mitochondria concurrently with a perturbation of mitochondrial bioenergetics leading to lactate accumulation. They also reveal a link between autophagy and ferroptosis, also known as ferritinophagy, by studying the activation of NCOA4 and TFR1 triggering the release of HMGB1. A final set of supporting studies center around differential phosphorylation of ULK1, which further stimulates autophagy. Conversely, the authors rescued cells from demyelination under inflammatory conditions by blocking key autophagy pathway proteins, including ATG7 (silencing RNA) and ULK1 (compound C), or the autophagosome itself (3-methyladenine). Since none of these strategies can be applied clinically, the authors used two antipsychotic agents, haloperidol and clozapine, with known autophagy-inhibitory properties to not only show an inhibition of autophagy but also a reversal of degeneration, with remyelination reverting MS deficits in animal models. Their comprehensive use of ex vivo, in vitro, and in vivo techniques thoroughly explored the contribution of auto/mitophagy to the pathophysiology of MS. Excitingly, the authors propose the practical application of two Food and Drug Administration–approved antipsychotics for the mitigation of MS through direct inhibitory interactions with autophagy pathway proteins, paving the way to envision repurposable uses for antipsychotics in MS. Leveraging the antiinflammatory properties of psychotropic agents in the treatment of MS in not a novel concept. In fact, the effectiveness of antidepressants such as selective serotonin reuptake inhibitors (7, 8), serotonin–norepinephrine reuptake inhibitors (9), tricyclic antidepressants (10, 11), and monoamine oxidase inhibitors (12, 13) has been well-demonstrated in experimental models of MS.

Autophagy represents an essential regulatory pathway triggered during stressful states to augment cellular survival by shifting critical nutrients for energy conservation and cellular growth during nutrient deprivation. MS, as an example of such a state, reveals how neuronal inflammation can dramatically up-regulate this process and concurrently exacerbate inflammation and trigger demyelination. That these processes are

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up-regulated as a natural response to, rather than a contributing part of, the disease is clarified by in vitro and in vivo studies demonstrating that blocking autophagy ameliorates inflammation, contrary to the contribution of amyloidogenic compounds in the same condition (14, 15). Moreover, Beclin-1 serves as a critical player connecting apoptosis, autophagy/mitophagy, and ferroptosis, all natural regulatory processes meant to enhance survival yet deregulated in multiple disease processes. Beclin-1 interacts with class III PI3K in the formation of the autophagosome, yet it also inhibits the activity of SLC7A11 to promote ferroptosis (3, 16). While the contribution of ferroptosis to demyelination was not thoroughly explored, the authors did specifically examine ferritinophagy in the context of inflammation. In the end, a selected group of antipsychotics were shown to effectively mitigate, reverse, and prevent demyelination, purportedly by their inhibitory effects on autophagy and mitophagy. However, the clinical duration, dose, and frequency that would bestow these protective effects have yet to be determined.

Taken together, Patergnani et al.'s (1) results make it seem plausible that antipsychotics could be repurposed for the treatment of MS. On closer inspection, the potential beneficial effects of antipsychotics on white matter are less clear. Preclinical studies have produced conflicting results. In macaque monkeys, for example, chronic exposure to haloperidol and olanzapine reduced oligodendrocyte numbers (17), suggesting a detrimental impact of antipsychotics on white matter growth. On the contrary, quetiapine, a second-generation antipsychotic, had a positive impact on oligodendrocyte recovery and myelin repair when tested in rats (18) and cell cultures (19), respectively.

Importantly, the majority of work on the effects of antipsychotics on white matter comes not from preclinical but clinical studies in schizophrenia, a disorder where antipsychotics have been the mainstay of treatment for over 60 y. This disorder is characterized by extensive white matter changes, although to a lesser extent than in MS, with reductions in oligodendrocyte densities and impaired myelination. These neuropathological findings are explored by diffusion tensor imaging (DTI), an imaging modality that enables the in vivo evaluation of brain microstructures and white matter integrity. In schizophrenia, DTI studies have shown white matter disruptions, with significantly lower fractional anisotropy (FA) in patients compared with controls. The effect of antipsychotics in white matter has been considerably explored, and although some studies have shown a positive correlation between fractional anisotropy and exposure to antipsychotics (20), the largest DTI meta-analysis to date showed no significant associations between FA and antipsychotic exposure (21).

One must wonder why no consistent effect of antipsychotics in white matter has yet been demonstrated, despite their extensive use in this disorder. One could argue that the magnitude of white matter changes in schizophrenia is minimal when compared to MS or that the underlying neurobiology has nothing in common. However, autophagic processes have also been shown to play a key role in the pathophysiology of schizophrenia (22) and a potential disease-specific effect of antipsychotics seems to be unlikely. Data from positron imaging tomography (PET) studies further support these findings. Translocator protein (TSPO) is a protein located on the outer mitochondrial membrane overexpressed when microglial cells are activated during neuroinflammation (23). TSPO can be measured in vivo with PET radiotracers, and increases in TSPO levels have been reported in conditions where neuroinflammation is a hallmark of disease, such as MS (24). Interestingly, TSPO can also regulate mitophagy. A recent PET study in Parkinson's disease showed TSPO levels' being inversely correlated with mitophagy, with TSPO down-regulation inducing a significant increase in mitophagy index (25). If TSPO levels serve as a proxy for neuroinflammation and mitophagy, antipsychotics' effects on these two markers should change TSPO levels. However, several studies and meta-analyses have shown no such effect on TSPO levels (26), casting doubt on the potential antimitophagic properties of antipsychotics in human neuroinflammatory conditions. Finally, one must consider the feasibility of using antipsychotic medication in MS. The recent Clozapine and Risperidone for the Treatment of Progressive Multiple Sclerosis trial in MS assessed the suitability of risperidone and clozapine in progressive MS but was prematurely halted due to participant withdrawal as a result of significant side effects. Researchers conjectured that individuals with MS may have had an unexpected sensitivity to antipsychotic agents, resulting in high attrition rates (27).

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Despite these potential drawbacks, results of Patergnani et al.'s (1) study are to be commended as they represent important pieces of a larger, more complex pathobiological puzzle. If autophagy and mitophagy play a critical role in the neurobiology of MS, and if blocking these processes has clinical benefit, future trials testing antipsychotics or other psychotropic agents with similar antiinflammatory and/or antimitophagic properties are needed. Hopefully, this study will galvanize the debate around the clinical efficacy of antipsychotics in neurodegenerative and neuroinflammatory conditions and heighten the interest in repurposing psychotropic agents for these indications.


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