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Novel Therapeutic Approaches in Multiple System Atrophy

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Abstract

Multiple system atrophy (MSA) is a sporadic, adult onset, relentlessly, progressive neurodegenerative disease characterized by autonomic abnormalities associated with parkinsonism, cerebellar dysfunction, pyramidal signs, or combinations thereof. Treatments that can halt or reverse the progression of MSA have not yet been identified. MSA is neuropathologically defined by the presence of α -synuclein-containing inclusions, particularly in the cytoplasm of oligodendrocytes (glial cytoplasmic inclusions, GCIs), which are associated with neurodegeneration. The mechanisms by which oligodendrocytic α -synuclein inclusions cause neuronal death in MSA are not completely understood. The MSA neurodegenerative process likely comprise cell-to-cell transmission of α -synuclein in a prion-like manner, α -synuclein aggregation, increased oxidative stress, abnormal expression of tubulin proteins, decreased expression of neurotrophic factors, excitotoxicity and microglial activation, and neuroinflammation. In an attempt to block each of these pathogenic mechanisms, several pharmacologic approaches have been tried and shown to exert neuroprotective effects in transgenic mouse or cellular models of MSA. These include sertraline, paroxetine, and lithium, which hamper arrival of α -synuclein to oligodendroglia; rifampicin, lithium, and non-steroidal anti-inflammatory drugs, which inhibit α -synuclein aggregation in oligodendrocytes; riluzole, rasagiline, fluoxetine and mesenchymal stem cells, which exert neuroprotective actions; and minocycline and intravenous immunoglobulins, which reduce neuroinflammation and microglial activation. These and other potential therapeutic strategies for MSA are summarized in this review.

Keywords

Parkinsonian Disorders; Therapeutics; Oligodendroglia; alpha-synuclein; Neurotrophic factors

1. Introduction

Multiple system atrophy (MSA) is a relentlessly progressive neurodegenerative disorder characterized by parkinsonian, cerebellar, pyramidal, and autonomic features in any combination. MSA is a rare disorder, affecting 4 in 100 000 people. Average survival from time of diagnosis remains fixed at 8 years^{1, 2}. Two main motor presentations can be

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distinguished clinically. Parkinsonian features (MSA-P phenotype) predominate in European¹ and North American cohorts². In contrast, cerebellar ataxia (MSA-C phenotype) predominates in the Japanese population³.

Currently available therapeutic interventions for MSA aim to improve symptoms such as orthostatic hypotension (OH), erectile dysfunction, and gastrointestinal disturbances rather than addressing the underlying ethiopathogenic mechanisms⁴. This is because neuroprotective or neurorestorative treatments, that can halt or reverse the progression of this devastating condition, have not yet been identified. Several compounds have shown promising results in animal studies or cell cultures. However, these therapeutic strategies either have failed to confirm their efficacy in human studies, or have not been tested in clinical trials yet. This article reviews the mechanisms involved in the physiopathology of MSA and summarizes emerging therapeutic approaches and strategies that might be applied to overcome each of the physiopathological mechanisms involved in MSA, with the final goal of hindering or ceasing disease progression.

2. Pathophysiology of multiple system atrophy

MSA is one of a group of diseases now classified as α -synucleinopathies as they appear to be caused by the abnormal, misfolded, accumulation of the natively soluble neuronal protein α -synuclein (α -syn). Native α -syn is abundant in the human brain. While its function is not completely known, a role in the regulation of neurotransmitter release and synaptic function has been suggested^{5–7}. It is unclear, however, whether native α -syn exists as a stable unfolded monomer⁸ or as a α -helical folded tetramer⁹, although a dynamic equilibrium among monomeric and oligomeric forms is likely (Figure 1). Certain pathogenic events (e.g., genetic mutations, oxidative stress, excitotoxicity) may potentially alter this equilibrium.

Abnormal, misfolded α -syn deposits in oligodendroglia are the pathological hallmark of MSA^{10, 11}. This is in contrast to Parkinson disease (PD), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), in which abnormal α -syn primarily accumulates in neurons. Abnormal α -syn burden in MSA is much higher than that found in PD and DLB; and also, MSA has higher levels of soluble α -syn in contrast to PD and DLB, which are characterized by higher levels of insoluble α -syn¹². In MSA, abnormal α -syn accumulates in the form of argyrophilic filamentous glial cytoplasmic inclusions (GCIs). These GCIs are primarily found in the oligodendrocytes, the myelin-producing cells of the central nervous system (CNS). GCIs have also been reported in neurons along with other neuropathological hallmarks such as neuronal loss in the striatum, cerebellum, brainstem and cortex, myelin loss, astrogliosis, and microgliosis^{13, 14}.

2.1. Factors that promote expression/arrival of α -syn to oligodendrocytes

In contrast to neurons, oligodendrocytes do not normally express α -syn. The mechanism by which abnormal α -syn emerge in oligodendrocytes is not completely understood. One possibility implies abnormal mRNA activation in oligodendroglia leading to overexpression of α -syn. This mechanism has been confirmed in murine models¹⁵, but not in humans in which oligodendroglial¹⁶ and whole brain¹⁷ mRNA levels of α -syn were not different

between MSA and healthy subjects. This suggests that the abnormal α -syn may have an ectopic, rather than an oligodendroglial origin.

In this regard, α -syn may arrive from the cytosol of adjacent cells. Although α -syn is a neuronal cytosolic protein, under certain circumstances it may be found on the extracellular space¹⁸. Then, extracellular α -syn from the surrounding media may reach the oligodendrocytes by non-selective endocytosis¹⁹, specific receptor-mediated endocytosis²⁰, and/or direct penetration through cell membrane²¹. Recent pieces of research emphasize the relevance of extracellular α -syn in the pathology of synucleinopathies²². Cell-to-cell transmission of α -syn from neurons to oligodendrocytes, or from oligodendrocytes to oligodendrocytes is an appealing mechanism that has been confirmed in several studies^{23–25}. Pathologic α -syn arriving at neurons and oligodendrocytes might induce a conformational change or other kind of modifications in native α -syn. These findings have led to the assumption that spreading of α -syn in the CNS resembles that of prion disorders^{26, 27}.

2.2. Factors that promote aggregation of α -syn in oligodendrocytes

Once the abnormal α -syn arrives to the oligodendroglia, it undertakes post-translational processes (e.g. oxidation, nitration, phosphorylation) that promote its aggregation into insoluble polymers and, eventually, into GCIs²⁸. These post-translational processes might be triggered and aggravated by oxidative stress²⁹. Oxidative stress is associated with increased production of reactive oxygen species (ROS), or a significant decrease in the activity of antioxidant defenses. High levels of ROS may result in significant damage to cell structures. Some studies have suggested that mitochondrial dysfunction³⁰, exposure to environmental toxins³¹, or certain genetic polymorphisms³² might contribute to oxidative stress in MSA. The activity of the enzyme myeloperoxidase (MPO) might be also a contributing factor for increased oxidative stress³³ (Figure 2).

Besides oxidative stress, the abnormal expression of protein p25 α is also implicated in the aggregation of α -syn. Under physiological conditions, p25 α (tubulin polymerization promoting protein, TPPP) is an oligodendroglial-specific protein involved in neuron myelination. In MSA, however, p25 α relocates from the myelin to the oligodendroglial cytoplasm where it is found associated with insoluble polymeric α -syn in the GCIs^{34, 35}. Interestingly, it has been shown that exogenous addition of p25 α stimulates α -syn aggregation in oligodendroglial cell cultures, which supports a pro-aggregation role for p25 α ³⁶. β -III tubulin, a microtubule protein, has been also implicated in the abnormal aggregation of α -syn³⁷, as well as a malfunction in the proteasomal degradation system³⁸. Proteasome inhibition has been specifically shown to accelerate neurodegeneration in a transgenic mouse model of MSA³⁹. Modulation of these mechanisms might constitute potential therapeutic targets, as discussed later.

2.3. Factors that lead to neuronal death

The mechanism by which the abnormal accumulation of α -syn in one type of cell (oligodendrocytes) leads to the death of a different type of cell (neurons) is far from being completely clear. Oligodendrocytes support neuronal survival and function, and their

dysfunction leads to neuronal degeneration in several diseases⁴⁰. Oligodendrocytes express neurotrophic factors that are required for neuronal survival, including brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). It is possible that aggregation of α -syn in oligodendrocytes hampers the expression of neurotrophic factors leading to early neuronal death. This mechanism is supported by the fact that postmortem brain samples from MSA patients show decreased levels of GDNF compared to controls⁴¹. Total brain lysates of α -syn transgenic mice also show a decrease in GDNF protein expression⁴².

Microglia (the CNS intrinsic macrophages) have an important role in triggering or potentiating oligodendroglia and neuronal injury by several mechanisms. Both “resting” and “activated” microglia release glutamate⁴³, as well as proinflammatory cytokines^{44, 45}. By using positron emission tomography (PET), there is evidence that microglia is highly activated in MSA patients⁴⁶.

Glutamate-induced excitotoxicity is an additional pathway by which neuronal death might occur in MSA⁴⁷. Oligodendrocytes are highly susceptible to glutamate-induced excitotoxicity. Oligodendrocytes are the predominant cells for glutamate clearance⁴⁸. Under certain conditions, reverse function of oligodendroglial glutamate transporters may lead to glutamate release from oligodendrocytes⁴⁹, giving rise to excessive Ca^{2+} influx⁵⁰. Accumulation of Ca^{2+} within mitochondria leads to release of proapoptotic factors, activation of nitric oxide synthase (NOS), and production of ROS and peroxynitrite, which perpetuate oxidative stress to oligodendrocytes and neurons⁵¹.

3. Potential therapeutic targets in MSA

All of the above-mentioned mechanisms by which the accumulation of α -syn in oligodendrocytes exerts its deleterious effects (arrival of α -syn to oligodendroglia, aggregation of α -syn monomers into GCIs, decreased production of neurotrophic factors, and microglial activation and neuroinflammation) constitute potential therapeutic targets in MSA (Table 1).

3.1. Blocking α -syn arrival to oligodendroglia

Sertraline, a second-generation selective serotonin reuptake inhibitor (SSRI) is one of the most promising therapeutic options for MSA. Sertraline has been shown to block the endocytic pathways by which α -syn is taken into oligodendroglia in in-vitro models. Sertraline also prevented α -syn uptake by human oligodendroglial cells in a dose-dependent manner and inhibited neuron-to-neuron transmission of α -syn⁵². Given its well-known adverse effect profile and its wide availability, a clinical trial with sertraline in MSA is warranted. Paroxetine, also a SSRI, has been shown to provide some clinical improvement in patients with MSA. A preliminary short-term, placebo-controlled, add-on trial with paroxetine 30 mg for 2 weeks in 20 patients with MSA patients showed a statistically significant, although clinically marginal, improvement in motor performance and, to some extent, in dysarthria⁵³. At doses up to 30 mg, paroxetine might also provide some improvement in the threshold of airway pressure required to maintain glottic opening in MSA, as shown in a study with 3 patients⁵⁴. Although the sample size was small, and the

observation period was short in both studies, these preliminary results deserve a larger, well-designed clinical trial with paroxetine.

3.2. Blocking α -syn aggregation

Treatment with the antibiotic rifampicin in a transgenic mouse model of MSA showed marked reductions in α -syn aggregation^{55, 56}. Based on these results, a randomized, double blind, placebo-controlled, multicenter clinical trial to test the efficacy and safety of 12-month treatment with rifampicin 600 mg/day in MSA was performed. 100 participants were randomized, 50 to rifampicin and 50 to placebo. The rate of change of the *United Multiple System Atrophy Rating Scale* (UMSARS), part I was not different between rifampicin and placebo (0.5 points per month)⁵⁷.

Lithium also showed promising results on animal models of MSA; it was shown to stimulate autophagy and removal of protein aggregates (including α -syn). Therefore, a randomized clinical trial of lithium in 9 MSA patients was performed in Italy⁵⁸. All patients in the lithium group abandoned because of adverse effects except for one who died. Further trials with lithium in MSA are discouraged.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to have a potent inhibitory effect regarding in-vitro formation of α -syn fibrils in a dose-dependent manner⁵⁹. Given their well-known profile of adverse effects and their wide availability, clinical trials with NSAIDs in MSA patients may be warranted.

Myeloperoxidase (MPO) is a heme protein expressed in phagocytic cells including activated macrophages and microglia that generates an array of cytotoxic oxidants, including ROS. MPO is also expressed in both human and mouse brains³³. Interestingly, the use of a MPO irreversible inhibitor in a transgenic mouse resulted in reduced motor impairment, less neurodegeneration, suppression of microglial activation, and reduction of intracellular α -syn aggregates³³. These results suggest that MPO could have a role in pathogenesis of MSA and may constitute a promising candidate therapeutic target in upcoming clinical trials.

The inhibition of p25 α and β -III tubulin, two of the crucial proteins involved in the aggregation of α -syn in oligodendrocytes, might be also a promising strategy. Nocodazole, an anti-neoplastic agent that interacts with free β -III tubulin to inhibit microtubule polymerization, prevented accumulation of the insoluble α -syn complex in cultures of murine neuronal and glial cells⁵⁶. Specific inhibitors of p25 α , though, have not been developed yet. An interesting approach is that of using synthetic peptides with ability to block α -syn aggregation or even destroy its β -sheet conformation⁶⁰. This methodology, however, has only achieved favorable results with in-vitro models^{61, 62}, and no animal studies have been conducted. Other molecules that have shown some promising results in inhibiting α -syn aggregation include dopamine⁶³, mannitol⁶⁴, catechol-o-methyltransferase inhibitors⁶⁵, cinnamon extract⁶⁶, and ring-fused pyridones (small organic molecules with antibacterial activity)⁶⁷.

3.3. Providing neuroprotection

Glutamate-related excitotoxicity is one of the most important mechanisms known to trigger neuronal death⁶⁸. Glutamate antagonists inhibit the binding of glutamate to NMDA receptors so that excitotoxicity can be avoided. A number of glutamate antagonists have been explored in CNS disorders, particularly riluzole, which is the only disease-modifying drug currently approved for amyotrophic lateral sclerosis (ALS). Riluzole blocks sodium and potassium channels, which indirectly prevents stimulation of glutamate receptors⁶⁹. In a rat model of MSA-P treatment with riluzole showed a significant reduction of motor deficits and a significant reduction in absolute striatal lesion volume, suggesting a potential neuroprotective effect⁴⁷. These encouraging findings resulted in a large randomized, double blind, placebo-controlled clinical trial using riluzole in 398 patients with MSA and 362 patients with progressive supranuclear palsy (PSP). To date, this is the largest clinical trial ever conducted in MSA. Disappointingly, there was no evidence of a drug effect on survival or rate of progression in either group of patients⁷⁰. Estrogens have also shown anti-glutamatergic neuroprotective effects⁷¹. However, an open-labeled pilot trial to assess the efficacy of estrogens in MSA-C failed to show any clinical benefit⁷².

Although trials with riluzole and estrogens were unsuccessful, anti-glutamatergic therapies are still promising strategies for MSA. For example, it has been shown that blockade of AMPA/kainate or NMDA receptors attenuates neuronal and oligodendroglial injury in animal models^{73, 74}, suggesting that both types of receptors mediate glutamate-induced toxicity. Modulation of purinergic pathways, such as P2X7 receptor blockade in oligodendrocytes, has also shown neuroprotective effects in vitro⁷⁵ and might be a promising target for the development of new MSA therapies.

Rasagiline is an irreversible inhibitor of monoamine oxidase-B (MAO-B), which demonstrated a symptomatic benefit and possible disease-modifying effect in PD patients⁷⁶. Functional neuroprotective actions of rasagiline, however, may not be dependent on MAO-B inhibition, but rather may be related to modulation of the mitochondrial metabolism⁷⁷. The strong biological plausibility for disease-modifying effects of rasagiline was confirmed in a transgenic mouse model of MSA, in which treatment with 2.5 mg/kg rasagiline led to improved motor behavior, and significant reduction in neuronal loss⁷⁸. Nevertheless, a double blind, randomized, placebo-controlled, clinical trial of rasagiline 1 mg/day in MSA-P has been completed recently and results were negative⁷⁹. Treatment with growth hormone was also unsuccessful to increase neurotrophic factors or provide significant symptomatic or motor improvement in MSA.⁸⁰

Another potential strategy to provide neuroprotection consists of increasing the levels of neurotrophic factors such as GDNF and BDNF. In this regard, the SSRI fluoxetine has been shown to increase GDNF and BDNF in a transgenic mouse model of α -syn⁸¹, to suppress pro-inflammatory factors in microglial cell cultures⁸², and to promote hippocampal neurogenesis⁸³. A clinical trial of fluoxetine in MSA patients has been recently completed but results have not been published yet⁸⁴.

The use of autologous mesenchymal stem cells (MSC) has emerged as an appealing therapeutic approach in MSA. MSC are multi-potent stem cells present in adult bone

marrow that are capable of differentiating into various cell types, including neurons⁸⁵. Additionally, MSC secrete a variety of cytokines and growth factors that exert neuroprotective effects⁸⁶. Animal studies have shown that human MSC had a protective effect against progressive dopaminergic and striatal neuronal loss⁸⁷. The neuroprotective and immunomodulatory effects of MSC have been also observed in a transgenic mouse model of MSA⁸⁸. An open-label, unblinded 12-month study performed in South Korea showed that intra-arterial infusion of MSC in 11 patients with MSA patients showed a significant improvement in the orthostasis and cerebellar dysfunction items of the UMSARS, with no serious adverse effects⁸⁹. Some severe methodological shortcomings were noted, including the likely possibility of a placebo effect⁹⁰. Subsequently, the same South Korean group performed a randomized, double-blind, placebo-controlled trial in 16 patients with MSA-C showing that those who received intra-arterial MSC infusions had a smaller increase in UMSARS scores (total UMSARS $p=0.047$; UMSARS-II: $p=0.008$) when compared to placebo⁹¹. A significant percentage (29% of MSC-treated and 35% of placebo-treated) of patients developed ischemic lesions on magnetic resonance imaging, including 1 subject who had a transient ischemic attack. Again, serious methodological issues were raised, such as the fact that this was a single-center study, only included MSA-C patients, and had potentially severe adverse effects⁹².

3.4. Decreasing neuroinflammatory response

The inflammatory process in the CNS triggered by the abnormal aggregation of α -syn plays an important role in the pathway leading to neuronal cell death in a number of neurodegenerative diseases including MSA. This inflammatory response is mediated by activated microglia, which normally respond to neuronal damage and remove the damaged cells by phagocytosis⁹³. Chronic activation of microglia may in turn cause neuronal damage through the perpetuation of the neuroinflammatory response and release of cytotoxic molecules such as pro-inflammatory cytokines⁹⁴. Therefore, suppression of microglia-mediated inflammation might be an important strategy in MSA therapy. Minocycline is a second-generation tetracycline, which crosses the blood-brain barrier and inhibits microglial activity and secretion of pro-inflammatory cytokines⁹⁵. In a transgenic mouse model of MSA, animals treated with minocycline showed a significant reduction of activated microglia in the substantia nigra compared to control mice. Minocycline-induced suppression of microglial activation also prevented loss of nigral dopaminergic neurons as well as loss of dopaminergic terminals in the striatum⁴⁵. Despite these promising results, a multicenter, randomized, double-blind, placebo-controlled clinical trial in 62 patients with MSA-P failed to show clinical improvement after 1 year of treatment with minocycline, although microglial activation, as measured by PET, was decreased, suggesting some biological effect⁹⁶.

Intravenous immunoglobulins (IVIg) have been used in a variety of immune-mediated disorders of the nervous system⁹⁷. Its mechanism of action, although not completely understood, is based on the fact that IVIg contains antibodies derived from human plasma with potential to block inflammatory responses in the nervous system. In a single-arm interventional, single-center, open-label pilot study, monthly infusions of IVIg (0.4 g/kg) were administered to 7 MSA patients for 6 months⁹⁸. Patients experienced a statistically

significant improvement on the UMSARS-I (pre-treatment 23.9 ± 6.0 vs. post-treatment 19.0 ± 5.9 ; $p=0.01$) and UMSARS-II (pre-treatment 26.1 ± 7.5 vs. post-treatment 23.3 ± 7.3 ; $p=0.025$) scales, suggesting that treatment with IVIg might be feasible and well tolerated, although a placebo effect cannot be completely excluded.

Interestingly, the preliminary efficacy of IVIg in MSA may be related to the presence of specific antibodies against soluble α -syn⁹⁹. In this regard, studies performed in animal models showed that passive immunization with a monoclonal α -syn antibody improved the deficits associated with α -syn accumulation, by promoting α -syn clearance via the lysosomal pathway¹⁰⁰, and microglial activation¹⁰¹, thereby preventing its spread to neighboring cells. Based on these results, clinical trials to evaluate the safety and clinical activity of α -syn targeting antibodies will be performed in the near future by the European project SYMPATH (SYnuclein-Mediated PATHology) in which two potential vaccines will be evaluated in patients with PD and MSA¹⁰².

4. Conclusions

As described in this review, several therapeutic approaches have shown potential to reduce the burden of misfolded α -syn in oligodendrocytes in cellular or murine models of MSA. Unfortunately, however, most of these strategies have failed in clinical trials. The only therapeutic options that have shown some promising results are SSRIs, autologous stem cells, and IVIg, but larger, well-designed clinical trials are still needed to confirm their efficacy. Understanding the origin of abnormal α -syn and the factors leading to its accumulation and aggregation in oligodendrocytes are essential in unraveling the pathogenesis of MSA, without which our therapeutic options remain dismal. Effective treatment may result from a multi-targeted approach addressing several pathophysiological mechanisms at once (i.e., blocking α -syn aggregation as well as enhancing neuroprotection and inhibiting neuroinflammation) and from multi-site collaborative efforts to test promising new therapies in properly designed clinical trials.

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Figure 1.

Figure 2.

Table 1

Therapeutic targets and strategies for MSA

Mechanism of action	Therapy	Efficacy in cellular or animal models of MSA	Clinical benefit in humans
Blocking of α -syn arrival to oligodendrocytes	Sertraline	Yes	Not tested
	Paroxetine	Yes	Yes
	Antibodies against α -syn	Yes	Not tested
Inhibition of α -syn aggregation in oligodendrocytes	Rifampicin	Yes	No
	Lithium	Yes	No
	MPO inhibitor	Yes	Not tested
	p25 α inhibitor	Not tested	Not tested
	Nocodazole	Yes	Not tested
	Synthetic peptides	Yes	Not tested
	COMT inhibitors	Yes	Not tested
	Mannitol	Yes	Not tested
	Cinnamon extract	Yes	Not tested
	Ring-fused pyridones	Yes	Not tested
Inhibition of glutamate-induced excitotoxicity	Riluzole	Yes	No
	Estrogens	Yes	No
	AMPA/kainate and NMDA blockers	Not tested	Not tested
	P2X7 blockers	Not tested	Not tested
Enhancement of neuroprotection	Rasagiline	Yes	No
	Growth hormone	Yes	No
	Fluoxetine	Yes	Unknown
	Mesenchymal Stem Cells	Yes	Yes
Inhibition of neuroinflammatory response	Minocycline	Yes	No
	Intravenous Immunoglobulins	Not tested	Yes