Inhibition of the mammalian target of rapamycin (mTOR): a potential therapeutic strategy for multiple system atrophy

Alain Ndayisaba¹ · Gregor K. Wenning¹

Received: 24 December 2019 / Accepted: 25 December 2019 / Published online: 9 January 2020
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Multiple system atrophy (MSA) is an aggressive neurodegenerative disorder characterized by the deposition of aggregates containing α -synuclein (α -syn) in oligodendrocytes and neurons. The disease is relentlessly fatal, and most patients die within 9 years of disease onset. While the events that trigger the presence and accumulation of α -syn in oligodendrocytes and neurons remains a mystery, the failure of intracellular protein clearance mechanisms appears to be a major pathophysiology pathway.

Pathways involved in autophagy and lysosomal function have received increased attention because their modulation could be a potential therapeutic strategy for neurodegenerative proteinopathies. One of such pathways is the mammalian target of rapamycin complex (mTOR) signaling pathway. Activation of the mTOR pathway promotes cell survival, growth and proliferation via increased protein synthesis, whereas inhibition of the mTOR pathway results in increased autophagy, among many other biological effects (Fig. 1). Thus, it is tempting to hypothesize that increased activation of autophagy via mTOR inhibition may result in reduced proteinopathy-related neurodegeneration [1, 3].

In keeping with this hypothesis, treatment with rapamycin (also known as sirolimus, a potent inhibitor of the mTOR pathway) in animal models of synucleinopathy reduced the amount of intracellular aggregated α -syn [6]. Similarly, treatment with rapamycin for 16 weeks in a transgenic mouse model of MSA overexpressing human α -syn exclusively in oligodendrocytes resulted in decreased α -syn levels in substantia nigra pars compacta, but not in striatum. Importantly, mice treated with sirolimus developed no motor improvement, consistent with decreased numbers of

tyrosine hydroxylase-positive neurons similar to untreated MSA mice. Yet, the overall number of Nissl positive neurons was comparable to healthy control mice suggesting that rapamycin exerts some degree of neuroprotection [8, 13]. On the other hand, inhibition of autophagy may not represent a primary or essential event in the pathogenesis of MSA since inhibition of macroautophagy via bafilomycin A1 did not promote α -syn aggregation in oligodendroglial cell lines and transgenic mice overexpressing human wild type α -syn [5, 6].

But the effects of mTOR inhibition go beyond the activation of autophagy and inhibition of apoptosis. Leigh syndrome is a severe neurological disease caused by mitochondrial dysfunction due to mutations in mitochondrial DNA or deficiency of pyruvate dehydrogenase. It manifests with neurological and psychomotor deficits with patients dying typically before age 3 [4]. In a recent study, treatment of cultured neurons obtained from patients with Leigh syndrome with rapamycin resulted in decreased energy consumption, presumably via a decrease of protein synthesis, which prevented glutamate toxicity [14]. Since mitochondrial dysfunction constitutes a central aspect in MSA pathogenesis [10], treatment with rapamycin in MSA may also have beneficial effects through mitochondrial pathways.

Patients with MSA also appear to have dysregulation of the upstream insulin/insulin-like growth factor (IGF)-1 pathway [12]. Putaminal neurons and oligodendrocytes of mice with MSA had increased expression of the insulin receptor substrate 1 phosphorylated at serine residue 312, which is a marker of insulin resistance, compared to neurons and oligodendrocytes from other, less affected brain areas in MSA, such as the temporal cortex [2]. Since IGF-1, also promotes mTOR activation via the PI3-K/Akt pathway (Fig. 1), mTOR inhibition with rapamycin/sirolimus may partially block the deleterious effects of excessive insulin and IGF-1 levels.

In summary, multiple sources of evidence support the rationale to test if rapamycin/sirolimus can effectively block

✉ Gregor K. Wenning
gregor.wenning@i-med.ac.at

¹ Division of Clinical Neurobiology, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria

Fig. 1 Simplified organization of the mTOR complex 1 (mTORC1) pathway. Rapamycin/sirolimus inhibits mTORC1 resulting in enhanced clearance and autophagy of intracellular proteins, such as alpha-synuclein. α -syn alpha-synuclein, *IRS1* insulin receptor substrate type 1, *PI3K* phosphoinositide 3-kinase, *Akt* serine/threonine kinase, *TSC* tuberous sclerosis complex, *mTORC* mammalian target of rapamycin complex

the mTOR pathway and enhance the autophagy of α -syn (Fig. 1). Sirolimus has been approved by most regulatory agencies since the 1990s as an immunosuppressant to prevent organ transplant rejection, and its profile of adverse events is very well known. An ongoing single-center phase-2 double-blind randomized placebo-controlled trial at New York University (NYU), led by Drs. Palma and Kaufmann, aims to determine whether sirolimus is of sufficient promise to slow the progression of MSA (ClinicalTrials.gov: NCT03589976). In this trial, patients receive oral sirolimus at dosages ranging from 2 to 6 mg/day, or matching placebo, for a year [11]. These dosages are well tolerated and associated with relatively low immunologic risk [7, 9]. The trial will be completed by late 2021 and first results are expected by early 2022. Since we are far from understanding the cause of this devastating disease, trials like this one with sirolimus are much needed. We owe it to all patients and their relatives in dire need for treatments.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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