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REVIEW

ANIMAL MODELS OF MULTIPLE SYSTEM ATROPHY

P.-O. FERNAGUT[a,b]* AND F. TISON[a,b]

[a]*Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France*

[b]*CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France*

Abstract—Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disorder clinically characterized by a variable combination of dysautonomia, levodopa-unresponsive parkinsonian and cerebellar symptoms. Neurodegeneration in MSA occurs in the substantia nigra, putamen, inferior olive, pontine and brainstem nuclei, as well as intermediolateral cell column of the spinal cord. MSA is recognized as a synucleinopathy due to the accumulation of insoluble alpha-synuclein in oligodendroglial cytoplasmic inclusions. Several animal models have been developed in order to reproduce various clinical and pathological features of MSA. Using "double toxin–double lesion" or "single toxin–double lesion", neurotoxin-based models were designed in rats, mice and non-human primates to reproduce the neuropathology of MSA in the nigrostriatal system while gene-based models were developed in mice to reproduce the accumulation of insoluble alpha-synuclein in oligodendrocytes. Both approaches have then been merged to create optimized, dual-hit models. This review describes the different animal models of MSA, their respective advantages and limitations and their usefulness to decipher the pathophysiology of MSA then to define efficient symptomatic and disease-modifying therapies.

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Key words: multiple system atrophy, parkinsonism, alpha-synuclein, levodopa, basal ganglia, oligodendrocyte.

Contents

*Correspondence to: P.-O. Fernagut, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo Saignat, Bat 3b. 33076 Bordeaux cedex, France. Tel: +33-557-571-685; fax: +33-556-986-182.
E-mail address: pierre-olivier.fernagut@u-bordeaux2.fr.

Abbreviations: CNP, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; GCI, glial cytoplasmic inclusions; MPP^+, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSA, multiple system atrophy; PLP, proteolipid; QA, quinolinic acid; 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine.

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MULTIPLE SYSTEM ATROPHY: DEFINITION, CLINICAL AND NEUROPATHOLOGICAL FEATURES

Multiple system atrophy (MSA) is a sporadic adult-onset neurodegenerative disorder of unknown aetiology affecting four to five cases per 100,000 habitants (Tison et al., 2000). Clinically, MSA includes a variable combination of dysautonomia, parkinsonian and cerebellar symptoms. Two main forms of MSA are recognized depending on the predominance of a parkinsonian or cerebellar syndrome: MSA-P (parkinsonian form, formerly known as striatonigral degeneration) and MSA-C (cerebellar form, formerly known as olivopontocerebellar atrophy) (Gilman et al., 1999). In addition, dysautonomia is present in both subtypes of MSA and includes urinary incontinence, respiratory failure, dysarthria, dysphagia and orthostatic hypotension (Gilman et al., 2008). The initial clinical manifestations of MSA can substantially differ among patients, and autonomic symptoms may precede motor signs (Lipp et al., 2009). Median life expectancy after disease onset is less than 9 years (Schrag et al., 2008) and no treatment is currently available to delay disease progression. Clinical management of dysautonomia includes the use of fludorcortisone for orthostatic hypotension and anticholinergic drugs for urinary dysfunction (Flabeau et al., 2010). L-DOPA is the first-line treatment for parkinsonism but dopaminergic responsiveness is poor and transitory, affording only 20–30% improvement of symptoms over 2–3 years (Hughes et al., 1992; Tison et al., 1995). In the absence of specific treatment, physiotherapy is beneficial for the management of ataxia and postural impairments.

In the nigrostriatal system, neuronal loss in MSA includes a progressive degeneration of the substantia nigra pars compacta (SNc) and of the sensorimotor striatum in somatotopically related areas. The loss of dopaminergic terminals affects principally the dorsolateral part of the posterior putamen, where the loss of striatal medium spiny neurons is the most pronounced (Fearnley and Lees, 1990). In the olivopontocerebellar system, neuronal loss predominates in the inferior olive and pontine nuclei, and to a lesser extent in the vermis where the loss of Purkinje cells is more pronounced compared with cerebellar hemispheres (Wenning et al., 1996b). In the brainstem, neuropathological alterations include depletion of chemosensitive respiratory neurons (Benarroch et al., 2007), neuronal loss in the pre-Bötzinger complex (Schwarzacher et al., 2011), depletion of serotonergic neurons in the raphé obscurus, raphé pallidus and ventrolateral medulla (Tada et

al., 2009). In the spinal cord, neuronal loss affects intermediolateral column cells (Kennedy and Duchen, 1985).

In addition to neuronal loss, MSA is characterised by the presence of argyrophilic glial cytoplasmic inclusions (GCIs). Like Lewy bodies in Parkinson's disease, these glial inclusions are the cytopathological hallmark of the disease. Following the identification of alpha-synuclein in Lewy bodies and GCIs (Spillantini et al., 1998), MSA, Parkinson's disease and dementia with Lewy body are now recognized as a unique family of neurodegenerative disorders designed as "synucleinopathies". Since alpha-synuclein is not expressed in oligodendrocytes in normal brain or in MSA (Miller et al., 2005), the origin of alpha-synuclein in GCIs is not a result of de novo expression but is rather attributable to an ectopic occurrence. Recent studies demonstrating cell-to-cell transmission of alpha-synuclein (Desplats et al., 2009) support the hypothesis that oligodendroglial accumulation of alpha-synuclein in MSA could arise from endocytosis of alpha-synuclein secreted by nearby neurons.

Even though MSA is a sporadic neurodegenerative disorder, several lines of evidence points to a genetic contribution to the pathogenesis of the disease. A recent genome-wide association study indicates that genetic variability at the alpha-synuclein locus is associated with an increased risk of MSA (Scholz et al., 2009). In addition, possible or probable MSA have been described in first degree relatives in several families and an increased incidence of parkinsonism has been reported in first degree relatives of MSA patients, further suggesting a genetic contribution (Wullner et al., 2004; Hara et al., 2007; Vidal et al., 2010).

The development of experimental models of MSA is a necessary step towards the understanding of the pathophysiology of this devastating disease. Because symptomatic treatments are of limited and/or transient efficacy and no disease-modifying therapy is currently available, such models that best recapitulate various aspects of MSA are also mandatory for the evaluation of therapeutic strategies. We will first describe neurotoxin-based models of MSA that have been developed in rodents and non-human primates. Using stereotaxic or systemic injections of neurotoxins, these models are based on a combined destruction of both sides of the nigrostriatal axis (either sequentially or simultaneously) in order to recapitulate the L-DOPA unresponsive parkinsonism occurring in the human disease. We will then review aetiological (gene-based) models developed to investigate the underlying mechanisms of neurodegeneration due to oligodendroglial and neuronal dysfunction. Following the recognition of MSA as a synucleinopathy, these models are based on the targeted expression of human alpha-synuclein in oligodendrocytes in order to recapitulate the cytopathological hallmark of the disease. The final part of this review will present the latest generation of MSA models that integrate the use of neurotoxins in genetically engineered mice.

STEREOTAXIC RAT MODELS

Parkinsonism is the main source of motor disability in MSA and is present in 90% of cases during the course of the disease (Tison et al., 1995). In addition, dopaminergic responsiveness is poor and temporary (Hughes et al., 1992). Toxin-based models were thus initially developed to reproduce the anatomical lesions underlying L-DOPA unresponsive parkinsonsism occurring in MSA. Neurotoxins used to develop animal models of Parkinson's and Huntington's disease were used to induce a sequential or simultaneous degeneration of both components of the nigrostriatal pathway (Table 1). This was first achieved by a "double toxin–double lesion" approach in rats, in which two neurotoxins are used to induce the degeneration of nigral and striatal neurons. Using 6-hydroxydopamine (6-OHDA) and quinolinic acid (QA) injected sequentially (3–4 weeks apart) in the median forebrain bundle (MFB) and the striatum respectively, the first model demonstrated the abolition of drug-induced rotational behaviour in double lesioned animals and a positive effect of fetal allografts (Wenning et al., 1996a). To explore the effects of the lesioning sequence (e.g. nigral first vs. striatal first), a subsequent study investigated the behavioural consequences of intrastriatal injection of QA, preceded or followed (8 weeks) by an injection of 6-OHDA in the MFB (Scherfler et al., 2000). Prior striatal dopaminergic denervation with 6-OHDA was found to decrease the neurotoxic effects of QA while prior striatal lesioning with QA did not affect 6-OHDA-induced nigral degeneration. At the behavioural level, bilateral stepping deficits were observed in double lesioned animals (Scherfler et al., 2000). Using simultaneous intrastriatal injection of 6-OHDA and QA in an attempt to overcome the reduced neuronal vulnerability due to dopamine depletion observed in previous rat models, this strategy resulted in an exacerbation of QA-induced striatal damage together with a slight reduction of 6-OHDA-induced dopaminergic loss. Abolition of rotational behaviour and additional ipsilateral deficits were observed in rats injected with both neurotoxins (Ghorayeb et al., 2001).

To prevent interactions between both sites of degeneration and the protective effect induced by a first nigral lesion, a "single toxin–double lesion" strategy was developed. In this case, a single neurotoxin is injected in the striatum to induce a combined degeneration of nigral and striatal neurons. This was performed using either the succinate dehydrogenase inhibitor 3-nitropropionic acid (3-NP) or the mitochondrial complex I inhibitor 1-methyl-4-phenylpyridinium ion (MPP^+) injected in the striatum (Waldner et al., 2001; Ghorayeb et al., 2002a). Both 3-NP and MPP^+ induced bilateral motor deficits associated with $>$40% neuronal loss in the substantia nigra and 47% (MPP^+) to 76% (3-NP) striatal loss. All stereotaxic rat models have enabled to produce a dopamine unresponsive motor phenotype, as shown with the abolition of apomorphine and/or amphetamine rotations. The striatal le-

Table 1. Overview of animal models of MSA

	Nigral cell loss	Striatal cell loss	Behaviour	Reference
Stereotaxic rat models				
6-OHDA followed by QA	>90%	56%	Bilateral paw reaching deficit	(Wenning et al., 1996)
QA followed by 6-OHDA	>90%	85%	Bilateral paw reaching deficit	(Scherfler et al., 2000)
QA+6-OHDA	15%	27%	Abolition of drug-induced rotations Bilateral paw reaching deficit	(Ghorayeb et al., 2001)
3-NP	45%	76%	Bilateral paw reaching deficit	(Waldner et al., 2001)
MPP+	48%	47%	Abolition of drug-induced rotations Bilateral stepping deficits	(Ghorayeb et al., 2002a)
Systemic models				
Non-human primate				
MPTP followed by 3-NP	70–90%	35–45%	Levodopa unresponsive parkinsonism, transient hind limb dystonia	(Ghorayeb et al., 2000; Ghorayeb et al., 2002b)
Mouse				
MPTP followed by 3-NP	44%	43%	↓ locomotor activity	(Stefanova et al., 2003)
3-NP followed by MPTP	26%	54%		
MPTP+3-NP	26%	36%	↓ locomotor activity, ↓ rotarod, ↓ pole test	(Fernagut et al., 2004)
T transgenic mouse models (oligodendroglial expression of human wild-type alpha-synuclein)				
PLP promoter	23%	—	↓ hindlimb stride length	(Kahle et al., 2002)
MBP promoter	≈40%	≈40%	↓ rotarod and pole test	(Shults et al., 2005)
CNP promoter	—	—	↓ rotarod	(Yazawa et al., 2005)
Dual-hit mouse models				
PLP+3-NP	≈50%	≈50%	↓ locomotor activity, pole test	(Stefanova et al., 2005)
MBP+3-NP	>70%	60%	↓ pole test	(Ubhi et al., 2009)

3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; CNP, 2',3'-cyclic nucleotide 3'-phosphodiesterase; MBP, myelin basic protein; MPP^+, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PLP, proteolipid; QA, quinolinic acid.

sion not only suppressed the behavioural response to dopaminergic drugs but also worsened behavioural deficits with the induction of bilateral sensorimotor impairments. The combined striatal and nigral degeneration does not simply result in superimposed striatal and nigral deficits but in a specific motor disorder. In addition, the reduced vulnerability of striatal medium spiny neurons observed following dopamine denervation is in accordance with a role for dopamine as a positive modulator of striatal neurodegeneration (Reynolds et al., 1998; Fernagut et al., 2002a). Based on the results obtained with the different stereotaxic rat models, it can be estimated that 25% of striatal degeneration is sufficient to abolish the dopaminergic response and induce a significant worsening of the behavioural phenotype. Despite this dopaminergic unresponsive motor phenotype, L-DOPA can still induce orolingual dyskinesia (Stefanova et al., 2004), as it is the case in the human disease (Hughes et al., 1992). The main advantage of stereotaxic rat models is the possibility to obtain various degrees of striatal and nigral degeneration that reproduce various aspects of MSA neuropathology in the nigrostriatal system, from early stages to the most advanced phases of the disease. Even though the limitation of these models is the fact that they only recapitulate a restricted part of MSA neuropathology and symptomatology without reproducing the widespread lesions outside the basal ganglia, they have a still underused potential to evaluate the antiparkinsonian potential of non-dopaminergic drugs.

SYSTEMIC MODELS

Using sub-chronic and chronic intoxication regimen, systemic neurotoxins allow inducing a progressive neuronal dysfunction. Such a dynamic approach thus take into account the temporal dimension of neurodegeneration occurring in the human disease. Systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 3-NP were thus used in mice and non-human primates to reproduce the core pathology of MSA in the nigrostriatal system (Table 1). In non-human primates, chronic administration of 3-NP in MPTP-treated monkeys provoked a progressive aggravation of parkinsonism. The subsequent appearance of a 3-NP induced hind limb dystonia and striatal degeneration were then associated with an abrupt deterioration of the motor status together with a loss of L-DOPA response and an abolition of MPTP-induced hyperactivity of the subthalamic nucleus (Ghorayeb et al., 2000, 2002b; Fernagut et al., 2010). In mice, systemic administration of 3-NP induces a distinct motor syndrome (hind limb dystonia and clasping, postural impairments) associated with neurodegeneration in the lateral part of the striatum and a moderate loss of dopaminergic neurons (Fernagut et al., 2002b). Sequential regimens of MPTP and 3-NP administrations (MPTP followed by 3-NP or 3-NP followed by MPTP) enabled to obtain a significant loss of nigral and striatal neurons. Administration of MPTP first reduced the striatal vulnerability to 3-NP while prior

administration of 3-NP reduced the vulnerability of nigral dopaminergic neurons to MPTP. Behavioural deficits were more pronounced when 3-NP was administered first and the alterations in locomotor activity correlated with the loss of striatal DARPP-32 neurons (Stefanova et al., 2003). Contrary to the reduced neuronal vulnerability observed using sequential intoxication regimens, the combined administration of MPTP and 3-NP over 9 days resulted in an increased magnitude and duration of the motor syndrome and alteration of sensorimotor performances compared with 3-NP or MPTP alone. Striatal damage, (neuronal loss and astrogliosis) was also significantly enhanced in animals receiving both neurotoxins (Fernagut et al., 2004). Similar to the stereotaxic rat models, systemic models only reproduce a pathological spectrum restricted to the nigrostriatal pathway. Nevertheless, these models have paved the way to the development of dual-hit models.

GENE-BASED MODELS

The identification of alpha-synuclein in GCIs and the subsequent recognition of MSA as a synucleinopathy provided a molecular lead to investigate the pathophysiological basis of the disease. Several transgenic mouse models expressing human wild-type alpha-synuclein under the control of oligodendroglial specific promoters were thus developed to reproduce the cytopathological hallmark of MSA (Table 1). Targeted expression of human wild-type alpha-synuclein in oligodendrocytes was achieved under the control of the proteolipid (PLP) promoter (Kahle et al., 2002), the MBP promoter (Shults et al., 2005) or the 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP) promoter (Yazawa et al., 2005). All three transgenic lines recapitulate the oligodendroglial accumulation of insoluble alpha-synuclein. In addition, hyperphosphorylation at serine 129 was shown in PLP- and MBP-driven alpha-synuclein (Kahle et al., 2002; Shults et al., 2005). All three lines have been shown to display various degrees of motor impairments such as a progressive reduction of rotarod performances (Yazawa et al., 2005), impairments of rotarod and pole test performances (Shults et al., 2005) or reduced hind limb stride length (Stefanova et al., 2005). Non-motor symptoms may also be recapitulated as shown with the olfactory dysfunction found in MBP-driven alpha-synuclein mice (Ubhi et al., 2010). Neuropathological investigations in the three transgenic models revealed that oligodendroglial expression of alpha-synuclein led to various ultrastructural and morphological alterations including myelin loss and axonal atrophy. A moderate loss of dopaminergic neurons in the substantia nigra was observed in mice expressing alpha-synuclein under the control of the PLP promoter (Stefanova et al., 2005) while MBP-driven alpha-synuclein induced a loss of nigral dopaminergic neurons, striatal tyrosine hydroxylase-positive fibres and striatal neurons (Shults et al., 2005; Ubhi et al., 2009). Spontaneous neuronal loss in the cerebellum and pontine nuclei has not been reported in any of these transgenic mouse models of MSA. Results obtained during the generation of several lines of MBP-driven alpha-synuclein mice strongly suggest that the levels of oligodendroglial expression have a significant effect on the behavioural and pathological outcomes (Shults et al., 2005). Whether the differences observed between the three lines are mainly due to gene dosage has not been directly assessed. If the level of oligodendroglial expression of alpha-synuclein is critical to induce behavioural impairments and neurodegeneration, crossing two of the existing transgenic lines together could be a simple strategy to increase it. MBP-driven oligodendroglial expression of alpha-synuclein was also found to alter the expression of several neurotrophic factors including insulin-like growth factor-1 and glial-derived neurotrophic factor, thus suggesting that a deficit in oligodendroglial neurotrophic support may be a key element in the disease process (Ubhi et al., 2010). In addition, recent evidence suggests that the oligodendroglial expression of alpha-synuclein may also recapitulate the degeneration of some brainstem nuclei involved in autonomic functions (Stemberger et al., 2010). However, autonomic functions (cardiac, respiratory, urinary. . .) have not yet been explored in genetic mouse models of MSA.

Gene-based models have the strong advantage to recapitulate the cytopathological hallmark of MSA and have proven useful to elucidate pathogenic mechanisms linked with the oligodendroglial accumulation of alpha-synuclein. However, the extent of neurodegeneration remains modest compared with toxin-based models or with the human disease. Since these models are based on the constitutive expression of alpha-synuclein in oligodendrocytes, it remains to be determined if the conditional expression of alpha-synuclein in adult oligodendrocytes could better replicate the human disease.

DUAL-HIT MODELS

All models have intrinsic limitations. Toxin-based models recapitulate the pattern and extent of neuronal loss in the nigrostriatal system but fail to reproduce lesions outside the basal ganglia and the accumulation of insoluble alpha-synuclein in oligodendrocytes. On the other hand, transgenic models do reproduce the oligodendroglial accumulation of alpha-synuclein but do not recapitulate the full pattern and extent of neurodegeneration occurring in the human disease. To circumvent these limitations, the systemic toxin-based approach developed in mouse with 3-NP (Fernagut et al., 2002b) was then applied to transgenic mice expressing human wild-type alpha-synuclein in oligodendrocytes (dual-hit model, Table 1). Administration of 3-NP in mice expressing human wild-type alpha-synuclein under the control of the PLP promoter enabled to induce widespread neurodegeneration in the nigrostriatal and olivopontocerebellar systems together with enhanced motor deficits (Stefanova et al., 2005). Exacerbation of 3-NP-induced motor deficits and neurodegeneration, together with increased oxidative modifications of alpha-synuclein were also demonstrated in mice expressing human wild-type alpha-synuclein under the control of the MBP promoter (Ubhi et al., 2009). The dual-hit approach incorporates the advantages of the systemic and gene-

based models, thus providing robust neurodegeneration together with oligodendroglial alpha-synuclein pathology. Therefore, dual-hit models represent the best experimental models of MSA available to date.

RELEVANCE TO THE HUMAN DISEASE AND FUTURE ISSUES

Despite the inherent limitations of toxin- and gene-based models, the development of experimental research on MSA during the past 15 years has yielded significant progress in our understanding of this devastating disease. Toxin-based models have proven useful to analyse basal ganglia alterations leading to L-DOPA unresponsive parkinsonism and have a good face validity to evaluate the potential of non-dopaminergic therapeutic options to alleviate motor symptoms. Gene-based models have a good aetiological validity and are thus very valuable to investigate how a primary oligodendroglial dysfunction can promote neuronal dysfunction and degeneration. They will also be useful to investigate gene-environment interactions or the contribution of additional genetic factors. In addition, gene-based models will be the best experimental test-bed to investigate disease-modifying strategies. Translation from bench to clinical trials has started, as evidenced by a growing number of clinical trials. However, there is still a lot to accomplish, as currently available therapeutic options are very limited to alleviate the motor and autonomic symptoms of MSA.

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