Mouse Models of Cognitive Deficits Due to Alpha-Synuclein Pathology

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Abstract. Synucleopathies are neurodegenerative disorders characterized by abnormal accumulation of alpha–synuclein, most often in neurons. Familial forms are due to mutations or multiplications of the gene encoding for alpha-synuclein but most synucleopathies occur sporadically. They include Parkinson’s disease (PD) and dementia with Lewy Bodies (DLB), which are both linked to cognitive decline. In DLB, dementia dominates the symptoms whereas in PD, subtle cognitive deficits are frequent and may appear even before motor symptoms, but only a fraction of patients develop severe dementia-type cognitive deficits. Several lines of mice were developed to model human synucleopathies by over-expressing the wild type or the mutated human alpha-synuclein under a variety of promoters. In addition, mice lacking alpha-synuclein have been used to determine the role of this protein in cognitive function. This chapter will review cognitive alterations observed in these models and discuss how they may help understand the various forms and stages of cognitive deficits observed in patients with synucleopathies.

Keywords: Cognition, memory, alpha-synuclein, Parkinson’s disease, overexpression, promoter

INTRODUCTION

Alpha-synuclein (α-syn), a 140 amino acid protein encoded by the SNCA gene, is normally found in neurons throughout the brain and the peripheral nervous system. Three missense mutations (A30P and A53T, E46K) in the SNCA gene cause familial forms of Parkinson’s disease (PD) [1–3]. Although not mutated in idiopathic PD cases, α-syn accumulates in Lewy bodies and Lewy neurites, which are key pathological features of the disease [4]. Moreover, duplication or triplication of the SNCA gene leads to PD, with a clear relationship between level of α-syn expression and age of onset of the disease [5, 6]. Interestingly, these genetic alterations in α-syn cause cognitive dysfunction: carriers of the E46K, A30P and A53T mutations displayed dementia and cognitive deficits [3, 7–9], and α-syn multiplications caused cognitive deficits in PD patients, whose frequency and severity were dependent on the number of gene copies [10–12]. Furthermore, α-syn duplication also caused cognitive deficits in healthy siblings of PD patients [13], and different haplotypes of the α-syn gene associated with risk for, or protection against PD differentially affected cognitive sequence learning [14]. Polymorphisms in the microtubule-associated protein tau (MAPT) were also strongly associated with dementia in PD [15]. Hence, it is not surprising that synucleopathies usually include cognitive deficits of variable severity. In PD mild cognitive deficits can appear in the pre-manifest stage of the disease, before any severe motor symptoms are observed. These deficits are primarily observed in the attentional and executive domains [16, 17]. As disease progresses, a subset of patients develops severe cognitive deficits leading to dementia [18, 19]. A main risk factor for the development of severe cognitive deficits in PD is age, but the presence of early cognitive deficits may also increase the risk of later, more severe, cognitive symptoms [20, 21]. The same is true for mutations in the glucocerebrosidase (GBA) or PRKN [22, 23] genes and for AD neuropathology like Aβ.
and tau [24]. In contrast to PD, dementia with Lewy bodies (DLB) is characterized by predominant early cognitive deficits, which are linked to the presence of extensive α-syn pathology in the cerebral cortex from an early stage of the disease [25]. In the majority of patients, these two synucleopathies can be differentiable from the clinical perspective, with predominance of dementia in DLB and of extrapyramidal symptoms in PD [26, 27]. Specifically, cases where extrapyramidal symptoms occur in succession with dementia are classified as DLB if dementia occurs within 12 months of parkinsonian features and as PD with dementia (PDD) if dementia occurs a year or more after the clinical diagnosis [26, 27]. However, it is still under debate whether DLB and PDD are neuropathologically distinguishable [26, 28]. Cognitive deficits are also present to a lesser extent in multiple system atrophy (MSA) [29], a disorder in which α-syn accumulates in oligodendrocytes rather than in neurons. Recently, a highly significant and negative correlation between the density of α-syn pathology and the Mini-mental state examination (MMSE) score that is used to screen cognitive impairments was demonstrated in a large cohort of patients that were diagnosed with different disorders characterized by Lewy body pathology (including DLB and PD) [30]. This suggests a possible causal relationship between the burden of α-syn pathology and cognitive deficits and highlights the importance of further exploring, using mouse models, the mechanisms downstream to α-syn pathology, which may cause cognitive deficits.

Numerous transgenic lines of mice overexpressing either wild type or mutated human α-syn in neurons or oligodendrocytes were created to mimic the pathological and clinical features of PD and other synucleopathies [31, 32]. Mice with α-syn deficiency, which are less relevant to the naturally occurring human disorders related to α-syn pathology, were also created, in order to study the role of this protein in molecular and cellular processes in neurons [33]. This chapter will review studies that have investigated the cognitive aspects associated with α-syn pathology induced in these various mouse models, excluding MSA models, for which there are no reports in the literature about cognitive deficits.

**MOUSE MODELS OF ALPHA-SYNUCLEIN DEFICIENCY**

In view of the clear involvement of α-syn in a number of human disorders that include cognitive deficits, it was of interest to determine whether or not α-syn plays a role in cognition. Indeed, even excess accumulation of a pathological protein can lead to loss of function by recruitment of the normal protein into pathological aggregates, as proposed for Huntington’s disease [34]. A natural model was provided by a subpopulation of C57BL/6J mice previously used for cognitive studies, the C57BL/6JOlaHsd mice, that was discovered to carry a chromosomal deletion encompassing the SNCA gene encoding for α-syn [35]. This raised the possibility that differences in fear extinction between this line and the 6N line resulted from the absence of α-syn in the former line [36], but a comparison of fear extinction behavior between these lines and the B6fax line that expresses α-syn ruled out an effect of α-syn expression on fear extinction [37]. This suggests that the differences found initially in fear extinction between the mouse strains C57BL/6JOlaHsd and 6N [36] are related to differences in the expression of other genes. Likewise, the similar performance of α-syn knock-out mice and wild type mice in the Morris water maze at 6 months of age ruled out the relation of α-syn deletion to cognitive function in this test, which was a potential concern regarding the interpretation of cognitive data obtained from C57BL/6JOlaHsd mice [38]. Other lines of mice deficient for α-syn were further created to rule out or confirm the involvement of this protein in cognitive function. Senior et al. have found that deletion of either alpha or gamma synuclein alone did not impair cognition, but deletion of both impaired cognitive function in the T-maze at 12–20 weeks [39]. Additionally, electrically-evoked striatal DA release was two-fold higher in the double-null mice than in either alpha or gamma synuclein deficient mice, with no change in striatal dopamine levels [39], consistent with previous reports of no change in dopamine levels following deletion of synucleins [40]. These results suggest that gamma synuclein may compensate for the absence of α-syn in regulating synaptic function, and thus may prevent cognitive decline in the α-syn deficient mice. These data support the hypothesis that cognitive deficits in synucleopathies are more likely related to a gain rather than a loss of α-syn function. Table 1 below summarizes the cognitive phenotype found in the different models of α-syn deficiency.

**MICE OVER EXPRESSING HUMAN ALPHA-SYNUCLEIN**

Many genetic models of Parkinson’s disease are based on overexpression of either the mutated or the wild type human α-syn under various promoters. These models are summarized in details in our previous work.
Table 1

<table>
<thead>
<tr>
<th>References</th>
<th>Genetic background</th>
<th>Neuropathology</th>
<th>Cognitive phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al. (2002)</td>
<td>129/Ola backcrossed to C57BL/6</td>
<td>Not documented</td>
<td>No deficits in Morris water maze</td>
</tr>
<tr>
<td>Siegmund et al. (2005)</td>
<td>B6J/Ola</td>
<td>No change in DG</td>
<td>No differences in fear conditioning</td>
</tr>
<tr>
<td>Senior et al. (2008)</td>
<td>C57BL/6</td>
<td>↑ release of DA in STR</td>
<td>↓ alternations in T-maze only when combined with gamma-synuclein deletion</td>
</tr>
</tbody>
</table>

DA, dopamine; DG, dentate gyrus; STR, striatum

review [31]. Most studies of these models focused on their motor deficits with less attention paid to their eventual cognitive deficits despite the frequency and severity of cognitive symptoms in human synucleopathies. We will first describe mice with predominant overexpression in the cerebral cortex, as they are more likely to model human pathologies in which cognitive deficits are early and severe as in DLB. Table 2 summarizes the various models of α-syn overexpression and the resulting pathological and cognitive alterations in these models.

**Mouse models of predominant forebrain cortico/hippocampal-limbic α-syn pathology**

Several lines of mice show extensive cortical α-syn pathology, which led the authors to conclude that these models reproduce DLB [41–45]. Nevertheless, it is important to mention that despite the predominant cortical pathology, nigral pathology also existed to some extent in the PDGF-α-Syn and CaMKIIα-Syn models, which could perhaps explain the impaired rotarod performance in these models [46, 47].

**Mice overexpressing human wild type alpha-synuclein under the PDGF promoter**

This line was the first published line of mice overexpressing human α-syn [46]. These mice displayed intraneuronal inclusions immunoreactive for α-syn and sometimes ubiquitin in regions typically affected in synucleopathies such as the neocortex, olfactory bulb, and to a lesser extent, midbrain [46]. Nevertheless, TH-positive terminals in the striatum, as well as striatal TH levels and activity were reduced in the line with the highest transgene expression [48]. Although further examination of this line also revealed a 25–50% decrease in striatal dopamine at 12 months of age and increased thigmotaxis [48], the extensive cortical pathology led the authors to state that this model more faithfully reproduces DLB than PD [41].

These mice did not show any loss of cholinergic neurons in the basal nucleus, a region that provides a major cholinergic projection to the cerebral cortex and has been linked to cognitive deficits [49]. In contrast, tests of hippocampal function such as the Morris water maze were impaired at 9 [50] but not 6 months of age [49]. This deficit could be related to a decrease in hippocampal neurogenesis [51] or to an upregulation of the metabotropic glutamate receptor (mGluR5) in the frontal cortex [50]. In accordance with these findings, MPEP, an mGluR5 antagonist, ameliorated the deficits in the Morris water maze [50]. Deficits in Morris water maze performance in the same line of mice at 12 months were associated with a decrease in both the post-synaptic densities and diameter of pre-synaptic terminals in the temporal cortex [52]. The number of neurons expressing α-syn in the neuropil and in the cell body also increased in the hippocampus and the neocortex of PDGF-α-Syn mice, as well as the expression of markers of autophagy [52]. Passive immunization with an antibody against the C-terminus (CT) of α-syn was able to clear α-syn aggregates in PDGF-α-Syn mice, restore pre-synaptic terminals diameter and post-synaptic densities, and ameliorate cognitive deficits at 12 months of age [52]. The results of these studies offer novel therapeutic approaches for synucleopathies and suggest that the associated cognitive deficits may be improved.

**Mice overexpressing human A53T alpha-synuclein under the prion promoter**

The A53T mutation causes a rare form of familial PD [1] and increases α-syn aggregation and pathology when expressed in mice under the mouse prion promoter, usually leading to more severe phenotypes than the wild-type form of the protein [53]. This line of mice displays a severe, even fatal, motor phenotype due to pathological alterations in motoneurons of the spinal cord [53]. In contrast to the clear motor phenotype, these mice were not cognitively impaired when tested in the Barnes Maze (a dry form of the
### Table 2

Different models of alpha-synuclein overexpression, grouped by the promoters to induce transgene expression; the data in each model are further subgrouped by different lines of mice generated by different research groups, with the first reference referring to the originator of the line and followed by other groups using the same line in chronological order. The different models are ordered chronologically (by the year of the first report of the model), and so are the different lines within each model. 0–6 Months of age are considered "young age", 6–12 months "middle age", and over than 12 months "old age". In cases where two age ranges appear separated by a slash (e.g., young/middle), the onset was either in the borderline between two ranges or was reported in different age ranges by different groups using the same mice.

<table>
<thead>
<tr>
<th>References</th>
<th>Human syn</th>
<th>α-Promoter</th>
<th>Genetic background</th>
<th>Expression levels</th>
<th>Neuropathology</th>
<th>Cognitive dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Rockenstein et al. (2002)</td>
<td>WT</td>
<td>Mu Thy-1</td>
<td>C57BL/6 x DBA2</td>
<td>2-3 fold of expression in WT</td>
<td>Young mice: ↓ SN, LC, other brain regions, ↓ TH+ cell loss in SN or LC up to 18 m, Decreased cortical NE, 7 m, decreased striatal TH and DA 14 m</td>
<td>4.5 m: deficits in reversal learning (and reversal by L-DOPA), in novel object recognition, novel place recognition, 5.6 m, 7-9 m: deficits in Y-maze</td>
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<td>Feimling et al. (2007)</td>
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<td>Magen et al. (2008)</td>
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<tr>
<td>Kahl et al. (2006)</td>
<td>A30P</td>
<td>Mu Thy-1</td>
<td>C57BL/6</td>
<td>~two fold of expression in WT</td>
<td>↓ A, B, Cx, SC, SN, STR; ↓ phos- Ser129 staining in A and Cx; ↓ phos-Ser-Ser129 staining, ubiquitin+, apoptosis. No TH+ cell loss in SN</td>
<td>Old age onset: ↓ fear response (freezing and active avoidance), deficits in probe trial in Morris water maze</td>
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<td>Frechel et al. (2007)</td>
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<td>Schell et al. (2009)</td>
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<td>Zhou et al. (2008)</td>
<td>Y39C</td>
<td>Mu Thy-1</td>
<td>FVB/N</td>
<td>2.5-fold of expression in WT</td>
<td>↓ DA levels in STR; ↓ post-synaptic density and pre-synaptic terminals diameter in Cx, ↓ markers of autophagy, ↑ number of α-syn expressing neurons in H and Cx, reversed by antibody against α-syn C-terminus</td>
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<tr>
<td>Masliah et al. (2000)</td>
<td>WT</td>
<td>PDGF-β</td>
<td>C57BL/6 x DBA2</td>
<td>10-40% of human loading control</td>
<td>↓ Neurogenesis and ↑ apoptosis in DG; ↓ post-synaptic density and pre-synaptic terminals diameter in Cx, ↓ markers of autophagy, ↑ number of α-syn expressing neurons in H and Cx, reversed by antibody against α-syn C-terminus</td>
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<td>Masliah et al. (2001)</td>
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<td>Hashimoto et al. (2003)</td>
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<td>Winner et al. (2004)</td>
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<td>Price et al. (2010)</td>
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<tr>
<td>Masliah et al. (2011)</td>
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Note: ↓ and ↑ indicate decreases and increases, respectively.
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<th>Neuropathology</th>
<th>Cognitive dysfunction</th>
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</thead>
<tbody>
<tr>
<td>Giasson et al. (2002)</td>
<td>A5T</td>
<td>Mouse prion</td>
<td>C57BL/6</td>
<td>∼5–30-fold of</td>
<td>I: B, C, SC, STR, Th; GFAP+ and gliosis in SC; altered neuronal morphology, diffuse accumulation of α-syn, Wallerian degeneration in ventral root of SC, axonal degeneration of sciatic nerve; Trend to ↓ TH+ neurons in SN; ↓ DA in OB (reversed by ceasing gene expression); ↓ neurogenesis in DG (reversed by ceasing gene expression)</td>
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<td>Clinton et al. (2010)</td>
<td></td>
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<td>end. α-syn</td>
<td></td>
<td>Old age onset: ↓ Barnes circular maze</td>
</tr>
<tr>
<td>Nober et al. (2008)</td>
<td>WT</td>
<td>CaM-tTA</td>
<td>C57BL/6</td>
<td>Less (&lt;90%) than human</td>
<td></td>
<td>Old age onset: ↓ retention in the Morris water maze</td>
</tr>
<tr>
<td>Lim et al. (2011)</td>
<td>WT, A5T</td>
<td>CaM-tTA</td>
<td>B6C3/H</td>
<td>Not documented</td>
<td></td>
<td>A5T</td>
</tr>
</tbody>
</table>

A, amygdala; ACh, acetylcholine; B, brainstem; BG, basal ganglia; C, cerebellum; CaM, calmodulin; Cg, cingulate; ChAT, choline acetyltransferase; Cx, cortex; DA, dopamine; DG, dentate gyrus; end. α-syn, endogenous levels of α-syn; GFAP, glial fibrillary acidic protein; H, hippocampus; I, inclusions; LC, locus coeruleus; M, midbrain; MB, mammillary bodies; mGluR5, metabotropic glutamate receptor 5; NBM, nucleus basalis of Meynert; NE, norepinephrine; OB, olfactory bulb; S, septum; SC, spinal cord; SN, substantia nigra; STN, subthalamic nucleus; STR, striatum; T, telencephalon; Tg, transgenic; Th, thalamus; TH, tyrosine hydroxylase; TS, thioflavine S; WT, wild type.
Mice overexpressing mutant human alpha-synuclein under the Thy1 promoter

The α-syn overexpressing mouse that has so far been the most extensively studied for cognitive function is a transgenic line of mice expressing the A30P mutated human α-syn under the murine Thy-1 promoter, created by Kahle et al. [55]. At 12 months of age, these mice exhibited deficits in the probe trial of the Morris water maze that were not related to decreased swimming speed [42]. Impairments in fear-conditioning behavior were found at 17–20 months and were associated with distinct staining patterns of phosphorylated serine residue (phospho-serine-129 (PSer129)) [43], which is one of the features of neuropathological lesions in PD patients [56, 57]. Somal and nuclear PSer129 immunoreactivity increased with age in hippocampal and cortical areas as well as the lateral/basolateral amygdala nuclei and were also present in young, presymptomatic mice but not WT controls [43]. These mice further developed age-dependent, specific neuritic/terminal α-syn pathology in the medial parts of the central nucleus of the amygdala nucleus and one of its projection areas, the lateral hypothalamus. This suggests that α-syn becomes phosphorylated in distinct parts of the brain in this mouse model, showing age-dependent increases of nuclear PSer129 in cortical brain areas and the formation of neuritic/terminal PSer129 neuropathy within the fear-conditioning circuitry [43].

A line of transgenic mice overexpressing the human α-syn with the mutation Y39C under the Thy-1 promoter, showed cognitive impairments in the Morris water maze starting at 15–18 months and deteriorating at 21–24 months. This mutation is not observed in human patients but was used to enhance neurotoxicity by promoting protein aggregation. These mice widely expressed the mutant protein in the brain, including the cortex, hippocampus, striatum, thalamus, and substantia nigra, resulting in 2.5 fold higher level of expression than the wild type endogenous protein. At 24 months, transgenic mice developed neuropathology, such as α-syn and ubiquitin-positive inclusions, phosphorylation at Ser129 of human α-syn, and increased apoptotic cell death in the cortex, which were not present at 18 months. Therefore, these pathological anomalies seem to follow the progression of cognitive dysfunctions [44].
Mouse models of predominant brainstem cortico/subcortical-limbic α-syn pathology

Several lines of mice have been generated to reproduce the predominantly subcortical pathology associated with PD, which according to the Braak staging, starts in the olfactory bulb and ventral medulla, then progressively include raphe, locus coeruleus, and subsequently substantia nigra, basal nucleus of Meynert and amygdala, before invading the cerebral cortex at the latest stages of disease [58, 59]. As discussed earlier, this pattern of α-syn pathology is compatible with the progressive nature of cognitive deficits in PD, that consists of subtle impairments in executive function and attention at early stages of the disease [16, 17] and only evolve toward frank dementia at later stages in a subset of patients [18, 19]. Furthermore, the cognitive decline was found to correlate with the neuropathological stages of PD, suggesting that the risk to develop dementia increases with disease progression [60]. Although several lines of mice were generated to over-express α-syn specifically in catecholaminergic neurons under the tyrosine hydroxylase promoter, the cognitive function of these lines has not been characterized yet [61–65].

Mice overexpressing wild-type human α-synuclein under the Thy1 promoter

More recently, our laboratory has characterized the cognitive deficits of mice over-expressing human wild-type α-syn under the Thy1 promoter, generated in the laboratory of E. Masliah [41], with a focus on the early impairments that could correspond to cognitive deficits reported during the pre-manifest phase of disease [66, 67]. This mouse model of α-syn overexpression recapitulates most of the other non-motor symptoms typical to the preclinical stage of PD [31]. As PD patients display difficulties in reversal learning [66], Thy1-αSyn and WT mice were tested in a reversal learning task that assesses cognitive flexibility. Male Thy1-αSyn mice at 4-5 months of age learned a simple operant strategy as well as controls but showed greater difficulty than WT littermates in switching their responses at reversal, although they were eventually able to achieve criteria and learn the reversed contingency [68]. These mice also showed memory deficits in the novel object recognition (NOR) and novel place recognition tests at 4-5 months, and in the Y-maze test at 5-6 and 7-9 months. However, they showed no deficits in the cognitive aspects of the holeboard at 3-4 months, and in the Y-maze at 3-4 months and 11–13 months [69 and Magen et al. unpublished]. The latter observation is in agreement with previous evidence that deficits in Y-maze performance are associated with increased extracellular levels of dopamine [70]. Indeed the time course of increase in extracellular dopamine levels parallels that of the Y-maze performance as the earliest time point when dopamine was shown to be elevated in the striatum in Thy1-αSyn mice was 6 months while at older ages the hyperdopaminergic tone subsides, leading to loss of striatal dopamine by 14 months of age [71]. However, the deficits in the Y-maze and NOR test, both of which involve the cholinergic system [72, 73], also point to cholinergic deficits in the Thy1-αSyn mice. Human α-syn was indeed found to be expressed in cholinergic neurons in the basal nucleus and medial septum of Thy1-αSyn mice, which might have implications on the function of these neurons, and ACh levels decreased in the cortex of 6 month old Thy1-αSyn mice by 30% [Magen et al. unpublished], consistent with reports of degeneration of cortical cholinergic fibers in Thy1-[A30P]-αSyn mice at the same age [74].

CONCLUSION

In summary, although cognitive deficits have been less studied in mouse models of α-syn overexpression than motor function, a number of models have proven to show reliable deficits that can provide end-point measures to test new therapies for cognitive deficits in patients with synucleinopathies. Like in humans with DLB, some models show predominant cortical and hippocampal pathology with associated deficits in hippocampal function. In these models, hippocampal dependent functions such as contextual fear memory and long-term spatial memory in the Morris water maze, as well as amygdalar functions like cued fear memory, were impaired beginning at middle or old age (8-9 months at the earliest) [42–45, 47, 50]. α-syn overexpression could also worsen associated amyloid pathology [54] and cognitive deficits could be reversed in some models by turning off the transgene [45]. In contrast, models with predominantly subcortical pathology more closely mimic the pathology seen in PD than in DLB, since the former is restricted to the brain stem in the early stages of the disease and only invades the cortex in the final stages [58, 59]. These models show early deficits at 4–6 months of age in a wide range of cognitive domains, such as short-term spatial working memory (Y-maze and novel place recognition tests), short-term non-spatial recognition memory (novel object recognition test) and cognitive flexibility (reversal learning) [68, 69, and Magen et al.].
used so far to reverse cognitive deficits. However, the predominant subcortical pathology, no treatment was cognitive deficits in DLB. In the accumulation, like the mGluR5 antagonist MPEP [50] and dysfunctional mechanisms resulting from other drugs target specific neurotransmitter systems promising because they not only reverse cognitive deficits but also prevent their main potential cause. The availability of multiple genetic models even though a direct causal link has not been demonstrated. The benefit of multiple genetic models of synucleopathies provides a tool to investigate new neuroprotective therapies, and treatments specifically directed at cognitive dysfunction. Strategies found to improve cognition in models with predominant forebrain cortico/hippocampal-limbic pathology include turning off the transgene expression with doxycycline towards hippocampal involvement with deficits in the Morris water maze only at ages >12 months, compared to the earlier deficits in the WT aSyn model. Although few mouse models develop the characteristic pathological finding of PD – dopaminergic cell loss in the substantia nigra – the presence of multiple deficits, including cognitive deficits in several lines of mice implicates an effect of the transgene on brain function at a relatively young age. Indeed, a-syn pathology and neurochemical changes were present in regions involved in cognition in a number of models, even though a direct causal link has not been demonstrated. The transgenic effect on a-syn protein [52], thereby preventing its aggregation and accumulation and the resulting downstream behavioral and neurochemical abnormalities. These strategies are particularly promising because they not only reverse cognitive deficits but also prevent their main causal factor. Other drugs target specific neurotransmitter systems and dysfunctional mechanisms resulting from a-syn accumulation, like the mGluR5 antagonist MPEP [50] and can be potentially employed for the treatment of cognitive deficits in DLB. In the a-syn models with predominant subcortical pathology, no treatment was used so far to reverse cognitive deficits. However, the early cognitive phenotype of the Thy1-aSyn model has only been characterized recently [69 and Magen et al. unpublished], and it is possible that novel therapeutic approaches currently under study may lead to the development of drugs for the early cognitive impairments in PD which, although mild, significantly affect the quality of life of patients and represent an unmet medical need in the treatment of the disease.

ACKNOWLEDGMENTS

Supported by PHS grant P50 NS38367 (UCLA Morris R. Udall Parkinson’s Disease Research Center of Excellence), and gifts to the Center for the Study of Parkinson’s Disease at UCLA.

REFERENCES


I. Magen and M.-F. Chesselet / Alpha-Synuclein and Cognitive Deficits


[38] Chen PE, Specht CG, Morris RG & Schoepfer R (2022) Spatial learning is impaired in mice containing a deletion of the alpha-synuclein locus. Eur J Neurosci, 18, 154-158.


