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The MPTP marmoset model of Parkinsonism: a multi-purpose non-human primate model for neurodegenerative diseases

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Aging societies face an increasing prevalence of neurodegenerative disorders for which no cure exists. The paucity of relevant animal models that faithfully reproduce clinical and pathogenic features of neurodegenerative diseases is a major cause for the lack of effective therapies. Clinically distinct disorders, such as Alzheimer's and Parkinson's disease, are driven by overlapping pathogenic mechanisms that converge onto vulnerable neurons to ultimately cause abnormal clinical outcomes. These similarities, particularly in the early phases of neurodegeneration, might help identify appropriate animal model systems for studying of cell pathology. While reviewing some of the cellular mechanisms of disease progression, we discuss the MPTP-induced model of Parkinsonism in marmoset monkeys as a model system for construct, face and predictive validity in neurodegenerative studies.

Overlapping pathogenic mechanisms and modeling neurodegenerative states

Aging Western societies face a steadily increasing prevalence of neurological diseases caused by a progressive degenerative process within the central nervous system (CNS). Neurodegenerative disorders as diverse as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) have for a long time been regarded as different pathological entities because of their specific clinical symptoms, unique cell pathology and response to drug treatment. These diseases, however, exhibit overlapping pathogenic mechanisms that are conspicuously present throughout the brain parenchyma (Fig. 1). For instance, specific defects in cellular repair mechanisms and inability to maintain neuronal (e.g. Ca^{2+}) homeostasis can threaten cell function and viability, particularly in genetically prone individuals [1]. The etiology of AD, PD, ALS and HD seems to be woven by similar molecular threads: the aggregation and deposition of microscopically visible abnormal proteins that are causally linked to cellular stress and inflammation. It is not clear, however, how abnormal proteins lead to synaptic damage and then faulty neurotransmission. Understanding the mechanism of toxicity of aggregation-prone proteins for each of these diseases represents the most compelling research endeavor in the neurosciences. Unfortunately, it has come as an acute disappointment that most first clinical trials of therapies designed to mitigate the toxicity of mutant or aggregation-prone proteins have failed to help patients. Furthermore, the paucity of relevant animal models that faithfully reproduce clinical and pathogenic features of neurodegenerative states have also failed to identify basic intracellular events that are causal for the human disease. An exception to this exasperating situation might be the toxin-induced model of idiopathic PD (Box 1). The observation in the early 1980s of early-onset Parkinsonism in some Californian drug users who inadvertently injected themselves with 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP, desmethylprodine; a synthetic opioid with effects similar to those of morphine and pethidine) led to the identification of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) as a

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GLOSSARY

Disturbed Ca^{2+} homeostasis [34] Regulation of intracellular Ca^{2+} is vital for proper CNS function. However, relatively high Ca^{2+} levels during aging might be responsible for age-dependent vulnerability to cell injury. In neurodegenerative diseases, neuronal Ca^{2+}-regulation is compromised by depletion of energy supply owing to metabolic arrest and loss of mitochondrial function. This invariably leads to synaptic dysfunction, impaired protein plasticity and overall cell degeneration.

Excitotoxicity [33] In excitotoxicity, cell death is initiated by the overstimulation of excitatory amino acid receptors by high glutamate concentrations, leading to high intracellular Ca^{2+} levels. Excitotoxicity also generates ROS accompanied with ATP depletion. Excitotoxicity has been implicated in progressive neurodegenerative disorders through a process in which otherwise healthy neurons are unable to withstand non-lethal glutamate concentrations.

Glia activation [12,35] Glia cells play an active part in neurodegenerative processes. After harmful signals to neurons, microglia produce substances (such as cytokines) that keep certain neurodegenerative processes in a constant state of inflammation. There is evidence that clusters of microglia abound in the senescent brain, thus suggesting that activation and proliferation of these cell types could account for age-related neurodegenerative states.

Mitochondrial dysfunction [3] Mitochondria organelles, the source for most of the cell's adenosine triphosphate (ATP) supply, are responsible for regulating membrane potentials and cellular metabolism through Ca^{2+}-dependent autonomous channels. Mitochondrial dysfunction contributes to protein misfolding and aberrant oxidative stress and plays a central part in age-related neurodegeneration.

Oxidative stress [10,32] An imbalance in redox homeostasis causes toxic effects on proteins, lipids and DNA strands through the production of ROS. Oxidative stress is one of the key mechanisms involved in neurodegenerative diseases. The primary sources of ROS are mitochondrial dysfunction and microglia oxidative burst.

Protein aggregation [5] Several age-related neurodegenerative diseases are associated with protein aggregation or misfolding. It is still unclear whether the protein aggregation is generally toxic or the result of a protective mechanism initiated by injured neurons; however, in inherited forms of neurodegeneration, misfolded proteins often lead to an earlier onset and more severe clinical phenotype than sporadic forms. The current understanding is that microscopic aggregates are protective and that monomers and/or oligomeric precursors of the aggregates are pathological.

drug derivative with discrete neurotoxic properties. Subsequent studies in non-human primates (e.g. squirrel monkeys, rhesus macaques and common marmosets) confirmed that injections of MPTP lead to a gross depletion of dopamine (DA) neurons in the *substantia nigra pars compacta*. This depletion causes a spectrum of movement disorders, including the clinical triad of resting tremor, rigidity and bradykinesia. In general, these initial findings have led to the development of the MPTP-induced model of Parkinsonism in marmoset monkeys (*Callithrix jacchus*), which is currently used as a valid preclinical model of idiopathic PD. It should be noted that rodents are a less useful model for neurodegenerative studies because rats are not sensitive to systemic MPTP treatment and DA cell death in mice usually does not lead to the full spectrum of Parkinsonian symptoms. The aim of this review is to list several pathological similarities of the marmoset MPTP-based model with a broad spectrum of neurodegenerative diseases (Fig. 2) and to discuss the possibility of using this non-human primate as an alternative model system for preclinical neuroprotective drug development.

BOX 1

The MPTP model of neurodegeneration

Since the discovery of MPTP, this drug has become the preferred toxin to induce Parkinsonism in laboratory animals. MPTP selectively damages DA neurons, which invariably leads to impaired DA neurotransmission. The toxin is highly lipophilic and after systemic administration rapidly crosses the blood–brain barrier to cause cellular havoc. Within the CNS, MPTP is converted into $MPDP^+$ in astrocytes by the enzyme monoamine oxidase-B; it then spontaneously oxidizes into the metabolite MPP^+. MPP^+ is released into the extracellular space by an as yet unknown mechanism. MPP^+ is taken up by DA neurons vi a the DA transporter. Inside the neuron, MPP^+ can be stored either in the vesicular monoamine transporter or mitochondria. MPP^+ impairs mitochondrial respiration pathways by inhibiting complex 1 of the electron transfer chain. In this context, MPTP toxicity can be efficiently counteracted by riluzole (a drug already approved for the treatment of ALS [30]) when used in models of DA neuron degeneration [29,31]. Thus, the MPTP model of neurodegeneration can be used for rapid drug discovery and as an *in vivo* screening assay for drugs and nutritionals that reduce the risk of excitotoxic damage to neurons.

Mitochondrial defects and neurodegenerative diseases

Early indications for the role of mitochondrial dysfunction (see Glossary) in neurodegenerative states [2] came from studies showing that increases in mitochondrial oxidative stress and/or accumulation of protein aggregates could produce a devastating pathological and clinical phenotype [3].

This possibility was further supported by the discovery that MPTP inhibits the first enzyme complex of the mitochondrial electron transfer chain (complex I) in brains and platelets of patients with PD [4]. Moreover, the finding that systemic administration of the lipophilic complex I inhibitor rotenone could recapitulate many of the symptoms of PD further highlighted the interrelationship of mitochondrial proteins, oxidative stress and DA cell function [5]. Since then, mitochondrial defects have been implicated in a variety of clinical cases, commonly involving cell networks that have high energy requirements such as those found in the CNS. For example, recessive mutations in the genes encoding DJ-1 and PTEN-induced kinase 1, both localized to mitochondria (or at least to the outer mitochondria membrane), have recently been linked to familial forms of PD [6,7]. Furthermore, several pathogenic mitochondrial DNA (mtDNA) base substitution mutations and mtDNA deletions and insertions have been identified in a variety of other neurodegenerative diseases. For instance, cortical mtDNA deletion levels are elevated in both AD and HD, and AD brains show increased oxidative damage in their mtDNA [8]. Similarly, oligomerized amyloid-β peptide, a large component of plaque pathology in the AD brain, seems to trigger mitochondrial fission or fragmentation via S-nitrosylation of dynamin-related protein [9]. Collectively, these observations rekindle the debate over mechanistic theories of neurodegenerative diseases and also revive interest in oxidative stress as an underlying mechanism for the selective demise of certain neurons. It is worth noting that mitochondrial-based diseases commonly have a delayed onset and a progressive course, very much like those seen in a broad range of neurodegenerative disorders. This is now being studied in the marmoset monkey model of PD, which might provide insights into several novel mechanisms for mitochondrial pathology.

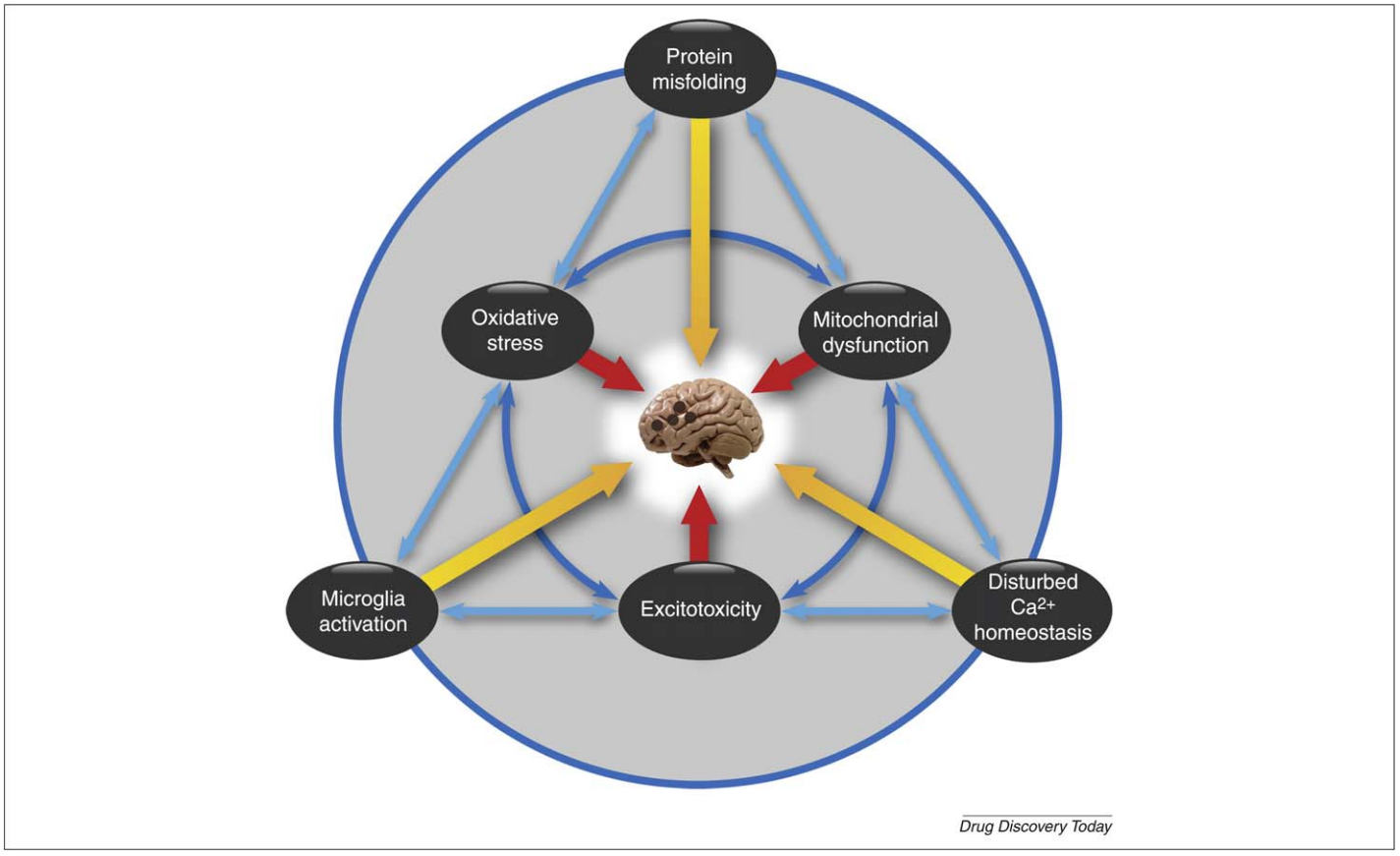

FIGURE 1

Schematic diagram depicting several pathogenic features found in a broad range of neurodegenerative diseases. The features in the inner circle are responsible for the initial cellular insult that causes failure of neuronal homeostasis. The features in the outer circle are responsible for the maintenance and progression of disease pathology. In some cases, such as in inherited PD or HD, the pathogenic process can originate from the outer circle. All of these intracellular processes of disease are potential targets for drug therapy.

Oxidative stress and brain pathology

Oxidative stress (e.g. reactive oxygen species, or ROS) can damage proteins overtly prone to changes in redox-signaling pathways [10]. Fortunately, the burden of ROS production is largely neutralized by a complex anti-oxidant arsenal of enzymatic scavengers including superoxide dismutase, catalase and glutathione peroxidase; however, these protective mechanisms are often weakened by chronic oxidative stress, particularly during senescence. Thus, it is generally accepted that a crucial balance between ROS production and anti-oxidant defenses determines the degree of oxidative stress in the aging nervous system [10]. Neurodegenerative diseases might, therefore, represent the effects of a chronic imbalance between ROS production and ROS clearance. Is there any supporting evidence for this working hypothesis? Indeed, alterations in mitochondrial respiratory capacity and age-dependent increases in oxidative damage are seen in AD, PD, HD and ALS [11]. The relative contribution of oxidative stress to neurotoxicity is not yet clear, but one possibility is that AD, PD, HD and ALS all share early common mechanisms of oxidative pathology, which later become specific to certain brain regions with different clinical end points. Nonetheless, the observation that diverse brain pathologies show oxidative damage reinforces the central role of mitochondrial metabolism and subsequent energy-dependent ROS production in neurodegenerative states. This link provides a useful framework for understanding disease progression in the marmoset monkey model of PD.

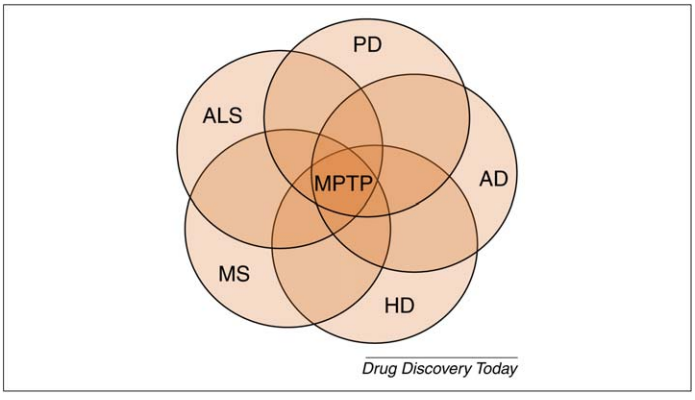

FIGURE 2

MPTP causes brain damage with phenotypes overlapping those caused by different etiologies. Neurons are particularly vulnerable to both the toxic effects of MPTP and aggregation of misfolded proteins. Each of these toxic effects converges on pathways that cause motor deficits or dementia. The common characteristics of these neurodegenerative disorders suggest parallel approaches to drug therapy.

Microglia activation and neurodegenerative diseases

For decades, glia cells were thought to have only a passive, supporting role in the CNS. It is now becoming increasingly clear, however, that glia cells, particularly microglia, have an active role in inflammatory response signaling events. For instance, microglia cells continuously survey the brain for injury and infection, both during development and during adulthood. Microglia cells promptly migrate to areas of injury and release cytokines such as tumor necrosis factor-α, interleukin-1β and interleukin-6, which dramatically increase the excitability of nearby neurons. Similar migratory patterns of microglia are found in AD, PD and multiple sclerosis (MS) patients, where they often interact with neurons and surrounding blood vessels. Whether these interactions are helpful or harmful in these clinical conditions is a matter of debate. Regardless, several *in vitro* studies have demonstrated co-localization of activated microglia cells with amyloid fibrils and α-synuclein aggregates remarkably similar to that seen in neural tissue extracted from patients afflicted with protein-folding-related diseases. This observation implies that aberrant folded proteins might directly injure the synapses and neurites of neurons, in addition to activating microglia cells. Thus, microglia activation as seen in certain neurodegenerative states might result from changes in protein metabolism that occur before widespread cell death ensues, the characteristics of which are often disease specific. Abnormally high levels of activated microglia have also been associated for decades with senescence, thus indicating that the inability to maintain glia cell homeostasis is sufficient to cause common end points in both aging and neurodegenerative states [12]. Work in non-human primates also implicates microglia activation as an early step for many of the underlying mechanisms that provoke neuronal death in AD, PD and MS. For example, injections of MPTP into marmoset monkeys selectively damages DA cells in the *substantia nigra pars compacta*, a pathogenic event that is immediately followed by the clustering of microglia around injured neurons [13]. Of interest, activated microglia in MPTP-treated monkeys remain considerably elevated in the midbrain one year after MPTP exposure [14]. This observation suggests that activation of microglia in areas of injury might be more protracted than previously thought. Furthermore, in an autoimmune model of MS in marmoset monkeys, degeneration of white matter seems to be indirectly mediated by infiltrated inflammatory cells, whereas degeneration of grey matter in the same non-human primate is ascribed to highly concentrated recruitment of microglia cells [15]. Of interest, in a superoxide dismutase mutant mouse model of ALS, neurodegeneration can be mitigated by inhibiting the actions of microglia cells, suggesting that – in this particular case, at least – degeneration could be triggered by the abnormal release of microglia-derived cytokines that bind and perturb cell-surface receptors and/or channels rather specifically [16]. Although the 'microglia cascade hypothesis of degeneration' offers a broad framework to explain certain pathological features of AD, PD and MS, it is currently hampered by a lack of detailed mechanistic understanding.

Aggregation and deposition of abnormal proteins

Several age-related degenerative diseases, including AD, HD, dementia with Lewy bodies and PD, are associated with aggregation and accumulation of misfolded proteins, the characteristics of which are often disease specific [5]. For instance, in AD, the aberrant deposition of amyloid-β occurs in the form of fibrils or extracellular plaques, whereas in HD, the polyglutamine-containing protein accumulates in the form of nuclear and cytoplasmic inclusions. In PD, the toxic protein is represented by α-synuclein that 'seeds' the brain to produce intracellular Lewy bodies [17,18]. It should be noted that the ability of proteins to form highly organized aggregates is not restricted to the few proteins associated with recognized clinical disorders but seems to be a generic propensity of all polypeptide chains. Studies in animal models of AD and PD further support the ability of proteins to change conformation and form small, soluble aggregates that assume toxic states with a wide range of cellular targets. For example, microinjections of fibrillar amyloid-β into the aged marmoset brain induces typical pathogenic aspects of AD [19]. In addition, rat studies show that intracerebral injections of misfolded α-synuclein cause degeneration of vulnerable neurons that recapitulate the pathogenic features often seen in sporadic PD [20]. Finally, mice systematically treated with MPTP spontaneously develop protein aggregates that could be equally toxic to the nervous system [18]. Despite the rapid advance in the molecular dissection of protein folding and misfolding, including the identification of several pathogenic proteins, it is not yet known whether clearance of soluble aggregates correlate with disease improvement. There is still considerable work to be done, particularly in non-human primate models of neurodegenerative diseases, to determine whether therapeutic agents can prevent aggregates from forming or dismantling those already rooted in the brain parenchyma.

Modeling certain pathogenic features of neurodegeneration

Animal models offer a useful experimental platform for target identification (e.g. pathogenic mechanism) and validation (e.g. face validity) of candidate drugs (Table 1). Target identification in neurodegenerative diseases is a major challenge, however, because a 'spider web' of pathological events – acting separately or synergistically – exist in certain individuals who are at risk of developing a specific-degenerative phenotype (Fig. 1). Furthermore, the multiple and diverse cellular mechanisms that characterize most neurodegenerative diseases conspire to develop an all-inclusive animal model that mimics the most obvious symptoms of the brain disease. Non-human primates, in particular the marmoset monkey, bridge this gap by providing an appropriate animal model for construct, face and predictive validity ('face validity' refers to the perceived similarity of the symptoms observed in the model and in the human disorder). More importantly, the close genetic, anatomical, physiological and immunological synteny of marmoset monkeys with humans makes them the preferred species for replicating brain diseases. Besides the anatomical and physiological similarities with humans, behavioral and cognitive deficits, which frequently represent the main source of disability in patients, can be assessed very accurately in the marmoset monkey [21]. There are, however, substantial ethical hurdles and acute differences associated with using monkeys for mimicking neurodegeneration in humans. For instance, potential side-effects associated with invasive approaches to disease replication (e.g. intracerebral injections of pathogenic molecules such as amyloid-β or α-synuclein) considerably limit the use of marmoset monkeys for certain clinical studies. In regards to MPTP, this toxin does not produce dementia with Lewy bodies, amyloid-β or polyglutamine-containing proteins, which are common pathological features of neurodegenerative disorders. Thus, the MPTP-treated marmoset monkey can only serve as a template model for understanding disease mechanisms and potential new drug treatments, rather than predicting different clinical manifestations of a particular brain disorder. This difference in essence relates back to the difficulty of finding an all-inclusive animal

TABLE 1

Neuroprotective compounds used in MPTP-based pathologies, which are also currently approved for preclinical phases of several neurological studies

	Mechanism of action	Target	Application	Status	Reference
Coenzyme Q10	Anti-oxidant Mitochondrial energy enhancer	Oxidative stress Mitochondrial dysfunction	PD, HD AD	Research	[24]
Creatine	Mitochondrial energy enhancer	Brain atrophy Inclusion formation	ALS, HD, PD	Research	[2]
Apocynin	Anti-oxidant Anti-inflammatory	Oxidative stress Microglia activation	ALS, MS, stroke, PD	Research	[25]
Minocycline	Anti-inflammatory anti-apoptotic	Microglia activation Apoptosis	PD, MS, HD, AD, ALS	Research	[24]
Lipoic acid	Anti-oxidant Anti-inflammatory	Mitochondrial decay Oxidative stress	PD, AD, HD	Research	[26]
EGCG[a]	Anti-oxidant Anti-inflammatory	Oxidative stress	PD, stroke, AD, ALS	Research	[27,28]
Memantine	NMDA[b] antagonist	Excitotoxicity	PD, AD	Approved/research	[29]
Riluzole	NMDA[b] antagonist Ca^{2+} channel blocker	Excitotoxicity	ALS PD	Approved/research	[30,31]
Rasagiline	Monoamine oxidase-B inhibitor Anti-apoptotic GDNF[c] activation	β-amyloid, glutamate Apoptosis	PD AD	Approved/research	[24]

[a] Epigallocatechingallate
[b] N-methyl-D-aspartate
[c] Glial-cell-line-derived neurotrophic factor

model that could point the way to common therapeutic approaches. In this regard, it is certainly conceivable that some of the therapeutic drugs listed in Table 1 could be applied across multiple neurodegenerative diseases. Indeed, memantine 10 mg twice daily has been used to treat several neurological diseases, including those associated with excessive glutamate release (e.g. AD and PD with dementia [22]). Both AD and PD with dementia, regardless of their respective protein aggregate profiles and anatomical lesion loci, are often accom-

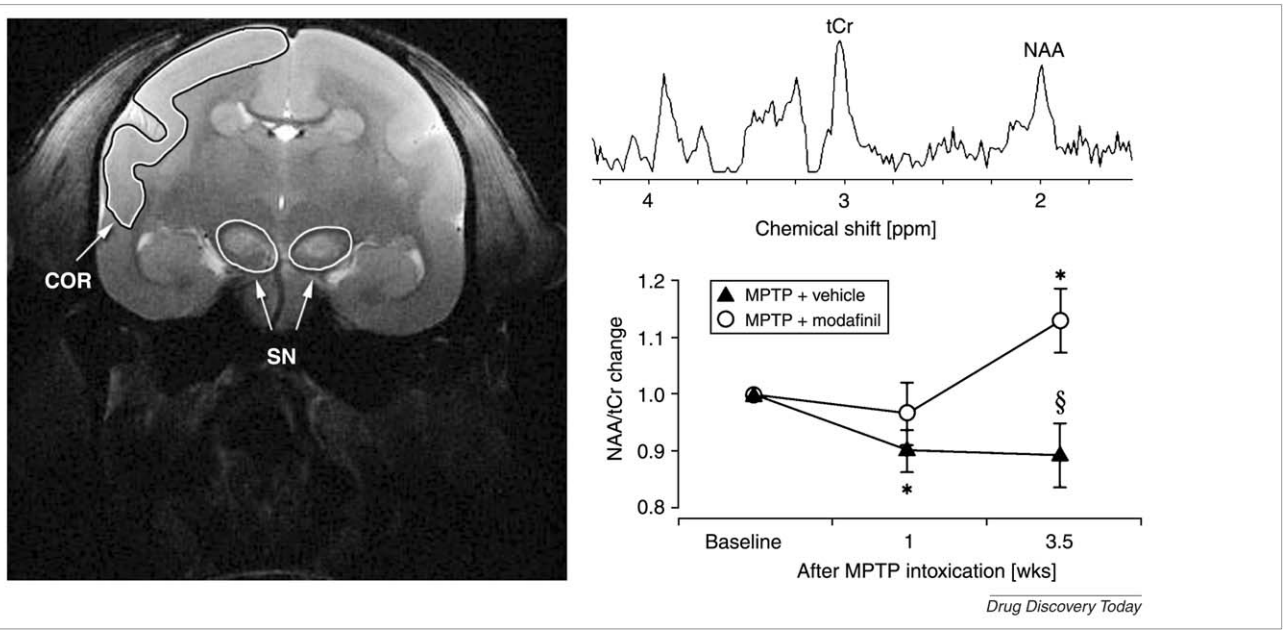

FIGURE 3

Magnetic resonance spectroscopy (MRS) imaging analysis of the MPTP-treated marmoset brain [23]. MRS imaging permits *in vivo* analysis in a regionally specific manner of brain metabolites relevant to neuronal density (*N*-acetylaspartate, or NAA). In these studies, we hypothesized that in the same MPTP-treated animal, the ratios of NAA to total creatine (tCr, the standard denominator in MRS ratio analyses) would be decreased. This pattern would reflect diminished neuronal viability to MPTP toxicity. Left panel: T2-weighted axial brain section oriented to the SN and reference area in the cortex (COR). Right panel (upper): Representative spectrum from one voxel is shown with peaks identified for NAA and tCr. Right panel (lower): Relative changes in NAA/tCr ratios (means ± SEM) across defined times (weeks) in the marmoset SN. Note that modafinil (already approved for narcolepsy) also minimizes MPTP-based toxicity. Significant differences compared to baseline (*) and between treatments (§) (one-way ANOVA followed by Bonferroni *post hoc* tests; $P \leq 0.05$).

panied by non-motor complications, such as dementia, sleep disturbances, depression and psychotic symptoms, which invariably worsen their prognoses. This strategy provides rationale for the use of drugs for wider applications than conditions in which cholinergic (for AD) or DA (for PD) are considerably impaired. Furthermore, as better *in vivo* imaging methods become more widely available in non-human primates (Fig. 3), ambiguities related to cholinergic, glutamatergic or DA function in the brain of living marmoset monkeys suffering from MPTP toxicity will probably become better elucidated [23]. Nevertheless, the well-established MPTP model of idiopathic PD in marmoset monkeys recapitulates most of the core pathogenic mechanisms of the human condition, including mitochondrial dysfunction, oxidative stress, and activation and proliferation of microglia [14]. Furthermore, the neuronal cell loss and neurodegenerative cascade of events after MPTP administration are stable over time, thus providing a window of opportunity for testing pharmacological therapies that modify the temporal and kinetic states of brain pathology. These useful characteristics of MPTP, when applied to the marmoset monkey, can provide relevant mechanistic and therapeutic information that could be used to delay or perhaps even arrest the disease before the more typical symptoms emerge and the damage caused by the neurodegenerative state becomes irreversible.

Concluding remarks

Despite the advances in clinical pharmacology and state-of-the-art of animal modeling, innovative approaches to neurodegenerative states are still needed. Rather than placing a lot of effort in the creation of disease-specific animal models, we propose that research efforts should focus on the implementation of a generic model that covers core principles of pathogenetic processes. The MPTP-treated marmoset monkey, for instance, resembles human PD with respect to pathology, biochemistry, symptomatology and response to treatment. Thus, knowledge gained from this animal model will aid in the development of drug therapies for several forms of neurodegenerative diseases.

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