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N-Methyl D-Aspartate (NMDA) Receptor Antagonists and Memantine Treatment for Alzheimer's Disease, Vascular Dementia and Parkinson's Disease

David Olivares[1], **Varun K. Deshpande**[2], **Ying Shi**[2], **Debomoy K. Lahiri**[3], **Nigel H. Greig**[4], **Jack T. Rogers**[5], and **Xudong Huang**[2,5,*]

[1]Service of Clinical Pharmacology, Hospital Clinico San Carlos, C/Professor Martin Lagos s/n, 28040, Madrid, Spain

[2]Conjugate and Medicinal Chemistry Laboratory, Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

[3]Departments of Psychiatry and of Medical & Molecular Genetics, Institute of Psychiatric Research, Indiana University School of Medicine, 791 Union Drive, Indianapolis, IN 46202, USA

[4]Laboratory of Neuroscience, Intramural Research Program, National Institute on Aging, Baltimore, MD 21224, USA

[5]Neurochemistry Laboratory, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Charlestown, MA 02129, USA

Abstract

Memantine, a partial antagonist of N-methyl-D-aspartate receptor (NMDAR), approved for moderate to severe Alzheimer's disease (AD) treatment within the US and Europe under brand name Namenda (Forest), Axura and Akatinol (Merz), and Ebixa and Abixa (Lundbeck), may have potential in alleviating additional neurological conditions, such as vascular dementia (VD) and Parkinson's disease (PD). In various animal models, memantine has been reported to be a neuroprotective agent that positively impacts both neurodegenerative and vascular processes. While excessive levels of glutamate result in neurotoxicity, in part through the over-activation of NMDARs, memantine—as a partial NMDAR antagonist, blocks the NMDA glutamate receptors to normalize the glutamatergic system and ameliorate cognitive and memory deficits. The key to memantine's therapeutic action lies in its uncompetitive binding to the NMDAR through which low affinity and rapid off-rate kinetics of memantine at the level of the NMDAR-channel preserves the physiological function of the receptor, underpinning memantine's tolerability and low adverse event profile. As the biochemical pathways evoked by NMDAR antagonism also play a role in PD and since no other drug is sufficiently effective to substitute for the first-line treatment of L-dopa despite its side effects, memantine may be useful in PD treatment with possibly fewer side effects. In spite of the relative modest nature of its adverse effects, memantine has been shown to provide

*Address correspondence to this author at BWH Radiology, 75 Francis Street, Boston, MA 02115, USA; xhuang3@partners.org.

CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

only a moderate decrease in clinical deterioration in AD and VD, and hence efforts are being undertaken in the design of new and more potent memantine-based drugs to hopefully provide greater efficacy.

Keywords

Alzheimer's disease; Parkinson's disease; vascular dementia; memantine; NMDAR; amantadine

INTRODUCTION

Alzheimer's disease (AD), a neurodegenerative disorder characterized by irreversible, progressive loss of memory followed by complete dementia, is marked by cognitive decline accompanied by impaired performance of daily activities, behavior, speech and visual-spatial perception. It is the most common type of dementia among people older than 65, accounting for about 60%-70% of cases [1], associated with heterogeneous risks including genetic, epigenetic, dietary, and lifestyle factors [2].

The most striking and early symptom of AD is a loss of short-term memory (amnesia). When AD is suspected, the diagnosis is usually confirmed with behavioral assessments and cognitive tests, often followed by a brain scan. As the disorder progresses, cognitive impairment includes difficulty in producing or comprehending spoken or written language (aphasia), difficulty of execution of movements (apraxia), loss of perception (agnosia) [3], and disorientation [4]. AD may also involve behavioral changes, such as outbursts of violence or excessive passivity in people who have no previous history of such behavior [5, 6]. Gradually, basic physiological functions are lost, ultimately leading to death.

AD afflicts at least 26 million people throughout the world [7] of which 5.4 million are Americans [8]. In the US, in 2011, it is estimated that at least $183 billion will be spent on direct AD care [8] and these costs will rise as the population ages. Several FDA-approved drugs are currently in use for the treatment of AD, however they mostly bring symptomatic relief and do not cure AD. Such an absence of treatment options sets the stage for the present review, which is primarily focused on the physiological role and utility of NMDAR antagonists, especially memantine, and its treatment not only for AD but other neurodegenerative disorders also, such as Vascular Dementia (VD) and Parkinson's Disease (PD). The present review summarizes the recent advances in pathogenic processes underlying these diseases, including the amyloid pathway, pharmacology of NMDARs, glutamatergic transmission and the utility of NMDAR antagonists for therapy. Keeping the current interest of the field in mind, we will place a special emphasis on memantine treatment. It is worth mentioning that several aspects of memantine, such as its molecular basis [9], pharmacology [10] and clinical trials [11] have been previously discussed in this journal. However, the present review brings forward distinctly the unique role of memantine in treating AD, VD and PD in a comprehensive manner.

ALZHEIMER'S DISEASE PATHOGENESIS, NMDARS AND MEMANTINE TREATMENT

Alzheimer's Disease Pathology and NMDARs

Cognitive impairment in AD is caused, in large part, by the death of cholinergic neurons in the basal forebrain area [12]. Therefore, well characterized in the AD brain are a deficit in acetylcholine (ACh) and classical cholinergic markers, epitomized by choline acetyltransferase and acetylcholineseterase [2, 13].

AD neuropathology is routinely characterized by the accumulation of insoluble amyloid protein that originates from the amyloidogenic processing of a much larger metalloprotein – amyloid precursor protein (APP) [14] that leads to the formation of extracellular neuritic amyloid plaques containing the peptide- beta amyloid peptide (Aβ, see Fig. 1). The other major pathological hallmarks include neurofibrillary tangles (NFTs) that are comprised of misfolded, abnormally phosphorylated microtubule-associated tau protein [15], inflammatory changes with astrocytosis and microgliosis [16], oxidative stress [17, 18] and neuropil threads that have been found in the post-mortem AD brain [19], and in addition, a variety of other neurochemical and cellular alterations that result in anatomic as well as functional impairment of the neurotransmitter systems.

Although genetic, biochemical and neuropathological data strongly point to Aβ and amyloid plaque formation as a central event in AD pathogenesis [20], the etiopathology of AD remains unclear. A considerable weight of data suggests that it is polygenic and multifactorial [21] and that, likely, Aβ metabolism is sensitive to a range of influences and multiple mechanisms that can cause a shift towards the pathogenic pathways that lead to AD [22]. A small fraction of patients develop AD before the age of 65 known as early onset familial AD (FAD) that is believed to be caused by ~200 mutations in one of three genes: APP (on chromosome 21), and presenilin-1 and −2 (PS1, PS2) (31, 177 and 14 mutations, respectively) [http://www.molgen.ua.ac.be/ADMutations]. A commonality of these numerous mutations is that they, albeit via different routes, increase generation of Aβ and, in particular, the ratio of $A\beta_{42}$: $A\beta_{40}$ [23]. Major evidence indicates that soluble aggregates of Aβ and Aβ-derived diffusible ligands (ADDLs) target synapses and impair memory and also can induce cellular dysfunction. Recently, it has been suggested that APP proteolysis generates additional fragments that contribute to neuronal dysfunction [24].

$A\beta_{40}$ (40 amino acid residues) is the main soluble Aβ species that is found in the cerebrospinal fluid at low nanomolar concentrations [25]. $A\beta_{42}$ (42 residues) is a minor Aβ species that is more fibrillogenic than $A\beta_{40}$ and heavily enriched in interstitial plaque amyloid [26]. It is generally agreed that Aβ peptide neurotoxicity is dependent on its conformational state [27]. The *in vitro* solubility of synthetic $A\beta_{42}$, in neutral aqueous solutions is lower than $A\beta_{40}$, consequent to the hydophobicity of the additional carboxylterminal amino acids. Also, it has been demonstrated that soluble $A\beta_{40}$ can be destabilized through seeding with $A\beta_{42}$ fibrils [28]. However, the presence or overproduction of $A\beta_{42}$ alone appears to be insufficient to initiate Aβ amyloid deposition. Overexpression of APP and consequential Aβ overproduction in transgenic mice models

rarely results in mice bearing full-blown Alzheimer's-like neuropathology [29]. Rather, it appears more likely that additional neurochemical factors are required for Aβ amyloidosis.

Some of the potential disease-modifying treatments for AD include NMDAR blockade, use of P-sheet breakers, antioxidant strategies, Aβ-peptide vaccination, secretase inhibitors, APP synthesis inhibitors, cholesterol-lowering drugs, metal chelators and anti-inflammatory agents. Strategies targeting the Aβ protein directly include anti-Aβ immunization, γ- and P-secretase inhibitors, aggregation inhibitors and copper/zinc chelators. Interest in the use of metal chelator drugs stems from recent research suggesting that Aβ plaque formation relies upon the binding of metal ions [22]. Cholinergic drugs such as donepezil, rivastigmine and galantamine represent primary treatments for AD and are based on increasing available levels of ACh to surviving neurons. However, they have not been shown to prevent neuronal death [30] or disease progression [31]. Therefore, the evaluation of potential AD treatments that target other mechanisms is a major focus of current investigation and offers the greatest potential to enhance clinical management.

Considerable evidence supports the role of dysregulated glutamate in the pathophysiology of neurodegenerative disorders and excitotoxicity [32]. Therefore, glutamate NMDARs have emerged as key therapeutic targets for AD.

Glutamate is the main excitant neurotransmitter in the mammalian brain, implicated in the excitatory postsynaptic transmission through several ionotropic and metabotropic glutamate receptors. There are three classes of glutamategated channels and a group of G-protein coupled glutamate receptors (which cause mobilization of Ca^{2+} from internal stores) [33, 34] named according to their activating synthetic agonist: the α-amino 3-hydroxy 5-methyl 4-isoxazole-propionic acid (AMPA) activated receptors, kainate activated receptors, and the N-methyl D-aspartate (NMDA) receptors, have great importance in long-term adaptive processes [35]. Among these, the ion channels coupled to classical NMDARs are generally the most permeable to Ca^{2+} [36], that can in turn function as a second messenger in various signaling pathways.

NMDA glutamate receptors are abundant and ubiquitously distributed throughout the central nervous system (CNS), playing a critical role in synaptic plasticity and the cellular processes that underlie learning and memory [37]. Long-term potentiation (LTP) is a representation of neuronal synaptic plasticity that consists of a brief induction phase that elicits a long-lasting enhancement in signal transmission between two neurons. A stimulus into a presynaptic cell releases neurotransmitters, mostly glutamate, onto the postsynaptic cell membrane. There, glutamate binds to AMPA receptors in the postsynaptic membrane and triggers the influx of positively charged Na^{+} ions into the postsynaptic cell, causing a short-lived depolarization called excitatory postsynaptic potential. In synapses that exhibit NMDAR-dependent LTP, sufficient depolarization plus binding of glutamate can unblock NMDARs and relieve the Mg^{2+} blockade of the NMDAR [38] allowing Ca^{2+} to flow into the cell.

NMDARs are tetrameric complexes (see Fig. 2) composed by two NR1 subunits (eight splice isoforms, see Fig. 3) that form the channel itself, and two NR2A, NR2B, NR2C or NR2D subunits (derived from four independent genes) [39]. NR2 subunits modulate the

characteristics of the NR1 channel; therefore each combination shows different physiological and pharmacological properties [34]. For example, *in vitro* recombinant NMDARs composed by NR1 and NR2B subunits result in much more sensitivity to the non-competitive antagonist ifenprodil than the NR1/NR2A combination [40]. Recently, NR3 subunits have been found [41], although NR1/NR3A or NR1/NR3B complexes are not activated by glutamate but rather elicit an excitatory response through glycine activation that is independent of Ca^{2+} influx. Glycine is a mandatory co-factor with glutamate for NMDA channel opening [42] for binding sites onto NR1 and NR2 subunits, respectively, although a more potent inducer than glycine, an uncommon amino acid, D-serine, has been found [43].

NMDARs have been implicated as a mediator of neuronal injury associated with many neurological disorders including ischemia, epilepsy, brain trauma, dementia, and neurodegenerative disorders, such as PD [44]. Pathological elevations of glutamate levels and possibly other disturbances that alter resting membrane potential (e.g. impaired metabolism) can cause over-stimulation of the NMDAR that can lead to cellular dysfunction and death [45]. Under normal conditions of synaptic transmission, the NMDAR channel is blocked by Mg^{2+} sitting within the channel and only activated for brief periods of time. However, under pathological conditions, the normal block of the ion channel by Mg^{2+} is removed and abnormally enhances NMDAR activity [46]. Over-activation of the receptor causes an excessive amount of Ca^{2+} influx into a neuron to then trigger a variety of processes that can lead to necrosis or apoptosis [47]. The latter process includes Ca^{2+} overload of mitochondria and the activation of caspases and Ca^{2+}-dependent activation of neuronal nitric oxide synthase (nNOS), leading to increased nitric oxide (NO) production [48]. Mitochondrial Ca^{2+} overload disables the membrane electrochemical gradient and, therefore, the ATP synthesis [49]. In addition, as consequence of electron chain failure, there is an excessive reactive oxygen species (ROS) production, such as the superoxide anion (O_2^-) that reacts with NO producing peroxynitrite ($ONOO^-$) that can in turn oxidize lipids, proteins and DNA [50]. Interestingly, Ca^{2+}-triggered neurotoxicity depends on the activation of a determinate pathway, since Ca^{2+} influx through L-type voltage-gated channels or non-NMDA receptors was not toxic to cells, while a similar Ca^{2+} load via NMDRs was neurotoxic [51]. Increased activity of nNOS is also associated with excitotoxic cell death [52]. The nNOS is physically tethered to NMDAR through the postsynaptic density protein of 95 kDa (PSD-95) [53] and is activated by Ca^{2+} entry via calmodulin [41]. In fact, increased levels of NO have been detected in animal models of stroke and neurodegenerative diseases [54, 55]. It has been shown that in *PSD-95* mutant mice, the production of NO induced by Ca^{2+} entry via NMDR is blocked without affecting nNOS expression, indicating the specificity of NMDAR in neurotoxicity [53].

Importantly, elevations in extracellular glutamate are not necessary to invoke an excitotoxic mechanism. Excitotoxicity can come into play even with normal levels of glutamate if NMDAR activity is increased, e.g. when neurons are injured and, thus, become depolarized [56]. Much evidence shows that the AD pathogenic cascade includes an excitotoxic component. Application of Aβ has been shown to promote endocytosis of NMDARs in cortical neurons [57]. However, the specific effects of Aβ on excitotoxicity are not yet fully understood, and the exact role of NMDAR activation in AD remains unclear, although

several studies have evidenced that Aβ could bind to NMDAR and increase Ca^{2+} influx into the cell [58].

Many potential neuroprotective agents block virtually all NMDAR activity and therefore, have unacceptable adverse effects, such as psychosis, nausea, vomiting, and a state called dissociative anesthesia, marked by catalepsy, amnesia, and analgesia. Neuronal cell death may accompany complete NMDAR blockade that may occur with high binding affinity of some drugs towards NMDARs [59]. Such possibilities dramatize the crucial role of the NMDAR in normal neuronal processes and explain why many NMDAR antagonists have disappointingly failed to advance in clinical trials for a number of neurodegenerative diseases. To be clinically acceptable, an anti-excitotoxic therapy must block excessive activation of the NMDAR while leaving normal function relatively intact to also avoid side effects. Drugs that simply compete with glutamate for the agonist binding site and block normal physiological functions do not meet this requirement. Both competitive glutamate and glycine antagonists, even although effective in preventing glutamate -mediated neurotoxicity, cause generalized inhibition of NMDAR activities [60]. Non-competitive antagonists, like MK-801, is an effective suppressor of excitotoxicity that acts allosterically (i.e. its binding site is other than the agonist's) in the ion channel, but due to its high affinity, slow off-rate kinetics and a lesser voltage-dependent activity, blocks the channel for a clinically unacceptable period of time [60]. Such drugs have thus failed in clinical trials to date because of the development of adverse events occurring when the drugs are administered in their therapeutic range [59].

One mechanistic type of drug that can preferentially block higher, pathological levels of glutamate is an 'uncompetitive' antagonist that differs from non-competitive antagonists in that it requires receptor activation by an agonist before it can bind to a separate allosteric binding site. This uncompetitive mechanism of action, unlike competitive or non-competitive antagonists, yields a drug that blocks NMDAR channels preferentially when it is excessively open and prevents an excessive flux of calcium inside the cell [61]. Most importantly, it does not substantially accumulate in the channel to interfere with normal synaptic transmission [60]. Evidence suggests that memantine acts by such a mechanism, given that it is a low, moderate affinity, uncompetitive NMDAR antagonist.

MEMANTINE TREATMENT FOR ALZHEIMER'S DISEASE

Memantine (1-amino-3,5-dimethyladamantane), an amino-alkyl cyclohexane derivative was first synthesized by Eli Lilly and Company (Indianapolis, IN) and patented in 1968, as documented in the Merck Index, as a derivative of adamantine, an anti-influenza agent. It possesses a three-ring (adamantane) structure with a bridgehead amine ($-NH_2$) that, under physiological conditions, carries a positive charge that binds at or near the Mg^{2+} site within the NMDAR-associated channel.

Memantine was relatively ineffective at blocking the low levels of receptor activity associated with normal neurological function but becomes increasingly effective at higher concentrations of glutamate associated with over-activation of NMDARs [60]. During normal synaptic activity, NMDA channels are open on average for only several milliseconds,

and memantine is unable to act or accumulate within the channels; accordingly, synaptic activity continues largely unabated [56]. During prolonged activation of the receptor, however, as occurs under excitotoxic conditions, memantine becomes a highly effective blocker.

In addition to its low to moderate affinity, memantine blocks/unblocks the NMDAR ion channel with rapid kinetics and high voltage dependency [62]. These properties are thought to underlie the apparent ability of memantine to allow normal physiological function of the receptor while impairing pathological activation. Blocking NMDARs has also been reported to mitigate Aβ-induced degeneration of cholinergic neurons in the rat magnocellular nuclear basalis and in rat hippocampal neurons [63–65]. Preclinical data suggest that NMDAR-mediated excitotoxicity may be linked to the effects of abnormal Aβ deposition in AD. More recently, memantine has been found to lower levels of secreted APP and Aβ peptide levels in neuronal cultures and in APP-$_{Swe}$+PS1 AD transgenic mice [66, 67]. This is important as Aβ accumulation is the precipitating event in AD that leads to synaptic loss among other pathological features. Aβ is known to alter neuronal structure by mechanisms that involve the NMDARand inhibition of the NMDAR can reduce the toxic effects of Aβ.

As a currently approved drug, memantine is indicated for the symptomatic treatment of moderate to severe AD, and has been associated with a moderate decrease in clinical deterioration in AD [68]. Its usefulness has been proved in several clinical trials in which it has shown little but statistically significant improvements [69–72], also assessed by brain imaging [73]. Several systematic reviews of randomized controlled trials have established that memantine has small but helpful actions on cognition, mood, behavior, and the ability to perform daily activities in moderate to severe AD [74–76] nevertheless, the action of the drug in mild to moderate AD remains largely unknown. Importantly, memantine appears capable of achieving its pharmacological actions in a clinically well-tolerated manner and does not show the adverse effects typically associated with high-affinity NMDA-blockers. In trials reporting adverse effects, the primary memantine-induced adverse actions found were infrequent and comparable to placebo such as dizziness, occasional restlessness/agitation, constipation, ocular effects (cataracts, conjunctivitis), nausea, dyspnea, confusion, headache, fatigue, rash, diarrhea and urinary incontinence [77, 78]. On the basis of successful clinical trials, the use of memantine in the modulation of glutamatergic function may therefore represent a useful strategy for the treatment of AD. Furthermore, *in vitro* and clinical data indicate no adverse interactions between the approved cholinesterase inhibitors and memantine [79, 80].

Because memantine has exhibited efficacy and safety in placebo-controlled trials in patients with moderate to severe AD, the combination of memantine and various cholinesterase inhibitors appears well tolerated and they seem act synergistically due to their distinct mechanisms of action [81–85].

At present, a series of second generation memantine derivatives are currently in development and may have even greater neuroprotective properties than memantine [9, 86]. Whether and how these drugs translate to clinical medicine are awaited with interest.

MEMANTINE TREATMENT FOR VASCULAR DEMENTIA

Memantine has also been described as effective and well tolerated for the treatment of mild to moderate VD in several randomized clinical trials [87–89]. VD ranks second in prevalence as a form of dementia after AD [1], and they often co-exist. It is not infrequent that confusion can occur between both disorders, due to the similarity of their clinical symptoms. VD is a degenerative cerebrovascular disease that leads to a progressive decline in memory and cognitive functioning. The root of this issue relates to a chronic reduced cerebral blood flow (vascular insufficiency) carrying oxygen and nutrients to the brain that may be impaired by a strategic infarct (ischemia) or small (silent) multi-infarcts, hemorrhagic cerebrovascular disease, or can derive from small vessel disease (including lacunar lesions and Binswanger's disease) [90]. Apart from acute ischemia from embolic or atherothrombotic large vessels occlusion, ischemic-hypoxic brain lesions also can be originated by cardiovascular diseases, such as hypertension or diabetes, which cause a narrowing of the lumen of small vessels [91]. In addition, senile arteriolosclerosis produces tortuosity and elongation of arterioles [92].

Since it may be partly preventable, VD needs to be differentiated from other causes of dementia such as AD, Lewy body-type dementia and PD. Special attention has to be given when attempting to make a differential diagnosis, to the following steps that may lead to a diagnosis of VD [93]:

- Detection of vascular risk factors, including hypertension, diabetes, orthostatic hypotension, smoking, cardiac arrhythmias and heart failure.
- Examination of the cardiovascular system that may be a cause of thromboembolism that results in transient ischemic episodes and a history of strokes.
- Neurological and psychometric assessments to evidence particular neurological deficits.
- A search for treatable factors that might lead to VD, such as hypothyroidism, neurosyphilis, vitamin B12 deficiency, cerebral vasculitis or frontal lobe tumors.

Oxygen and glucose deprivation are followed by an elevation of extracellular glutamate both in ischemic brain damage and traumatic brain injury [50] that results in consequent NMDR overactivation and massive Ca^{2+} influx. Failure of astrocyte functions also has been reported [94] such as maintenance of blood-brain barrier (BBB) cells in cerebral microvasculature and endothelial permeability [95]. Disruption of tight junctions among endothelial cells, degradation of the basal lamina and extracellular matrix by metalloproteinases-2 and −9 are involved in BBB breakdown and cerebral hemorrhagia [96–98]. In addition, adhesion and transmigration of leukocyte occurs, leading to activation of an inflammatory response [99]. For a review of downstream processes after calcium entry in ischemia, see Ref. [48].

In general, cerebral lesions after ischemic injury begin with an initial reversible stage where neurons finally become necrotic [100]. The cells of the ischemic core undergo anoxic depolarizations that expand to the penumbral region and a lack of energy that leads to

necrosis [101]. Since the ischemic area grows as the number of peri-infarct depolarizations increases, the extension of severe damaged area can be attenuated by blocking NMDAR-mediated depolarizations [102].

PARKINSON'S DISEASE PATHOGENESIS, NMDARS, GLUTAMATERGIC TRANSMISSION AND MEMANTINE TREATMENT

Parkinson's Disease Pathology, NMDARs and Glutamatergic Transmission

PD is the second most frequent progressive-type neurodegenerative disorder after AD [103] and represents, like AD, a large health burden to society. Approximately 1% of the population over 60 years of age is affected [104]. Classical clinical symptoms include tremors; bradykinesia, or slowness of movement; and rigidity, or akinesia.

The primary underlying pathology of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) that innervates the striatum. At post-mortem examination, the depletion frequently exceeds 90% [105] with consequent loss of neuronal systems responsible for motor functions. Besides, cell death is not limited to dopaminergic neurons in SNpc and can expand to other areas of the brain, leading to extensive neuronal death. It is not infrequent to find dementia in patients afflicted by PD. A further archetypal hallmark is the formation of intracytoplasmic inclusions, termed Lewy bodies, in remaining neurons [106].

To date, no curative treatment for PD exists but symptomic control can be achieved. The most effective treatments are based on the replacement of dopamine (DA) loss using either the precursor of DA, L-dihydroxyphenylalanine (L-dopa), or agonist-mediated stimulators of DA receptors, epitomized by pramipexole or ropinirole. Essentially, all patients require L-dopa at some stage of disease progression, in spite of its adverse effects, such as the "wearing-off" phenomenon – relating to the shortening of sustainable pharmacological activity [107] as occurs when the symptoms of PD, attenuated by the treatment, become more intense prior to the next expected dose. Albeit that L-dopa is associated with dyskinesia or diminished voluntary movements and the presence of involuntary movements, it must be recognized that, since L-dopa's clinical introduction, survival with PD has been considerably prolonged [108].

NMDARs are very abundant in the striatum [109], comprised by putamen and caudate nucleus, where they regulate the release of neurotransmitters like γ-aminobutyric acid (GABA) and ACh [110]. NMDARs downstream of the striatum also participate in modulating the activities of basal ganglia circuit and are present in the subthalamic nucleus (STN), globus pallidus internus (GPi) [111], and cerebral cortex [112]. The activity of NMDARs is largely regulated by dopaminergic afferents. D1 receptor agonists elicit a fast enhancement of NMDA-induced depolarization of striatal cells, whereas D2 receptor agonists attenuate this [113].

Execution of voluntary movement starts with the cortex (executive) signaling the caudate and putamen via glutamatergic projections or from the SNpc via dopamine. The Striatum then sends inhibitory GABAergic signals to GPi leads to disinhibition of the thalamic ventral

anterior (VA). This leads to stimulatory signaling of the motor cortex by the thalamic VA and initiation of movement. As described, PD is characterized by depletion of dopaminergic neurons, leading to a disinhibition of striatal neurons that have inhibitory D2 dopaminergic receptors and project to the globus pallidus externus (GPe), and to a decrease of striatal neuron activity projecting to the GPi and the substantia nigra pars reticulata (SNpr) that have D1 excitatory dopaminergic receptors [114]. All these striatal efferent pathways are mediated by GABA and are inhibitory so that GPe projection to the STN (also inhibitory) is reduced. Therefore, the suppression of dopaminergic modulation disinhibits STN neurons, rendering them overactive [115]. The enhanced activity of excitatory glutamatergic STN projections to GPi and SNpr (besides lack of inhibitory input from the GPe stated above) further enhance the activity of their GABAergic neurons [116]. Spontaneous movement is reduced by inhibiting the activity of thalamic glutamatergic and excitatory VA projections VA to the motor frontal cortex (see Fig. 4A and B). Acetylcholinergic neurons in the brainstem and basal forebrain areas, are regulated by prefrontal cortex glutamatergic projections, and seem to be of special relevance in modulating motor, emotional and mnemonic functions [117], therefore a decrease of thalamocortical input entails a deficit of ACh, leading to a decline in voluntary movements. Likewise, the striatum and SNpc can receive glutamatergic excitatory input from the neocortex [118].

Accordingly, increased activity of STN neurons has been described in monkeys treated with 1-methyl 4-phenyl 1, 2, 3, 6-tetrahydropyridine (MPTP), a neurotoxin that induces parkinsonism in animal models [119], and NMDAR antagonists have been reported to provide potent neuroprotective action [120]. NMDARs localized to the STN also play a role in sustaining pathological hyperactivity observed in a 6-hydroxydopamine rat model of parkinsonism, and the infusion of a NMDAR antagonist into the STN normalized the activity of the basal ganglia [121].

NMDARs are also found on dopaminergic neurons in the SNpc [122]. Increased glutamatergic input to dopaminergic neurons through NMDARs might accelerate the degenerative process [118]. It has been reported that NMDAR antagonists elevate striatal DA release *in vivo* [123–125] and, given this, would likely be beneficial in PD. In testing this conjecture, the initial class of selective antagonists' studies in parkinsonism were the phenylethanolamines. One of them, ifenprodil, shows anti-parkinsonian activity in reserpine-treated rats and MPTP-treated monkeys [126].

The effect of an anti-PD medication can be enhanced by NMDAR antagonists. In animal models of PD, NMDAR antagonists have shown a potentiation of the anti-parkinsonian effect of L-dopa and locomotion [109]. Some anticholinergic drugs are also non-competitive antagonists of the NMDAR and, at therapeutic concentrations, may interact with NMDARs and palliate PD [127]. Just as anticholinergics are able to work as NMDA antagonists, NMDA antagonists also can function as anticholinergic agents [128] and normalize the glutamatergic control of corticostriatal ACh release. In the striatum, NMDA stimulation enhances the release of ACh, and antagonists can effectively inhibit this release [110].

Since oxidative products of DA play a role in dopaminergic cell death [129], the use of NMDA antagonists could additionally allow for a decrease in L-dopa dosage and, thereby,

diminish any potential oxidative damage. Other NMDA antagonists, such as dextromethorphan, have been reported to suppress dyskinesia in PD patients, but adverse effects (primarily drowsiness) at higher doses would likely limit such a treatment strategy [130]. On the other hand, amantadine (1-amino adamantine) a non-selective NMDA antagonist used to treat PD, provides mild L-dopa-induced anti-dyskinetic benefit with a moderate degree of NMDA antagonist activity [131]. Furthermore, in a large retrospective study, amantadine was associated with an increased lifespan in patients with PD, suggesting that it may have neuroprotective properties [132].

Memantine Treatment for Parkinson's Disease

Given that memantine carries out its therapeutic action by targeting the glutamatergic transmission, and the role of NMDARs in basal ganglia for the development of PD symptoms, memantine has also been tested in parkinsonian patients with a degree of moderate success.

Although memantine's chemical structure is related to amantadine's, and they act in a somewhat similar pharmacological fashion, memantine does not appear to share the anti-dyskinetic activity of amantadine [133]. However, like DA agonists and other NMDA antagonists, memantine is able to reverse neuroleptic-induced catalepsy [134].

Using patch-clamp techniques, it has been reported that memantine blocks the NMDA ion channel [135], binds to the MK-801 binding site of the NMDAR [136], and decreases NMDA-induced membrane currents. The mechanism of action postulated is a normalization of the corticostriatal glutamatergic activity and/or the subthalamopallidal pathways that are overactive in PD (see Fig. 4C and D). Contrasting with amantadine, in which anti-dyskinetic activity could be rationalized by blocking subthalamic activity, the anti-parkinsonian and synergistic effect of memantine could be due to the inhibition of glutamatergic transmission in the striatum, whereby striatonigral neurons are GABAergic and inhibitory, causing a decreased inhibition of nigrostriatal dopaminergic neurons in SNpc and thereby an elevation in DA release [137].

To investigate the primary efficacy of memantine, a double-blind crossover exploratory trial was designed [133], in which 12 patients with idiopathic PD were randomized to memantine or placebo during two weeks in an escalated dosage from 10 mg/day to 30 mg/day at day 7, and after this time, a single dose of L-dopa was administrated to each arm. Five patients were taking concomitant PD medication (but not amantadine). As expected, a clear anti-parkinsonian activity was observed in terms of counteracting bradykinesia and resting tremor. A synergistic enhancement of L-dopa and memantine seemed evident with motor function. Side effects, mainly drowsiness and nausea, occurred with a similar frequency in both groups.

To further assess the efficacy of memantine, a randomized controlled study was performed with patients suffering from dementia with Lewy bodies or PD dementia that resulted in an improvement in the majority of variables stated in the clinical global impression of change test for the memantine group compared to placebo [138, 139] and a better response assessed

in other useful rating scales [140], while the proportion of adverse events was similar to placebo and improved L-dopa-related dyskinesia and the “off” effect [141].

CONCLUDING REMARKS

Several studies show how memantine positively impacts cognition and, hence, they lend credence to the hypothesis that neurotoxicity of glutamatergic overstimulation is involved in dementia. The neuroprotective properties of memantine have also been demonstrated in several *in vitro* experimental settings, albeit further studies are needed to examine whether memantine treatment and cholinergic treatments could ultimately prove to be complementary or even synergistic. Memantine has also shown efficacy in PD, revealing itself as a potentially promising new therapeutic option. Importantly, as memantine treatment is generally well tolerated, combining it with other therapies is a valuable and feasible option both with AD and PD. However, although memantine was approved for treating mild to moderate AD, its results are modest; therefore, a second generation of adamantane-based drugs are being designed in the hope of improving its clinical efficacy. In conclusion, given the wealth of data on NMDAR activity in AD, VD, and PD, memantine and other drugs that emerge in the NMDAR antagonist class are likely to have an increasingly significant role to play in the future treatment of these diseases.

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LIST OF ABBREVATIONS

Ach	Acetylcholine
AD	Alzheimer’s disease
ADDLs	Aβ-derived diffusible ligands
Amantadine	1-Amino adamantine
AMPA	α-Amino 3-hydroxy 5-methyl 4-isoxazolepropionic acid
APP	Amyloid precursor protein
Aβ	Beta amyloid peptide
BBB	Blood-brain barrier
CNS	Central nervous system
DA	Dopamine
FAD	Familial Alzheimer’s disease
GABA	γ-Aminobutyric acid

GPe	Globus pallidus externus
GPi	Globus pallidus internus
L-dopa	L-dihydroxyphenylalanine
LTP	Long-term potentiation
Memantine	1-Amino-3,5-dimethyladamantane
MPTP	1-Methyl 4-phenyl 1, 2, 3, 6-tetrahydropyridine
NFTs	Neurofibrillary tangles
NMDA	N-Methyl D-Aspartate
NOS and NO	Nitric oxide synthase and nitric oxide
PCP	Phencyclidine
PD	Parkinson’s disease
PS1 and PS2	Presenilin-1 and Presenilin-2 protein
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulate
STN	Subthalamic nucleus
VD	Vascular dementia

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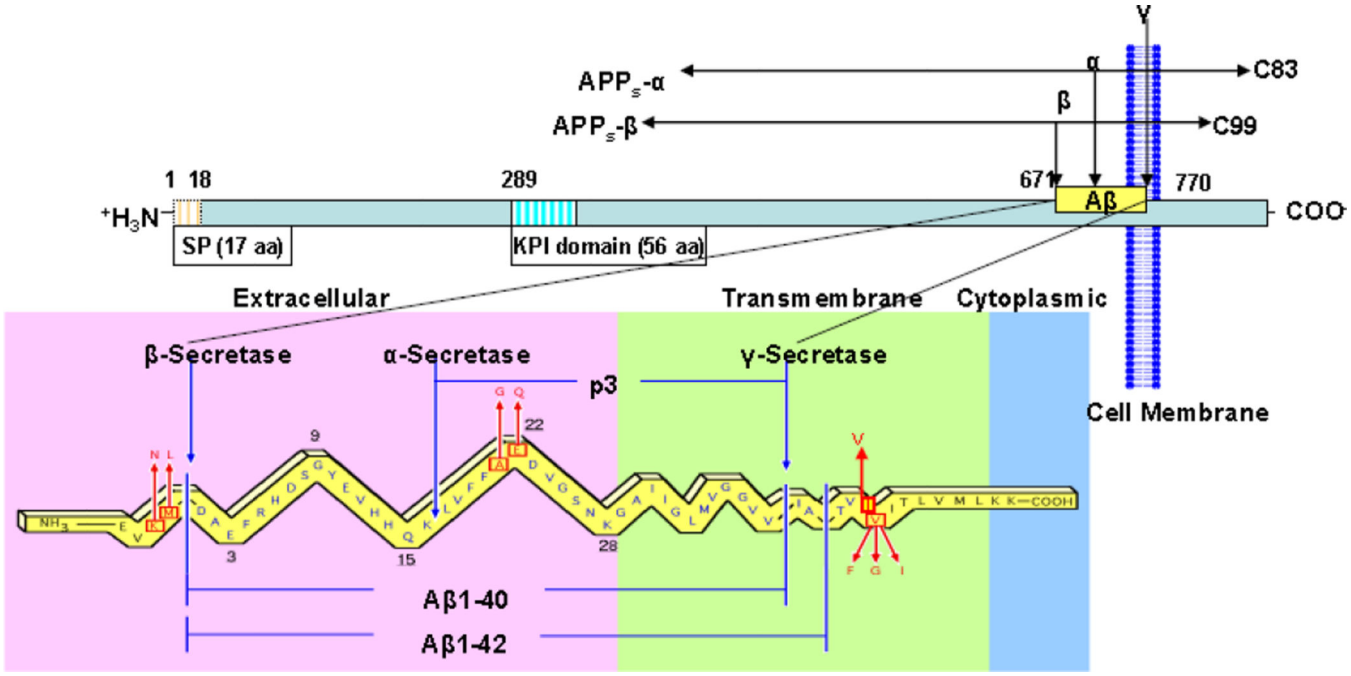

Fig. (1).

Schematic illustration of APP protein and its Aβ product after cleavage by α-, β- and γ-secretases. β- and γ-secretase cleaves on the N- and C-terminal ends of the Aβ region respectively. γ-Secretase cleavage yields a 39–43 amino acid product. Long and more fiblillogenic 42–43 amino acid Aβ species are implicated in AD pathogenesis and may seed the formation of Aβ40 fibrils. Mutations in the APP gene and in genes encoding proteins known as presenilins increase the production of long Aβ. Presenilins-1 and −2 is thought function as γ-secretases (for a review, see [142]).

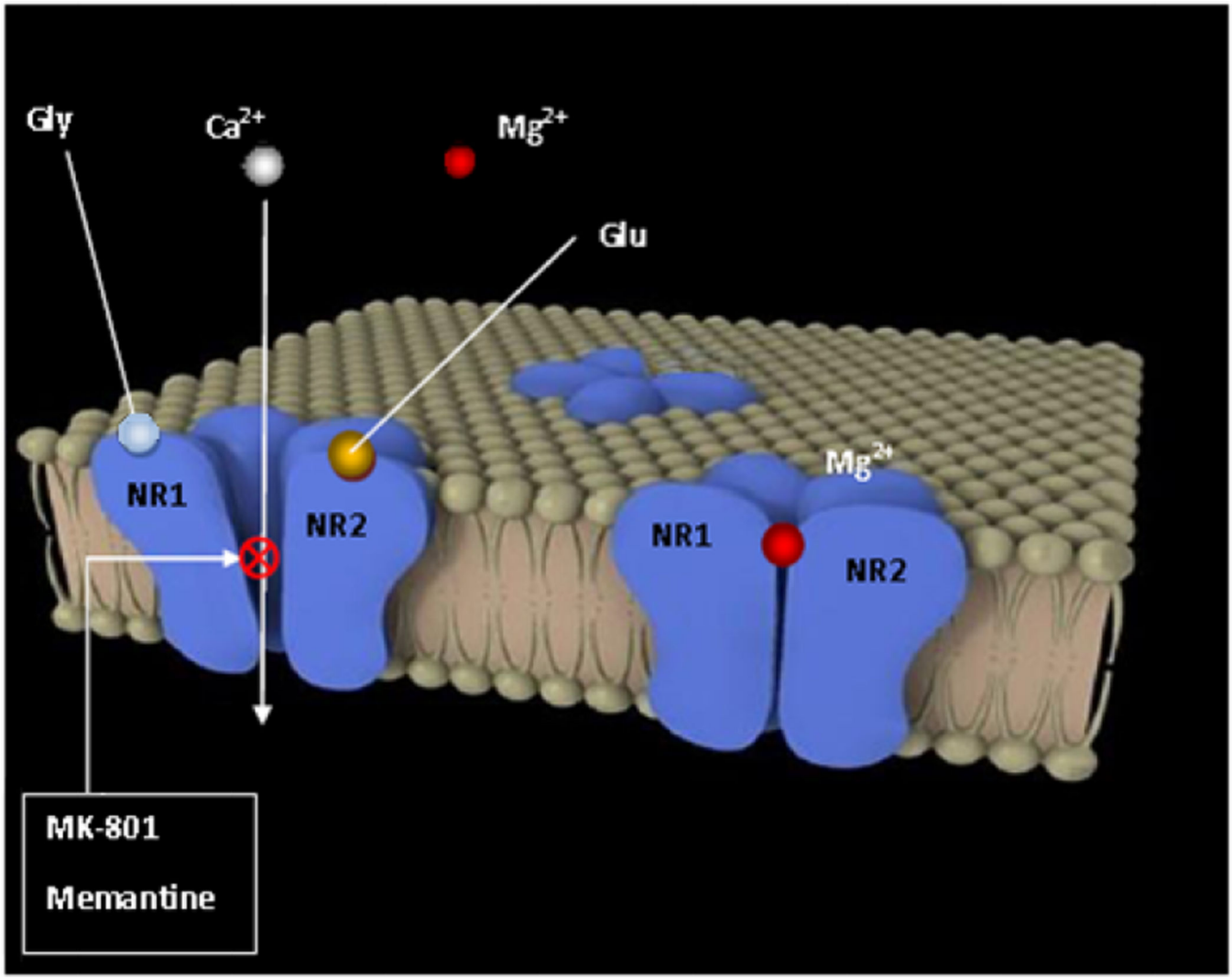

Fig. (2).

Depiction of the tetrameric NMDAR at rest (right) and activated after depolarization and binding of agonists glycine and glutamate, suppressing the magnesium channel blockade (left), where antagonists MK-801 and memantine have their allosteric binding site.

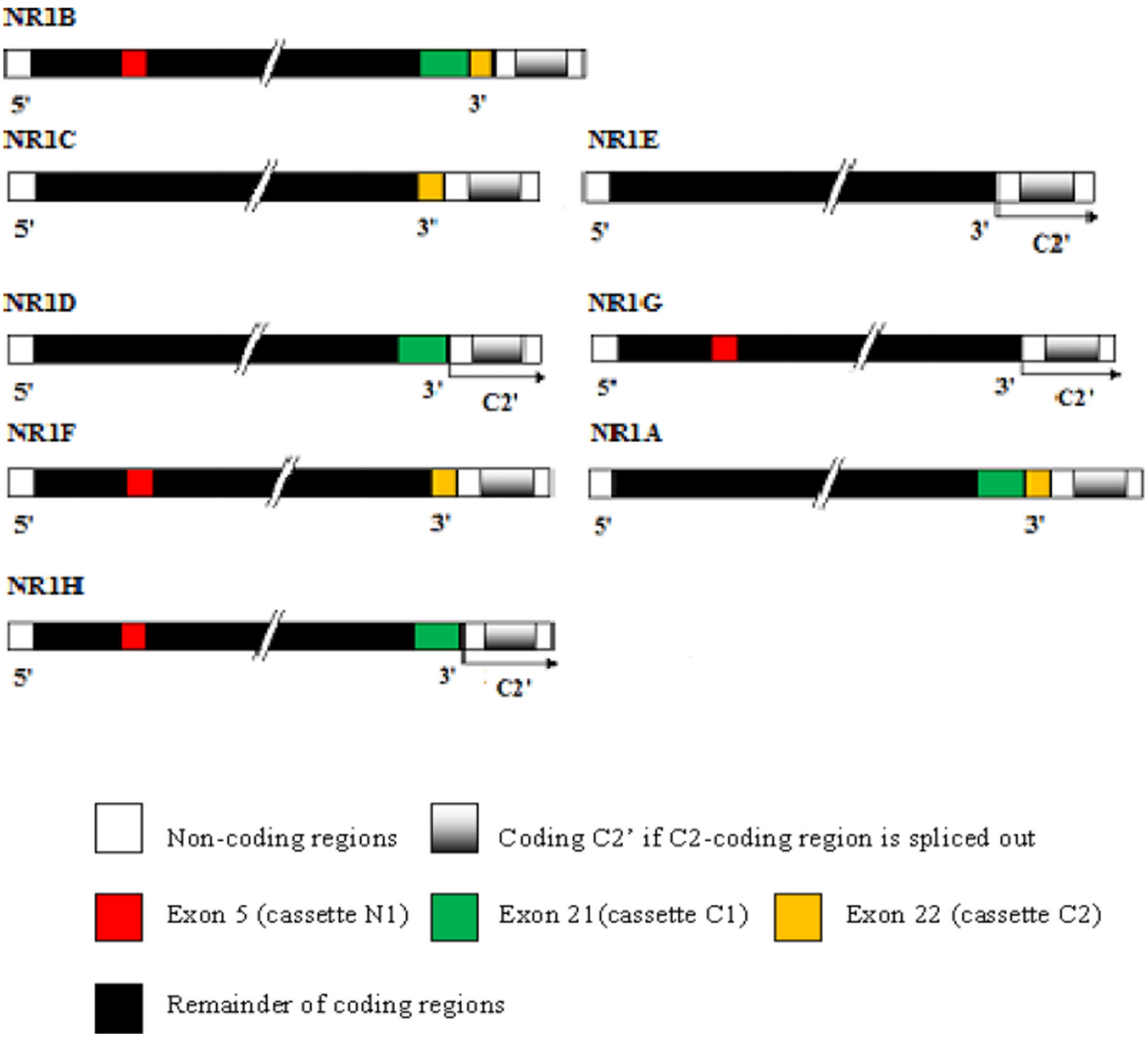

Fig. (3).

Schematic structure of eight NR1 receptor isoforms (NR1A–H). Exons 5, 21 and 22 encode three splice cassettes named N1, C1 and C2. Carboxy-terminals variants are generated by splicing out of cassettes C1 and/or C2; and amino-terminal variant, by splicing out of N1. If C2 is excised, the first stop codon is suppressed, resulting in a new open reading frame that encodes the sequence named C2' [143].

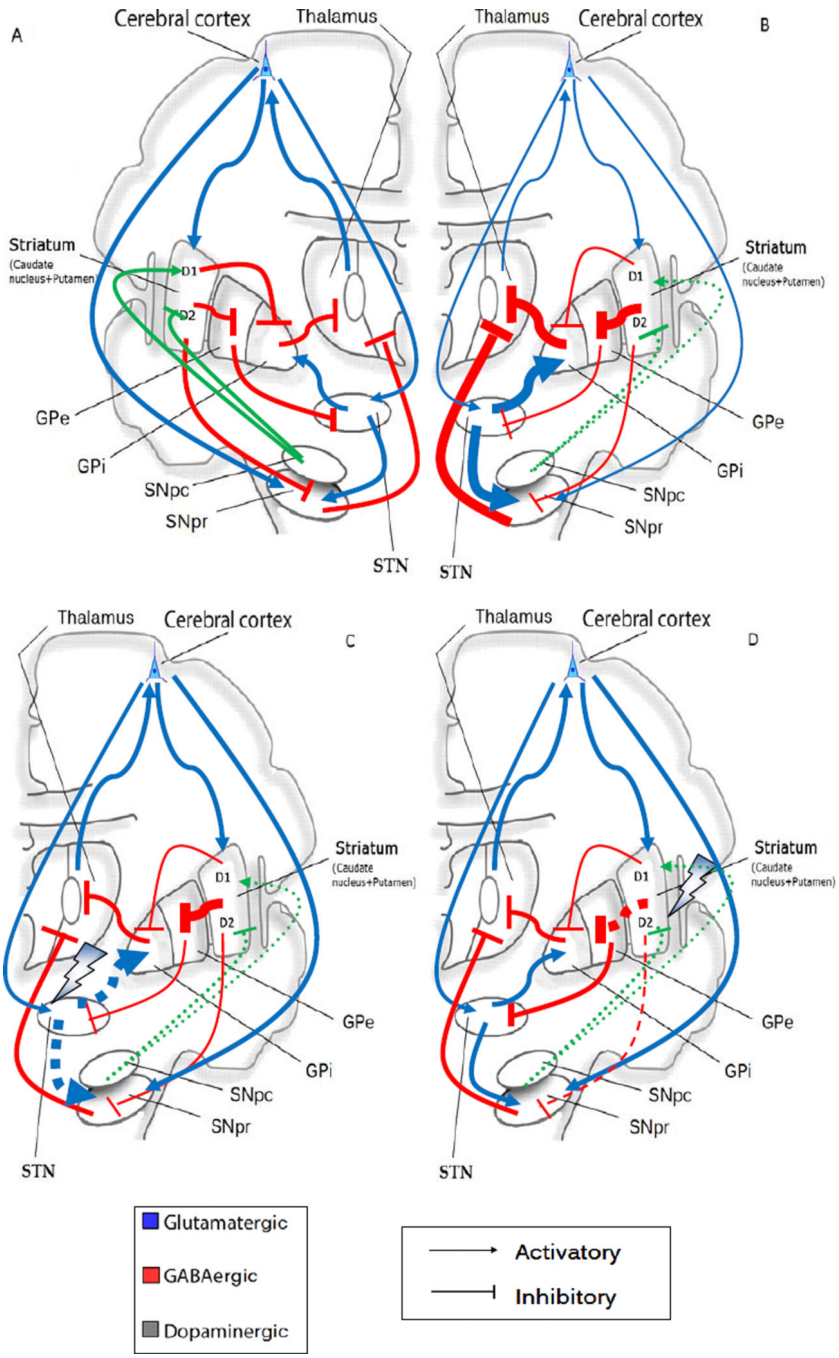

Fig. (4).

Classical model of normal activity of the basal ganglia and malfunctioning in PD (reviewed in Ref. [114]). Thin arrows indicate downregulation and thick arrows upregulation. Blue arrows show glutamatergic activatory efferents, red arrows indicate inhibitory GABAergic efferents and green arrows, activatory/inhibitory projections. **(A)** The ‘direct pathway’ is comprised of striatal neurons with D1 activatory dopaminergic receptors and their GABAergic efferent projections to the globus pallidus internus (GPi) which together the SNpr transmit inhibitory signals via GABAergic output to the thalamic ventral anterior (VA)

nucleus. The ‘indirect pathway’ is comprised of striatal neurons with D2 inhibitory dopaminergic receptors. The striatum (composed of caudate and putamen) projects GABAergic output to the globus pallidus externus (GPe). From this point, they synapse to the nucleus subthalamicus (STN), from which glutamatergic activatory projections reach the GPi and the substantia nigra (SNpc/SNpr). The subthalamic nucleus also gets excitatory input directly from the cortex and induces the GPi to increase GABA release in the VA. While GPe keeps it in check, the SNpc dopamine binds D2 receptors to inhibit this pathway, blocking the inhibition of the subthalamic circuit by GPe. Additionally, the striatum and the SNpc receive glutamatergic efferents from the neocortex.

(B) Loss of dopaminergic afferents (broken green arrows) entails a dis-repression of striatal D2 neurons leads to over-activity of their GABAergic projections to the GPe, and this in turn decreases its GABAergic efferent activity to the STN. As a consequence, STN glutamatergic projections to the GPi render over-active, increasing GABAergic output from the GPi to the VA. On the contrary, the D1 striatal neurons are underactive, therefore the GABAergic output to the GPi and to the SNpr are reduced and consequently the GABAergic output from both to the VA is increased. As a consequence in both cases, the loss of dopaminergic projections causes a failure to desinhibit the thalamocortical output, leading to bradykinesia, a typical symptom in PD. **(C) (D)** Possible targets at the basal ganglia level of NMDAR antagonists amantadine and memantine. Broken arrows mean suppression of output projections. A putative target is the STN (C), overactive in PD by blocking the subthalamic stimulation of GPi and a normalization of downstream thalamocortical connections. Other target could be the indirect pathway from the striatum (D), triggering a dis-repression of SNpr and leading to a normalization of STN activity and therefore a thalamic-cortical neuron well-functioning.