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Memantine and its benefits for cancer, cardiovascular and neurological disorders

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ABSTRACT

Memantine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that was initially indicated for the treatment of moderate to severe Alzheimer's disease. It is now also considered for a variety of other pathologies in which activation of NMDA receptors apparently contributes to the pathogenesis and progression of disease. In addition to the central nervous system (CNS), NMDA receptors can be found in non-neuronal cells and tissues that recently have become an interesting research focus. Some studies have shown that glutamate signaling plays a role in cell transformation and cancer progression. In addition, these receptors may play a role in cardiovascular disorders. In this review, we focus on the most recent findings for memantine with respect to its pharmacological effects in a range of diseases, including inflammatory disorders, cardiovascular diseases, cancer, neuropathy, as well as retinopathy.

1. Introduction

Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is used as a monotherapy or in combination with acetylcholinesterase inhibitors such as galantamine, donepezil, and rivastigmine to treat Alzheimer's disease (Folch et al., 2018; Matsunaga et al., 2015; Schmidt et al., 2015). Unlike high-affinity antagonists of NMDA receptors, such as ketamine, memantine is a low-affinity antagonist that is displaced rapidly from the NMDA receptor, an effect that lessens the negative side-effects of NMDA receptor inhibition on learning and memory. Moreover, memantine is well tolerated, and has a suitable safety and acceptable therapeutic index (Folch et al., 2018). However, memantine is associated with a range of side-effects, such as headache, dizziness, hypertension, drowsiness, restlessness, constipation, diarrhea, nausea, anorexia, coughing, and dyspnea (Blanco-Silvente et al., 2018; Thomas and Grossberg, 2009). Memantine inhibits the effects of excessive glutamate activity, which causes neuronal damage and cell death (Kumar, 2004). Previously, memantine was proposed as a possible treatment of various neurological disorders (Lipton, 2006, 2007) and it was finally approved in 2003 for the treatment of moderate-to-severe Alzheimer's disease by the Food and Drug Administration (FDA) (Sestito et al., 2019). Although memantine continues to be used as one of the main treatment options for Alzheimer's disease in the last two decades, numerous studies have investigated its other potential uses (Table 1).

2. NMDA receptors

In the central nervous system (CNS), glutamate is an excitatory neurotransmitter that participates in many neurological activities such as learning and memory. Studies have shown that increasing levels of glutamate can lead to excitotoxicity and death of neuronal cells, as well as possessing a toxic role in the pathophysiology of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (Willard and Koochekpour, 2013). Glutamate receptors are widely expressed in the body (Gill et al., 2007). Some studies have shown that glutamate signaling plays a role in cell transformation and cancer progression in various organs, such as the brain, skin, breast, and prostate (Prickett and Samuels, 2012). Studies have also recently shown that glutamate receptors are present in the cardiac cells, and are involved in important cardiac functions such as contraction, rhythmicity, and coronary circulation, and may play a role in heart diseases (Gill et al., 2007).

Glutamate receptors are divided into 2 families, including ionotropic

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Table 1
Several studies with memantine on various disorders.

First author's name/Year	Cell line/Animal model used	Dose of Memantine	Main Finding
Li et al./2013	Wistar rats	5, 20 and 40 mg/kg	Attenuate of the Aβ-induced rapid disruption of hippocampal LTP in vitro.
Reisberg et al./2003	Human	20 mg	Reduction of glutamate-induced excitotoxicity and symptoms of Alzheimer's disease.
Motaghi et al./2016	Mice	12.5, 25 and 50 mg/kg	Attenuation of IL-1β, IL-6, TNF-α and MPO in the model of ulcerative colitis
Cheng et al./2019	C57BL/6 J mice	5 mg/kg	Reduction of NR-1 expression, glutamate release and Ca2+ influx and amelioration of pulmonary inflammation in a mice model of COPD induced by cigarette smoke combined with LPS.
Salih et al./2019	BALB/c mice	5 and 10 mg/kg	Reduction of BUN, Scr, MDA, MPO, ALT, AST and ALP levels in cisplatin-induced renal cellular damage.
Srejovic et al./2017	Wistar rats	100 μmol/l	Reduction of most cardiodynamic parameters and some oxidative stress biomarkers in isolated rat heart.
Abbaszadeh et al./2018	Wistar rats	5 and 20 mg/kg	Improvement of electrocardiogram (ECG) pattern and reduction of cardiac remodeling, lipid peroxidation and neutrophil infiltration in isoproterenol induced heart failure.
Albayrak et al./2017	Androgen-dependent prostate cancer cell line LNCaP	2.5,5,7.5,10, 12.5 and 15 mM	Antineoplastic activity by triggering Bax-dependent pathway of apoptosis.
North et al./2010	Human breast adenocarcinoma cell lines MCF-7, and SKBR-3	25 μM–800 μM	Expression of NMDAR1 and NMDAR2 in breast cancer cells. Reduction of the viability of MCF-7 and SKBR3 breast cancer cells by treatment with memantine.
Yoon et al./2017	Glioma cell lines (T-98 G and U-251 MG)	10–600 μM	Induction of NMDAR1- mediated autophagic cell death in malignant glioma cells.
Medvedev et al./2004	Wistar rats	1–10 mg/kg	Reduction of tactile allodynia induced by sciatic nerve ligation. Inhibition of formalin-induced grooming behavior and effective in chronic pain management
Chen et al./2009	Harlan Sprague-Dawley rats	20 mg/kg	Improvement of mechanical hyperalgesia and allodynia in diabetic neuropathic pain
Rojas et al./2008	CBA/J mice	0.7, 7 and 70 μg/kg	Prevention of the *in vivo* morphological damage induced by complex I inhibition with the natural xenobiotic rotenone and oxidative stress. Elevation of retinal metabolic capacity in the presence of rotenone. Neuroprotective effects against rotenone-induced retinal toxicity.
Kim et al./2002	Rabbit	1 mg/kg	Neuroprotective effect of memantine in optic nerve ischemia.

receptors (ligand-gated channels) and metabotropic receptors (G protein-coupled receptors). The ionotropic receptors are divided into three sub-families: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors (Willard and Koochekpour, 2013).

Ionotropic NMDA receptors are permeable to Na+, K+, and especially Ca2+ which acts as a secondary messenger to modify synaptic activity (Fig. 1) (Liu et al., 2019). These receptors are involved in excitatory neurotransmission in the CNS and play an important role in brain function such as neurodevelopment and synaptic plasticity (Hansen et al., 2017). Abnormal NMDA receptor activity plays a key role in the pathophysiology of some neurological and psychiatric disorders, such as ischemic stroke, Alzheimer's disease, epilepsy, traumatic brain injury, mood disorders, and schizophrenia (Hansen et al., 2017; Pérez-Otaño et al., 2016).

In addition to the CNS, NMDA receptors are found in other tissues such as kidney, bone, parathyroid gland (Bozic M, 2015), heart, and endothelium (Makhro et al., 2016; Qureshi et al., 2005). In addition, NMDA receptors are expressed in immune cells, including lymphocytes, neutrophils, thymocytes where their hyper-activation can disrupt immune system function, which may contribute to several pathological states. Glutamate receptors are also present in glial cells. There is now convincing evidence of a mutual relationship between glia and neurons, that implies a role in neuropathological events. It is noteworthy that microglial-derived proinflammatory molecules are associated with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease as well as multiple sclerosis and amyotrophic lateral sclerosis (Boldyrev et al., 2012; Glezer et al., 2004).

NMDA receptors are heteromeric complexes consisting of several subtypes that differ in molecular composition (Paoletti et al., 2013). To date, 7 subunits of NMDA receptors have been identified, showing different pharmacological activity and signaling. Our current understanding is that the NMDA receptor consists of assemblies of a glycine-binding NR1 subunit with a glutamate-binding NR2 and/or glycine-binding NR3 subunit (Chaffey and Chazot, 2008; Paoletti et al., 2013). The presence of the NR1 subunit is essential for NMDA receptor activity and is combined with at least one NR2 (A-D) subunit or more infrequently an NR3 (A, B) subunit (Chaffey and Chazot, 2008). NMDA receptor subunits are expressed in different regions of the CNS, such as cortex, hippocampus, Purkinje, thalamic regions (Chaffey and Chazot, 2008; Takai et al., 2003), and in human astrocytes (Lee et al., 2010; Conti et al., 1996). Recently, some studies have revealed the expression of NMDA receptor subunits in extra-neuronal tissues (Seeber et al., 2001). In peripheral tissues, the NR1 subunit is found in greater abundance in heart and kidneys, and of the NR2 subunits, only the NR2C subunit is expressed in the kidney (Leung et al., 2002, 2004). NR1, NR2B and NR2D subunits are also expressed in rat colon (Del Valle-Pinero et al., 2007). Additionally, the NR2D subunit of NMDA receptor is expressed in the retina, specifically in rod bipolar cells (Wenzel et al., 1997). Also, some studies have shown that the NR2B subunit of the NMDA receptor is expressed in the neonatal rat heart (Seeber et al., 2001, 2004).

In the next sections, we will focus on the role of over-activity of NMDA receptors in the pathophysiology of various diseases and the effects of memantine as an antagonist of these receptors.

3. Pharmacology of memantine

Memantine (1-amino-3,5-dimethyladamantane) is a non-competitive NMDA receptor antagonist and is an amantadine derivative with a low to moderate affinity for NMDA receptors with a plasma elimination half-life of 60–80 h in humans (For Pharmacokinetic Parameters see Table 2). Memantine acts as an open NMDA channel blocker with fast blocking and unblocking kinetics that are strongly voltage dependent (Fig. 1). These properties enable memantine to unbind quickly from the NMDA channel upon transient and strong synaptic depolarization such as occurs during transient physiological activation by glutamate. Memantine at therapeutic concentrations, is also able to suppress NMDA receptor activation in pathological conditions (Amidfar et al., 2018; Johnson and Kotermanski, 2006). These properties allow

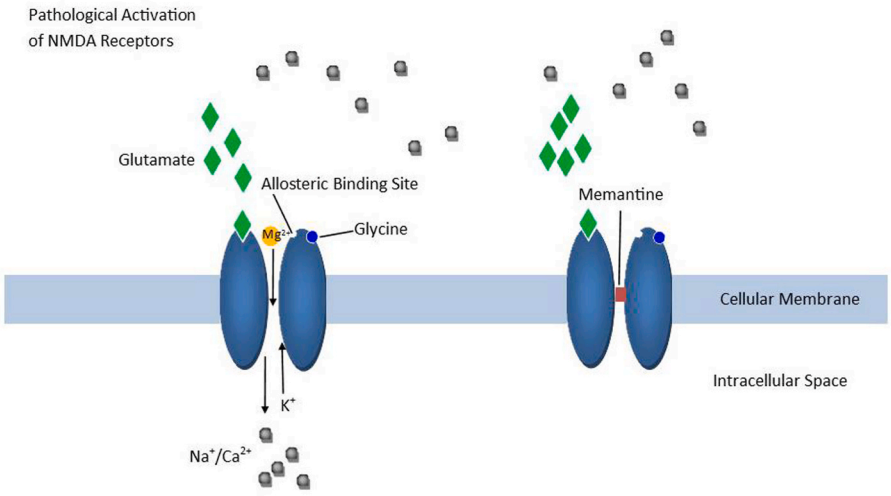

Fig. 1. Mechanism of action of memantine. NMDA receptors are permeable to Na+, K+, and especially Ca2+ which acts as a secondary messenger to modify synaptic transmission and is blocked by endogenous Mg^{2+}. Memantine acts as an open NMDA channel blocker with fast blocking and unblocking kinetics that are strongly voltage dependent.

memantine to provide both neuroprotection and improvements in memory and learning with infrequent adverse effects (Amidfar et al., 2018). It is important to note that memantine at higher concentrations has been reported to have antagonistic effects on 5-HT_3 receptors as well as on multiple subtypes of nicotinic receptors. It also inhibits 5-HT and dopamine transporters and voltage–gated Na^+ channels (Amidfar et al., 2018; Johnson and Kotermanski, 2006). As NMDA receptors are voltage-dependent channels that exhibit high permeability to Ca^{2+} and subject to blockade by endogenous Mg^{2+}, the physiological activation of NMDA receptors allows Ca^{2+} ions to enter the cell in a Mg^{2+}-dependent manner (Montemitro et al., 2017). However, as Mg^{2+} and memantine share similar binding sites, Mg^{2+} competes with memantine for NMDA receptor binding and thus may lead to reduced memantine effectiveness (Johnson et al., 2015).

Some studies have shown that memantine can prevent neurotoxicity caused by excitotoxic mechanisms (Pellegrini and Lipton, 1993). Memantine was approved for the treatment of moderate to severe Alzheimer's disease in 2003 (Sestito et al., 2019). Long-term potentiation (LTP) is the main mechanism in learning and memory that is mediated by glutamate-induced activation of NMDA receptors. Despite the link between LTP and learning, elevated glutamate levels are associated with excitotoxicity. Therefore, elevated glutamate levels can lead to Ca^{2+} accumulation and consequently apoptosis. In addition, amyloid-beta (Aβ) plaques, as a pathological feature of Alzheimer's disease, increase neuronal susceptibility to excitotoxicity. In this way, the extracellular accumulation of glutamate and intracellular Ca^{2+} are increased. Therefore, the glutamate-induced excitotoxicity pathway is an attractive target for the treatment of Alzheimer's disease. Antagonists of NMDA receptors can therefore be considered as an effective treatment for neurodegenerative diseases due to prevention of Ca^{2+} influx (Thomas and Grossberg, 2009).

Memantine has been proposed as a neuroprotective agent (Wenk et al., 1995; Jain, 2000) and reduce neuronal damage in cerebral infarction (Stieg et al., 1999), intracerebral hemorrhage (Sinn et al., 2007), traumatic brain injury (Mei et al., 2018) and neuropathic pain (Nair and Sahoo, 2019) partially through reduction in the accumulation of glutamate, over-activity of NMDA receptors, and reduction in tau phosphorylation. Memantine is also considered as a potential therapy for Parkinson's disease (Schneider et al., 1984) by targeting the glutamatergic transmission and reducing oxidative stress. Other potential uses of memantine include treatment of bipolar disorder through prevention of dopamine receptor sensitization (mania) and the ensuing desensitization (depression) (Serra et al., 2014), post-traumatic stress disorder (PTSD) (Battista et al., 2007), and attention-deficit/hyperactive disorder (ADHD) (Mohammadzadeh et al., 2019). Studies have shown that memantine may have beneficial effects on other neurological disorders such as schizophrenia and depression, where improper glutaminergic transmission has been implicated. In schizophrenia, memantine has the potential to treat both positive and negative symptoms, while it may be an appropriate adjunctive antidepressant agent (Czarnecka et al., 2021).

Moreover, some studies suggest memantine may have antiproliferative effects on human prostate, breast, and colon cancer cell lines (Hoosein and Abdul, 2004). Interestingly, recent studies have shown that memantine has beneficial effects on oxidative stress (Abbaszadeh et al., 2018) and inflammation (Wu et al., 2009). Furthermore, our recent study showed that memantine attenuates cardiac remodeling, lipid peroxidation and neutrophil recruitment in a rat model of heart failure suggesting it may be effective in the treatment of cardiovascular disease (Abbaszadeh et al., 2018) (Fig. 2).

Table 2
Pharmacokinetic parameters of memantine in human and rodents.

	Rat (10 mg/kg)	Mouse (10 mg/kg)	Human (10 mg)
Plasma Protein Binding (%)	41	NA	45
T_{max} (hr)	0.5–1	0.5–1	3–7
Elimination (%)	Kidney (80–90)	Kidney (80–90)	Kidney (80–90)
	1 mg/kg (IV)	**1 mg/kg (IV)**	
Vd (L/kg)	8–9	8–9	9–11
Cl_p (L/hr/kg)	4.15	3.81	0.16
$t_{1/2}$ (hr)	4	3	60–80

Abbreviations: T_{max}: Time at maximal concentration. Vd: Volume of distribution. Clp: Plasma clearance. t1/2: Half-life. NA: Not available.

4. Memantine and inflammatory disorders

Inflammation is a biological reaction of the immune system that can be triggered by various factors, including pathogens and damaged cells. Although inflammation is a defensive response, hyper-activation of the immune system may cause secondary complications. Therefore, inflammation is an important pathological factor in various organs disorders (Cui et al., 2018; Rameshrad et al., 2015). Numerous studies have shown that the immune system plays a major role in regulating

glutamate neurotransmission and the maintenance of synaptic integrity. Furthermore, glutamate can markedly affect the function of immune cells in the brain including microglia (Haroon et al., 2016), the immune cells of the CNS that play an important role in the pathogenesis of neurological disorders such as Alzheimer's disease and Parkinson's disease. As NMDA receptors are present on microglia of the human CNS, their over-activation may elicit an inflammatory response that eventually leads to the death of neocortical neuronal cells. This neocortical damage is significantly reduced by pharmacological inhibition of NMDA receptors (Kaindl et al., 2012b; Bachiller et al., 2018; Perry et al., 2010). In addition, there is evidence to suggest that NMDA receptors in microglia play an important role in the secretion of neurotoxic factors, including pro-inflammatory cytokines such as tumor necrosis factor-α (TNF –α) (Folch et al., 2018).

Anti-inflammatory and neuroprotective effects of memantine have been reported in several studies, actions mediated by the prevention of over-activation of microglia (Wu et al., 2009). Furthermore, several studies have suggested that memantine elicits anti-inflammatory effects outside of the CNS. Motaghi and colleagues have reported a protective effect of memantine in a mouse model of ulcerative colitis by a reduction in neutrophil infiltration and release of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin 6 (IL-6) and TNF-α (Motaghi et al., 2016). In addition, pulmonary inflammation associated with over-activation of NR-1 subunits of NMDA receptors in chronic obstructive pulmonary disease (COPD) is reduced by memantine via reducing NR-1 expression, glutamate release, Ca2+ influx, and by inhibiting the release of TNF-α, IL-6 and interferon gamma (IFN-γ) (Cheng et al., 2019). In addition, our own recent study, which aimed to investigate the effects of memantine on a rat model of heart failure, showed that memantine inhibits neutrophil recruitment and reduces myeloperoxidase (MPO) levels, a biomarker of inflammation in myocardial tissue. Thus, an anti-inflammatory activity may underly the cardioprotective activity of memantine (Abbaszadeh et al., 2018). In another study from our research team, we reported an anti-inflammatory effect of memantine in a rat model of carrageenan-induced paw edema (Azarbaijani et al., 2021).

Overall, due to the role of over-activation of NMDA receptors in causing inflammatory responses and elevation of inflammatory mediators, memantine, by inhibiting these receptors, can effectively ameliorate inflammation and should be considered as an effective therapeutic agent in inflammatory disorders.

5. Memantine and oxidative stress

Imbalance between the production of reactive oxygen species (ROS) and antioxidant capacity causes oxidative stress (Betteridge, 2000). ROS are mainly produced by mitochondria, both under physiological and pathological conditions. Increased production of ROS damages important cellular components such as proteins, lipids, and nucleic acids (Pizzino et al., 2017). Oxidative stress has been related to several neurological diseases, such as Parkinson's disease, Alzheimer's disease, and depression, and may play a role in neuronal loss and dementia (Pizzino et al., 2017; Christen, 2000). In addition, in the CNS inflammatory responses of glial cells play an important role in the induction of oxidative stress (Folch et al., 2018).

Furthermore, numerous *in vivo* and *ex vivo* studies show that oxidative stress plays an important role in atherosclerosis, ischemic damage, and heart failure (Pizzino et al., 2017). Other studies also show the effect of oxidative stress in the onset and/or progression of several diseases, including cancer, diabetes, and metabolic disorders (Pizzino et al., 2017). On the other hand, over-activation of NMDA receptors may lead to increased intracellular Ca2+ accumulation and mitochondrial dysfunction resulting in the production of ROS and oxidative stress (Liu et al., 2013). Blockade of NMDA receptors by memantine inhibits the production of ROS (Folch et al., 2018; Pieta Dias et al., 2007) and also reduces oxidative stress via anti-inflammatory mechanisms. Importantly, inhibition of glial NMDA receptors is neuroprotective (Kaindl et al., 2012a). According to some studies, memantine reduces oxidative stress in the cortex and hippocampus, two important areas of the brain involved in memory, and thus it can produce neuroprotective effects and may limit memory loss. (Pieta Dias et al., 2007; Liu et al., 2013). However, some studies suggested antioxidant effects of memantine in

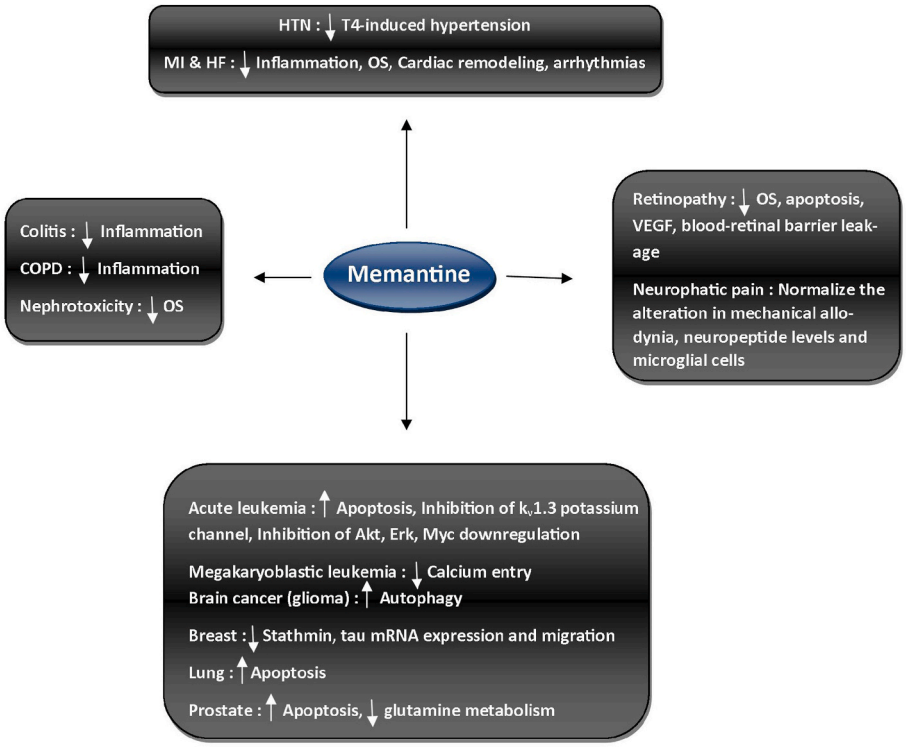

Fig. 2. Reported mechanisms of memantine in various disorders.

non-neurological disorders as well. For example, in a study conducted by Salih and colleagues with the aim of investigating the toxic side effects of cisplatin in the kidneys, the results showed that treatment with memantine could reduce malondialdehyde (MDA) levels, a biomarker of oxidative stress in kidney tissue. They reported that memantine ameliorates oxidative stress in cisplatin-induced nephrotoxicity (Salih and Al-Baggou, 2019). In addition, the results of our recent studies on the effects of memantine on heart failure and myocardial infarction showed that memantine could have cardioprotective effects by reducing the tissue MDA level in the heart. (Abbaszadeh et al., 2018).

6. Memantine and cardiovascular diseases

In addition to the CNS, NMDA receptor expression in other tissues such as the heart and endothelial cells has also been reported (Gao et al., 2007; Qureshi et al., 2005). NMDA receptors in the heart are predominantly localized at nerve terminals, ganglia, conductive fibers and atrial myocytes (Gao et al., 2007). The activation of NMDA receptors in the heart plays an important role in the electrical activity of the heart and the occurrence of ventricular arrhythmia (Bozic and Valdivielso, 2015). Moreover, activation of these receptors increases intracellular Ca2+, leading to atrial fibrillation and interstitial fibrosis (Bozic and Valdivielso, 2015; Shi et al., 2017). In addition, studies by Gao and colleagues showed that stimulation of NMDA receptors in the heart results in increased ROS production, mitochondrial dysfunction, and the release of apoptotic factors, which lead to cardiomyocyte apoptosis (Gao et al., 2007). The toxic effects of NMDA receptor activity are reduced by antagonism of these receptors (Bozic and Valdivielso, 2015). The results of some studies suggest that memantine plays a protective role in the heart by inhibition of NMDA receptor activity. However, to date, there is little information about the cardiovascular effects of memantine.

Ventricular arrhythmias including ventricular tachycardia or ventricular fibrillation, are one of the major causes of mortality associated with cardiovascular diseases. One of the major underlying causes of arrhythmia is myocardial ischemia, determined by an imbalance between myocardial oxygen supply and demand, and leads to cardiac dysfunction, arrhythmias, myocardial infarction, and sudden death (Shimokawa and Yasuda, 2008). Furthermore, abnormal ROS production plays an important role in pathogenesis of cardiovascular diseases such as myocardial infarction (Moris et al., 2017) and recent studies suggest that NMDA receptor antagonists can reduce arrhythmias and limit cardiac ischemic damage (Makhro et al., 2016). According to a study by D'Amico and colleagues, memantine was used to investigate the effects of NMDA channel blockers on ventricular arrhythmias induced by myocardial ischemia/reperfusion (D'amico et al., 1999). In that study, interestingly, the authors showed that the effect of NMDA receptor antagonists was evident during reperfusion, but not ischemia. This suggests that arrhythmias that occur under pathological conditions are caused or facilitated by the endogenous activation of excitatory amino acid receptors during reperfusion. In agreement with the observation that excitatory amino acid receptors containing NMDA subunits are present in cardiomyocytes, memantine reduces the incidence of ventricular tachycardia, ventricular fibrillation, and reperfusion-induced arrhythmias in the reperfused myocardium. Moreover, memantine reduces indices of mechanical function, production of superoxide, a biomarker of oxidative stress, in isolated rat heart (Srejovic et al., 2017).

More recently, we described the cardioprotective effects of memantine on myocardial ischemic injury both in *ex vivo* and *in vivo* studies where it improved recovery of cardiac function and reduced cardiac remodeling, arrhythmias, and infarct size (Jannesar et al., 2020).

Heart failure is another cardiovascular disease, commonly associated with left ventricular remodeling, myocardial hypertrophy, necrosis, and fibrosis (Timmers et al., 2008), in which over-production of ROS can play a role in its pathogenesis. Additionally, heart failure can be associated with elevation of pro-inflammatory cytokines such as IL-1β and TNF-α (Janahmadi et al., 2017). Our previous study demonstrated the cardioprotective effects of memantine in a rat model of heart failure through reduction in lipid peroxidation, neutrophil recruitment, and cardiac remodeling (Abbaszadeh et al., 2018). In that study, pre-treatment with memantine attenuated cardiac remodeling including fibrosis, necrosis, and hypertrophy. In addition, pre-treatment with memantine attenuated neutrophil recruitment and the MPO level, as a biomarker of inflammation, and the MDA level, as a biomarker of lipid peroxidation. In addition, memantine prevented ischemia-induced changes in the electrocardiogram (ST segment depression) in heart failure. Memantine-induced cardioprotection has also been observed in a cold-stress model in which it inhibited hypothermia-induced cardiomyocyte nuclear size reduction and apoptosis that resulted from activation of a mitochondria-dependent signaling (Meneghini et al., 2009). Recently, Repas and colleagues demonstrated the involvement of NMDA receptors in thyroxin (T4)-induced cardiovascular complications. They investigated whether memantine, as an antagonist of NMDA receptors, could alter T4-induced elevation in blood pressure and the development of cardiac hypertrophy. They showed that memantine prevents T4-induced hypertension, but it had no effect on cardiac remodeling (Repas et al., 2017). Other studies have reported bradycardia and QT prolongation in response to memantine administration (Gallini et al., 2008; Takehara et al., 2015) and intracoronary administration of memantine elicits negative inotropic and chronotropic effects in association with alterations in intracellular Ca2+ concentrations (Srejovic et al., 2017). Clinically, the common adverse cardiovascular effect of memantine is bradycardia, but the underlying mechanism remains unclear (Howes, 2014; Gallini et al., 2008). Also, PR prolongation is observed in Alzheimer's disease patients treated with a combination of memantine and donepezil (Igeta et al., 2013).

Collectively, although several studies have recently shown the cardioprotective effects of memantine, cardiovascular properties of memantine are still complex and largely unclear, demonstrating the need of further study.

7. Memantine and cancer

Currently, cancer is becoming a leading cause of death all over the world and is a major economic burden for health care systems (Ferlay et al., 2020). Cancer treatment employs different strategies depending on cancer type and includes surgery, radiation therapy, and chemotherapy. Despite great improvements in cancer chemotherapy using anticancer drugs, either alone or in combination, there are still limitations against successful chemotherapy such as the high cost of chemotherapeutic agents, toxic adverse effects to otherwise healthy tissues, such as the heart, and the development of multidrug resistance (Pucci et al., 2019). Therefore, investigation of new compounds or the repurposing of existing drugs with low prices and minimal adverse effects is desirable to enhance the efficacy of chemotherapeutic approaches.

Cancer cells often have altered metabolic pathways in comparison with normal cells in order to meet their often-higher metabolic requirements required by their high rate of growth and proliferation. This high metabolic demand is mainly met by the utilization of glucose and glutamine (Bahrambeigi and Shafiei-Irannejad, 2020). Although, glucose metabolism in cancer cells has been extensively investigated, glutamine metabolism in cancer cells is also drawing attention due to its multiple cellular functions. To investigate glutamine metabolism in cancer cells, Albayrak and colleagues treated LNCaP prostate cancer cells, known to express active NMDA receptors (Abdul and Hoosein, 2005) with memantine. They hypothesized that NMDA receptor blockade with memantine inhibits excess glutamate which is needed for cancer cell growth (Albayrak et al., 2018). Exposure of prostate cancer cells to memantine (0.25 mM) elicited a potent anticancer response that was accompanied by activation of the Bcl-2-associated X protein (Bax)-dependent pathway. They suggested memantine is an effective compound to target glutamine metabolism in the chemotherapy of

prostate cancer cells (Albayrak et al., 2018).

Small cell lung cancer (SCLS) cells have also been shown to express functional NMDA receptors, which are associated with tumor growth. North et al. demonstrated that SCLS classical cell lines, including DMS 53, NCI H345, NCI H146, and NCI H82 (variant cell line), all express functional NMDAR1 and NMDAR2 receptors. NMDAR1 antagonists, memantine and MK-801, and NMDAR2B antagonists, ifenprodil and Ro25-6981, significantly decreases the viability of these cells. Immunohistochemistry investigation of SCLS tumors also indicated that 8 of 10 tissues are positive for NMDAR1 receptors (North et al., 2010a). A role of these receptors in cancer biology is supported by studies that showed the viability of SCLS xenografts in mice is decreased by memantine, when used either alone or synergistically when in combination with the chemotherapeutic agent, topotecan (North et al., 2019).

Other NMDA receptor antagonists, such as MK-801, also possess antiproliferative and anti-invasive effects (Deutsch et al., 2014) and since NMDA receptor signaling facilitates cancer cell growth and proliferation, the existence of these receptors on breast cancer cells suggests their inhibition with antagonists such as memantine, may have potential utility in breast cancer treatment (Mehrotra and Koiri, 2015). Based on this hypothesis, North and colleagues investigated the expression of NMDAR1 and NMDAR2 in breast cancer cells and found that both receptors are expressed in MCF-7 and SKBR3 breast cancer cells at both gene and protein levels. Furthermore, treatment with the NMDAR1 antagonists, memantine and MK-801, significantly decreased the viability of these cells. Immunohistochemical analysis of tumor tissues from 10 patients also showed positive staining for NMDA receptors in all 10 cases (North et al., 2010b).

Effects of memantine on motility of metastatic breast cancer cells have been also demonstrated (North et al., 2010b). The expression of tau and stathmin, cell motility regulator proteins, has been shown to be associated with poor prognosis in breast cancer (North et al., 2010b). With attention to the finding that memantine can inhibit tau protein in neurons, Seifabadi and colleagues investigated the effects of memantine on the motility of metastatic breast cancer cells and observed that memantine could significantly decrease their viability and migration and expression levels of stathmin and tau. They also found a synergistic effect of memantine when combined with paclitaxel. (Seifabadi et al., 2017).

Memantine also shows potential in the treatment of hematologic malignancies. In acute leukemia cells, memantine inhibits Kv1.3 potassium channels, and when combined with citarabine, it decreases their viability. Furthermore, co-treatment with memantine resulted in inhibition of AKT serine/threonine kinase 1 (Akt 1), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and S6, and boosted Myc down-regulation. In addition, memantine-induced mitochondrial dysfunction leads to cytochrome *c* release, caspase 9 and caspase 3 activation, and enhanced apoptosis (Lowinus et al., 2019). Memantine, by inhibiting NMDA receptors and by blocking Ca^{2+} entry, has also been reported to inhibit the proliferation of leukemic megakaryoblasts (Kamal et al., 2015).

There is also evidence concerning the beneficial effects of memantine in brain cancers. Yoon et al. indicated that memantine could exhibit antiproliferative effects in T98-G glioma cells, which express NMDAR1, through autophagic cell death. This finding was confirmed by increasing autophagy-related protein levels, such as beclin-1, and conversion of light chain protein 3II (LC3-II/LC3-I). Autophagic vacuoles were also increased by memantine, as detected by transmission electron microscopy (Yoon et al., 2017). Memantine was reported as a safe compound for adjuvant therapy with temozolomide in patients with glioblastoma (Maraka et al., 2019). Memantine has been also shown to improve cognitive function in whole brain radiotherapy in patients with brain metastases. Whole brain radiotherapy has been considered as the basic treatment in patients with various brain metastases for decades. However, there are serious toxicities associated with whole brain radiotherapy including nausea, fatigue, alopecia, and irreversible cognitive decline (Chang et al., 2009). Due to the neuroprotective effects of memantine, its administration before and during whole brain radiotherapy resulted in a significant delay in the decline in cognitive function, memory, and processing speed (Lynch, 2019).

Taken together, the results of these preclinical and clinical studies suggest that memantine can be considered as a potent adjuvant in chemotherapy and radiotherapy approaches for the treatment of many types of cancer, however, complementary studies are still needed.

8. Memantine and neuropathic disorders and retinopathy

Peripheral neuropathy (commonly shortened to neuropathy) is defined as damage to peripheral nerves (nerves other than brain and spinal cord). The symptoms of neuropathic disorders may vary depending on the nerves involved (autonomic, sensory, or motor nerves). Neuropathy can occur due to various reasons including chronic diseases (e.g., diabetes mellitus), chemotherapy, some types of antibiotics, vitamin deficiencies, ischemia, or trauma, viral infection, and immune system diseases. The consequences of neuropathy include pain, numbness, bone and muscle degeneration, and many other defects depending on whether sensory or motor nerves are involved (Hughes, 2002).

Treatment for neuropathy, especially for neuropathic pain, includes symptomatic treatment with medications used for CNS disorders. Previous studies have shown that an NMDA-subtype of the glutamate receptor is crucial for development of neuropathic pain and in the acquisition and development of pain related behaviors (Parsons, 2001). Therefore, it seems logical that NMDA receptor antagonists might have beneficial effects in neuropathic pain. However, as glutamate is the main excitatory neurotransmitter in the CNS, blocking glutamate receptors will have undesirable side-effects, which are likely to obscure its therapeutic potential. Therefore, moderate-affinity NMDA receptor antagonists, such as memantine, may be more acceptable due to their stronger voltage-dependency and faster receptor unblocking kinetics (Parsons et al., 1999). In a study carried out by Medvedev and colleagues, memantine was active against tactile allodynia induced by sciatic nerve ligation. Furthermore, memantine exerted beneficial effects in chronic pain as confirmed by inhibition of formalin-induced grooming behavior (Medvedev et al., 2004). In another study, a single treatment with memantine in adult male Wistar rats showed dose-dependent anti--allodynic activity, suggesting the analgesic activity of the compound in neuropathic pain model.

It is known that induction of neuropathic pain by sciatic nerve injury can affect cortical and subcortical parts of the brain in addition to causing peripheral nervous system dysfunction. To assess the effects of the neuropathic pain on behavioral and neurochemical levels in the CNS, Takeda and colleagues treated rats with memantine and applied a chronic constriction injury. They observed that treatment with memantine inhibited the mechanical allodynia. Furthermore, memantine could reverse reductions of somatostatin and substance P in the brain. In animals exposed to sciatic nerve injury, the expression levels of the microglia marker, CD11b, were increased, which was suppressed following treatment with memantine, suggesting a microglia involvement in the pain mechanism (Takeda et al., 2009). Memantine, in another study, could reverse the neurotoxic effects induced by atypical sphingolipids, such as 1-deoxysphingolipids. In that study, the authors reported that the neurotoxic effects of 1-deoxysphingolipids are mediated through NMDA receptor pathways as only neuronal cells that express functional NMDA receptors responded to treatment with 1-deoxysphingolipids. Moreover, treatment with non-competitive antagonists, memantine or MK-801, reversed this neurotoxicity (Güntert et al., 2016).

As diabetes mellitus is a common cause of neuropathy, Chen and coworkers investigated the antinociceptive effects of the non-competitive NMDA receptors antagonists, memantine and neramexane, in a rat model of diabetic neuropathic pain. They observed that chronic

administration of memantine or neramexane exhibited significant and persistent reductions of mechanical hyperalgesia and allodynia, suggesting these compounds are potential therapeutics for diabetic neuropathic pain (Chen et al., 2009).

Other reasons for development of neuropathic pain include treatment with various types of chemotherapeutics such as the platinum-based drugs, vincristine, and paclitaxel. Treatment with oxaliplatin, a third generation platinum-based chemotherapeutic, induces early phase cold hyperalgesia and late phase mechanical allodynia in rats (Sakurai et al., 2009). Mihara and colleagues showed that intrathecal injection of memantine reverses oxaliplatin-induced neuropathy (Mihara et al., 2011). In another study, anti-nociceptive effects of memantine were investigated on neuropathic pain induced by vincristine treatment in rats. The results indicated that systemic administration of memantine can be a possible and potential strategy for treatment of vincristine-induced neuropathic pain (Park et al., 2010).

Within the CNS, while glutamate is a main excitatory neurotransmitter and plays an important role in information processing and neural development, enhanced levels of glutamate lead to increased receptor stimulation, resulting in neurotoxicity (Nakanishi et al., 1998). Indeed, glutamate-mediated excitotoxicity, involving NMDA receptor over-activation, is implicated in many neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, Huntington's disease, schizophrenia, and epilepsy (Hallett and Standaert, 2004; Tzschentke, 2002; Kieburtz, 1999).

Retinal ganglion cell (RGC) death occurs with a mechanism similar to above-mentioned neurodegenerative disorders (Seki and Lipton, 2008). Based on the ability of memantine to exert beneficial effects in several CNS disorders, it is likely that memantine may also have protective effects on RGC death and retinotoxicity. Memantine (12 μM) prevents NMDA receptor-induced cytotoxicity in neonatal rat RGCs in primary culture (Pellegrini and Lipton, 1993). In another study, the neuroprotective effects of memantine were demonstrated in a murine model of retinal toxicity, where the intravitreal injection of rotenone, a known inhibitor of complex I of the mitochondrial respiratory chain, induces retinal toxicity (Zhang et al., 2006). In the study of Julio and co-workers, the neurotoxic effects of rotenone were reflected as increased RGC cell death, oxidative stress, reduction in RGC cell density, and RGC + nerve fibre layer thickness. All these changes were prevented by co-treatment with memantine in a dose-dependent manner. Furthermore, long-term retinal energy capacity was increased after memantine treatment (Rojas et al., 2008).

Ethambutol is another compound that can induce retinal injury. Ethambutol is a widely used drug for tuberculosis, although optic nerve toxicity and neural retinal injuries are inevitable side-effects (Ezer et al., 2013). The effects of memantine in ethambutol-induced retinal injury were investigated in a study by Ahmed and colleagues. Administration of ethambutol in rats induced changes similar to rotenone such as decreased neural retina thickness and cellularity along with an increase in expression levels of glial fibrillary acidic protein (GFAP), B-cell lymphoma protein 2 (Bcl-2), caspase 3 and oxidative stress biomarkers. When memantine was combined with ethambutol therapy, neural retinal thickness and cellularity were reversed to amounts close to control group. Furthermore, a significant decrease in expression of Bcl-2 and caspase 3 and minimal GFAP expression were observed after memantine co-administration. These results suggested that memantine can be considered as a possible compound to protect from ethambutol-induced retinal injuries (Abdel-Hamid et al., 2016). The protective effects of memantine on ethambutol-induced retinal toxicity in Wistar rats were confirmed in another study, using a flash electroretinogram (ERG) protocol. The duration of treatments in that study was 28 days and ERG waves were recorded on day 0 and 21. Ethambutol had no significant effect on 'a'-wave amplitude of ERG but resulted in a significant decrease in 'b'-wave amplitude which was reversed and protected by memantine therapy (Vijayakumar et al., 2016).

Memantine can also exhibit neuroprotective features in secondary neurodegeneration of dorsal lateral geniculate nucleus (dLGN) and superior colliculus (SC) following retinal injury caused by intravitreal NMDA injection. Pre-treatment with memantine could also protect from both retinal injury and secondary neurodegeneration in dLGN and SC. Although post-treated groups did not show significant reversion in NMDA-induced retinal damage, it could protect against neurodegeneration in dLGN on SC of brain (Ito et al., 2008). In another study, Kim et al. reported the neuroprotective effects of memantine on ischemic damage of the optic nerve in rabbits. They induced optic nerve ischemia by endothelin-1 delivery to the optic nerve, and evaluated the morphological changes by a confocal scanning laser ophthalmoscope. In rabbits receiving memantine concurrently with endothelin-1, no obvious alteration was observed in topometric parameters of optic nerve in comparison with rabbits which only received endothelin-1, suggesting that memantine could exert neuroprotective effects for optic nerve ischemia (Kim et al., 2002).

Beneficial effects of memantine in experimentally-induced glaucoma in monkeys was also reported in a study carried out by Hare and co-workers. They induced chronic ocular hypertension in monkeys through argon laser treatment of the anterior chamber angle in the right eye. Results indicated that animals treated with memantine exhibited increased survival of RGCs. Measurement of optic nerve morphology by confocal laser scanning indicated less topometric alterations in memantine-treated animals compared with untreated animals (Hare et al., 2004). In a mouse model of glaucoma, treatment with memantine significantly enhanced RGC survival and inhibited apoptotic ganglion cell layer death, which was accompanied by down-regulation of Bax expression and up-regulation of Bcl-2 expression. Furthermore, memantine significantly decreased OPA1 isoform release in comparison with vehicle-treated animals (Ju et al., 2009). It has also been reported that retinal damage induced by NMDA injection is accompanied by ERK1/2 activation. Nakazawa et al. showed that following intravitreal injection of NMDA, activation of ERK1 can be observed in retinal Muller cells (Nakazawa et al., 2008). Activation of the renin-angiotensin-aldosterone system (RAAS) is also implicated in RGC death. However, it has been reported that there is no relation between NMDA signaling and the RAAS system. This finding was confirmed when spironolactone, an antagonist of the receptor for mineralocorticoids (e.g., aldosterone), was shown to have no effect on NMDA-induced retinal injury, while, memantine could decrease RGC death. Conversely, memantine had no neuroprotective effect, in aldosterone-induced retinal damage, while spironolactone could decrease retinal neurodegeneration (Kobayashi et al., 2017). The neuroprotective effects of memantine have also been reported in a immunohistochemical study by Yigit and colleagues. They reported that memantine significantly enhanced the number of live RGCs after induction of retinal injury by increasing intraocular pressure. In addition, the mean apoptotic index in animals treated with memantine was significantly decreased in comparison with untreated group (Yiğit et al., 2011).

Diabetic retinopathy is one of the most common diabetic complications, which occur in nearly 90% of patients with diabetes mellitus. Although, diabetic retinopathy has been previously viewed as a microvascular disorder, it has recently been considered as a neurodegenerative disease. To investigate the effects of memantine in diabetic retinopathy, Kusari and colleagues demonstrated that chronic treatment with memantine significantly enhanced retinal function and inhibited RGC death. Furthermore, memantine modulated the increased levels of vascular endothelial growth factor (VEGF) and improved blood-retinal barrier breakdown, suggesting that memantine has beneficial effects in retarding diabetic retinopathy (Kusari et al., 2007).

Taken together, the results of these studies suggest that inhibition of glutamate excitotoxicity in the peripheral nervous system by the NMDA antagonist, memantine, may have beneficial neuroprotective effects in both neuropathy and retinopathy.

9. Conclusion

Memantine is a drug used to treat Alzheimer's disease, and inhibition of the NMDA receptors is its main mechanism of action. Abnormal NMDA receptor activity plays a key role in the pathophysiology of a range of neurological and psychiatric disorders. Several studies have reported that memantine can be used as a neuroprotective agent and plays a neuroprotective role in infarction, intracerebral hemorrhage, traumatic brain injury, and neuropathic pain, partially through reductions in the accumulation of glutamate, over-activity of NMDA receptors, and tau phosphorylation. In addition to the CNS, NMDA receptors are also found in peripheral tissues. Glutamate receptors are present on cardiac cells and are involved in important cardiac functions including contraction, rhythmicity, and the coronary circulation. The pathophysiological impact of NMDA receptor activity can be reduced by blockade of these receptors and recent studies have shown that NMDA receptor antagonists reduce arrhythmias and cardiac ischemic damage. On the other hand, some studies have reported bradycardia and QT prolongation with memantine administration. Although our recent studies show that memantine could be an effective cardioprotective agent for the treatment of a range of cardiovascular diseases, the effects of memantine on the cardiovascular system are complex, still largely unclear, and require further detailed investigation.

In addition, studies have suggested memantine, through its anti-proliferative effects, is a potent compound to target glutamine metabolism in the chemotherapy of several cancers including prostate cancer, lung cancer, breast cancer, brain cancer, and acute leukemia, indicating that memantine can be considered as a potent adjuvant in chemotherapy and radiotherapy for treatment of many types of cancer, however, additional studies are still needed. Recent studies have shown that memantine has beneficial effects on oxidative stress and inflammation. Memantine inhibits the production of ROS by blockade of NMDA receptors and also reduces oxidative stress via anti-inflammatory mechanisms. It has been reported that memantine demonstrates anti-inflammatory and neuroprotective effects in neurodegenerative diseases. Overall, due to the role of over-activation of NMDA receptors in causing inflammatory responses and elevation of inflammatory factors, memantine, by inhibiting these receptors, can effectively ameliorate inflammation in CNS, colitis, COPD, myocardial infarction (MI), heart failure (HF), and carrageenan-induced paw edema model in rats. As a result, memantine can be considered as an effective agent in inflammatory disorders. Finally, we conclude that memantine can be a useful drug in the treatment a plethora of diseases, and further research into its impact is clearly warranted.

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CRediT authorship contribution statement

Vahid Shafiei-Irannejad: Conceptualization, Writing – original draft. **Samin Abbaszadeh:** Writing – original draft. **Paul M.L. Janssen:** Writing – review & editing. **Hamid Soraya:** Conceptualization, Writing – review & editing.

Declaration of competing interest

None declared.

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