Review

Physiopathology of ischemic stroke and its modulation using memantine: evidence from preclinical stroke

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Abstract

Ischemic stroke is the most common type of cerebrovascular disease and is caused by an interruption of blood flow in the brain. In this disease, two different damage areas are identifying: the lesion core, in which cells quickly die; and the penumbra (surrounding the lesion core), in which cells are functionally weakened but may recover and restore their functions. The currently approved treatments for ischemic stroke are the recombinant tissue plasminogen activator and endovascular thrombectomy, but they have a short therapeutic window (4.5 and 6 hours after stroke onset, respectively) and a low percentage of stroke patients actually receive these treatments. Memantine is an approved drug for the treatment of Alzheimer's disease. Memantine is a noncompetitive, low affinity and use-dependent antagonist of N-methyl-D-aspartate glutamate receptor. Memantine has several advantages over developing a new drug to treat focal ischemic stroke, but the most important is that it has sufficient safe probes in preclinical models and humans, and if the preclinical studies provide more evidence about pharmacological actions in tissue protection and repair, this could help to increase the number of clinical trials. The present review summarizes the physiopathology of isquemic stroke and the pharmacological actions in neuroprotection and neuroplasticity of memantine in the post stroke stage of preclinical stroke models, to illustrate their potential to improve functional recovery in human patients.

Key Words: focal ischemic stroke; memantine; neuroplasticity; neuroprotection; stroke therapy

Introduction

Among cerebrovascular diseases, stroke is the most frequent. Worldwide, stroke is the second most common cause of death and the third most common cause of disability (Feigin et al., 2017). There are two main types of stroke, hemorrhagic and ischemic. The former represents about 15% while the latter accounts for the remaining 85%. Focal ischemic stroke is the most common and is caused by the occlusion of a cerebral artery and can be local or distal. Locally, the main cause is the formation of a thrombus or an atherosclerotic plaque. Distally, an embolus (clot) forms in another blood vessel and travels to the brain and occludes a cerebral artery (Brouns and De Deyn, 2009; Moskowitz et al., 2010).

Currently approved treatments for ischemic stroke are the recombinant tissue plasminogen activator and endovascular thrombectomy, which focus on saving the penumbra cells and limit the infarct core enlargement by removing the occlusion in the artery, but they are effective only if started within a few hours of the onset of the stroke. Treatment with recombinant tissue plasminogen activator, a fibrinolytic agent, is effective if applied within the first four and a half hours of stroke onset, however, there is a potential risk of hemorrhage (del Zoppo, 2013). Mechanical thrombectomy, on the other

hand, shows benefits when applied within the first six hours of ischemic stroke onset, but the patients should be selected by appropriate imaging and treated by experienced operators (Asadi et al., 2015). Both treatments are effective but have a very limited therapeutic window and few patients have access to them or are suitable candidates. Moreover, in some cases, these treatments may cause reperfusion injury, leading to brain blood barrier disruption and hemorrhagic transformation or massive brain edema (Molina and Alvarez-Sabín, 2009). Therefore, finding new treatments with wider therapeutic windows is necessary to help more patients. Hundreds of drugs have been studied in animal stroke models, many with positive results but there is not yet an approved medication for helping recovery rehabilitation after a stroke. Many aspects are involved in this failure, including the high cost of developing a new drug, insufficient basic research, including no beneficial effect or serious side effects in clinical trials and lack of safety testing. Drug repurposing (or reprofiling) is a strategy to find a new therapeutic use for a drug approved for a different condition. This approach has many advantages over developing a new drug. For example, approved drugs are sufficiently safe in preclinical models and humans, there is a lot information regarding cellular and molecular effects generally available, the drug is probably available in the

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market and could be used in a clinical trial (phase II and III). Taking these advantages into consideration, we will analyze the effects of memantine and its potential as a repurposed drug to help human stroke patients. In the followings sections, we will briefly describe the physiopathology of ischemic stroke and the evidence of the benefits of memantine used after stroke in experimental animal models.

Electronic databases were searched for articles to collect all data since 2000, related to preclinical studies, involving memantne and focal ischemic stroke, using the following terms: Ischemic stroke OR Cerebral ischemia OR Oxygen-glucose deprivation AND memantine, using Pubmed. For ongoing clinical trials, the ClinicalTrials.gov electronic database was searched with the terms Stroke and Memantine. If the abstract meets the inclusion criteria, the full-text article was obtained and reviewed.

Stroke

The brain depends on a continuous and regulated blood supply to support its functional integrity. It receives nearly 15% of the cardiac output and consumes more than 20% of the metabolic substrates (oxygen and glucose), though neurons have very limited energy reserves. This suggests that neurons extract oxygen and glucose from the blood on an as-needed basis to support ongoing neural function to meet the physiological demands imposed by neural activation (Lourenço et al., 2017). The reduction or cessation of blood flow in the brain may produce different levels of damage depending on the time elapsed, cell resistance and magnitude of the ischemia, and activates a very complex cascade of interrelated cellular and molecular events with a temporal overlapping profile that evolves over minutes, hours or days, inducing injury in all cell types and damage that can range from transient to irreversible (e.g., cell death) (Brouns and De Deyn, 2009; Deb et al., 2010). This event produces two different areas of damage: the ischemic core and the penumbra. In the ischemic core, blood flow is abruptly reduced and the cells are permanently injured and die rapidly by necrosis. The size of this area will depend primarily on the duration and magnitude of the ischemia and the location of the stroke. The penumbra is located around the ischemic core. This zone is perfused by collateral blood vessels which allow cells that are structurally intact but functionally weakened (Brouns and De Deyn, 2009; Deb et al., 2010). These functionally impaired cells can be slowly incorporated into the ischemic stroke or saved. Some studies have shown a certain degree of spontaneous recovery in the weeks or months after a stroke in both humans and mice (Clarkson et al., 2013; Bergsma et al., 2017; Delavaran et al., 2017). This recovery involves adaptive changes in neurons and glial cells to partially reverse the alterations caused by an ischemic stroke. Many factors can delay or impair recovery, for example, tissue susceptibility, age, and comorbidities.

Ischemic Cascade

Ischemic cascade refers to several interrelated and overlapped pathological mechanisms that are activated after a few minutes of blood vessel occlusion and whose progress occurred on a different time scale. The first event of the ischemic cascade is the reduction of oxygen and glucose which leads to a failure to produce high-energy molecules to maintain the cellular homeostasis. This sets off several mechanisms that include ionic imbalance, excitotoxicity, calcium overload, cytotoxic and vasogenic edema, peri-infarct depolarization, oxidative and nitrosative stress, blood-brain barrier (BBB) disruption, inflammation, and apoptosis. These mechanisms are briefly described below.

Energy Failure and Ionic Imbalance

Severe decrease of blood perfusion produces a depletion of oxygen and glucose and a consequent decline of ATP levels in neurons and glial cells, which leads to the failure of ion transport pumps (e.g. sodium/potassium pump) and depolarization. Subsequently, this causes an influx of sodium, chloride and calcium ions along with water and the output of potassium ions. Moreover, there is an increase of neurotransmitter release (e.g., excitatory amino acids) and inhibition of neurotransmitter reuptake systems that enhance the accumulation of neurotransmitters in the extracellular space (Nicholls and Attwell, 1990; Katsura et al., 1994; Martin et al., 1994). Additionally, the low availability of oxygen induces anaerobic glycolysis and increases the levels of lactate, which can cause acidosis cell damage (Brouns et al., 2008).

Excitotoxicity and Calcium Overload

Excitotoxicity refers to damage caused by pathological depolarization due to the abnormal release of excitatory neurotransmitter glutamate and calcium overload (Lai et al., 2014). The extracellular glutamate interacts with ionotropic receptor subtypes N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-propionate or kainate, which depolarize the cell membrane and this event, open voltage-gated ion channels, and dramatically contributes to increase the influx of sodium, chloride and calcium ions (Meldrum et al., 1985; Rothman and Olney, 1986; Choi, 1988; Chen et al., 2008). Height calcium influx activates several calcium-dependent enzymes such as proteases, lipases, and nucleases that cause damage to macromolecules resulting in extensive cell damage that lead to cell death from liquefactive necrosis (Choi, 1988, 1995).

Cytotoxic and Vasogenic Edema

Cytotoxic edema is described as cell swelling and is caused by passive water influx that follows the abnormal accumulation of sodium ion. This type of edema is observed a few hours after ischemic stroke onset and declines within 1 day. The dramatic increase the influx of sodium, chloride and calcium ions is passively followed by water resulting in cell swelling that can cause cell death. Vasogenic edema is due to extravasation and extracellular accumulation of fluid into the cerebral parenchyma and is caused by the disruption of the BBB. Vasogenic edema develops within two or three days and last several days. Abnormal accumulation of fluids produces increased brain volume and intracranial pressure, which can induce hypoxia and blood flow reduction (Michinaga and Koyama, 2015).

Peri-Infarct Depolarizations

Peri-infarct depolarizations are spontaneous depolarization waves that propagate at slow velocity (3–5 mm/min) and occur in the penumbra due to ionic imbalance. Moreover, these waves are accompanied by prolonged recovery of cortical function, or no recovery at all, and are a causal factor in the expansion of experimental infarcts (Lauritzen et al., 2011). The number of peri-infarct depolarizations and the cumulative duration have a positive correlation with the expansion of infarct size (Mies et al., 1993; Dijkhuizen et al., 1999). The extracellular accumulation of potassium ions, glutamate, and increase of intracellular calcium in astrocytes are important conditions to trigger peri-infarct depolarizations (Fabricius et al., 1993; Duffy and MacVicar, 1996; Murphy et al., 2008).

Oxidative and nitrosative stress

Stroke activates several pathways that produce reactive oxygen and nitrogen that surpass the cellular mechanism to free radical scavenging. Calcium overload produces several effects in relation to oxidative stress, such as mitochondria depolarization and a large amount of superoxide. It also activates NADPH oxidase which produces superoxide and induces the conversion of xanthine dehydrogenase to xanthine oxidase, which generates different oxygen species, for instance, superoxide and hydrogen peroxide (Abramov et al., 2007; Brennan et al., 2009; Girouard et al., 2009). Oxidative stress can produce lipid peroxidation, protein dysfunction and DNA damage (Allen and Bayraktutan, 2009). Nitrosative stress is due mainly to the generation of the strong oxidant peroxynitrite from the combination of superoxide and nitric oxide, produced by nitric oxide synthase activated during the stroke (Beckman et al., 1990).

Brain-blood barrier disruption

BBB disruption starts with an inflammatory process caused by stagnant blood flow, due to the release of proinflammatory mediators from the endothelium activation of intravascular leukocytes, and brain parenchyma. The intravascular inflammation establishes the conditions for BBB breakdown and leukocyte invasion of the ischemic tissue (Anrather and Iadecola, 2016). Other factors released by glia and neuron cells also contribute to BBB disruption such as oxidative stress and inflammatory responses that change the endothelial tight junctions (Michinaga and Koyama, 2015).

Inflammation

After parenchyma injury, damaged cells release damage-associated molecular patterns and these molecules activate receptors such as toll-like receptors in microglia and astrocytes to initiate immune responses. A few minutes after damage onset, microglia become reactive and accumulate at the lesion core and in the penumbra. The gradual alteration in the BBB allows the infiltration of leucocytes, which occurs hours after ischemic stroke onset (Gelderblom et al., 2009; Grønberg et al., 2013). On the first day, reactive microglia show an anti-inflammatory profile or M2 phenotype, but after this period, they switch to M1 phenotype with a pro-inflammatory profile (Hu et al., 2012). Microglial cells release several pro-inflammatory mediators, such as reactive oxygen species and tumor necrosis factor-α, which promote the infiltration of circulating leukocytes (Ritzel et al., 2015). Cytokines released by M1 microglia can induce the reactivity of astrocytes (astrogliosis) within 4 to 24 hours after stimulation (Zhu et al., 2000; Nowicka et al., 2008). Moreover, leukocytes release several pro-inflammatory cytokines, such as interleukin-1β and interferon-γ to damage neural structure directly or indirectly and contribute to the enlargement of the lesion core (Lambertsen et al., 2004; Allan et al., 2005). The peak inflammatory response is within 7 days after stroke onset and then slowly declines (Dirnagl et al., 1999).

Apoptosis

In the penumbra, cells die generally in a regulated manner known as apoptosis which presents a defined morphological pattern that is characterized by cell shrinkage, membrane-bound vesicles (apoptotic bodies) and pyknosis (chromatin condensation) (Puig et al., 2018). This process can be triggered by several events such as DNA damage, excessive activation of the NMDA receptor, acid-sensing ion channels, and transient receptor potential channels, among other factors (Budd et al., 2000; Broughton et al., 2009). Apoptosis can be initiated by internal (intrinsic pathway) or external events (extrinsic pathway). The intrinsic pathway involves calcium overload, disruption of mitochondria and the release of the cytochrome C, which leads to the downstream activation of caspases that damage the DNA. The extrinsic pathway is activated by specific extracellular ligands (e.g. Fas ligand) that bind to transmembrane death receptors such as Fas, TNFR-1 and p75[NTR]. The extracellular Fas ligand binds to Fas death receptors which trigger a series of events, including caspase 3 to damage DNA (Broughton et al., 2009). Pro and anti-apoptotic proteins have been observed in the penumbra of experimental stroke after 0.5–1 hour of model cerebral artery occlusion (Ferrer et al., 2003) and markers of apoptosis peaked at 1–2 days and persisted for 4 weeks after stroke onset (Li et al., 1995). **Figures 1** and **2** show the interaction between different pathological processes in the ischemic core and penumbra, respectively.

Mechanism of neuroprotection and neuroplasticity

Although after a stroke neuroprotective and neuroplastic mechanisms overlap, they can be differentiated as follows: after damage, all the cells activate a series of mechanisms against the harmful factors to avoid damage (neuroprotection). In the infarct core, these mechanisms exceed their capacity to protect and the cells die. In the penumbra this mechanism contributes to limit the expansion of the infarct core and include: 1) homeostatic regulation of ions and fluids, 2) free radical scavenging, 3) neurotransmitter re-uptake, 4) production and release of anti-inflammatory cytokines, 5) BBB and neurovascular unit repair, 6) isolation of the injury site through scar formation, and 7) phagocytosis and debris clearance (Li et al., 2008; Sofroniew and Vinters, 2010; Burda and Sofroniew, 2014; Pekny and Pekna, 2014). Neuroplasticity involves the activation of mechanisms to restore the homeostatic function of the tissue previously damaged through reorganization and compensation of structural and functional deficiencies and includes: 1) production and release of growth factors, 2) angiogenesis, gliogenesis, and neurogenesis, 3) reorganization of microvascular and neuronal networks, and 4) synaptic contact growth (Ko and Yoon, 2013; Dąbrowski et al., 2019).

Stages of ischemic stroke

The classification of stroke stages used here is commonly utilized in imaging studies (Birenbaum et al., 2011). The main characteristics of these stages are summarized following.

Acute stage

The acute stage starts immediately after injury and covers the first 24 hours. In the ischemic core, the events progress rapidly, and within minutes or hours there is depletion of cellular energy stores, ionic imbalance, release of excitatory neurotransmitters and inhibition of their reuptake, peri-infarct depolarization, BBB disruption, cellular edema, and excitotoxicity, causing irreversible injury and cell death, mainly caused by excitotoxicity, ionic imbalance and oxidative and nitrosative stress (Brouns and De Deyn, 2009; Deb et al., 2010). In the penumbra, the damage is less severe since the collateral blood flow provides sufficient oxygenated blood for cells to partially preserve their energy metabolism and survive, and all cells are exposed to several deleterious mechanisms, such as excitotoxicity, oxidative and nitrosative stress, cytotoxic edema, peri-infarct depolarization, inflammation and BBB dysfunction, and apoptosis which can eventually cause cell death (Brouns and De Deyn, 2009; Deb et al., 2010).

Subacute stage

This stage includes the time period from 24 hours to 5 days after stroke onset. All the events occur in the penumbra. Several pathological mechanisms present in the acute phase
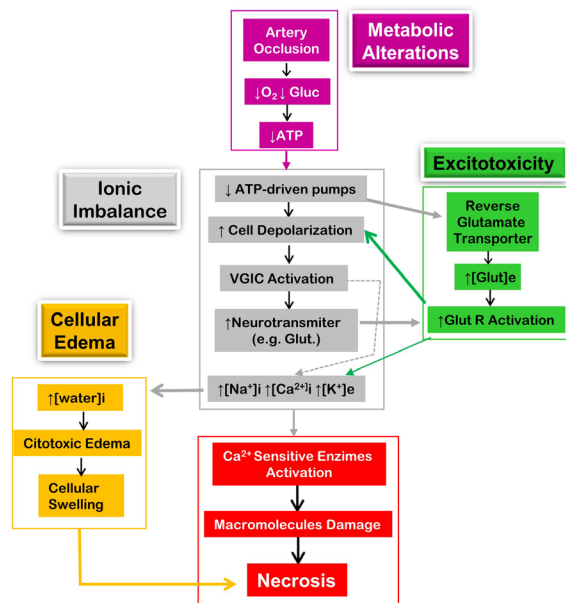
Ischemic Core

Figure 1 │ **Diagrammatic representation of the main pathological mechanism in the ischemic core leading to cell death by necrosis.**
[ ]: Concentration; e: extracellular; Glu: glucose; Glut: glutamate; Glut R: glutamate receptor;i: intracellular; VGIC: voltage-gated ion channels. Adapted from López-Valdés et al. (2020).
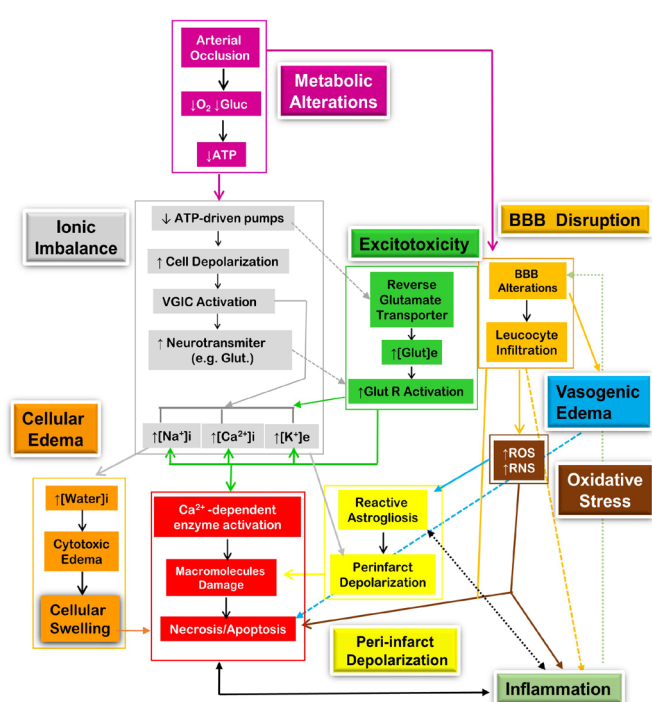
are still active in this area as vasogenic edema, BBB disruption, oxidative and nitrosative stress, inflammation and apoptosis (Brouns and De Deyn, 2009; Deb et al., 2010).

Chronic stage
This stage includes the period of time after 5 days to months following stroke onset and all the events occur in the penumbra. Several processes are still active, such as vasogenic edema, apoptosis, astrogliosis, and inflammation (Brouns and De Deyn, 2009; Deb et al., 2010). On day 6 after injury, a subset of reactive astrocyte, NG2 cells, and reactive microglia start the glial scar formation (Ding, 2014; Adams and Gallo, 2018), which is completed between 2 and 4 weeks after stroke onset, beginning a chronic state that lasts many months. The perimeter of astrocyte scars has a variety of cells formed by reactive microglia, hypertrophic reactive astrocytes, viable neurons and other cell types with a long-term potential for remodeling and forming new circuits (Clarkson et al., 2013; Li et al., 2010; Overman et al., 2012), and in fact, considerable functional recovery can occur in the first weeks after stroke, mostly due to spontaneous active mechanisms (Cramer, 2008; Grefkes and Fink, 2014).

Memantine
Memantine or memantine hydrochloride, are the generic names for 3,5-dimethyladamantan-1-amine hydrochloride (PubChem CID: 181458). The drug was officially launched in Germany in 1989 to treat dementia and in 2003, the FDA approved it to treat patients with moderate to severe Alzheimer's disease (Rogawski and Wenk, 2003; FDA, 2004). Memantine is absorbed by the gastrointestinal tract with an absolute bioavailability of 100% and follows a linear dose–concentration pattern. The peak plasma levels are reached within 3–7 hours and the elimination half-life in man is between 60 and 80 (Schmitt et al., 2007). Memantine crosses the BBB to distribute to many areas within the brain (Kornhuber and Quack, 1995; Parsons et al., 1999). Three major metabolites of memantine have

Penunbra

Figure 2 │ **Diagrammatic representation of the main pathological mechanism in the penumbra leading to cell death by apoptosis.**
[ ]: Concentration; e: extracellular; Glu: glucose; Glut: glutamate; Glut R: glutamate receptor; i: intracellular; RNS: reactive nitrogen species; ROS, reactive oxygen species; VGIC: voltage-gated ion channels. Adapted from López-Valdés et al. (2020).

been characterized and include an N-glucuronide conjugate, 6-hydroxymemantine, and 1-nitroso memantine, but between 57–82% of the memantine dose is eliminated unchanged in the urine, which suggests that the drug does not undergo extensive metabolism, besides, all major metabolites have minimal NMDA receptor activity (Schmitt et al., 2007). Due to memantine being an uncompetitive, voltage dependent NMDA receptor antagonist with moderate affinity and fast on–off kinetics, one of its main therapeutic actions is it selectively blocks the pathological over-activation of the NMDA receptor in excitotoxicity (Parsons et al., 1999; Lipton, 2006). However, evidence from *in vivo* and *in vitro* experiments, showed that memantine has pleiotropic effects that include brain-derived neurotrophic factor (BDNF) (Marvanová et al., 2001; Meisner et al., 2008; Jantas et al., 2009; Réus et al., 2010) and glial cell-derived neurotrophic factor upregulation (Wu et al., 2009), anti-apoptotic effects (Jantas et al., 2009) and reduction of neuroinflammation (Rosi et al., 2009; Wu et al., 2009).

Memantine in experimental stroke
In this review, we will analyze separately studies that applied memantine after focal permanent vessel occlusion in adults, because this is more relevant to translate into clinical stroke trials, and then, we will look at those that applied the drug in the model of occlusion/reperfusion in adults, which is similar to interventional thrombectomy (Hossmann, 2012; Sommer, 2017).

Memantine in permanent vessel occlusion models
Neuroprotective and neuroplasticity effects have been demonstrated when memantine is given acutely and chronically. Culmsee et al. (2004) showed that memantine (20 mg/kg) intraperitoneally (IP) decreased the infarct area by 10% when the drug is applied 5 minutes after stroke in mice,

but failed to protect when administered at 30 or 90 minutes after stroke. Another study conducted in rabbits (Lapchak, 2006), showed improved behavior when the memantine (25 mg/kg) was applied intravenously (IV) acutely (≤ 60 minutes after stroke). López-Valdés et al., (2014) treated mice with memantine (30 mg/kg) in drinking water for 28 days after stroke and the treatment significantly improved their functional locomotor performance, increased the forepaw sensory map area, vascular density, BDNF, and phosphorylated-tropomyosin–related kinase-B receptor in the penumbra and a decrease in reactive astrogliosis was observed in the same area. Lastly, no differences were identified in infarct and glial scar size between memantine and control animals.

Memantine in occlusion/reperfusion models

Seif el Nasr et. al. (1990) used a rat model of transient forebrain ischemia induced by clamping both carotid arteries for 10 minutes to study the effects when the drug (10 and 20 mg/kg) is applied I.P. immediately after ischemia. They found that only 10 mg/kg significantly decreased the neuronal damage. Another study also in rats showed that memantine (30 mg/kg) administered via nasogastric intubations after reperfusion, showed significant reductions in the infarct volume and significant improvement in the neurological score at 24 and 72 hours after treatment (Aluclu et al., 2008). Killic et al. (2013) analyzed the effects of memantine (20 mg/kg) alone or in combination with melatonin on pathways related to vascular leakage after stroke, when applied immediately after reperfusion. They evaluated the effects 24 hours after treatment and found that memantine significantly decreases the stroke volume, the BBB permeability, and the fragmented DNA. Another research group used memantine (20 mg/kg) immediately after artery occlusion, followed by a maintenance dose of 1 mg/kg at 12 hours intervals. After 24 hours of artery occlusion, they found that memantine improved neurological deficits, decreased infarct volume, decreased apoptosis and calpain (a calcium dependent protease) in the penumbra (Chen et al., 2017). Wang et al. (2017) studied the effect of memantine (20 mg/kg per day) applied in the subacute stage (72 hours after stroke) and delivered it subcutaneously over 28 days. They found that memantine significantly decreased astrogliosis and increased concentrations of BDNF, glial cell-derived neurotrophic factor and the vascular endothelial growth factor in the cortex and striatum (Wang et al., 2017). Some of the effects mentioned above, can be supported by the results obtained *in vitro* with brain slices and cell culture exposed to oxygen-glucose deprivation, a common model of stroke *in vitro* (Holloway and Gavins, 2016). Rat hippocampal slices exposed to oxygen-glucose deprivation and treated with memantine (1–30 μM) produced a concentration-dependent neuroprotection (Öz and Saybaşılı, 2016; Landucci et al., 2018). In the same preparation, memantine (10 μM) reduced lactate dehydrogenase (LDH) by 40%, a marker of tissue damage (Sobrado et al., 2004). In primary cultured hippocampal neurons, ATP-depleted by sodium azide (5 mM NaN_3) treated with memantine (10 or 50 μM) significantly increased survival neurons and decreased the lactate dehydrogenase release (Chen et al., 2017). In another study in primary cultured cortical neurons, memantine (10 μM) significantly decreased the apoptosis and increased cell viability (Chen et al., 2016). Another source that can also help, are the results obtained in experiments that applied memantine before the artery occlusion and the results show that memantine decreased oxidative stress (Tanaka et al., 2018), the number of reactive microglia and astrocytes, endothelial cells damaged, matrix metallopeptidase 9 secretion, an enzyme involved in the degradation of extracellular matrix, and improved the BBB

integrity (Chen et al., 2016). Furthermore, indirect evidence from the effects of memantine in another disease can also help. For example, in preclinical models of Alzheimer's disease, chronic treatment with memantine decreases neuroinflammation, oxidative stress, improves memory, and increases synapse density and BDNF concentration (Folch et al., 2018).

Conclusions

Memantine, an approved drug to treat patients with moderate to severe Alzheimer's disease, showed pleiotropic effects in models of experimental stroke (**Figure 3**), suggesting that it participates in different regulatory pathways of neuroprotection and neuroplasticity. The protective role of memantine is expressed as the reduction of infarct volume and neurological deficits if the drug is applied (IP) immediately or a few minutes after artery occlusion, which suggests its utility in the acute phase as a complement to thrombolytic therapy and endovascular thrombectomy. Moreover, some results suggest that memantine decreases apoptosis, proteases, and BBB permeability, which can contribute to the protective effect. Long-term use (28 days, oral administration) showed neuroplastic effects such as reconfiguration of optical maps, significant increase of BDNF, angiogenesis, and functional recovery, decrease of astrogliosis, but no difference in the infarct size, which suggests that memantine could be useful in the chronic poststroke stage, which is a more realistic possibility. Although the results of the experiments included in this analysis showed that memantine has neuroprotection and neuroplasticity effects, more experiments are needed to confirm and expand the knowledge of the molecular mechanism involved in the therapeutic actions of memantine, particularly at the subacute and chronic stages. It is clear that all the evidence presented above contains some caveats because all the experiments were performed using young male animals without comorbidities and it is known that stroke is more severe in older animals and humans, and human patients generally show comorbidities (Sohrabji et al., 2013; Barnes, 2015), consequently animals with these conditions and females should be included in the experiments.
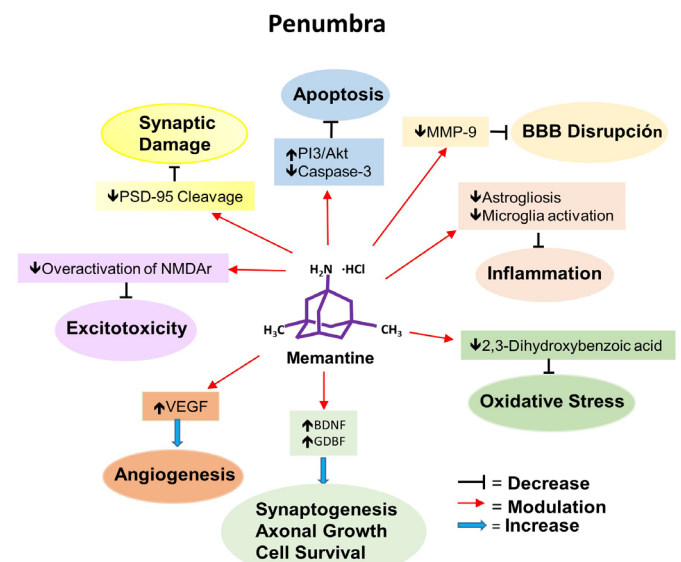

Figure 3 │ Diagrammatic representation of the main therapeutic effects of memantine on penumbra.
Akt: Protein kinase B; BBB: brain-blood barrier; BDNF: brain-derived neurotrophic factor; GDNF: glial cell-derived neurotrophic factor; MMP-9: matrix metallopeptidase 9; NMDAr: N-methyl-D-aspartate receptor; PI3-K: phosphatidylinositol-3 kinase; PSD-95: postsynaptic density protein 95; VEGF: vascular endothelial growth factor.

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Finally, at this time, only two ongoing clinical trials are testing the efficacy of memantine on patients with ischemic stroke, one is recruiting patients (ClinicalTrials.gov identifiers: NCT02144584) and the status of the other (NCT02535611) is unknown. Therefore, more clinical trials are needed to evaluate the effects of this drug in improving the outcomes of stroke patients.

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