Chapter

Available Therapeutics after a Stroke: Current and Promising Options

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Abstract

Morbidity and mortality after a cerebrovascular event have increased during the past few years, even after extensive efforts have been made concerning research in prevention, acute treatment, pharmacotherapy, revascularization, and rehabilitation. The functional deficits that arise from an ischemic event are related to the increasing chronic disability that results from lower mortality rates. More people are becoming chronically disabled; currently, as much as 90% of survivors are affected and face difficulties to continue with daily life activities. In this chapter, we briefly review the pathophysiology of ischemia and immediate clinical attention to the event. We argue about the need to seek new pharmacological and non-pharmacological alternatives and discuss the most representative in the field of neuroprotection and neurorestoration. In addition, we review the most relevant dietetic strategies and physical rehabilitation therapies, all aimed at improving the survivors' quality of life.

Keywords: cerebral ischemia, neuroprotection, neuroregeneration, rehabilitation, immunomodulation

1. Introduction

Acute ischemic stroke (AIS) remains the second cause of death worldwide [1], despite showing a mortality rate reduction of 1.19% [2]; only in 2017, there were 6 million 167, 291 deaths; 1, 291,000 more with respect to 1997. During the same period, the survival rate increased by 0.02%; this caused an increment in the disability-adjusted life years percentage (DALYs), which went from 4.17 to 5.29% [2].

Data from the World Health Organization (WHO) indicate that stroke represents the third cause of permanent adult disability worldwide [3], and is present in 90% of survivors. Motor deficits after stroke account for the high rates of long-lasting disability. The most common impairments are related to speech, or language and communication disorders (aphasia and dysphasia), apraxia [4], swallowing, depression, cognitive impairment, and hemiparesis of the contralateral limb [5] characterized by muscle weakness or spasticity in distal rather than proximal muscles [6]. These deficits ultimately cause chronic disability, affecting the ability to

work and the patient's independence and autonomy for performing daily life activities such as dressing or eating, ensuring they will require long-lasting care, which also deteriorates their quality of life and that of the patients' caregivers.

Stroke complications represent a considerable economic burden both individually and as a society; such complications are associated with a substantial increase in household expenses related to a higher requirement of medical attention, medication, lost workdays, and payment to external or additional caregivers, and in several cases, physical rehabilitation. It is estimated that the United States alone had an annual expenditure of 45.5 billion dollars during the 2014–2015 period, which is only expected to increase through 2035, according to estimations of RTI international [7].

It is therefore fundamental to revisit the procedures regarding basic and clinical research points of view, as well as the most recent recommendations issued by the American Heart Association/American Stroke Association (AHA/ASA), which endorse multiple-component quality improvement initiatives including emergency department education and multidisciplinary teams with neurological management experience, thus increasing the application of fibrinolytic treatment IV.

The strategies that are currently being studied in search of treatments for cerebral ischemia can be categorized into four areas: clinical care, neuroprotection, neurorestoration strategies, and rehabilitation therapy.

The term neuroprotection is defined as the intentional intervention, either inhibition or modulation, that takes place at a certain point during the ischemic cascade, to intervene in a specific mechanism of damage to prevent tissue injury from increasing during the acute phase of ischemia [8]. The neurorestoration is developed through the stimulation of neurogenesis and neuroplasticity to restore the tissue and functional integrity of the neural tissue.

In the clinical setting, several recanalization strategies have been explored to restore blood flow to the injured area of tissue as soon as possible, to assure the lesser damage and decrease secondary sequelae to the original lesion. Finally, physical therapy has become a rehabilitation tactic that has positively impacted the recovery of patients' independence, autonomy, and quality of life, which is worth reviewing.

2. Pathophysiology of stroke

Cerebral ischemia is caused by an abrupt and sustained occlusion of blood flow to a large artery that unties a series of biochemical alterations that are known as the ischemic cascade, **Figure 1** [9]; during the development of such changes, a set of mechanisms that lead to cell death occurs: ionic imbalance and excitotoxicity, oxidative stress, and inflammation [10].

The reduction of blood flow leads to a depletion in levels of glucose and O_2, which alters aerobic metabolism, increasing lactic acid accumulation. Simultaneously, astrocytes use stored glycogen to provide energy to the neurons in the form of lactate [11]; but, because aerobic metabolism is interrupted at this time, lactic acid continues to accumulate, causing lactic acidosis, which causes ionic dysfunction [12]. Ionic alterations, together with Na^+/K^+ pump inactivity, give rise to neuronal depolarization, which leads to the opening of the Ca^{2+} channels and the subsequent release of excitatory neurotransmitters such as glutamate, causing increased activation of ionotropic receptors, especially NMDA, increasing the Ca^{2+} flux into the cell [13].

Ca^{2+} is an essential protagonist within the ischemic cascade since it is capable of activating a significant amount of proteins that lead to cell death, and

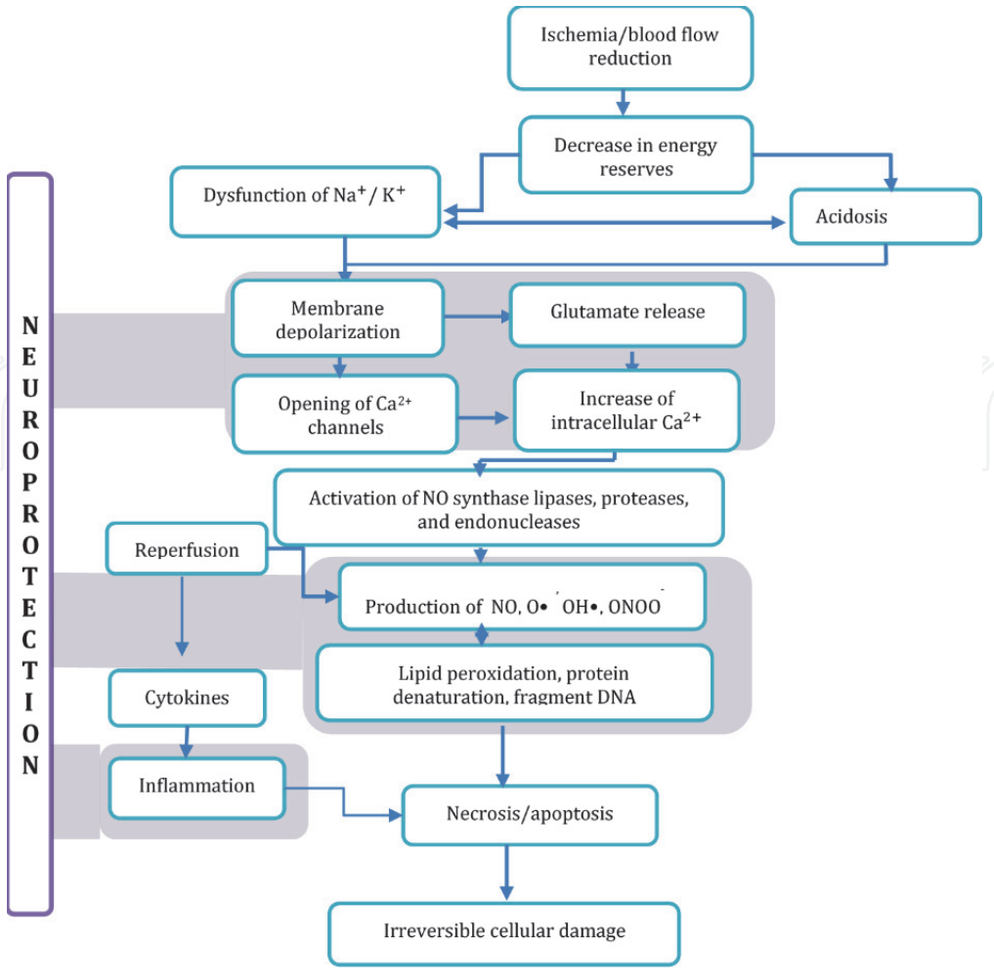

Figure 1.
Key points to the pathophysiology of stroke.

overproduction of free radicals; such proteins are calpains [14], endonucleases [15], calmodulin [16], and A2 phospholipase (**Figure 1**) [17]. Activation of these proteins leads to a further increase in free radical production and other oxidant species that directly damage structural molecules and activate inflammatory processes [18].

The mitochondria are where the highest production of free radicals takes place; under normal conditions, superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) are produced continuously and eliminated by antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase [19]. Alternatively, under ischemic conditions, reperfusion provides sufficient substrate for different enzymatic oxidation reactions to take place, causing an overproduction of free oxygen radicals (ROS) and the inactivation of antioxidant enzymes [20]. Concurrently, nitric oxide (NO) increases due to the activation of endothelial and neuronal nitric oxide synthases as a result of increased Ca^{2+} concentration, NO reacts with ROS and forms a highly toxic peroxynitric acid (ONOOH) [21].

Free radicals promote mitochondrial membrane permeability and allow for cytochrome c to be released into the cytosol, where the intrinsic pathway of apoptosis becomes activated, the concentration of free radicals also increases lipid peroxidation and protein denaturalization [22], DNA fragmentation, and activate several signaling pathways that lead to neural death, such as PI3K/AKT [23], Bcl2, p53 [24] and others. From the moment of the occlusion, endothelial cells express damage-associated molecular patterns (DAMPs), produce ROS and adhesion molecules that allow for their activation and that of surrounding mast cells and macrophages, which, as a consequence, release histamine, proteases, TNF-a, and

chemokines [25]. The production and release of these molecules promote the blood-brain barrier (BBB) rupturing, thus causing peripheral leukocyte invasion into the injured brain parenchyma [26].

Microglial cells are then activated in the non-perfused region of the brain parenchyma [27], microglial cells acquire phagocytic characteristics and a predominantly pro-inflammatory phenotype (M1), which in turn increases the release of interleukin-6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor-alpha (TNF-α), NO molecules, and prostanoids [28]. Peripheral immune cells such as neutrophils, B lymphocytes, T lymphocytes, and NK are recruited into the injured tissue, this event is thought to contribute both beneficially by inducing the release of anti-inflammatory cytokines and growth factors, and negatively by increasing the lesion through a sustained release of proinflammatory cytokines and free radicals [29].

Within the process of the ischemic cascade, three points are identified that could classify as strategic to restore neuroprotection (ionic imbalance, excitotoxicity, and inflammation); nonetheless, most neuroprotective drugs act in many of the phases of the ischemic cascade, which is why they cannot be classified into a single step of neuroprotection.

3. Current stroke management in the clinical setting: the first step after the stroke

Early diagnosis of stroke is a predictor for better clinical outcomes [30]; therefore, its confirmation is a pressing matter for the treatment to begin as soon as possible from the recognition of symptoms onset [31]. Currently, different strategies for acute ischemic stroke are being used in the clinical setting and are part of the AHA/ASA clinical practice guidelines [32].

The differential diagnosis for stroke includes transient ischemic attacks, seizure, syncope, migraine, and brain tumors [33]. To establish a correct and timely diagnosis and to determine the best course of action, the clinician must rely on laboratory testing [34] (blood glucose is usually high, total cholesterol, LDL, HDL, AST, CPK-MB), and although the gold standard for diagnosis is a cerebral angiography, clinicians try to avoid it by choosing different methods such as imaging testing, including the first-line non-contrast CT scans, CT angiography, MRI, and MRI angiography [32, 35, 36]. In the earliest stages of acute stroke, CT scans are less useful for ischemic stroke diagnosis but can rule out hemorrhagic stroke [36]. Other clinical tests such as EKG, EEG, and the National Institutes of Health Stroke Scale (NIHSS) help establish differential diagnosis and treatment plan [35].

Specific and timely reperfusion treatment is essential to determine the course of the clinical outcome and to improve survival. Once the ischemic etiology has been established, and the patient is stable, treatment should start promptly. Currently, two major therapeutic strategies are being used to treat cerebral ischemia to allow for recanalization and reperfusion. The treatment of choice will depend on time to treatment and etiology of the injury; these therapies are thrombolysis using pharmacological agents and mechanical thrombectomy [35, 37–39].

At present and still after decades, the FDA only approves the use of recombinant tissue plasminogen activator (rTPA), also known as alteplase, as the sole pharmacological option for recanalization [35, 39]. Alteplase initiates local fibrinolysis when administered intravenously by hydrolyzing the peptide bond in plasminogen to form plasmin [40]. The standard IV dosage is 0.9 mg/kg for 60 min, with a 10% bolus over 1 min within 4.5 h of AIS onset [31].

Although alteplase is the only drug available for thrombolysis, most stroke sufferers do not receive this drug as treatment. There usually is a delay in

recognition of the symptoms and the time window in which rTPA must be administered is from 3 to 4.5 h from onset of symptoms, and benefits diminish over time [39, 41], which is why the new AHA/ASA guidelines recommend not waiting for clinical improvement before administration [32]. Also, not all patients are eligible, since candidates must be ≤80 years of age, without diabetes or stroke history, with an NIHSS score ≤ 25, not currently taking oral anticoagulation, and without radiologic evidence of ischemic injury involving more than one-third of the MCA territory [42].

Complications that are associated with its use are limited: BBB integrity alterations, and hemorrhagic transformation, granting that other studies have shown it to be well tolerated by patients using warfarin or other anticoagulants [38], in controversy with the new AHA/ASA guidelines that suggest it should not be administered if the patient received heparin 24 h before [32, 35, 43]. Other drugs are also available, such as aspirin, which must be delivered within 24–48 h after stroke onset. Although the guidelines emphasize that it should not be used to replace mechanical thrombectomy or IV alteplase, aspirin continues to be the choice for secondary prophylaxis [32, 44], even when the 2018 guidelines find no benefit from its use for the treatment of an ongoing AIS [32].

Furthermore, the FDA approves of endovascular treatments, which are reported to have a time window of up to 8 hours from the onset of symptoms [38].

For patients with large vessel occlusion, less responsive to rTPA, intra-arterial therapy is recommended, since it leads to higher recanalization rates by being able to infuse the drug directly into the occluded area or the clot itself [35, 45]. About 10% of patients with AIS fall into this category, but only a few centers can perform endovascular procedures in proper conditions [46].

Also, endovascular mechanical thrombectomy using contact aspiration (CA) [47], which has been described before [48], and stent retrievers (SR), especially those of new generations [49], for clot rupturing and aspiration has shown significant benefits in large vessel occlusion [50] regarding clinical outcomes and lower complication rates [49]. Notwithstanding, CA alone, without the use of a SR, is associated with a greater need for rescue treatment, and thus, worse outcomes [51]; the SR might also increase the risk for hemorrhagic transformation and neurological deficit [52].

Increased costs of endovascular treatments, as well as their complexity and need for trained personnel, cause patients to have less access to them. Therefore, exploring new pharmacological therapies should be continued.

4. First neuroprotective pharmacological and non-pharmacological treatments

In the search to find new alternatives of neuroprotective agents, a great variety of molecules have been explored that affect one or several strategic points of the pathophysiology, and that promise good results; some are mentioned below.

During the onset of AIS, glucose and oxygen concentrations decrease, and this promotes the activation of adenosine monophosphate-activated protein kinase (AMPK). This process upregulates cellular pathways that control energy metabolism through catabolic pathways such as glycolysis and lipid oxidation to increase adenosine triphosphate (ATP) production and decrease its consumption through the inhibition of gluconeogenesis. Observations have been made regarding the fact that the activation of this enzyme for short periods increases neural survival, but its activation for extended periods will lead to cell death through apoptosis, necrosis, and autophagy [53], which is why several drugs that modulate AMPK activation have been tested recently in search for beneficial effects.

To mention some, metformin has been widely studied for cerebral ischemia since it possesses pleiotropic activity and modulates AMPK activation [54]. In 2016, Zhang et al. administered 7 mg/kg of metformin intraperitoneally to C57BL/6 mice for 7 days, before middle cerebral artery occlusion (MCAO). After MCAO, the authors observed that it induced neuroprotection by reducing infarct size, through lower AMPK, results that were not observed if administered for short periods of 1–3 days before MCAO, or after the occlusion; also, these benefits were not found in the case of reperfusion [55]. Also, the neuroprotective effect of metformin was observed in a global ischemia model in rats; after administration, apoptosis decreased, and mitochondrial biogenesis was induced [56]. Other experiments have demonstrated that metformin has the potential to improve memory and learning through the increase in brain-derived neurotrophic factor (BDNF) and p7056k protein [57]. On the other hand, it has also been implicated in the reduction of IL-6, IL-1β, TNF-α, and adhesion molecule levels, as well as a decrease in neutrophil infiltration [58]. Considering these results, it is crucial to clarify how this modulation is carried out since there is some controversy about the mechanism (**Table 1**).

Atorvastatin is a statin that has pleiotropic effects, since it allows angiogenesis and synaptogenesis, increases blood flow, blunts atherosclerotic plaque formation, and provides neuroprotection in cerebral ischemia model [59] by reducing aquaporin 4 expression (AQP4) [60], thus, preventing cerebral edema and the increase of infarct size. This statin has also been reported to attenuate cognitive deficit [61] through caspase 3 inhibition and avoiding neural death in the CA1 region of the hippocampus.

There is also a great variety of neuroprotective drugs or molecules that act closer by modulating inflammation, through the promotion of an anti-inflammatory microglial phenotype activation; only the most representative will be mentioned below.

DRα1 recombinant protein linked to the MOG peptide has demonstrated the ability to decrease macrophage migration and monocyte activation through its binding to CD74, which translates to a reduction in infarct size [62]. It has also been shown that it reduces proinflammatory cytokine expression, such as IL-1β, I-17, TNF-α, and INF-ϒ, as well as lowers T lymphocyte infiltration and promotes a polarization toward an M2 phenotype macrophage activation [63].

Cop-1 or glatiramer acetate is a copolymer formed by four amino acids (L-alanine, L-lysine, L-glutamic, and L-tyrosine) that has shown to exert neuroprotective effects by being able to reduce infarct size and improve neurological deficit [64]. Cop-1 increases the expression of IL-10, BDNF, Insulin-like growth factor-1 (IGF-1), and neurotrophin (NT-3) in the choroid plexus [65], and the cortex, which stimulates greater neurogenesis [66]. Mangin et al. and their study group obtained similar results; they reported that Cop-1 is capable of reducing COX-2, CD32, TNF-α, and IL-1β, as well as inducing greater neurogenesis and thus, reducing memory loss in mice with cerebral ischemia [67].

On the other hand, food strategies have also been proposed; for example, diet-induced ketosis has demonstrated its neuroprotective effects. Xu et al. observed, in 2017, that the ketogenic diet induced a reduction in infarct size through the overexpression of transcription factors HIF-1α, pAKT, and AMPK [68]; in 2018 Stefanovic, beneficial effects of administering exogenous β-hydroxybutyrate intraperitoneally were also observed in a model of cerebral ischemia induced by endothelin-1 in rats. He reported that the ischemic penumbra cells had a diminished glucose uptake, which translated into less ROS production, astrogliosis, and neuronal death [69]. Ketone bodies or ketosis is worth further exploration since clinical

Drug	Mechanism	Observed effect	Authors
Metformin	↓ AMPK ↓ Apoptosis	↓ Infarct size ↓ Neurological deficit	Deng et al. [55]
	↑ AMPK ↓ Apoptosis	↓ Infarct size ↓ Neurological deficit	Ashabi et al. [56]
	↓ AMPK ↑ BDNF ↑ P70S6K	↑ Memory ↑ Learning	Ghadernezhad et al. [57]
	↓ AMPK ↓ NFkβ ↓ IL-6 ↓ IL-1β ↓ TNF-α ↓ ICAM ↓ Neutrophils	↑ Protection of blood-brain barrier	Liu et al. [58]
Atorvastatin	↓ Aquaporin AQP4	↓ Infarct size ↓ Neurological deficit ↓ Edema	Cheng et al. [60]
	↓ pJNK3 ✥ Caspase 3	↑ CA1 neurons of the hippocampus	Shao et al. [61]
Ketosis	↑ HIF-α ↑ AMPK ↑ pAKT	↓ Infarct size ↑ Neural survival	Xu et al. [68]
	↓ ROS ↓ Astrogliosis	↑ Neural survival	Bazzigaluppi et al. [69]
DHA	↓ ● Macrophages ↓ ● Microglia ↓ Leukocyte infiltration ↓ TNF-α ↓ IL-6 ↓ IL-1β	↓ Infarct size ↓ Edema ↑ Protection of blood-brain barrier	Chang et al. [70]
	↓ Macrophages Neutrophils T lymphocytes B lymphocytes Infiltration ■ Polarization of macrophages to M2	↓ Infarct size ↓ Neurological deficit	Cai et al. [71]
	↑ Neurogenesis	↓ Infarct size ↓ Neurological deficit	Belayev et al. [72]

Drug	Mechanism	Observed effect	Authors
DRα-1MOG35-55	↓ Macrophages migration ↓ ● Monocytes	↓ Infarct size	Benedek et al. [62]
	↓ TNF-α ↓ IL-17 ↓ IL-1β ↓ INF-ϒ ↓ T lymphocytes ↓ Infiltration	↓ Infarct size ↑ Motor functions	Wang et al. [63]
Cop-1	Immunomodulation	↓ Infarct size ↓ Neurological deficit	Ibarra et al. [64]
	↑ IL-10 ↑ BDNF ↑ IGF-1 ↑ NT-3	↓ Neurological deficit	Cruz et al. [65].
	↑ Neurogenesis ↑ NT-3	↓ Neurological deficit	Cruz et al. [66]
	↓ COX2 ↓ Cd32 ↓ TNF-α ↓ IL-1β	↓ Infarct size ↓ Neurological deficit ↓ Edema ■ Memory	Mangin et al. [67]

◆, *regulation ;* ●, *activation.*

Table 1.
Main neuroprotective agents in ischemia.

trials in Alzheimer's patients with mild cognitive decline have shown improvements in verbal memory after being treated with a ketogenic diet [73].

Dietary administration with docosahexaenoic acid (DHA) has also proven to have anti-inflammatory and neuroprotective effects in cerebral ischemia through the reduction of proinflammatory cytokine expression, such as TNF-α, IL-1β and IL-6; even, a decrease in macrophage and microglial activation and a decrease in leukocyte infiltration to the lesion site [70]. Similar observations were made by Cai et al. who noted that macrophage, neutrophil, and T and B lymphocyte infiltration was significantly decreased, besides stimulating an anti-inflammatory macrophage (M2) activation [71]; DHA is also capable of inducing neurogenesis and angiogenesis [72], which makes it a promising molecule for future experimental research.

5. Neurorestoration

Many of the cytokines and growth factors that result from immunomodulation processes are directly involved in neurorestoration processes, the latter understood as the set of strategies that seek to reconstruct the affected neural circuits through neuroplasticity or neurogenesis [74].

Neurotrophins are a group of proteins that are involved in the maintenance and survival of the central nervous system [75]; this includes BDNF, NT-3, NT-4, NT-5, nerve growth factor (NGF), and IGF-1. Neurotrophins interact with two types of receptors, Trk (tyrosine kinase receptors) and the p75 receptor that belongs to the TNFR receptor family, implicated in apoptosis processes.

Among the most studied neurotrophins are BDNF and NT-3; BDNF is produced by almost all brain cells and is known to participate in processes of proliferation, survival, and neuronal differentiation. Its receptors are widely distributed [76] and activate critical signaling pathways such as PLCγ, PI3K, and ERK, which ultimately lead to phosphorylation and activation of the transcription factor CREB that mediates the expression of genes that are essential for the survival and differentiation of neurons [77]. NT-3 has also been involved in the processes of cell proliferation and differentiation through the notch pathway [78], as well as participating in processes of memory and learning [76].

Experiments have shown that the increase of neurotrophic factors in the ischemia model is commonly related to a better functional or memory recovery and that it is usually associated with neurogenesis or neuroplasticity—as in the case of metformin, which showed an increase in BDNF expression and that induced a more significant recovery of memory and learning [57]. Also, Cop-1 was able to induce the increase of BDNF, IGF-1, and NT-3; which correlated with the increase in neurogenesis [65]; and the experiments of Luan et al. showed that patients with cerebral ischemia who presented higher levels of NGF obtained a better functional recovery at 3 months after the ischemia [79].

Stem cell transplantation has also been linked to better neurological recovery; although clinical trials have not reported the expected results [80], basic research using stem cells has shown an increase in neurological rehabilitation and suggested mechanisms include the overexpression of BDNF and IGF-1 [81, 82], as well as immunomodulatory cytokines like IL-10, which together induce a polarization toward an anti-inflammatory M2 microglial phenotype [83].

In recent years, there has been an increase in the interest of studying how the external environment has a direct effect on the structure and neuronal function, that is, on neuroplasticity [84], and that is why researchers keep studying what kind of external characteristics (specifically physical and social activity) can increase these factors and thereby obtain more significant benefits.

In 2017, Chen et al. explored whether a specific type of environment stimulated the production of BDNF in rats with cerebral ischemia, and what they observed was that physical stimulation increases the expression of neurotrophic factors more than social stimulation and obtains a higher neurological recovery [85]. Mang, on the other hand, observed that the increase in BDNF after an ischemic event is determined by the type of aerobic exercise and the val66met variant of the BDNF gene [86].

The effects on NT-3 have also been evaluated, and the results have been very similar; there is an increase in its levels with physical stimulation after the ischemic event and a more significant functional recovery [87]. Other proteins have also been associated with neuronal plasticity through axonal growth, such as the growth-associated protein 43 (GAP-43), which has been observed to increase when rats with cerebral ischemia undergo fastigial electrostimulation [88].

Electrical stimulation directly into the fastigial nucleus (FNS) has proven to be beneficial in a model of MCAO [89]. The mechanism through which FNS has shown to improve walking balance and neurological scores is due to the activation of the PKA/cAMP pathway, suppressing the expression of Rho-Kinase, and through the overexpression of GAP-43 protein [89].

In this sense, experiments continue to be designed to establish the efficacy of training types and times to modulate inflammation, the production of

neurotrophins, and the impact on patient mobility, as in the proposal developed by Scalzo et al. [89] that gives rise to the continued development of a well-founded physical therapy for patients with cerebral ischemia.

6. Physical therapy as a coadjuvant to neural restoration through stimulation of neural plasticity

Post-stroke physical rehabilitation (PR) is of utmost importance as a non-pharmacological strategy for neuroprotection and neurorestoration but, most significantly, should be aimed at restoring and regaining motor impairment during the chronic period [90], and to promote the functional autonomy of the patient [4]. Recovery of body function assessment depends on whether the patients can perform everyday activities on their own and is measurable by several different scales such as UE-FM score for the upper extremity, and the Barthel Index for Activities for Daily Living scale [4].

Functional and cognitive deficit severity is related to tissue integrity [91], and it is not clear whether recovery results from biological processes or physical rehabilitation [91, 92]. Some clinical parameters that can be observed at the bedside, such as early finger extension and shoulder abduction, can act as predictors of long-term (over 6 months) recovery after stroke [93]. Spontaneous recovery of upper and lower limbs occurs depending on the type, location, and severity of the lesion, in approximately 60–70% of cases [93] during the first 2–6 months [4, 94], period after which most people believe they have achieved maximal recovery and stop with either physical or pharmacological therapy [4, 95]. Interventions should be designed according to the stage of neurological recovery the patient is in, with the consideration that early chronicity is not a contraindication for continuing rehabilitation [4].

Physical rehabilitation must start early, if possible, during the first week post-stroke [96], because there is an intensification in neuroplasticity during the early stages [91], employing different mechanisms such as the axon regeneration [88], and the higher expression of growth-promoting genes, such as GAP-43. This lesion-induced plasticity that happens during the first days post-stroke [90, 97, 98] reportedly lasts around 6 months after stroke [4, 91, 95, 97]. Also, therapy must continue after such a period, to take advantage of behavior-induced plasticity [95], which is still possible after 1 year of having had the stroke [4].

PR has also been proven to elicit neuroprotection and neurorestoration in other neurological disease models, such as Parkinson's, through the upregulation of BDNF and GDNF and prevention of inflammatory response [99]. The following therapies are currently under study for neurorestorative purposes during the post-stroke chronic period:

Environmental enrichment focuses on inducing adaptation to different environments, including toys and complex tasks, to improve functional outcomes [97]. Also, this type of therapy has shown to enhance angiogenesis by increasing CD31 and VEGF [97]. Furthermore, environmental enrichment upregulates BDNF secretion, and other neurotrophic factors [85, 90].

Wang et al. found improvements in spatial learning and memory, number of synapses, and an increase in the expression of synaptogenesis markers. GAP-43, a protein involved in neural plasticity through axonal growth, is upregulated during the first 28 days after stroke in mice exposed to environmental enrichment. Likewise, other markers involved in synaptogenesis like SYN and PSD-95 achieve better concentrations in the brains of mice treated with environmental enrichment [97].

Functional electrical therapy has been used alongside other types of electrical stimulation to induce repetitive muscular contraction to mobilize certain joints [6]. Somatosensory stimulation might enhance neurorehabilitation after stroke through the stimulation of corticomotoneuronal excitability [6]. It has been proposed that this type of therapy increases muscle strength, reduces spasticity, and facilitates voluntary movements, among other motor benefits [6].

Guided self-rehabilitation (GSR) is a method in which the intensity of training can be increased inside the home environment. While combined with conventional rehabilitation, it has proven to be efficacious in engaging the patients in their recovery through a contract between the patient and the therapist, allowing for an increased sense of responsibility and motivation for the patients, who are required to register their progress in a diary [100]. Although not many physical therapists accept such an approach [100], positive changes have been observed after 1 year of GSR and conventional rehabilitation in ultrasound measuring of the soleus' and medial gastrocnemius' thickness and fascicle length, as well as clinical improvement, observed in soleus extensibility and ambulation speed [101] in chronic stroke patients.

Constraint-induced therapy requires constraining the non-affected limb for 90% of the waking hours, forcing the patient to use the paretic limb, inducing the increase of use-dependent plasticity, although this therapy is not practical for most of the population [6].

Videogame- or virtual reality-based (VRb) therapies have been under study for upper extremity functional recovery in acute and subacute or chronic patients [91, 96, 99, 102]; the rationale for such approaches is that they promote motor learning and repetitive, intense movements, and in the specific case of virtual reality, the patient is exposed to interactive visual, auditive, and proprioceptive feedback [91, 102]. Different videogame and VRb therapies have reported improvements in fine dexterity, grip strength [96], and grasp force [99] in upper extremities, and, activities of daily living [91] and cognition [102] in young and elderly patients after several weeks of rehabilitation. Better results have been observed when combined with conventional therapy, although it is still not known whether it enhances or speeds up recovery [91].

7. Final remarks and future directions

In addition to continuing the search for pharmacological agents that allow the neuroprotection and neurorestoration of tissue affected by cerebral ischemia, the development of physical therapy and diet modification offers new horizons that have shown satisfactory results in the clinical setting in short times. However, it has not yet been possible to establish a protocolized treatment that can be added to the health care guidelines; so it is important to continue exploring all possible strategies to improve the quality of life of people who have suffered a cerebral infarction and that of their caregivers.

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