

The Importance Of Neuronal Plasticity In The Prognosis Of Cases Of Cerebral Ischemia: A Systematic Review

REVIEW

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Abstract

Background: Neuronal plasticity is the capacity that the neurons have to make new connections and enable new ways of transmitting information. Under this context, new methodologies are being addressed in order to measure how important this neuronal capacity is in the process of full recovery of learning in subjects who suffered damage from cerebral ischemia.

Methods: A systematic review was performed on the online databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) and Scopus, between 1998 and 2014. The MeSH (Medical Subject Headings) descriptors used in this review were: "neuronal plasticity", "brain ischemia" and "learning". We found 164 articles that, when screened, resulted in 46 articles that met the criteria of evidence and were included in this review.

Results: There are several ways available in the literature to increase neuronal plasticity to keep the learning process after bad conformations resulting from cerebral ischemia. We highlighted the most elucidated: those promoted by SMe1EC2 antioxidant, which brings therapeutic benefits when neuronal plasticity is impaired; and Atorvastatin, a statin which facilitates recovery of spatial learning. It is further observed that the body has a number of intrinsic devices,

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such as the endogenous compensatory mechanisms that contribute to the development of neuronal plasticity when there is brain damage caused by ischemia.

Conclusion: The improvement of neuronal plasticity appears in several studies mapped as a new and still little explored possibility of treatment of damages caused by brain processes of oxygen deprivation. Multiple devices, endogenous and exogenous, that promote an increase in neuronal plasticity, are being elucidated in an attempt to promote the full recovery of the learning process, decreased by brain damage from ischemic processes. Thus, it is pointed the necessity of scientific studies that allows to define and maximize the potentials of the neuronal plasticity.

Keywords

Cerebral Ischemia, Neuroplasticity, Neuronal Recovery, Learning Enhancement

Introduction

Chronic cerebral ischemia is the common pathological process of the development of various diseases, such as Vascular Dementia, Alzheimer's disease and Binswanger's disease, and eventually cause cognitive impairment [1, 33]. It was also noticed that the cerebral ischemia resulting from an inadequate supply of blood and oxygen to the brain due to cerebrovascular disease, cardiac arrest, or traumatic brain injury is often accompanied by neuropsychiatric symptoms [2, 3, 4, 92]. In an attempt to mitigate these negative consequences, the body develops some defenses, such as motor cortex neuronal changes within motor cortex that include up regulation of trophic factors, like BDNF, attacking increase in protein synthesis, synaptogenesis, and map reorganization [5, 120], because recovery might be enhanced not only by dampening inflammation, but also by increasing synaptic and structural plasticity [6].

Thus, it was realized that studies have their focus on endogenous conformations or procedures/exogenous substances that can mitigate the damage.

As examples of these, there Bone Marrow Stromal Cells (BMSC), which, when transplanted, were demonstrated to improve from the function of spatial learning and memory of rats with chronic cerebral ischemia [7, 33] and Netrin-1, a laminin-related protein, which ameliorates spatial memory impairment and improves synaptic dysfunction as observed by the recovery of population spike component of basal evoked potential and LTP in rats with global ischemia [8]. As example of these, there are atorvastatin (ATV), a statin that protects against ischemia-induced misbalance by blocking NMDA receptor downregulation GluN1, decreasing GluN2B upregulation, and restoring the association of GluN1 / PSD5 in clusters [9], and ceftriaxone, a β -lactam antibiotic that, when administered before the onset of the cerebral artery occlusion, was found to reduce infarct size [10].

Knowing that neuronal plasticity plays an important role in trying to recover the normal function of neurons after cerebral ischemia processes, this study was based on the following question: neuro-

nal plasticity, after the occurrence of cerebral ischemia, may reintroduce the learning process? And, if so, how is this reintroduction? Thus, this research was conducted through a systematic review aims to update the knowledge about the ability of neuronal plasticity in the reintroduction of learning after brain ischemia, identifying which are the endogenous and exogenous substances and conformations involved in such a process and, finally, identifying therapeutic approaches to guide the development of new research in the area.

Methods

With emphasis on prognosis in cases of cerebral ischemia, a qualitative systematic review of articles about the importance of neuronal plasticity was carried out on a basis of preselected data. A search of the literature was performed from the online databases MEDLINE and SCOPUS, between June 5 and July 18, 2014, from 1995 to 2014. The reason to establish the time limit between 1995 and 2014 was because there were more published articles in this period. However, it was noted the high visibility of this thematic field due to the higher proportion of current articles compared to the old. The search was focused on the MEDLINE and SCOPUS data from the following terms: 1. "Neuronal plasticity" (Medical Subject Headings) [MeSH term]; 2. "Brain ischemia" (Medical Subject Headings) [MeSH term]; 3. "Learning" (Medical Subject Headings) [MeSH term].

The choice of these three MeSH terms was made from a careful concatenation, which sought to define our central question of the article based on demand descriptors. Therefore, research strategies and articles were evaluated in different situations and with great scientific rigor to ensure proper sampling.

The analysis of the articles followed predefined eligibility criteria. We adopt the following inclusion criteria: (1) Original articles with full text online ac-

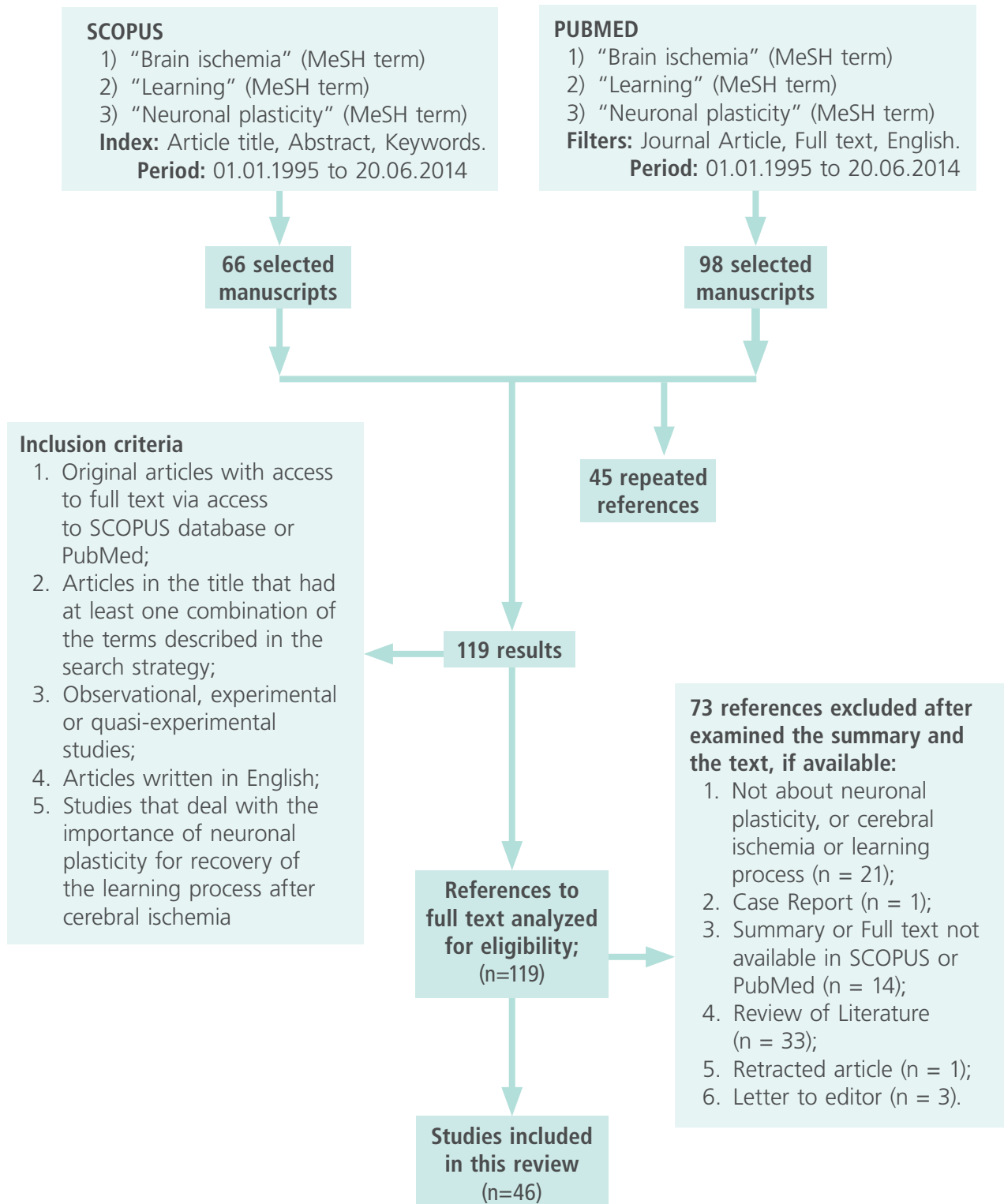
cess; (2) studies that contained in the title at least a combination of the descriptors; (3) observational, experimental or quasi-experimental studies; (4) Writings in English only; and (5) studies which focus on the importance of neuronal plasticity in the recovery of learning process after cerebral ischemia. Exclusion criteria were: (1) other projects, such as case reports, case series, literature review and comments; (2) The non-original studies, including editorials, comments, prefaces, brief comments and letters to the editor; (3) Items pictured; (4) productions that did not address the neuronal plasticity and cerebral ischemia or the learning process; and (5) the articles in which the objective of the study did not matched the theme pursued by the systematic review in question.

Then each item was read in its entirety and compositional elements extracted from them came in an array that included authors, publication year, sample description of the study and the main findings. Some studies dealing with pre-ischemic neuroprotection were also availed by the understanding that they have an intimate relationship with the post-ischemic neuronal plasticity.

Results

Initially the search using the strategies and criteria mentioned resulted in 98 articles in the PubMed and 66 articles in SCOPUS. 45 titles were excluded because they belonged to both databases. After an analysis of the title, abstract and body of the remaining references based on inclusion criteria of the study, the eligibility of those articles able to appear in the final text of the review, 73 articles were excluded and 46 articles were retrieved and included in the present study and in the final tables (**Figure 1**).

Table 1 shows an overview of selected articles as well as their main findings, methods of control and data publication

Figure 1: Flow diagram summarizing the procedure for selection of studies for review.

Abbreviations: MeSH, Medical Subject Headings

Table 1. Overview of selected articles.

Authors	Journal	Sample	Main findings
Gutierrez-Vargas et al. [9] 2014	Journal of Neuroscience Research	Male Wistar albino rats from our in-house, pathogen-free colony of the species at the vivarium at SIU, University of Antioquia, were kept on a 12 hr dark–light cycle and received food and water ad libitum. Three-month-old rats weighting 250–310 g were used. Fifteen rats per group were used for neurological scoring. Of these, nine rats in each group were subjected to spatial-learning and memory evaluation. Four or five rats per experimental group were dedicated for histological and biochemical assessments.	Our findings suggest that acute ATV administration after cerebral ischemia protects against morphological and functional brain damage and facilitates long-term spatial-learning and memory recovery by a GluN2B NMDA receptor subunit-dependent mechanism. ATV treatment restored neurological scores faster than placebo, prevented the appearance of pyknotic neurons, and restored MAP-2 and NeuN staining to control values in the somatosensory cerebral cortex and the hippocampus.
Tang Q et al. [60] 2013	Behavioural Brain Research	A total of 114 adult male Sprague Dawley rats weighing 200 to 250g were used In the study. All animals were kept on a 12 h light/dark cycle at 23±2°C room temperature. Rats with a neurological deficit score of 2 and 3, as evaluated at 2h after recirculation, were use in this study. Littermate rats were randomly assigned to one of four groups: normal control rats that did not receive middle cerebral artery occlusion (MCAO) (NC, n=18), rats that received only MCAO (MCAO, n=18), rats that additionally experienced environmental modification (EM, n=18), and rats that additionally received willed-movement therapy (WM, n =18).	Our previous [4] and present data indicated That WM training for rats could improve neurobehavioral Performance relative to EM and MCAO rats. The improvement of the motor performance might Be the result of a change in basal synaptic transmission Following the WM training
Li J et al [92] 2013	Biomedical Research (Japan)	Male mongolian gerbils, aged 13 to 16 weeks with a body weight of 60 to 80 g, were housed one to a cage in the Animal Center of our university on a 12-h/12-h light/dark cycle at a room temperature of about 23°C with free access to rodent food.	These results suggest that the recovery of spatial learning in group T-20 might not be due to functional recovery or cellular regeneration of hippocampal CA1 neurons themselves from the severe ischemic damage, but rather to functional compensation for the ischemia-induced damage to hippocampal CA1 neurons by neural networks of learning in the extra-CA1 regions.
Undén et al. [102] 2013	BMC Neuroscience	The animal experiments were performed on male Wistar rats, weighing 300-350 g (Møllegaard ' s Breeding Center, Copenhagen, Denmark), which were fasted overnight with free access to tap water.	We show that EPO has no influence on neuronal survival and delayed neuronal cell death in the CA1 region in the hippocampus, cortex and striatum of rats subjected to ischemia but treatment significantly preserved memory function.
Kim, S.Y. et al. [10] 2013	Restorative Neurology and Neuroscience	Twenty-three male 4 month-old Long-Evans hooded rats were used. Rats were received from Harlan Laboratories three months before the onset of experimental procedures, and made tame by handling to minimize stress during training. Animals were housed in pairs on a 12: 12 hour light:dark cycle, receiving water ad libitum.	The present findings of detrimental effects of ceftriaxone on motor behavioral outcome indicate the need for a more thorough characterization of dose-response and temporal profiles of post-ischemic treatment effects on behavioral function, and for careful consideration of the timing of its administration post-stroke.

Bayat et al. [8] 2012	Brain Research	Sixty male Wistar rats (Pasteur institute, Tehran, Iran; weighing 300–320 g) were used in this study. They were housed 3 per cage at a room with controlled temperature (23 ± 2 °C) and a relative humidity of $50\pm 10\%$, and maintained on a 12-h light–dark cycle with ad libitum access to food and water unless otherwise indicated.	The major findings of the present study showed that the intra hippocampal injection of netrin-1 dose-dependently and significantly ameliorated memory impairment and improved synaptic dysfunction as observed by recovery of population spike component of basal evoked potential and LTP in rats with global ischemia.
Zhang et al. [33] 2012	Life Science Journal	Bone marrow was obtained under sterile conditions from an 8-week-old rat	The mechanisms of spatial learning and memory improvement caused by BMSCs transplantation may be correlated with down-regulation of P75NTR and up-regulation of BDNF which thereby mediated synaptic activity, promoted dendritic and axonal growth, improved self-repair of the nervous system
Pagnussat et al. [120] 2012	Brain Research	Forty three male Wistar rats from a local breeding colony (ICBS, Universidade Federal do Rio Grande do Sul, Brazil) weighing approximately 300 g at the time of surgery were housed in standard plexiglass boxes, under 12:12 h light/dark cycle, in a temperature-controlled environment (20 ± 1 °C), with food and water available ad libitum, except during behavioral training and testing periods.	Our results support that skilled motor activity can induce brain plasticity after brain ischemia despite of no functional improvement in this experimental model of focal ischemia.
Adelson et al. [6] 2012	Neuron Report	KbDb KO mice, offspring of breeding pairs on a C57BL/6 background, were generously provided by H. Ploegh. C57BL/6 (i.e., KbDb WT) controls were purchased (Charles River). PirB KO and PirB WT controls were previously generated in C.J.S.'s laboratory. Mice were maintained in a pathogen-free environment	Motor performance in KO mice recovered to a greater degree than in WT, and infarct area was smaller in KO but only after 7 days and not 24 hr post-MCAO. This delay is consistent with the idea that mechanisms of synaptic plasticity and functional recovery take time and may be more fully engaged in KO mice.
Costa C et al. [58] 2011	Neurobiology of Disease	Hippocampal slices (thickness, 400 μ m) were cut from 1 to 2-month-old male Wistar rats (n=38) (Harlan, Italy) using a vibratome. Preparation and maintenance of hippocampal slices have been described previously. A single slice was transferred to a recording chamber and submerged in a continuously flowing Krebs' solution (34 °C; 2.5–3 ml/min) bubbled with a 95% O ₂ –5% CO ₂ gas mixture. The composition of the solution was as follows (in mol/L): 126 NaCl, 2.5 KCl, 1.2 MgCl ₂ , 1.2 NaH ₂ PO ₄ , 2.4 CaCl ₂ , 10 glucose and 25 NaHCO ₃ .	We found that NO/cGMP/PKG pathway exerts a critical role in the induction of the hippocampal iLTP and ZNS, at a non- anticonvulsant dose, reduces this pathological plasticity by modulating this biochemical pathway.
Cao et al. [154] 2011	Chinese Journal of Physiology	Adult male Wistar rats. Rats were randomly divided into 3 groups for treatment: sham operation (S, n = 8), I/R (I/R, n = 40), and I/R + UTI treatment (U, n = 40). The last 2 groups were divided into 5 sub-groups (8 rats each) for different I/R times (12, 24, 48, 72 and 168 h after reperfusion).	We found that UTI could improve spatial reference learning and memory in rats with I/R by down regulating S100 β -positive cells and preventing the loss of neural cells

List J et al. [40] 2011	Cerebral Cortex	Twelve patients with CADASIL (aged 48.3±8.3 years, range 36-67 years, 8 females) from 8 different families and 12 healthy volunteers (HV) (49.9±8.3 years, range 39-67 years, 8 females) were included in the present study.	The present findings suggest that in middle-aged individuals, the brain uses endogenous compensatory mechanisms, as indicated by increased rapid-onset cortical plasticity, to successfully counteract damage.
Spaccapelo L et al. [170] 2011	European Journal of Pharmacology	Male Mongolian gerbils (Charles River Breeding Laboratories, Calco, Italy) weighing 70-80 g were used. The animals were acclimatized to our housing conditions for at least 1 week before use, and were kept in air-conditioned colony rooms (temperature 21±1 °C, humidity 60%) on a natural light/dark cycle, with food in pellets and tap water available ad libitum.	The present data give direct evidence for the first time of the neuroprotective effect of melanocortin MC 4 receptor agonists.
Li et al. [88] 2011	Neurochemical Research	Male Wistar rats. The rats were randomly divided into four groups (n = 26), which were sham group (n = 6, normal saline 5.6 mg/kg/day, i.p.), NaHS group (n = 6, NaHS 5.6 mg/kg/day, i.p.), 2VO group (n = 6, normal saline 5.6 mg/kg/day, i.p.) and 2VO-NaHS group (n = 8, NaHS 5.6 mg/kg/day, i.p. post-2VO). Rats were reared for 3 weeks	We demonstrated the H 2 S content in hippocampus could be increased by treating with a certain concentration of exogenous H 2 S. H 2 S could improve impairment of learning and memory in brain-ischemic rats. The underlying mechanism was associated with improvement of synaptic plasticity
Zhu H et al. [144] 2011	Neuroscience Letters	Sixty-four male Wistar rats weighing 180-200 g. Rats were housed at 25 +1°C with a 12-h light/dark cycle with free access to food and water.	Our current study demonstrated that EE reversed spatial cognitive impairment and LTP deficits induced by CCH and enhanced expression of pCREB, synaptophysin, and MAP-2. Our study elucidated possible underlying mechanisms of cognitive impairment and improvement after CCH or exposure to an EE. Thus, exposure to an EE may be a promising therapy for reversing cognitive impairment after CCH.
Zhao Y et al. [104] 2011	Synapse	One hundred and forty-four male adult Sprague-Dawley (SD) rats (280-320 g) were used for experiments and were randomly divided into four groups of thirty-six rats in each: sham-operated 1 vehicle-treated (S 1 V), sham-operated 1 PROG (S 1 P), ischemia 1 vehicle-treated (I 1 V) and ischemia 1 PROG-treated (I 1 P). In each group, GAP-43 and SYP were detected on Day 3 (n 5 6), Day 7 (n 5 6), Day 14 (n 5 6), Day 21 (n 5 6), and Day 35 (n 5 6) after global cerebral ischemia. Twenty-four rats (six in each group) were used to count neuronal cell density 14 days after operation. Rats were kept under a 12-h light-dark cycle and allowed free access to food and water.	PROG stimulated the expression of GAP-43, blocked the down regulation of SYP and improved post ischemic synaptogenesis in the CA1 region of the hippocampus.

Gáspárová et al. [79] 2011	Interdisciplinary Toxicology	Male Wistar rats, 2 months old, weight 221 ± 11 g, n=40, from the breeding station Dobrá Voda (Slovak Republic, reg. No. SK CH 4004) were used. The rats had free access to water and food pellets and were kept on 12/12 h light/dark cycle. Animals were acclimated one week prior to the experiments.	The LTP-protective effect of SMe1EC2 found in the rat hippocampus exposed to model ischemia may prove beneficial in therapeutic application when neuronal plasticity is injured in some conditions including ischemia, trauma and aging in man. The mechanism of pyridoindole antioxidant effect in ischemic conditions may differ from the mechanism of its effect in control "normoxic" conditions.
Li S. et al. [57] 2010	Neuroscience	Twenty-six adult male Sprague–Dawley rats weighing 200–250 g were used to carry out the experiments (Experimental Animal Center, Tongji Medical College, Huazhong University of Science and Technology). They were housed with five per cage in a temperature and humidity-controlled room (temperature: 1 °C, humidity: 60%) with free access to food and water. The rats were kept in a 12-h light and dark cycle. The rats were adapted to housing conditions for at least 7 days before experiments. All of the rats were randomly divided into groups of sham-operated and ischemia	Our report would be the first to describe that the down regulation of HCN1 mRNA in the condition of chronic incomplete global cerebral ischemia induced by bilateral carotid artery ligation. The phenomenon opened new insights for further investigation of the physiological and pathological significances of HCN1 in chronic incomplete global cerebral ischemia
Gutiérrez-Vargas, J et al. [74] 2010	Neurochemistry International	Wistar albino male rats from the house colony of SPF (Species Pathogen Free) vivarium of SIU (Sede de Investigación Universitaria), at the University of Antioquia, Medellín-Colombia, were kept in a 12:12 h dark:light cycle and received food and water ad libitum. Three-month-old, adult, male Wistar rats weighting 300-350 g were used	Rac1 is a molecular pivot and convergent target of neuronal survival and plasticity pathways, and its feedback plays a crucial role depending on the specific ticular context and the time period after the cerebral damage to achieve structural and functional recovery
Samson, M.L. et al. [103] 2010	Journal of Pharmacology and Experimental Therapeutics	The animal holding rooms were on a 12-h dark/ light cycle, and water and food were provided ad libitum. Male Sprague- Dawley rats 250 to 330 g obtained from Charles River Canada (Montreal, QC, Canada) were used for experimentation	Taken together, these findings suggest that darbepoetin alfa reverses pre-existing spatial working memory deficits resulting from transient global ischemia by increasing the activity of nitric-oxide synthase, an enzyme implicated in synaptic plasticity.
Sun et al. [56] 2009	Nature Neuroscience	Stroke rats 72 h after 4VO; Sham surgery rats 72 h after 4VO.	TRPM7 suppression in hippocampal CA1 neurons in vivo is well tolerated, imparts resilience to ischemic damage, and preserves neuronal function and performance for hippocampus-dependent learning tasks after ischemic brain injury

Yao Y et al. [80] 2009	Phytotherapy Reserach	Male Wistar rats (6 weeks, 250 ± 10 g) were obtained from the Chinese Academy of Medical Sciences and were randomly divided into three groups, i.e. vehicle group, sham-operated group and quercetin-treated group. Rats in the vehicle and quercetin-treated groups were subjected to permanent bilateral occlusion of their carotid arteries to induce chronic cerebral ischemia and model the effects of VD. In the sham-operation group, the carotid arteries were exposed but not occluded.	In summary, this work showed that quercetin improved the performance of learning and memory of chronic cerebral ischemic rats, reversed the LTP deficit induced by ischemia and inhibited voltage-dependent sodium channels.
Giuliani D et al. [65] 2009	Brain, Behavior, and Immunity	We used male 8-9 week-old Mongolian gerbils (Charles River Breeding Laboratories) weighing 70-80 g (No. 116). They were kept in air-conditioned colony rooms (temperature 21 ± 1 C, humidity 60%) on a natural light/dark cycle, with food in pellets and tap water available ad libitum.	Here we show, for the first time, that short-term treatment of ischemic stroke with nanomolar amounts of the melanocortin NDP-a-MSH (agonist at MC 1, MC 3, MC 4 and MC 5 receptors produces long-lasting functional recovery associated with overexpression of the activity-dependent gene Zif268 in the hippocampus.
Ploughman et al. [28] 2009	Stroke	Thirty-two male Sprague-Dawley rats (Charles River Laboratories, Montreal, Canada) weighing 250 to 275 grams at the time of surgery were used in this study. Animals were housed in pairs in Plexiglas cages on a 12-hour reverse light/dark cycle with water and food ad libitum. All procedures were performed during the animals' dark phase.	BDNF is crucial for mediating the motor relearning that takes place as a result of post stroke rehabilitation. Strategies that increase BDNF broadly within the nervous system, such as exercise or BDNF infusion, may enhance neuroplasticity processes in multiple neuronal systems involved in motor relearning during stroke rehabilitation.
Askim et al. [121] 2009	Neurorehabilitation and Neural Repair	Patients admitted to the Stroke Unit, St Olavs Hospital, Trondheim, Norway, were screened on the following criteria: age 50 to 75 years, right-handedness, first-ever acute stroke diagnosis, 23 modified Rankin Scale (mRS) score of less than 3 before admission, paresis but no paralysis of the hand or arm item on the Scandinavian Stroke Scale (SSS), 24 Mini-Mental State Examination score exceeding 20, no language impairment, no intra cerebral hemorrhage on computed tomography, no previous neurological or psychiatric disease, living within 60-minute driving distance from the hospital, no MR imaging contraindications, and first fMR imaging within 4 to 7 days after stroke onset.	The main results showed that successful functional recovery was associated with similar activation patterns in acute and chronic phases, despite significant differences in hand function.
He et al. [75] 2008	Cellular and Molecular Neurobiology	Adult male Sprague-Dawley rats weighing 200-250 g were used (Experimental Animal Center, Tongji Medical College, Huazhong University of Science and Technology). They were housed 5 per cage in a temperature and humidity-controlled room (temperature: 22 ± 1 C, humidity: 60%) with free access to food and water. The rats were kept on a 12-h light/dark cycle. The rats were acclimatized to housing conditions for at least 4 d before being used.	Our findings suggest that chronic hypoperfusion decreases the contents of excitatory and inhibitory amino acids in rat brain and up-regulates the apoptosis-related protein: P53 and BAX. Piracetam inhibited the decrease amino acid content induced by chronic hypoperfusion, ameliorated the dysfunction of learning and memory in HP rats, down-regulated P53 and BAX protein, facilitated the synaptic plasticity, and may be helpful in the treatment of vascular dementia.

Maldonado et al. [112] 2008	Neurorehabilitation and Neural Repair	Twenty-eight 4-month-old and twelve 1- to 1.6-year-old female Long-Evans hooded rats that were bred at the University of Texas at Austin were pair housed and kept on a 12/12 h light/dark cycle with water access ad libitum. Animals were frequently handled 2 to 3 weeks prior to the experiment, and all behavioral procedures were carried out in the same room in which the animals were housed.	We did find a significant effect of rehabilitative training alone for spinophilin, a dendritic spine protein in the perilesion motor cortex, which may indicate that tray reaching produced synaptogenesis in this region
R.P. Allred, T.A. Jones [44] 2008	Experimental Neurology	Well-handled rats were pair housed with standardized housing supplementation (a PVC pipe piece and small wooden objects) on a 12:12 light/dark cycle. Animals were maintained on scheduled feeding (15-17 g/day) to motivate reaching performance.	The present results indicate that experiences with the less-affected forelimb can disrupt neuronal activity in the infarcted hemisphere in a manner linked to greater injury-induced impairments. Additional research is needed to address the timing and persistence of intact forelimb training effects, the causality of its relationship with peri-infarct neural activity, its molecular mechanisms, and the involvement of interhemispheric communication and corticospinal tract in these effects
He Z et al. [81] 2008	European Journal of Pharmacology	Adult male Sprague–Dawley rats weighing 200–250 g were used (Experimental Animal Center, Tongji Medical College, Huazhong University of Science and Technology). They were housed with 5 per cage in a temperature and humidity-controlled room (temperature: 22±1 °C, humidity: 60%) with free access to food and water. The rats were kept on a 12-h light (07:00-19:00) and dark (19:00-7:00) cycle. The rats were adapted to housing conditions for at least 7 days before experiments. All rats were randomly divided into groups of sham-operated, ischemia and ischemia treated with DDPH.	Administration of DDPH daily for 30 days abolished almost total inhibition of long-term potentiation in rats with chronic cerebral ischemia. These data suggested that DDPH could facilitate the synaptic transmission in hippocampus. These electrophysiology data also support our other results from cognitive studies and from morphology examinations that DDPH could ameliorate the learning and memory impairment and reduce neuronal injury in those chronic ischemic rats.
Huang et al. [73] 2008	Cellular and Molecular Neurobiology	Adult male Sprague-Dawley rats weighing 200-250 g were used (Experimental Animal Center, Tongji Medical College, Huazhong University of Science and Technology). They were housed five per cage in a temperature and humidity-controlled room (temperature: 22 ± 18C, humidity: 60%) with free F33access to food and water. The rats were kept on a 12-h light/dark cycle and adapted to these conditions for at least 7 days before experiments. All rats were randomly divided into groups of sham, ischemia and ischemia treated with hydroxyfasudil (1 mg/kg and 10 mg/kg).	In conclusion, our results demonstrated that activation of the Rho/Rho-kinase pathway is related to the neuronal damage and the pathogenesis of the spatial learning and memory impairment in BCAL rats. The relative long-term hydroxyfasudil treatment improved spatial learning and memory performance, increased the induction rate and amplitude of LTP and attenuated neuronal damage in this model. The neuroprotective effects of Rho-kinase inhibition by hydroxyfasudil could be attributed to at least two aspects: (1) up regulation of NR2B mRNA and protein expression; (2) reduction in oxidative stress.

Clarke, J. et al. [109] 2007	European Journal of Neuroscience	The experiments used adult male hAPP695 Tg rats (APP; n ¼ 22) and their non-transgenic littermates (NT; n ¼ 19), weighing 375-425 g at the time of surgery. A separate group of intact adult rats (n ¼ 6 APP, 5 NT) were used for biochemical analyses. Animals were individually housed in a temperature-controlled environment (20 ± 1C), with lights on 07.00-19.00 h. Food and water were available ad libitum, except during periods of food restriction for behavioral testing.	The current findings indicate that while APP overexpression does provide some histological neuroprotection following MCAO in rats, this does not translate into significant functional benefit. We suggest that while increased APP expression is protective acutely after stroke, the subsequent accumulation of Ab peptides in the brain may impede, and possibly worsen, functional outcome and recovery.
Hsu, J.E et al. [52] 2006	Experimental Neurology	Thirty-three male Long-Evans hooded rats (purchased or bred from Charles-River Laboratories) that were 3 to 4 months of age at the time of surgery were used. Animals were handled briefly everyday for a month before the onset of the experiment. The rats were housed in pairs in transparent cages and received water ad libitum.	Unilateral ischemic SMC lesions enhanced performance of a new motor skill task with the less-affected forelimb compared with sham operates.
Ruan Y.-W. et al. [14] 2006	Neuroscience	Male adult Wistar rats (200-300 g, Charles River, Wilmington, MA, USA) were used in the present study	In the present study, quantitative analysis indicates that CA1 pyramidal neurons undergo dendritic plasticity change after ischemia. A significant outgrowth occurs in the apical dendrites at 24h, which mainly results from the dendritic sprouting in the middle segment. In addition, many neurons display dendritic disorientation after ischemia with some basal dendrites coursing to the apical dendrite territory, and vice versa. These results demonstrate an ischemia-induced dendritic plasticity in CA1 neurons within 48 h after transient forebrain ischemia.
Ai and Baker [48] 2006	Experimental Brain Research	Animals were deeply anesthetized with 2.0-2.5% halothane and decapitated. The forebrain from rats was immediately removed (within 1 min) and maintained in an ice-cold artificial cerebrospinal fluid (ACSF) aerated with 95% O ₂ and 5% CO ₂ . Transverse slices of the forebrain containing the hippocampus (400 µm) were prepared from Sprague-Dawley rats 50-60 days old using a Vibratome	We have demonstrated a presynaptic hyperexcitability at the CA3-CA1 synapses following ischemic insult, and this enhanced response is Ca ²⁺ dependent. This ischemia-induced presynaptic hyperexcitability may at least partially account for the increased extracellular glutamate and the postsynaptic anoxia-LTP.
Matsumori Y et al. [152] 2006	Neurobiology of Disease	Male adult Sprague-Dawley rats (2.5 months of age, 230-0280 g) from Charles River Laboratory (Wilmington, MA) were used for all experiments and were housed in the institutional standard cages (41 25 19 cm; 2 rats per cage) before the procedures.	The main findings of this study are that post-ischemic EE combined with spatial learning increased DG neurogenesis and the neural stem/progenitor cell pool, enhanced neuronal differentiation, restored the perturbed DG immature neuroblast production

Briones TL et al. [59] 2006	Experimental Neurology	Adult male Wistar rats 3-4 months of age (with mean body weight of 325 g) were used in the study and transient global cerebral ischemia was induced by the four-vessel occlusion method as previously described. Wistar rats were used in the present study since this rat strain is commonly utilized in cerebral ischemia because it provides a good model for examining cerebral blood flow and metabolism.	The main findings of the present study are that: (1) ischemic injury and EC housing resulted in synaptic and dendritic changes in the hippocampal area adjacent to the site of injury, and (2) EC housing-induced synaptic and dendritic changes were accompanied by enhanced functional recovery after cerebral ischemia. Our results showed that transient global cerebral ischemia and behavioral experience in the complex environment independently resulted in increased number of synapses per neuron, and increased volume of dendritic processes and surface area of dendritic membrane per neuron in the CA2-CA3 of the hippocampus
Hwang IK et al. [41] 2006	Journal of the Neurological Sciences	This study utilized the progeny of Mongolian gerbils (<i>Meriones unguiculatus</i>) obtained from the Experimental Animal Center, Hallym University, Chunchon, South Korea. The animals were housed at constant temperature (23 °C) and relative humidity (60%) with a fixed 12 h light/dark cycle and free access to food and water.	Our results suggest that the impairment of AC-I may occur in the hippocampal CA1 region without any neuronal loss at early time after transient forebrain ischemia and that AC-I may be associated with impairment of neurodevelopment and neuroplasticity including learning and memory in the hippocampus after transient ischemic insult.
Dahlqvist P. et al. [145] 2004	European Journal of Neuroscience	Before operation male Sprague-Dawley rats (7-8 weeks old; B & K Universal Laboratory, Sollentuna, Sweden) were group housed four to five per cage in standard laboratory cages (595X380X200mm) at a temperature of 20-21°C with lights on 06:00-18:00h and with free access to water and food(standard rat chow).	The main finding of this study is that postoperative housing in an EE restored the spatial memory impairment after MCAo in rats. Furthermore, EE housing extinguished the association between poor spatial memory and large infarct volumes that was seen after MCAo in deprived rats
Dahlqvist P. et al. [145] 2004	European Journal of Neuroscience	Before operation male Sprague-Dawley rats (7-8 weeks old; B & K Universal Laboratory, Sollentuna, Sweden) were group housed four to five per cage in standard laboratory cages (595X380X200mm) at a temperature of 20-21°C with lights on 06:00-18:00h and with free access to water and food(standard rat chow).	The main finding of this study is that postoperative housing in an EE restored the spatial memory impairment after MCAo in rats. Furthermore, EE housing extinguished the association between poor spatial memory and large infarct volumes that was seen after MCAo in deprived rats
YOSHIOKA et al. [84] 2002	Pharmacological Research	Male Wistar rats (SLC Japan, Shizuoka) weighing 290-320 g were used at 9-10 weeks of age. They were housed in an animal room controlled at 22±2°C with a light/dark cycle of 12 h (light from 7:00 to 19:00) and given free access to food and water.	Ibudilast protects nerve cells from death due to cerebral ischemia by inhibiting Ca ²⁺ influx into cells or by inducing favorable changes in cerebral metabolism in addition to uncertain mechanism(s).

Farrell, R. et al. [148] 2001	Neuroscience	This experiment used 84, 4-5-month-old female Mongolian gerbils (<i>Meriones unguiculatus</i>) weighing 50 [^] 76 g (High Oak Ranch, Baden, ON, Canada). Animals were housed in groups of five in standard plastic laboratory cages on a 12/12-h light/dark cycle. All experimental manipulations were performed during the light phase. Food and water were freely available. Three days after surgery/sham occlusion (see below) animals were housed either five per cage (enriched condition) or singly (non-enriched condition)	The main findings of this study were that environmental enrichment attenuated the behavioral abnormalities associated with IP but paradoxically, enrichment increased the loss of CA1 neurons
Mori K. et al. [83] 2001	Behav Brain Res.	Adult male Wistar rats (280-360 g b.w. and 8–13 weeks old) were used (Slc:Wistar:ST, Shizuoka Laboratory Animal Center, Hamamatsu, Japan). The animals were housed in a room with a 12-h light (07:00-19:00 h)-dark (19:00-07:00 h) cycle and were allowed food and water freely. In each experiment, different rats (five-ten) were used except in the behavioral studies. In the behavioral studies, a Y-maze test was conducted 1 day after the open field test using the same rats.	These results suggested that reduction of LTP in the perforant path-dentate gyrus synapses, a gate for novel information, might result in faulty passing of information to the CA3 and/or CA1 region resulting in memory dysfunction. In contrast, restoration of LTP in the perforant path–dentate gyrus by administration of aminoguanidine might open the gate to novel information resulting in the successful passage of information to the CA3 and/ or CA1 region. Since LTP in mossy fiber–CA3 synapses was not influenced by 4-VO or administration of aminoguanidine, processing of novel information in the CA3 region instead of the CA1 region via the dentate gyrus might contribute to the prevention of memory dysfunction.
Briones et al. [153] 2000	Biological research for nursing	Thirty-eight adult female Wistar rats age 65 to 75 days old and weighing 275 to 350 g at the time of surgery were included in the study. Female animals were used in this study because it has been shown that they are more sensitive to plastic changes (Woolley and McEwen 1994). All animals were housed individually in a temperature-controlled environment (25 °C) with free access to standard rodent food and water. The animals were handled daily and maintained on a reverse light-dark cycle (lights on at 6:00 PM and off at 6:00 AM).	Our results showed that ischemic rats exposed to an enriched environment performed as well as controls in the spatial learning task. In comparison, ischemic rats housed in standard environment, although able to learn, demonstrated a slower rate of learning and a higher asymptotic level of learning (did not reach control levels even on days 5 and 6) in both swim latency and directional heading error.

Kiprianova I et al. [34] 1999	Exp Neurol.	Global cerebral ischemia was achieved in adult male Wistar rats (450-600 g) with four-vessel occlusion under halothane/nitrous oxide. Both vertebral arteries were coagulated, followed by the transient occlusion of both common carotid arteries for 10 min. In sham-operated control animals, both vertebral arteries were coagulated and the carotid arteries were exposed, but not occluded. The left femoral artery was cannulated with PE-50 polyethylene tubing for continuous monitoring of arterial blood pressure and blood sampling for analysis of arterial blood gases. The temperature was recorded with a rectal thermistor and maintained between 37.0° and 37.5°C with a feedback-controlled heating lamp. Animals were returned to their cages after the surgical procedure with free access to water and standard rat chow. BDNF was administered by an osmotic minipump which was implanted after the reopening of the carotid arteries.	We described for the first time improved cognitive functions associated with a recovery of synaptic transmission after transient forebrain ischemia. These data provide further evidence for the neuroprotective effects of BDNF after lesions of the adult brain and indicate a therapeutic potential in acute neurovascular disease
Stroemer et al. [89] 1998	Stroke	Nonfasted male SHR (weight, 260 to 300 g) were anesthetized with halothane (4% induction/1% maintenance), placed on a heating pad, and given an antibiotic (streptomycin, 0.10 mL, 150 mg/mL IP). SHR were used to ensure constant infarction volume and placement because of poor collateral circulation and consistent vascular anatomy.	D-AMP treatment in concert with performance of behavioral tasks can selectively up regulate neurite growth in those neural circuits able to subserve the behavioral function tested, despite the loss of the original pathways. Thus, physical therapy during the effective window of D-AMP treatment may improve recovery in patients with cortical ischemia and trauma.
Mizumori SJ et al. [123] 1995	Behav Neurosci.	Nineteen Wistar male rats (175-225 g; 6-8 weeks old; Hilltop, PA) were housed, 2 each, to a hooded, ventilated cage in animal quarters that were temperature and humidity controlled and on a controlled light-dark cycle. They were fed ad libitum and had free access to water for 7 days prior to the surgical procedure.	The results of this study provide the first evidence that the ischemic hippocampus undergoes long-term functional reorganization that might contribute to the initially impaired acquisition of a spatial task

Discussion

Generally, the reviewed articles were based on the mensuration of the influences, in the prognosis of the cerebral ischemia, of some predetermined exogenous substances, some already known endogenous substances or of the behavior of the sample studied. Nevertheless, to provide better analysis and following the progress of the investigation, the articles that focused on these three main themes were discussed in other themes that they also have pointed interesting views, such as Enriched Environment (EE), Endogenous Conformations and The Effects of Motor Activities Practice on Neural Plasticity.

Endogenous Conformations

There are several unique mechanisms developed by the body, seen in the present study, which are important to the control of the cerebral damage caused by ischemic processes, once ischemia induces changes in neuronal excitability and alters dendritic spines within hours. [11-13, 6] The alteration of dendritic arborization directly affects the number of spines, and thus the function of the neurons [14]. It was proved that one of the main factors underlying learning and memory formation at the cellular level is long-term potentiation (LTP), [15, 16, 40] considered a major synaptic mechanism underlying hippocampus-dependent learning and memory, [17-19, 34] which is N-methyl- D -aspartate (NMDA) receptor and voltage dependent and requires an increase in intracellular concentrations of calcium ions. [20, 21, 48]

One mechanism possibly contributing to sensorimotor deficits and recovery is an altered balance between excitatory and inhibitory neurotransmitter receptors [22]. Previous work suggests that blockade of α_2 adrenoceptors enhances sensory responses at the spinal cord level, possibly contributing to the improved performance of ischemic rats in a test assessing tactile/proprioceptive limbplacing reactions [23, 22]. Besides, there is significant neuroprotection in the absence of either the innate immune receptor

PirB or two of its MHCI ligands Kb and Db by using *in vivo* and *in vitro* ischemia models [6]. It was also demonstrated that Rho/Rho-kinase pathway is involved in the modulation of N-methyl-D -aspartate (NMDA) receptor function, [24, 25, 73] which may be associated with learning and memory processing and disruption of the gene for NR2B in mice causes perinatal lethality. [26, 73]

Another important endogenous molecule that significantly contributes to the learning recovery in post-ischemic processes is the BDNF (Brain Derived Neurotrophic Factor), which is one of a family of neurotrophins that influences neuronal proliferation, survival, and differentiation [27, 28] as a result of binding to its tyrosine kinase receptor and subsequent downstream activation of several signal transduction pathways, [28] in addition to has pleiotropic effects on modulating activity-dependent forms of synaptic plasticity, neuronal survival, neuronal development, dendritic arborization and axon growth. [29, 30, 33]

It has been speculated that BDNF is involved in the maintenance of LTP, [31, 32, 34] fact that occurs because a decrease in BDNF expression can cause neuronal death or axonal damage. [33] It was demonstrated that intracerebroventricular infusion of BDNF can restore almost completely both synaptic transmission and memory capacity [34] and that strategies that increase BDNF broadly within the nervous system, such as exercise or BDNF infusion, may enhance neuroplasticity processes in multiple neuronal systems involved in motor relearning during stroke rehabilitation. [28] This motor learning increases BDNF levels in the cortex, which may contribute to cortical map reorganization, increased synaptogenesis, enhanced dendritic spine formation and branching, and other forms of neuronal plasticity implicated in recovery after stroke. [35-38, 28] This occurs because BDNF elevates intracellular Ca^{+2} in hippocampal neurons, stimulates phospholipase C/protein kinase C pathways, and increases the number of calbindin containing neu-

rons in hippocampal slice cultures. Several lines of evidence indicate that calcium ions play a central role in the delayed neuronal death observed in the CA1 region of the hippocampus after transient forebrain ischemia. [39, 34] It was also exposed that the mechanism of recovery of spatial learning and memory may be relevant to BMSCs (Bone Marrow Stromal Cells) transplantation by mediating the expression of BDNF and P75NTR, after transplanted the BMSCs. [33]

There is, also, other metabolic pathways necessary to combat the cerebral ischemia, like that present when chronic hypoperfusion, as in CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), might induce compensatory brain plasticity. [40] Besides, significant increases of AC-I immunoreactivity and its protein level were detected at 3h after ischemic insult. This result may be associated with the compensatory mechanisms to ischemic damage. [41] Among these subtypes of AC (Adenylate Cyclase), AC-I and AC-VIII are mainly detected in brain and play an important role in signal transduction underlying some forms of learning and memory function. [42, 41] The mechanisms underlying this increased plasticity may include release of neurotrophic factors. [40] As an example of these factors, there is the transcription factor, Δ FosB, which is cumulatively and persistently expressed in response to repeated neuronal activation. [43, 44] It was proved that it increased reliance on the intact forelimb in tests of coordinated forelimb movements, once that unilateral lesions increased FosB/ Δ FosB neuronal density in layer II/III of remaining SMC (Sensorimotor Cortex) near the infarct after impaired forelimb training; however, early intact forelimb training reduced this expression. [44] The glutamate, also, is very important because plays an important role in dendritic development via activation of AMPA and NMDA receptors, [45, 46, 47, 14], and, furthermore, an increased glutamate release is one of the mechanisms leading to neuronal death following ischemic

stroke. [48] As an example of an AMPA receptor dependent protein, there is the PICK1 (Protein Interacting with C kinase 1), which has been proven to be one of the key proteins in the regulation of synaptic plasticity. [49-51, 60]

A highlighted approach is the contralesional brain compensation after an ischemic damage. Some of the contralesional changes are associated with enhanced ipsilesional function. [52] Following unilateral cerebral damage, humans and other animals develop a compensatory hyper-reliance on the less-affected body side ipsilateral to the injury. [53, 44] The enhanced ipsilesional function might aid in behavioral compensation but might also make animals more prone to disuse the impaired forelimb, contributing to the phenomenon of learned-nonuse. [54, 52] The intact hemisphere develops an exaggerated disruptive influence over the infarcted hemisphere which is linked with worsened outcome. [55, 44] These findings suggest that the intact hemisphere can negatively impact function of the impaired body side. [44]

It is noted the influences of other endogenous mechanisms, such as TRPM7 (Transient receptor potential cation channel, subfamily M, member 7) suppression in hippocampal CA1 neurons in vivo is well tolerated, imparts resilience to ischemic damage, and preserves neuronal function and performance for hippocampus dependent learning tasks after ischemic brain injury. [56] The cationic channels are essential for the transport of ions such as Na⁺, because the long-lasting enhanced PR (Presynaptic Response) following ischemia may result in a significant enhancement of Na⁺ influx to the presynaptic terminals, which may play an important role in both Na⁺ - glutamate transporter - or exocytosis - mediated glutamate release that is detrimental to the postsynaptic neurons. [48] Besides the TRPM7, the HCN1 mRNA was shown to be decreased significantly in the hippocampal CA1 area and neocortex in the chronic ischemic rats with possible features of vascular dementia. Down regulation of

HCN1 mRNA led to decrease of HCN1 channels expression. It is definite that HCN1 channels play a key role in function of learning and memory. [57] There is, still, the endogenous Nitric Oxide, which plays a critical role in the induction of hippocampal iLTP (post-ischemic LTP). In fact, iLTP is blocked by either L-NAME, a non-selective NOS inhibitor, or 7-NINA, a relatively more selective inhibitor of nNOS. [58] The LTP is considered as one of neural activations for long term memory. [41]

There are studies that suggest that rehabilitation therapies may be able to remodel neuronal circuitry within the injury site and its surrounding region and that such restructuring contributes to "recovery" of function that is compromised by the injury. [59] There are data showing that WM (Willed Movement) training led to a larger amount of LTD (Long Term Depression) compared to MCAO (Middle Cerebral Artery Occlusion) rats and EM (Environmental Modifications) rats, and WM training facilitated motor recovery after focal ischemia in rats. It can be inferred that a 'therapeutic' effect that might be due, at least partially, to stimulation of LTD-related synaptic neuroplasticity. [60]

It is noted, also, that melanocortins afford a strong neuroprotection against damage consequent to global or focal cerebral ischemia in gerbils and rats. They act by blocking several ischemia-related mechanisms of damage, through the activation of central nervous system (CNS) melanocortin MC 4 receptors, and in a broad therapeutic treatment window. [61-64, 65] This effect occurs through a counteraction of the main ischemia-related, early developed mechanisms of damage, and is associated with long-lasting improvement in functional recovery accompanied by overexpression of Zif268, an immediate early gene required for synaptic plasticity and memory formation and involved in injury repair. [61, 62, 63, 65, 70] Also known as Egr-1, Krox-24, NGFI-A, TIS8 and ZENK, this gene belongs to the early growth response gene family, and the expression of these immediate early genes is de-

pendent on synaptic activity and is used as a marker of neuronal functionality. [66-69, 65] Thus, the data showing a significant increase in Zif268 levels in the whole hippocampus of melanocortin-treated animals point to a gain in the number of activated/functional neurons. [70]

Lastly, a neuronal plasticity involves cytoskeletal remodeling, where the Rho GTPases, a subgroup of proteins from Ras superfamily, are major players, participating in neuritic outgrowth, differentiation, axonal guidance, dendritic spine formation and maintenance. [71, 72, 74] Nevertheless, there is data providing novel information for the importance of Rho-kinase inhibition in improving the deficit of cognition and the ability of spatial learning and memorizing in chronic ischemia. [73] It is important to point, too, that in vitro studies revealed that the Rac1 inhibition (pharmacological and dominant negative mutant) induced neuronal death, and the Rac1 activation (constitutively active mutant) produced neuronal survival. [74]

The role of the exogenous substances

This systematic review notified the existence of several exogenous substances which, when actuate in many conformations of the organism, are important to the recuperation process provided by cerebral ischemic damages, related to cognitive impairment and neuronal death. [75] Among these, there are the Ceftriaxone, the Hydrogen Sulfide, the new pyridoindole antioxidant SMe1EC2, the Piracetam and the D-amphetamine sulfate.

The Ceftriaxone, a β -lactam antibiotic, selectively increases GLT1 expression and the functional capacity of glutamate uptake. [76, 10] On the other hand, the Piracetam, a gamma-aminobutyric acid derivative, attenuated apoptotic-like changes and neuron losses and reversed the shift in the expression pattern apoptosis-related proteins (BAX and P53) induced by ischemia in the cortex. [75] In experimental stroke, ceftriaxone injected prior to the onset of middle cerebral artery occlusions (MCAo) has been

found to reduce infarct volume. [77, 10] In a similar way, piracetam could facilitate the synaptic transmission in hippocampus. [75] Some findings suggest that the neuroprotective effects of ceftriaxone, in particular its ability to reduce infarct volume, may be maximized when ceftriaxone is injected prior to ischemia, enabling astrocytic glutamate uptake to be enhanced at the onset of the stroke. [10] This Ceftriaxone effect is similar to the mechanism of facilitating the electrophysiology in rat brain of piracetam, which may be explained by the effects of the increase of the content of glutamate, the key excitatory neurotransmitter in central nervous system and related to the excitatory synaptic transmission and neuron plasticity. [78, 75] Nevertheless, some other substances do not show a direct relation with the glutamate, such as the pyridoinole antioxidant SMe1EC2, which presumably contributes to the preservation of the neuronal cell membrane and to its permeability, and further by its inhibitory effect on carbonylation of proteins mediated by conditions involving oxidative stress, and thus SMe1EC2 might protect neurons from damage of membrane lipids and protein receptors. [79]

Other antioxidant substances play an important role on the post-ischemic damages recuperation and on the protection of endogenous mechanisms that control the spread of these damages, such as LTP. The Quercetin, for example, protects against LTP changes in the hippocampus induced by chronic cerebral ischemia. [80] Besides the Quercetin, the effect of the DDPH, 1-(2, 6-dimethylphenoxy)-2-(3, 4-dimethoxyphenylethylamino) propane hydrochloride, categorized as a competitive $\alpha 1$ -adrenoceptor antagonist, facilitates the synaptic plasticity, which might be related, at least, to its antioxidant property and the up-regulating expression of NR2B. [81] Similar as the quercetin can alter the cognitive deficits induced by different methods including transient cerebral ischemia, [82, 80] the DDPH was shown to significantly attenuate the neuronal damage and to ameliorate the cognitive deficits. [81]

Moreover, it was noted the influence of specific inhibitors in suppressing the expansion of the post-ischemic damage. Behavioral performance, i.e. Y-maze and contextual fear conditioning, was impaired following transient cerebral ischemia, and the impairment was ameliorated by the administration of aminoguanidine, a relatively selective iNOS inhibitor, [83] for example. Other notable substance involved in this inhibition process is the ibudilast, a phosphodiesterase inhibitor. It protects nerve cells from death due to cerebral ischemia by inhibiting Ca^{2+} influx into cells or by inducing favorable changes in cerebral metabolism in addition to uncertain mechanism(s). [84]

Studies suggests, still, that the Nitric oxide (NO) is an intercellular retrograde messenger, originally described as an endothelial relaxation factor, which has been shown to be involved in several physiological processes such as hippocampal long-term potentiation (LTP), plasticity, learning, and memory. [85, 86, 58] The levels of NO metabolites, NOx, were increased following transient cerebral ischemia. [83] Experimental studies have shown that ZNS (Zonisamide) inhibits NO synthase in the hippocampus following NMDA administration suggesting a possible neuroprotective effect via a reduction of NO formation. [87, 58] iNOS inhibitors seem to be more appropriate for clinical targets in ischemic insult. In the previous reports, the effects of nNOS on learning and memory were still controversial. [83] Besides, studies indicate that NOS inhibitors do not modify the iLTP once established indicates that NO production is necessary for the induction of this form of pathological synaptic plasticity, but not for its maintenance. [58]

The GAP-43 is a nervous tissue specific protein, which is highly expressed in neurons during development and nerve regeneration, and has been implicated in neurite outgrowth, long-term potentiation, signal transduction and neurotransmitter release. [88] Some exogenous substances could elevate the expression of this protein, such as the D-ampheta-

mine sulfate (D-AMP). Since an important outcome measure is recovery of function, it is meaningful to correlate the expression of GAP-43 and synaptophysin with functional outcome in D-AMP-treated compared with vehicle-treated rats. [89] Beyond this, there is, also, the H_2S , that could inhibit the edema around pyramidal neurons and the nuclear shrink induced by ischemia, promote the expression of GAP-43 in the CA1 region of post-ischemic hippocampus, and decrease the injury of neurons caused by ischemia. [88] D-AMP treatment improves behavioral recovery not only in the sensorimotor task of the forelimb behavior but also in the spatial memory tasks. [89] The spacial memory recovery is provided, also, by the atorvastatin administration. Findings suggest that acute ATV administration after cerebral ischemia protects against morphological and functional brain damage and facilitates long-term spatial-learning and memory recovery by a GluN2B NMDA receptor subunit-dependent mechanism. [9]

Behavioral determinants

It was shown that the hippocampal synaptic plasticity is considered to be the cellular basis of learning and memory in the brain. [90, 92] For example, in relation to the Gabaergic receptor, altered receptor binding in the hippocampus would contribute to spatial learning deficits. [22] There are findings indicating, also, that a different function for HCN1 channels is found in hippocampal CA1 neurons. Deletion of the HCN1 channel in forebrain neurons results in an unexpected exchange of spatial learning and memory. [91, 57] Besides, it was demonstrated that, after a transient cerebral ischemia, the number of CA1 neurons in the bilateral hippocampi decreased with increased time of occlusion of the bilateral carotid arteries. [92]

There is data that directly relate the hippocampal conformations to the post-ischemic behavioral consequences, because hippocampal [3H]AMPA receptors might be involved in compensatory behavior

developed by ischemic rats in order to overcome spatial learning deficits. [22] Results show, still, that the HCN1 channels play a key role in function of learning and memory. Both down regulation of HCN1 mRNA and knockout of HCN1 could lead to impairment of learning and memory function. [57] Data also suggests that the recovery of spatial learning in a group of rats after 20 days post ischemic procedure might be due to functional compensation for the ischemia-induced damage to hippocampal CA1 neurons by neural networks of learning in the extra-CA1 regions.[92]

The role of the endogenous substances

A variety of endogenous substances were observed, beyond those exogenous ones, which act by different mechanisms. These substances have an extremely importance to the complete recovery of patients affected by processes of oxygen deprivation. Among these, it is known the Ulinastatin, the melanocortins, the Netrin-1 protein, the amyloid precursor protein (APP), the hormones - progesterone and erythropoietin - and the synthetic form of this one, the darbepoetin alfa.

Melanocortins with the adrenocorticotropin/α-melanocyte-stimulating hormone (ACTH/α-MSH) sequences, as well as shorter fragments and synthetic analogs, have a protective and life-saving effect in animal and human hypoxic conditions. [93-97, 65] MC3 and MC4 are the predominant melanocortin receptor subtypes expressed in the CNS. [70] That short-term treatment of ischemic stroke with nanomolar amounts of the melanocortin NDP-α-MSH (agonist at MC 1, MC 3, MC 4 and MC 5 receptors) [61-63, 65] produces long-lasting functional recovery associated with overexpression of the activity-dependent gene Zif268 in the hippocampus. [65] Thus, there is data that give direct evidence, for the first time, of the neuroprotective effect of melanocortin MC4 receptor agonists. [70] Besides, Zif268 upregulation in the hippocampus of melanocortin-treated animals could have had

a key role in learning and memory recovery after stroke. [65]

Among the hormones involved with the enhancement of neuroplasticity, there is the Erythropoietin (EPO). The EPO gene is regulated by hypoxia inducing factor (HIF), where it stimulates erythropoiesis and proliferation of parenchymal cells. [98-100, 102] In the brain, EPO is neuroprotective and has also brain restorative properties in different models of acute neuronal death and neurodegenerative diseases, through effects on neurons and astrocytes by multimodal actions. [101, 102] Concomitantly, it was noted the influence of the synthetic form of the Erythropoietin, the Darbepoetin alfa, whereupon findings suggest that erythropoietins such as Darbepoetin alfa may improve cognitive performance in humans by activating the NOS signaling pathway. [103] Like its analogues covalents, we conclude that intravenous EPO administration after global ischemia does not protect against ischemic brain damage, but protects against loss of synaptic function important for working and spatial memory. [102] Other hormone involved in the enhancement of the neuroplasticity in patients affected by cerebral ischemic processes is the progesterone, which has several positives characteristics in relation to cerebral activity, because the progesterone increases GAP-43 and SYP levels in the CA1 region of the male rat hippocampus. In conjunction with previous studies, it appears that PROG-induced increases in the cognitive function of rats may be influenced by the effect of PROG on hippocampal synaptogenesis and synaptic plasticity. [104]

Among the important proteins in the ischemic process recovery, there are: Rac-1, Netrin 1 and BDNF. In vitro and in vivo findings suggest that the inactive state of Rac is present in neuropathological condition, even implying abnormal neuronal survival in a part of the neuronal population during the acute and middle phase after ischemia. [74] The intrahippocampal injection of netrin-1 dose-dependently and significantly ameliorated memory

impairment and improved synaptic dysfunction. [8] Results provide the first direct demonstration that BDNF is crucial for mediating the motor relearning that takes place as a result of poststroke rehabilitation. [28] It is also possible that netrin1 in some ways could act like growth factors including brain-derived neurotrophic factor (BDNF). [105, 8] Stroke rehabilitation strategies that increase BDNF broadly within the nervous system, such as exercise or BDNF infusion, may enhance neuroplasticity processes in multiple neuronal systems involved in motor relearning during stroke rehabilitation. [28] Besides these cited proteins, there is a specific class of proteins, the glycoproteins, highlighting two involved in neuronal plasticity process. Firstly, there is the Ulinastatin -a urinary trypsin inhibitor-, which became an endogenous positive factor, actuating in the neuroplasticity once it is considered cytoprotective against I/R injury in the liver, intestine, kidney, heart and lung through its anti-inflammatory activity. [106, 107, 154] Furthermore, there is the Amyloid precursor protein (APP) is a transmembrane glycoprotein, which is widely expressed in the brain. APP and its products are proposed to have a number of important physiological roles in the nervous system, including development, synaptic function and plasticity, and cellular response to stress. [108, 109] Nevertheless, there are findings indicating that while APP overexpression does provide some histological neuroprotection following MCAO in rats, this does not translate into significant functional benefit. [109]

The effects of motor activities practice on neural plasticity

The neuroplasticity involves various ways to establish that new connections in cortical networks could be effectuated, providing a new information flow. Studies suggest that motor learning mechanisms may be operative in stroke recovery and possibly reinforced by rehabilitative training. To maximize functional rehabilitation in patients with stroke, it is necessary

to explore the basic changes in brain plasticity in response to different treatment approaches. [121]

In view of the importance of the way that the approach is going to be made, it is noted that the enhancement of the cortical reorganization can be done by motor experience. These experiences shall be effectuated in a way to follow a specificity, because studies conclude that skilled motor can induce brain plasticity after brain ischemia. [120] In relation with it, it was performed a new way to improve the motor ability following a cerebral ischemia, such as the Willed-movement (WM) training, which is defined as a voluntary motor training through which an individual pays attention to a goal and makes an effort to accomplish it. [110, 60] WM therapy [111, 60] involves more coordinated activities of the whole body and limbs. [60] Nevertheless, some studies show that in a traumatic brain injury model, animals receiving voluntary exercise early post-injury (days 0-6) were found to have reduced expression of plasticity-related proteins in the hippocampus and worsened water maze performance compared to animals exercised between 14 and 20 days after injury. [113, 112] Despite this evidence, data also clearly showed that WM training led to a larger amount of LTD compared to MCAO rats and WM training facilitated motor recovery after focal ischemia in rats. [60] This apparent contradiction is explained when it is pointed that although exercise can be beneficial, learning motor skills results in neuronal structural and functional plasticity in the motor cortex and cerebellum that is not found with simple exercise or repetition of previously learned skill, [114-116, 112] since learning may more effectively induce activity-dependent plasticity than mere use, at least in some of the brain regions that mediate motor movements. [112] For example, the primary motor cortex- M1 is involved in the process of motor learning and that learning-associated activity in M1 can be greater in magnitude and areal extent than the activity associated with simple motor use

either in healthy or in lesion conditions. [117-119, 120]

Studies prove the occurrence of structural changes in the brain after the ischemia. The structural changes should require the synthesis and/or redistribution of various neuronal proteins necessary for motor learning. [120] They are, generally, beneficial, because the successful functional recovery after ischemic stroke seems to be linked to reemergence of a lateralized motor network combined with plasticity in bilateral somatosensory association areas and contralesional SII. [121] It was, nevertheless, observed no significant modification in protein expression in undamaged cortex. [120] Thus, such changes may be the natural evolution of functional recovery but may also be enhanced by the given treatment. [121] However, in patients with stroke, the underlying structural pathologic condition resulting from the ischemic episode will recruit additional regions or networks to compensate for the functional deficit, [122, 121] because the cellular activity in multimodal association cortex undergoes long-term functional reorganization. [123] Thus, a general principle of neuronal responses to brain injury may include the reorganization of representational systems. Such a process may reflect an alternate neurocognitive strategy for learning new information. [123]

A completely learning recovery, after an ischemic process, depends of several factors, including the stroke severity and type/intensity/duration of treatment. Skilled rehabilitation would be a good choice, even after a severe stroke and restricting the compensatory mechanisms during rehabilitation might be pivotal for functional improvement. [120] It is also known that early motor training seems essential for successful recovery, and motor learning mechanisms may be operative during spontaneous stroke recovery and interact with rehabilitative training. [112, 124, 125, 126, 127, 128, 121] Besides, many studies finding beneficial effects of exercise after injury used a regimen in which the animal

experienced the exercise before the application of the injury. [129-131, 112]

Enriched Environment

Environment, social interaction, and physical activity are determinants of functional outcome after experimental cerebral infarction. [132-135, 152]. Besides, exposure to complex spatial environments or environmental enrichment causes increased dendritic growth and spine formation, synaptogenesis and increased expression of growth factors in the cortex and hippocampus of both normal and injured animals. [136-143, 148]

It was showed that CCH (Chronic cerebral hypoperfusion) led to cognitive impairment in rats and exposure to an EE (Enriched Environment) attenuated the cognitive impairment induced by CCH by improving synaptic plasticity. [144] Besides, studies found that postoperative housing in an EE significantly attenuates the long-term spatial memory impairment induced by MCAO rats. [145] Several studies have shown that an EE can enhance learning and memory, enhance synaptic plasticity not only in lesioned rats but also in nonlesioned rats. [146, 147, 144] An important aspect of the enrichment environment is that animals are continuously exposed to a varied environment. During enrichment, objects were moved into different locations in the cage and the presence of other animals ensured changing sensory-motor stimulation. [148] Studies showed that CCH leads to decreased levels of NMDAR1, which are restored by an EE. [149, 144] Similar to this, for rodents, post-ischemic housing in an enriched environment (EE) improves functional outcomes and increases transcriptional factor expression including NGF-IA and IB expressions, enhances brain-derived neurotrophic factor (BDNF) mRNA and protein expression, decreases serotonin receptor expression. [150, 151, 152] It is conceivable that increased expression of growth factors or cell survival genes (e.g. Bcl-2) might 'rescue' CA1 neurons that otherwise would go on to die. [148]

However, studies made in animals subjected to ischemic preconditioning (IP) or ischemic tolerance, showed that the environmental enrichment did not attenuate the delayed loss of CA1 neurons after ischemic preconditioning. [148]

The studies aimed to analyze in which aspects the EE is more beneficial. For example, a related experiment using a focal ischemia model demonstrated an increase in infarction volume when rats were put into an enriched environment plus training on several motor tasks beginning 24 h after ischemia. [148] The inclusion of cognitive learning also simulates occupational therapy in humans. According to our results, EE/learning significantly enhanced neuronal differentiation and neurogenesis in both sham surgery and ischemic rats compared to standard housing. [152] It is questioned to what extent this improved behavioral outcome is due to recovery of lost functions or to compensation for lost functions is difficult to ascertain. However, in view of evidence of morphological plasticity and the absence of evidence of alternative learning strategies (swim latency and directional heading error were similar to controls) in ischemic animals exposed to enriched environment, it is likely that environmental enrichment facilitates recovery of lost function rather than compensation. [153]

Conclusion

This revision possible to infer that the brain plasticity allows the recovery of neurologic adult patient, even partially, and the interaction with the environment can promote structural and functional changes in the central nervous system. In addition, physical rehabilitation and endogenous and exogenous factors allow an increasingly efficient adjustment of motor responses issued. This means that this type of treatment, when properly developed, effectively contributes to neuroplasticity, and therefore allows the reintroduction of learning in patients suffering from cerebral ischemia.

One can see, however, that the human brain constantly undergoes structural and chemical changes, such as the regulation of neuronal plasticity after cerebral oxygen deprivation processes, and this is one of the main reasons that affects the clarify of its mechanisms. Therefore, it is necessary that further researches, especially in humans, could be performed so that there is a better understanding of neuroplastic changes in the neuronal recovery.

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The authors have no conflicts of interest or financial ties to report.

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