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Neuroprotection in Animal Models of Global Cerebral Ischemia

Miguel Cervantes[1], Ignacio González-Burgos[2], Graciela Letechipía-Vallejo[1], María Esther Olvera-Cortés[3] and Gabriela Moralí[4]

[1]*Laboratorio de Neurociencias. Facultad de Ciencias Médicas y Biológicas "Dr. Ignacio Chávez", Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Michoacán*

[2]*Laboratorio de Psicobiología, División de Neurociencias, Centro de Investigación, Biomédica de Occidente Instituto Mexicano del Seguro Social, Guadalajara, Jalisco*

[3]*Laboratorio de Neurofisiología Experimental, Centro de Investigación Biomédica de Michoacán, Instituto Mexicano del Seguro Social, Morelia, Michoacán*

[4]*Unidad de Investigación Médica en Farmacología, UMAE Hospital de Especialidades, CMN S XXI, Instituto Mexicano del Seguro Social, México, D.F. Mexico*

1. Introduction

The present chapter deals with some of the main lines of experimental research on global cerebral ischemia, through which a substantial knowledge has been generated, that has contributed in an important measure both to the understanding of the mechanisms of cerebral damage induced by ischemia, and of the subsequent post-ischemic neuroregenerative and cerebral plastic processes taking place in the remaining or newly differentiated neurons. Thus, data obtained from experimental designs in animal models of global cerebral ischemia, on key molecular and cellular events triggered by this condition, have provided a substantial background from which neuroprotection can be rationally approached, in order to develop strategies aimed to antagonize, to interrupt, or to slow the sequence of injurious biochemical and molecular events that would result in irreversible ischemic injury; as well as to promote brain repair and plasticity processes which can favor functional preservation or recovery after global cerebral ischemia.

Transient global cerebral ischemia, which can mainly occur during cardiac arrest and cardiopulmonary resuscitation, but also during asphyxiation, hypotensive shock, or extracorporeal circulation, is a pathophysiological condition that is associated with great morbidity and requires intensive medical treatment (Madl & Holzer, 2004). In certain clinical situations (surgical repair of the thoracic aorta, complex congenital heart lesions, and also during implantable cardiac defibrillator testing in patients with drug-resistant

ventricular fibrillation) the possible occurrence of transient global cerebral ischemia, and some neuroprotective procedures, can be anticipated (Hogue et al., 2008); however, this is not the case of cardiac arrest.

Cardiopulmonary arrest remains as one among the most frequent causes of death and disability around the world. Despite quick emergency responses and better techniques of defibrillation, the chances of survival following cardiac arrest are still poor, between 20-50% of patients in whom cardiopulmonary resuscitation is attempted. A complex pathophysiological condition is elicited by cardiac arrest, since it results in whole-body ischemia which compromises systemic circulatory homeostasis and cerebral, pulmonary, renal, and cardiac functions. In the course of cardiac arrest, global cerebral blood flow is severely impaired with the consequent risk of ischemic damage of brain cells, which magnitude seems to be associated with the cumulative time staying in cardiac arrest. Thus, most deaths (60%) during the post-resuscitation period have been attributed to extensive brain injury and neuronal damage that develops as a consequence of alteration of cell processes triggered by cerebral ischemia and reperfusion, during and after cardiac arrest. In addition, it is known that transient interruption or reduction of blood flow in the whole brain, are main causes of permanent brain damage and functional disruptions in human beings, and near around a half of surviving patients show permanent impairment of cognitive functions, such as learning and memory, attention, and executive functioning, and only a small proportion (less than 10%) of those survivors are able to reassume their former usual life styles (Geocardin et al., 2008; Grubb et al., 2000; Krause et al, 1986; Schneider et al., 2009). Thus, development of effective cytoprotective therapies that may be common to the organs more sensitive to cardiac arrest, such as heart or brain, could result in improvement of survival and better outcome following this whole ischemic episode (Karanjia & Geocardin, 2011).

Experimental protocols aimed to gain relevant information regarding those pathophysiological phenomena leading to cerebral damage elicited by ischemia have included, since long time, the use of animal models of cerebral ischemia, in order to support better diagnostic, prophylactic and clinical-therapeutic procedures for ischemic cerebrovascular diseases in human beings (Ginsberg & Busto, 1989; Gupta & Briyal, 2004; Hartman et al., 2005, Hossmann, 2008; Traystman, 2003). Thus, biochemical, electrophysiological, histological, and behavioral parameters of ischemic brain damage have been included in experimental designs to evaluate the efficacy and safety of pharmacological and non pharmacological neuroprotective procedures against brain injury resulting from the significant reduction of blood supply to the whole brain, in several animal models of global cerebral ischemia.

Even though a great number of pharmacological agents have proven to exert effective neuroprotective actions against cellular events leading to ischemic brain injury in experimental models of global cerebral ischemia, unfortunately they have not had enough clinical relevance to date. On the other hand, after evaluation of its effectiveness as a neuroprotective strategy in animal models of global cerebral ischemia, hypothermia has been tested in clinical trials in patients having suffered cardiac arrest, the most frequent cause of global cerebral ischemia in human beings (Castren et al., 2009; Geocardin et al., 2008; Greer, 2006; Inamasu et al., 2010; Knapp et al., 2011; Seder & Jarrah, 2008,). It seems that new and better strategies to translate preclinical data supporting the potential clinical usefulness of neuroprotective drugs to clinical trials, must be developed.

2. Animal models of global cerebral ischemia

Animal models of global cerebral ischemia allow studying, at different levels of biological organization of the central nervous system, the development and temporal course of those processes that may result in irreversible ischemic neuronal damage, as well as in the subsequent cell repair and plasticity underlying either permanent cerebral functional impairment or recovery as a result of intrinsic brain mechanisms or neuroprotective procedures. Thus, animal-related factors (species, strain, age, sex, co-morbidities), animal-model-related factors (choice of ischemic model, anesthetic procedures, duration of ischemia, reperfusion, survival, possibility of monitoring of physiological parameters), selective vulnerability of specific neuron types in several brain structures, outcome assessment (histopathological, biochemical, functional, parameters of brain injury in specific cerebral structures), short- or long-term experimental design, pharmacological characteristics of the presumptive neuroprotective agent itself, timing and dose-response of neuroprotective drug administration with reference to starting and ending of the ischemic episode, may account for the relevance of results from these investigations.

Models of cerebral ischemia have been also developed in *in vitro* models, in particular brain tissue slices and neuronal cultures, allowing to study in detail the cellular phenomena leading either to neuronal damage or to neural recovery and plasticity after ischemia (Benítez-King, 2006; Goldberg & Choi, 1993; Kasai et al., 2003; Whittingham et al., 1984).

Several conditions have to be fulfilled by animal models of global cerebral ischemia in order to become appropriate counterparts of these pathophysiological conditions in human beings, as well as to yield reliable and valid results in supporting clinical therapeutic approaches. Thus, it could be expected that in animal models of global cerebral ischemia the ischemic episode can be induced in a constant and reproducible manner: low variation for the extent, temporal course, and magnitude of the resulting ischemic brain injury under specific experimental conditions, including duration of the ischemic episode; easy control of possible deviations of important physiological variables, feasible neurological, neuropathological, and functional evaluations; lack of influence of anesthetic drugs and surgical procedures on the mechanisms of brain injury, brain recovery and/or neuroprotection; short-, intermediate- and long-term follow up of the outcome; and economical, easily available experimental animals of those species better accepted by public animal welfare concerns to be used in experimental protocols of cerebral ischemia and neuroprotection.

2.1 Main animal models of global cerebral ischemia

Models of global cerebral ischemia have been performed in both large (monkeys, sheep, dogs, pigs, cats, rabbits) and small animals (gerbils, rats, mice). Among these, both advantages and disadvantages can be recognized according to several practical aspects: main objectives of the model; monitoring procedures to be used; nature, number and timing of simultaneous parameters to be recorded in order to evaluate the ischemic brain injury and recovery; degree of similarity of structural and functional characteristics of brains of experimental animals to those of the human brain; and updated ethical outlines for the use of experimental animals in research protocols.

Since the whole brain is exposed to transient ischemia and reperfusion as a result of cardiac arrest and the subsequent cardiorespiratory resuscitation to allow survival in human beings, animal models of global cerebral ischemia have been designed attempting to totally or

partially mimic the consequences of this clinical condition on the brain (Ginsberg & Busto, 1989; Gupta & Briyal, 2004; Mc Bean & Kelly, 1998; Traystman, 2003), which are the main cause of neuronal injury to selective vulnerable brain regions, and neurological or cognitive impairment, in human beings.

Cardiac arrest (induced by injection of KCl, electric shock, thoracic compression, asphyxia, and mechanical obstruction of the ascending aorta) followed by cardiopulmonary resuscitation (by artificial ventilation, closed chest massage and electrical defibrillation), both in large experimental animals (formerly a common model, but nowadays rarely used) and also in rodents, has been a technique to produce global cerebral ischemia in an attempt to closely resemble the clinical situation of cardiac arrest, including complete ischemia and reperfusion in renal, splachnic and other peripheral organs. This technique seemed to be an excellent model of global cerebral ischemia, but it is expensive when large experimental animals are used, and intensive care (cardiopulmonary support under unconsciousness, control of blood pressure, pH, body fluids, and temperature) must be provided to the animals, especially during the first 24-48 h after the cardiac arrest. Complete acute global cerebral ischemia during cardiac arrest (8-20 min) and a variable period of incomplete cerebral ischemia during reperfusion, even after a successful cardiopulmonary resuscitation, as well as damage in those brain structures most vulnerable to ischemia, can be expected from this model (Berkowitz, et al., 1991; Bleyaert et al., 1978; Dave et al., 2004; Hossmann, 2008; Katz et al., 1995; Kofler et al., 2004; Radovsky et al., 1995; Safar et al., 1976; Todd et al., 1982). In particular, models of global cerebral ischemia in mice are currently of interest because of the availability of transgenic and knock-out strains for identification of cellular pathways of ischemic damage, and for neuroprotection studies.

Several other animal models of global cerebral ischemia have been designed in cats, monkeys, gerbils, mice, and rats, in order to circumscribe to the brain those harmful effects of the reduced blood flow that follows a cardiac arrest, avoiding affecting other vital organs in a whole body ischemia condition, as can be expected from animal models of cardiac arrest (Ginsberg & Busto, 1989).

Decapitation in small animals has been used as a model of global cerebral ischemia, only allowing the study of the immediate alterations of some biochemical and metabolic parameters elicited by ischemia in the brain contained into the head (Abe et al., 1983; Ikeda et al., 1986; Lowry et al., 1964; Yoshida et al., 1985).

A neck tourniquet or a neck cuff, whether they include or not arterial hypotension, have also been used to produce global cerebral ischemia in rats, cats, dogs, or monkeys. However, these techniques lead to variable ischemic outcomes since the produced ischemia may not be complete because of a remaining cerebral blood flow through the vertebral arteries, as well as complications due to vagal compression and venous congestion (Chopp et al., 1987, 1988; Grenell 1946; Nemoto et al., 1977; Sheller et al., 1992; Siemkowits & Gjedde, 1980; Siemkowitz & Hansen, 1978).

Reduction of cerebral blood flow near to zero has been accomplished in cats and monkeys, by occlusion of the innominate and left subclavian arteries near the aortic arch, and pharmacologically induced hypotension (below 80 mm Hg), without involvement of other organs in the ischemic phenomena**.** However, these experimental animals require intensive care procedures to their survival, and studies of long-term recovery are difficult to achieve (Bodsch et al., 1986; Clavier et al., 1994; Hossmann, 1971; Hossmann & Grose Ophoff, 1986; Zimmerman & Hossmann, 1975).

Gerbils usually lack of a common posterior communicating artery connecting the carotid and vertebro-basilar arterial system. Thus, the bilateral common carotid artery occlusion results in a reduction of global cerebral blood flow near to zero and injury of the most vulnerable brain structures (hippocampal CA1 pyramidal neurons after 5 min of ischemia) in most animals (Kirino, 1982). This model of forebrain global cerebral ischemia may fail in some animals in which a complete Willis circle persists, and the high susceptibility of gerbils to seizures may influence the ischemic outcome.

The four-vessel occlusion (4-VO) and the two-vessel occlusion with hypotension (2-VO) models in rats became, nowadays, the most widely used animal models that simulate the reduction of blood flow, as it would occur by effect of cardiac arrest, on the forebrain. The 4-VO model (Ginsberg & Busto, 1989; Pulsinelli & Brierley 1979; Pulsinelli & Buchan 1988; Pulsinelli & Duffy 1983; Pulsinelli et al., 1982) provides a method of reversible forebrain ischemia in awake, freely moving rats (but also in anesthetized rats). In a first step of the model procedures, vertebral arteries are permanently occluded and 24 or 48 hours later, the ischemia is produced through transient (10 – 20 min) occlusion of the common carotid arteries under light inhaled anesthesia so that the ischemic episode occurs while the animal is unanesthetized. Loss of the righting reflex, and unconsciousness persisting for at least 20 min after the onset of reperfusion have to occur for each animal to be included in the study. In this way, a reduction in cerebral blood flow to less than 5% of control values, which is followed by hyperemia during 5 to 15 min after reperfusion, and subsequent hypoperfusion lasting for 24 hr result in main ischemic neuronal damage in hippocampus, neocortex and striatum, along hours to days after ischemia, its magnitude relating to the duration of the ischemia. The effects of this insult are, however, quite variable between rat strains, as well as between those individuals surviving (survival rate, 50-75%) after having fulfilled the criteria required to be included in the experimental groups. Similar consequences in selectively vulnerable neurons in specific brain structures result from the 2-VO model of forebrain ischemia, in which bilateral common carotid artery occlusion and systemic hypotension (blood withdrawal and subsequent return with or without pharmacological procedures, leading to arterial blood pressure below 50 mm Hg) are combined to provoke reversible forebrain ischemia (Eklof & Siesjo 1972a, 1972b; Smith et al., 1984a, 1984b).

Mouse models of global cerebral ischemia have been developed through bilateral common carotid occlusion and controlled pulmonary ventilation (Traystman, 2003).

It is known that animal models of global cerebral ischemia require adequate control of certain variables, such as careful control of animal's temperature and blood glucose concentration, in order to achieve consistent pathophysiological effects and brain injury (Colbourne & Corbett, 1994; Lipton, 1999; Siemkowicz, 1981; Siemkowicz.& Gjedde 1980). Hyperthermia and hyperglycemia increase brain injury, while hypothermia results in neuroprotection by itself.

3. Cellular mechanisms of neuronal injury, neuronal repair and plasticity

Models of global cerebral ischemia in experimental animals, as well as *in vitro* models, in particular brain tissue slices and neuronal cultures, have allowed to study in detail the cellular phenomena leading either to neuronal damage, or to neural repair and plasticity after ischemia. From these studies it has been known that mechanisms of cellular damage, repair and plasticity may be the same, in general, both if reduction of blood flow to the brain tissue results from occlusion of one of the main cerebral arteries as would occur in focal

ischemia, and if it is the result of reduction of blood flow to the whole brain as it would occur after a cardiorrespiratory arrest.

3.1 Cellular mechanisms of neuronal injury

Interruption of blood flow and hence, of glucose and oxygen supply to the brain, results in an immediate severe energy failure in terms of ATP depletion that leads to alterations of the cell membrane ionic gradients and a severe breakdown in cellular homeostasis. Several mechanisms of neuronal damage are triggered and evolve both in cascade and as parallel pathways (Gwag et al, 2002; Lakhan et al, 2009; Lipton, 1999; Mehta et al, 2007; Schneider et al, 2009; Sugawara et al, 2004; Warner et al., 2004). In particular, a massive accumulation of intracellular calcium and sodium occurs because of failure of their energy-dependent efflux processes, and anoxic depolarization. This further leads to accumulation of lactate and hydrogen ions, and as a consequence, to decreased pH.

As a result of anoxic depolarization, excitatory aminoacids such as glutamate and aspartate are released, activating ligand-gated calcium and sodium channels with a further influx of these ions into the cells. Calcium is also released from intracellular pools, and its excessive, unregulated intracellular overload causes direct Ca^{2+}-dependent activation of lipases, proteases, and endonucleases leading to breakdown of structural and functional proteins, and damage to cytoskeleton and macromolecules including nucleic acids. A result of these phenomena is, among others, cell membrane lipoperoxidation.

Excessive intracellular calcium activate abnormal cell processes promoting functional derangements of mitochondria and an increased production of free radicals, exceeding the neuronal antioxidant reserves, and imposing risks to the structural and functional integrity of neuronal cells. The brain is highly susceptible to oxidative damage as a consequence of its high lipid and metal content, as well as other biochemical characteristics (Margaill et al., 2005; Reiter et al., 2005; Warner el al., 2004). Reperfusion and reoxygenation of the ischemic tissue, which must be reestablished within minutes in an effort to prevent severe neurological damage and favor survival of individuals, also may provide chemical substrates for further increasing cellular alterations, neuronal death and neurological deficits (Margaill et al., 2005).

Free radicals also contribute to the breakdown of the blood-brain barrier and brain edema. Reactive oxygen and nitrogen species including superoxide, hydroxyl free radical, and peroxylnitrite anion are also important mediators of inflammatory tissue damage, of activation and secretion of inflammatory cytokines such as tumor necrosis factor α, interleukin-1, and interleukin-6, and of expression of cyclo-oxigenase (COX)-2, and inducible nitric oxide synthase generating nitric oxide that also contributes to neuronal damage. These changes favor inflammatory reactions soon after cerebral ischemia/reperfusion (Barone & Feuerstein, 1999; Lakhan et al, 2009; Lipton, 1999; Mehta et al, 2007).

Calcium overload may additionally lead to mitochondrial damage and trigger an apoptotic cascade. The pro-apoptotic cascade involves nuclear factor κB- and p53-dependent pathways, changes in the Bcl-2 to Bax ratio, opening of the mitochondrial transition pore, release of cytochrome *c*, and activation of caspases (Chan, 2001; Chinopoulos & Adam-Vizi, 2006). In addition, caspase-independent pathways may also contribute to neuronal apoptosis.

Several gene families such as immediate early genes, heat-shock proteins, and inflammation-and apoptosis-related genes, are known to be differentially expressed during cerebral ischemia, and some neuropathologic processes triggered by ischemia seem to be mediated in part by alterations of molecular transcriptional and translational activities (Mehta et al, 2007).
Activation of DNA fragmentation enzymes and energy-consuming DNA repair enzymes, finally lead to DNA breakdown, interruption of protein synthesis, and cell death (Iadecola & Alexander, 2001; Leker & Shohami, 2002).
In addition to the above mentioned cellular processes of ischemic damage, brain ischemia/reperfusion may also trigger cellular mechanisms for neuronal repair, and functional recovery through neuronal plasticity involving remaining neurons in vulnerable damaged or undamaged brain structures (Barone & Feuerstein, 1999; Bendel et al., 2005; Crepel et al., 2003; Hurtado et al., 2006; Jourdain et al., 2002; Ruan et al., 2006). The different ischemia/reperfusion induced cellular mechanisms leading either to brain injury and neuronal death, or to neuronal repair, as well as plasticity and brain functional recovery, may occur in a sequential or simultaneous manner. Their latencies and temporal course, from minutes to weeks, are important references in attempting to establish their differential relevance in those critical periods for neuronal damage and death, as well as the "window of opportunity" for specific neuroprotective procedures (Barone & Feuerstein, 1999; Lipton, 1999; Leker & Shohami, 2002; Pulsinelli et al., 1997).

3.2 Differential neuronal vulnerability in animal models of global cerebral ischemia

Brain injury is expected to occur when cerebral blood flow is reduced to less than 10-20% of the normal value; the greater the reduction and/or longer lasting, the worst damage. Under these conditions, damage to specific brain structures due to immediate or delayed death of highly vulnerable neuronal groups, including the pyramidal neurons of the CA1 subfield of the hippocampus, and to a lesser degree those in layers 3 and 5 of the cerebral cortex, the Purkinje cells of the cerebellum, and spiny neurons in the striatum, take place after global cerebral ischemia (Ginsberg & Busto, 1989; Pulsinelli, 1985). Experimental models of global cerebral ischemia have allowed to know some neuronal characteristics that seem to account for selective vulnerability to ischemia, including a high density of excitatory glutamatergic synapses; low antioxidant enzyme reserves; high content of transition metals; increased expression of pro-apoptotic Bax protein; thus leading to differential susceptibility of some cell processes (Ca^{2+} homeostasis, oxidative-antioxidative balance, functional mitochondrial stability) to become out of physiological control under ischemia (Arai et al., 2001; Araki et al., 1989; Chen et al., 1996; Lipton 1999; Schmidt-Kastner et al., 2001; Sugawara et al., 1999). Brain injury after global ischemia/reperfusion is finally evidenced by neuronal death, affecting the neuronal population, circuit connectivity and functioning in specific brain structures involved in the neural integration of cognitive brain functions and behavior.

3.3 Cellular mechanisms of neuronal plasticity and repair

Cellular mechanisms of neuronal repair and plasticity have been observed to occur in vulnerable brain structures in which damage or death of neurons resulted from a sequence of pathophysiological phenomena triggered by global cerebral ischemia and the subsequent reperfusion. Thus, structural and functional characteristics of those neuronal components of circuits in the hippocampus and prefrontal cortex, which are identified, among others, as

highly vulnerable to ischemia, and their correlation with the integration of specific cerebral functions (mainly cognitive functions) after global cerebral ischemia, have been analyzed. In this sense, short- and long-term structural alterations have been shown to occur in the remaining pyramidal neurons of the hippocampus after ischemia; thus, axonal degeneration as well as reduction of dendritic length and arborizations, of number and shape of dendritic spines, and of number of synapses, are usually related to impairment of cognitive functions and recognized as degenerative changes. By contrast, cytoarchitectural adjustments such as axonal and dendritic sprouting, increase of number of dendritic spines and synapses, changes in the relative proportion of spine types, are interpreted as compensatory plastic responses of surviving neurons. They contribute to neuronal circuit remodeling and functional recovery, and have been correlated with preservation of cognitive functions after the ischemic insult, even in absence of neuroprotective procedures (Briones et al., 2006; Jourdain et al., 2002; Mudrick & Baimbridge, 1989; Neigh et al., 2004; Onodera et al., 1990; Ruan et al., 2006; Skibo & Nikonenko, 2010; Sorra & Harris, 2000). In addition, neurogenesis and integration of newly differentiated neurons into neuronal circuits in the Ammon's horn may contribute to recovery of hippocampal-dependent cognitive functions (Bendel et al., 2005; Bernabeu & Sharp, 2000).

Similarly, reductions of dendritic length, arborization, and dendritic spine density have also been described, among various cytoarchitectural adjustments, in sensorymotor cortex pyramidal neurons following global cerebral ischemia (Akulinin et al., 1997, 1998, 2004). These cytoarchitectural alterations could be influenced by the extent of neuronal remaining connections; thus, either reduction or increase of afferent connections may result in changes in dendritic arborizations and spine density (Fiala et al., 2002; Johansson & Belinchenko, 2002). It has been emphasized the functional relevance of neuronal connections from the hippocampus to the prefrontal cortex for synaptogenesis and neuronal plasticity accounting for learning and memory (González-Burgos, 2009; Laroche et al., 2000). Thus, a permanent deafferentation of pyramidal neurons at cortical layer V after the extensive reduction of pyramidal neuron population of the CA1 subfield of the Ammon's horn as expected to occur after global ischemia (Letechipía-Vallejo et al., 2007), may lead to changes in neuronal activity, which may in turn affect the cytoarchitectural characteristics of pyramidal prefrontal cortex neurons (García-Chávez et al., 2008; Wellman & Sengelaub, 1991).

These dendritic restructuring (Neigh el al., 2004; Ruan el al., 2006) and reactive synaptogenesis (Briones et al., 2005; Crepel et al., 2003; Jourdain et al., 2002, Kovalenko et al., 2006) among other phenomena including the activation of a variety of potential growth-promoting processes (Arvidsson et al., 2001; Gobbo & O´Mara, 2004; Schmidt-Kastner et al., 2001), that occur in neurons surviving to the ischemic insult in vulnerable brain structures, seem to be a part of mechanisms of adaptive changes, probably accounting for neuronal conditions favoring synaptic plasticity and functional recovery. In fact, a long-term progressive continuous plastic reorganization of the dendritic tree and dendritic spines, initially altered by acute global cerebral ischemia, has been shown to occur in pyramidal neurons at layers 3 and 5 of the sensorymotor cortex of the rat (Akulinin et al., 1997, 1998, 2004).

Thus, preservation or recovery of hippocampal- and pre-frontal cortex- dependent functions after global cerebral ischemia, may involve long-term cytoarchitectural modifications in those remaining hippocampal CA1 and prefronto-cortical (layers 3 and 5) pyramidal neurons, since their morpho-functional organization is critical for normal learning and memory performance (Block, 1999; McDonald & White, 1993; McNamara & Skelton, 1993; Olsen et al., 1994; Olvera-Cortés et al., 2002; Silva et al., 1998), on the basis of the major role

played by the CA1 region for the output of information flowing through the hippocampus, via the tri-synaptic circuit (Herreras et al., 1987). It is well known that the prefrontal cortex is directly involved in the organization of sequenced motor actions during working-memory performance (Fuster, 1999; I. Lee & Kesner, 2003), and that hippocampal projections supply of spatial information to the prefrontal cortex allowing suitability of motor responses in the spatial context (Jung et al., 1998). These phenomena may be altered not only by gross lesions of the prefrontal cortex, but fine alterations of its neuronal circuits may also result in impairment of the spatial working memory (Fritts et al., 1998; Lambe et al., 2000; I. Lee & Kesner, 2003; Olvera-Cortés et al., 2001; Taylor et al., 2003). Experimental data have shown that variations in cognitive behavioral performance are related to plastic changes in dendritic spines (Pérez-Vega et al., 2000). In addition, excitatory information flows mostly through dendritic spines-mediated synaptic contacts (Gray, 1959), which are highly sensitive to electrical stimulation and yet to mnemonic activity-related electrical phenomena (Harris, 1999; Hartman et al., 2005; Onodera et al., 1990).

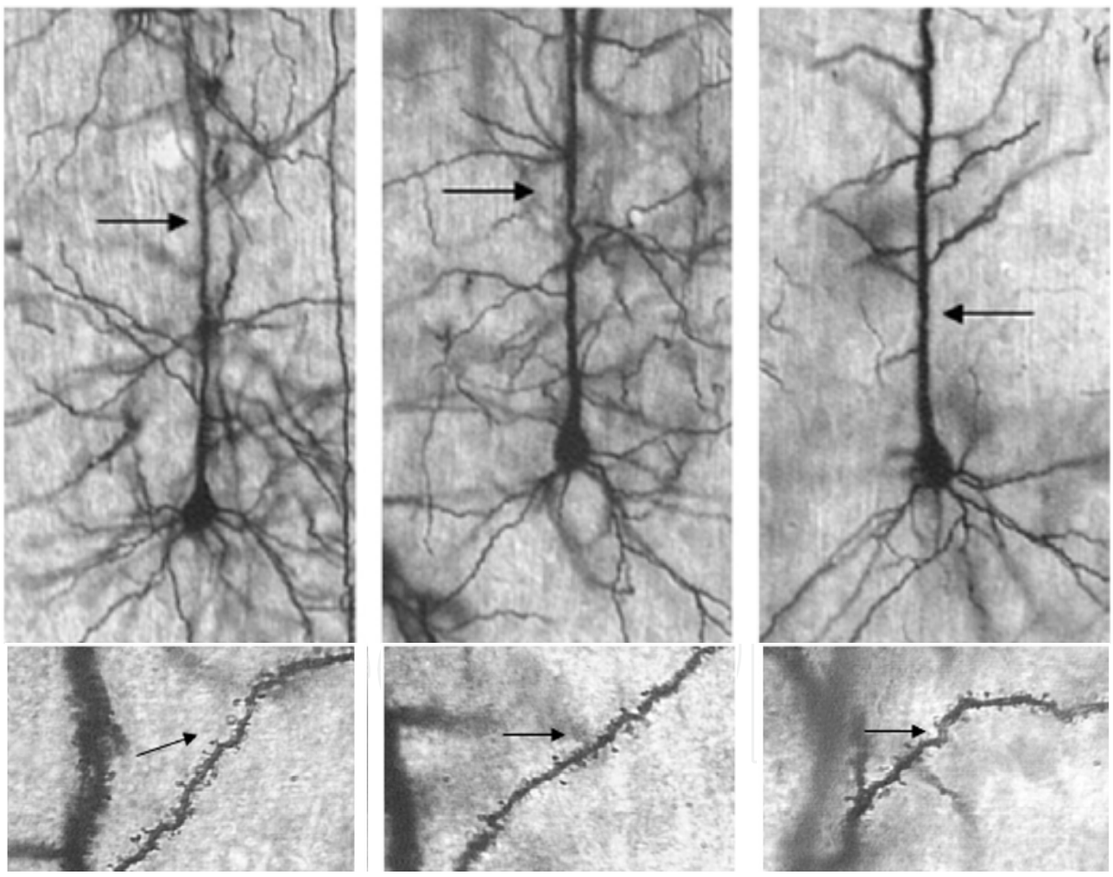

Fig. 1. Photomicrographs of prefrontal third-layer pyramidal neurons of rats: intact (left), after global cerebral ischemia and neuroprotective melatonin (centre) or vehicle (right) treatment. Note the reduction in dendritic arborization protruding from the apical dendrite, and dendritic spine reduction (arrows) in the ischemic and non treated cell in comparison with neurons from intact, and ischemia melatonin treated rats.
(Modified from: García-Chávez et al., 2008).

Since long-term preservation of the neuronal substrate in cerebral vulnerable structures underlying functional recovery after cerebral ischemia has been considered to be a major end point of neuroprotective strategies (STAIR, 1999) it can be expected that experimental designs for neuroprotection studies may lead to reliable interpretations of the efficiency of neuroprotective agents, in view of the proven capability of intrinsic cerebral mechanisms to promote , by themselves, neuronal repair and plasticity after ischemia.

Some neuronal proteins that are involved in structural and functional aspects of synaptic connectivity and neuronal circuits remodeling have been evaluated as parameters of ischemic damage and neuroprotection. In this sense, synaptophysin has been shown to be reduced in the frontal motor and temporal cortex of human beings that have been survived for 1 week to 1 year after a cardiac arrest (Akulinin et al., 1998). Besides, a reduction of synaptophysin 2, Munc-18-interacting proteins, 1-3 days after global cerebral ischemia in mice has been related to delayed neuronal death (Nishimura et al., 2000). On the other hand it has been proposed that progesterone-induced increase (3-35 days after ischemia) in the expression of synaptophysin and growth-associated protein 43, and the effects of venlafaxine preventing the decrease of synaptophysin, in the rat hippocampus are evidences of the neuroprotective effects of these drugs (Fang et al., 2010; Zhao et al., 2011).

4. Approaches to neuroprotection in animal models of global cerebral ischemia

The experimental approach to neuroprotection aimed to influence, through pharmacological and non pharmacological procedures, those early and late neural phenomena accounting either for brain damage or for neuronal repair, plasticity and functional recovery after global cerebral ischemia and reperfusion, has resulted in a considerable amount of reliable information along the last 40 years.

Different strategies of neuroprotection attempting to prevent, reduce, or stop the progress of the ischemic brain damage have been assayed in animal models of global cerebral ischemia, under the premise of an opposition relationship between the mechanism(s) of action of the presumptive neuroprotective drugs or non pharmacological procedures, and the pathophysiological mechanisms of brain damage, which has been maintained as targets of neuroprotective strategies.

Neuroprotection studies in animal models of global cerebral ischemia have maintained the main objective of support proposals of pharmacological and non-pharmacological neuroprotective procedures to be incorporated as a matter for clinical trials aimed to a better management of human beings exposed to global cerebral ischemia, frequently as a consequence of a cardiorespiratory arrest. Translation of knowledge about neuroprotection obtained from models in experimental animals, to clinical practice has not been successful. This situation has been also observed in the case of focal cerebral ischemia, leading to consensus meetings (Fisher et al., 2009; STAIR, 1999) attempting to establish the better conditions for preclinical studies of neuroprotection as to give reliable results to be applied in clinical conditions. If opinion of these consensuses may be recognized as applicable to preclinical studies of global cerebral ischemia, it is apparent that some factors must be taken in account for designing and carrying of the respective experimental protocols. Thus, studies in animal models of global cerebral ischemia should give information on effective neuroprotective doses in the case of drugs being tested; hence, dose-response relationships should be investigated. Routes of drug administration and pharmacokinetic characteristics

should also be taken in account as to be compatible with their potential use in human beings.

The time window of opportunity for the effective neuroprotective treatment is an important factor to be considered in preclinical models that may predict the timing of neuroprotective procedures in clinical situations with reference to the onset of global cerebral ischemia and subsequent reperfusion. The initial hypothesis that opportunity window for neuroprotective procedures would be limited to a short period after the ischemic episode has been changed in view of experimental evidence. Thus, different drugs or neuroprotective procedures having predominant mechanisms of action against specific cellular processes of ischemia damage occurring lately within the pathophysiological cascade, may allow to neuroprotection even when administered hours or days after ischemia. Besides, the opportunity time window may be further extended when it is expected that neuroprotective procedures act through promotion of cellular processes of neuronal repair and plasticity.

In view of the multiple pathophysiological processes occurring both in sequence and simultaneously after ischemia and reperfusion, it is considered as an advantage for presumptive neuroprotective drugs to have multiple cellular or molecular mechanisms of action, as occurring with some originally endogenous compounds, namely melatonin, estradiol and progesterone (El-Abhar et al, 2002; Hurn et al, 1995; Jover-Mengual et al, 2010; Lebesgue et al, 2009; Reiter et al, 2005; Wang et al, 2008). By contrast, most synthetic drugs only have one mechanism of action accounting for neuroprotection. Attempting to counteract several mechanisms of ischemic brain injury would require the simultaneous administration of several drugs (Hicks et al, 1999; Matsumoto et al, 1993; Pazos et al, 1999; del Pilar Fernández et al, 1998; Sánchez-Casado et al, 2007; Zapater et al, 1997) (Table 1).

Recommendations arisen from these consensuses of opinion have also highlighted the importance of long-term studies to identify whether functional preservation or recovery may be attributed to effects of the neuroprotective procedures, and/or to intrinsic mechanisms of plasticity and repair triggered by ischemia *per se*. Reliable parameters of long-term structural and functional outcome may allow to evaluate the final result of the neuroprotective procedures on cerebral structures vulnerable to ischemia. Thus, evaluation of neuronal population, cytoarchitectonic characteristics, and connectivity of the neural circuits in these vulnerable structures, as well as different aspects of cognitive functions depending on them should be included as a part of experimental designs of neuroprotection.

It has been described that the neuronal population of remaining neurons in CA1 at survival times of 2-3 weeks may be less than that evaluated 3-4 months after the ischemic episode, suggesting that, without exogenous intervention, CA1 neurons may have been repopulate, became integrated to the hippocampal neuronal circuits, and contribute to functional recovery (Bendel, et al 2005; von Euler et al., 2006, Hartman et al, 2005, Nakatomi et al., 2002). Obviously, the potential repopulation complicates the interpretation of learning and memory studies after global cerebral ischemia, because short-term studies may not give an adequate end point of the cognitive alteration after global cerebral ischemia, which seems to require a long-term follow up.

Experimental designs to evaluate the potential of neuroprotective drugs or hypothermia may have not met all requirements set by these consensuses in a single study, but integration of results of the many experimental studies may give enough information as to support proposals for their clinical usefulness.

Main Mechanism of Action	Neuroprotective Agent	References
PHARMACOLOGICAL AGENTS		
Increase of energy reserve	Creatine	Lensman et al., 2006; Otellin et al., 2003.
Calcium channel blockers	Nimodipine	Cervantes et al., 1992; Choi SK et al., 2011; Haddon et al., 1988; Lazarewicz et al., 1990; Lazarewicz et al., 1993; del Pilar Fernández et al., 1998; Rami & Krieglstein, 1994; Zornow et al, 1996.
	Levemopamil	Block & Schwarz 1998.
	Dantrolene	Nakayama et al, 2002
	Flunarizine	Lee Y.S. et al., 1999.
K^+ channel activators	Linoleic acid	Blondeau et al., 2002.
Glutamate antagonists	Dizocilpine	Bernabeu, R., & Sharp, 2000; Hicks et al., 1999; Janac et al., 2008; Kwon et al., 2000; Montero et al., 2007; Stevens & Yaksh, 1990; Selakovic et al., 2010; Zhang et al., 2009.
	Dextromethorphan	Block & Schwarz, 1998.
	Lamotrigine	Conroy et al., 1999 ; Crumrine et al., 1997; Lee Y.S. et al., 1999 ; Morimoto et al., 2002 ; Shuaib et al., 1995b ; Wiard et al., 1995.
	Lubeluzole	Koinig et al., 2001; Mueller et al., 2003; Haseldonckx et al., 1997
	$MgSO_4$	Meloni et al., 2009; Miles et al., 2001; Sirin et al., 1998.
	Zinc	Matsushita et al., 1996.
	Antiepileptic agents	Stepień et al., 2005.
GABAergic agents	Clomethiazole	Clarkson et al., 2005; Chaulk et al, 2003; Cross et al, 1995; Liang et al, 1997; Shuaib et al., 1995a; Sydserff et al., 2000.
	Diacepam	Corbett et al, 2008; Dowden et al, 1999; Hall et al, 1998; Johansen FF, Diemer, 1991; Schwartz et al, 1995.
	Thiopental	Kofke et al., 1979; Pappas & Mironovich, 1981; Todd et al, 1982 .
	Propofol	Cai et al., 2011 ; Cervantes et al., 1995 ; Ergün et al, 2002.
	Progesterone, allopregnanolone	Aggarwal et al., 2008 ; Cervantes et al., 2002 ; González-Vidal et al., 1998 ; Moralí et al., 2005 ; Moralí et al., 2011a, 2011b; Ozacmak & Sayan, 2009 ; J.M. Wang et al, 2008 ; Zhao et al, 2011.

Main Mechanism of Action	Neuroprotective Agent	References
Antioxidants	Tirilazad	Li et al., 2010; del Pilar Fernández et al., 2008; Selakovic et al., 2010; Stevens & Yaksh, 1990.
	Pentoxifylline	Sirin et al., 1998; Tuong et al., 1994.
	Edaravone	Kubo et al., 2009 ; Otani et al., 2005.
	Methylene blue	Wiklund et al., 2007.
	Melatonin	Cervantes et al., 2008; Cho et al, 1997; El-Abhar et al., 2002; García-Chávez et al., 2008; González-Burgos et al., 2007; Letechipía-Vallejo et al., 2001; Letechipía-Vallejo et al., 2007; Rennie et al., 2008; Weil et al., 2009.
	Other	Bashkatova et al, 2001; Fang et al, 2010; Gaur & Kumar, 2010; Nanri et al, 1998; Pazos et al., 1999; Sinha et al., 2001; Warner et al, 2004.
	Human albumin	Belayev et al., 1999.
Antiapoptotic agents	Estradiol	Dai et al., 2007 ; He et al., 2002 ; Hurn et al., 1995 ; Jover-Mengual et al, 2010; Koh et al., 2006 ; Lebesgue et al., 2009 ; Littleton-Kearney et al, 2005 ; Lu et al., 2002 ; Wang et al., 2006 ; Wappler et al., 2010.
Other mechanisms	Delta 9-tetrahydro-cannabinol	Zani et al., 2007.
	Linoleic acid and other PUFA's	Blondeau et al., 2002; Fernandes et al., 2008; Lauritzen et al., 2000; Ma et al., 2008; Plamondon & Roberge, 2008.
Cell proliferation stimulants	Erythropoietin	Cotena et al, 2008 ; Givehchian et al., 2010; Incagnioli et al., 2009; Zhang et al, 2007.
Growth Factors	BDNF	D'Cruz et al., 2002; Kiprianova et al., 1999a, 1999b; Larsson et al., 1999; Popp et al., 2004.
NON-PHARMACOLOGICAL AGENTS		
Reduction of: cerebral metabolism and oxygen demands, reactive oxygen species, release of excitatory aminoacids, apoptosis, inflammatory reactions. Enhancement of BDNF	Hypothermia	Asai et al., 2000; Baumann et al, 2009; Chopp et al, 1988; Colbourne & Corbett, 1994; Dong et al, 2001; Noguchi et al., 2011; Silasi & Colbourne, 2011; Webster et al., 2009; Zhang H. et al., 2010; Zhang Z, et al., 2001.

Main Mechanism of Action	Neuroprotective Agent	References
ASSOCIATION OF PHARMACOLOGICAL AND NON-PHARMACOLOGICAL AGENTS		
	Hypothermia + $MgSO_4$	Meloni et al., 2009.
	Hypothermia + $MgSO_4$ + tirilazad	Sánchez Casado et al., 2007

Table 1. Main pharmacological and non-pharmacological agents showing neuroprotective effects through molecular, biochemical , histopathological, behavioral, neurologic, and cognitive parameters.

These strategies have allowed identifying the neuroprotective characteristics of many agents, including non-pharmacological procedures like hypothermia, that have been tested in animal models of global cerebral ischemia from the knowledge of an opposition relationship between their mechanism(s) of action, and the nature of the pathophysiological phenomena of ischemic damage. They may be grouped in relation to their main predominant mechanism of action against ischemic damage: calcium channel blockers, glutamate antagonists, GABAergic drugs, antioxidant agents, anti-inflammatory compounds, etc. Many of these compounds are products of chemical synthesis; but endogenous compounds (melatonin, estradiol, progesterone, allopregnanolone, etc.) playing important physiological roles in mammals, have also been shown to exert potent neuroprotective effects. Table 1 presents some examples of the various groups of neuroprotective agents.

4.1 Outcome assessment of brain injury and neuroprotection in animal models of global cerebral ischemia

Assessment of brain injury and neuroprotection in animal models of global cerebral ischemia can be effected at different levels of biological organization of the central nervous system, from molecular and cellular phenomena to brain functions requiring highly integrated, behavioral expressions. In general, parameters of cellular and molecular processes leading to ischemic brain damage or neuroprotection require obtaining brain tissue samples at a selected time point after ischemia for these phenomena to be evaluated. On the other hand, a follow-up of damage and/or recovery through repeated bioelectrical, behavioral, and cognitive measurements is possible to be done in the same animal along extended periods. Parameters that allow evaluating the presence and magnitude of ischemic brain injury at the different levels of biological organization are also reliable indexes of neuroprotective actions, as they are induced by ischemia and may be counteracted by neuroprotective procedures. A similar consideration can be done regarding cell repair and plasticity mechanisms triggered by the ischemic insult, which are expected to be favored by neuroprotective agents.

Measurements have been done of parameters of each of the various phenomena affected by ischemia which constitute the starting point of ischemic brain injury. These include timely and topographically appropriate evaluation of ionic changes, release of neurotransmitters, modification of receptor molecular structure, excitotoxicy, morphological and functional mitochondrial alterations, reactive oxygen and nitrogen species, antioxidant enzymes and lipoperoxidation, activation of pro- and antiapoptotic cascades, DNA breakdown, pro- and

anti-inflammatory processes, among others (Lakhan et al, 2009; Lipton, 1999; Mehta et al, 2007; Schneider et al, 2009).
Neurological, behavioral, electrophysiological and histopathological correlates of the outcome after global cerebral ischemia being end points of cellular processes triggered by ischemia, give information about ischemic brain injury and neuroprotection.

4.1.1 Neurological assessment

Global cerebral ischemia usually does not result in long lasting focal neurological deficits in rats. Thus neurological deficit scores resulting from sensorimotor tests assessing motor-sensory functions in rats, including placement reactions, righting and flexion reflexes, equilibrium, spontaneous motility, among others may be altered shortly after (24 h) global cerebral ischemia, but they appear recovered 7 days after ischemia. These transient neurological deficits have been interpreted as functional alteration of hippocampus and striatum; though correlation between neurological deficit scores and ischemic neuronal damage in these structures, not always were found (Block, 1999; Hartman et al., 2005; Kofler et al, 2004).

4.1.2 Mood and behavioral assessment

Elevated, four (two open and two closed) arms plus maze, and open field tests have been used, among other to evaluate anxiety after global cerebral ischemia especially in rodents. Thus scores of latency to enter to open arms, the number of open and closed arms entries and rears are taken as parameters of anxiety in the elevated plus maze, while in the open field (circular arena 80 cm in diameter, three concentric rings and lines radiating from the center) tests, the number of segments entered with all the four paws, the number of rears, and the number of *faecal boli* are indexes of anxiety (Nelson et al., 1997).

4.1.3 Cognitive functions assessment

Since the clinical consequences of cardiac arrest, as the main cause of global cerebral ischemia, have been consistently described as long-term alterations of cognitive functions, it can be expected that similar cognitive deficits may be elicited by global cerebral ischemia in experimental animals. In fact, the most vulnerable neurons to ischemia are located in brain structures involved in cognitive processes (Ginsberg & Busto, 1989; Gionet et al., 1991; Pulsinelli, 1985); thus, evaluation of cognitive functions mainly dependent on hippocampus, striatum and prefrontal cortex, and its electrophysiological and morphological correlates may be reliable parameters of brain injury and neuroprotection after global cerebral ischemia.
The magnitude and type of cognitive deficits in experimental animals submitted to global cerebral ischemia may vary considerably depending on the animal model, the survival times of testing, and the specific behavioral tests that could have been used. Among these procedures to evaluate cognitive functions, the Morris water maze, the eight-arms radial Olton maze, and the T maze, have been widely used in assessing learning and memory in both 2VO and 4VO models in rats, and its correlation with neuronal loss (Block, 1999; Hartmann et al., 2005; Olsen et al., 1994; Volpe et al., 1984), and functional and morphological characteristics of the neural substrate underlying cognitive functions in brain structures vulnerable to ischemia. Novel object recognition tests have been shown to be a reliable index of cognitive functions since rats or mice normally spend more time exploring novel objects, whereas animals with recognition memory deficits will explore novel and

familiar objects equally (Hartman et al., 2005). Cognitive functions have also been assessed in rodents through conditioned avoidance tasks (Block, 1999; Kofler et al., 2004; Langdon et al., 2008).

Several paradigms in the Morris water maze and in the eight-arms radial Olton maze, that have been used in most of neuroprotection studies in which cognitive functions are assessed, have proven to be useful for testing hippocampal, striatum and prefrontal cortex functioning as end points of brain damage or neuroprotection after global cerebral ischemia (Morris, 1984; Olton et al, 1982).

Hippocampal functioning has been evaluated in rats and mice through some behavioral paradigms that require the integrity of this brain structure and related structures in the temporal lobe (Barnes, 1979; Morris et al., 1982, 1990), in order to configure cognitive spatial representations, i.e., a cognitive spatial map (Cassels, 1998; Jarrad, 1993; McDonald and White, 1994; 1995; Moser et al, 1993). Thus parameters of spatial learning training to locate a hidden platform, (escape latency: time spent by the animal to reach the platform; swimming path length: distance swam until reaching the platform; searching strategy: pattern of the swimming path towards the platform) and probe trial to evaluate retention of spatial learning (time spent, or the distance traveled by the animal in each of the four quadrants of the maze; number of crossings over the former platform location) in the Morris water maze including extra maze spatial clues, have been used in testing the morpho-functional state of the hippocampus (Dalm et al 2000; D'Hooge & De Deyn, 2001; Eichenbaum et al, 1990; Morris, 1984; Myhrer, 2003)..

Under these training conditions and since there are no intra maze clues to guide the animal's behavior, it is assumed that, to achieve the goal, the animal has to build the cognitive map and thus, a hippocampal processing of information occurs (Gallagher and Pelleymounter, 1988, O'Keffe & Nadel 1978). For this reason, studies of neuroprotection use the spatial learning in the Morris water maze paradigm, as a reliable index of the hippocampal functioning.

However, in addition to place learning, spatial navigation in the water maze may occur through at least, two additional strategies not depending on the hippocampus but on the striatum: signal learning and egocentric learning (Brandeis et al 1989; Gallagher & Pelleymounter, 1988; O'Keefe & Nadel 1978). Signal learning is displayed when the animal reaches a visible platform, or a visible stimulus indicating (signaling) the location of the platform within the maze. Learning of the association between the stimulus and the response is established and depends on the functioning of the striatum (McDonald & White, 1994). The egocentric learning occurs when the animal develops stereotyped motor patterns to locate the invisible platform on the basis of the proprioceptive information provided by its own movement. It is also an ability that depends on the memory system to which the striatum belongs (McDonald & White, 1994; McDonald & White 1995; Oliveira et al., 1997). Results obtained when evaluating both adult and aged male rats, show that some adult rats may use either place, hippocampal dependent allocentric, or striatum-dependent, egocentric strategies; on the other hand, aged rats use egocentric, as their main swimming strategy to solve the task (Dalm et al., 2000; Olvera-Cortés et al, 2011). Thus, deficits in the performance of this task may indicate an alteration of any of these two abilities, place and egocentric learning, so that different parameters should be evaluated to assess the mechanism underlying the observed deficit (D'Hooge & De Deyn, 2001). A qualitative analysis of the swimming paths both during the training period and the probe trial may allow a better determining of the strategy used by the rat in solving the task in the water maze.

Spatial working memory can be evaluated by using the 8-arms Olton radial maze (Myhrer, 2003; Olton**,** 1983, 1987; Olton et al., 1982; Shibata et al., 2007). For a daily standard evaluation all eight arms are baited and the rat is allowed to collect food from each arm; the number of errors, defined as a re-entry into an arm that had already been visited, is recorded in order to evaluate withholding and updating of information about each arm visited and rewarding obtained. An alternative maze configuration in which only some of the eight arms are baited allows to evaluate reference memory besides working memory through recording of the number of reference memory errors (number of entries into unbaited arms) and working memory errors (re-entry into an already visited arm). Performance in the Olton maze requires an adequate functioning of hippocampal-prefrontocortical neuronal circuits, and is a reliable parameter of morpho-functional integrity of these brain structures after ischemia and neuroprotection (Cassel et al., 1998; Fritts et al., 1998; Izaki et al., 2008; Kolb, 1990, Kolb et al 1982; Laroche et al., 2000; Olton et al., 1982; Seamans et al., 1995; Winocur, 1982). An aquatic version of the 8-arm radial maze has also been described (Kolb et al, 1982), and used to correlate hippocampal pyramidal neurons damage and working memory performance (Nelson et al. 1997).

4.1.4 Histopathological assessment

Neuronal population of different neuron types in brain vulnerable structures has been considered as a reliable parameter of ischemia brain damage and neuroprotection. Thus, pyramidal neuron population in the Ammon´s horn of the hippocampus and in the neocortex (Bleayert et al, 1978; Colbourne & Corbett, 1994; García-Chávez et al., 2008; Hartman et al, 2005; Johansen & Diemer, 1991; Kirino, 1982; Letechipía-Vallejo et al., 2007; Moralí et al., 2011b; Pulsinelli, 1985; Schmidt-Kastner & Freund, 1991; Shuaib et al, 1995), or different neuron types in other brain vulnerable structures (Block & Schwartz, 1998; Cervantes et al., 2002), have been evaluated through the number and proportion of surviving neurons. However, most of these studies deal with histopathological assessment of the hippocampus, the highest vulnerable brain region to global cerebral ischemia. Usually four separate counts of surviving neurons in selected areas of the Ammon´s horn are obtained from each of five coronal sections of the hippocampus per rat, stained with cresyl violet for a total of 20 counts per animal, under the different experimental conditions (Hartman et al., 2005). Similar procedures are followed for neuronal counting in other brain structures vulnerable to ischemia.

Immunohistochemical staining techniques have been also used in animal models of global cerebral ischemia and neuroprotection in order to identify specific proteins or fluorescent DNA labels that may selectively mark cells undergoing an acute necrotic or apoptotic process, as well as the activation of specific cellular processes involved in neuronal damage or repair and survival. Immunohistochemical marks (c-fos/c-jun, heat shock proteins, Bcl-2/Bax immunoreactivity, among others) allow to identify neuron types and neuroanatomical regions where ischemia-induced phenomena take place. Besides, immunohistochemical markers of glial fibrillary acidic protein (GFAP) as well as microglia cell surface components lead to identification of reactive gliosis in the hippocampus, as a consequence of global cerebral ischemia and ischemic neuronal death, which elicited activation of microglial cells and interleukine 1 release that may trigger an astrocyte reaction mainly located in the *stratum lacunosum-moleculare, stratum moleculare*, and *hilus*, and

persisting for weeks after ischemia (Buffo et al., 2010; Choi JS et al, 2008; Mori et al, 2008; Morioka et al., 1991, 1992; Nikonenko et al., 2009; Petito & Halaby, 1993). The efficacy of neuroprotective agents can also be determined on the basis of the success in preventing the occurrence of necrosis, apoptosis, heat shock expression, gliosis, etc., as indicated by the immunohistochemical biomarkers (Scallet, 1995). Different parameters of the glial reaction elicited by global cerebral ischemia have been used as indexes of brain damage or neuroprotection (Cervantes et al., 2002; de Yebra et al., 2006; Duan et al., 2011; Korzhevskii et al., 2005; Piao et al., 2002; Soltys et al., 2003).

Neuronal cytoarchitecture and fine structure parameters of synaptic connectivity have also been used for histopathological assessment after brain damage and neuroprotection (Briones et al., 2006; García-Chávez et al., 2008; González-Burgos et al., 2007; Johansson & Belichenko, 2002; Kovalenko et al., 2006, Moralí et al., 2011a; Nikonenko et al., 2009; Ruan et al., 2006).

4.2 Therapeutic opportunity window in animal models of global cerebral ischemia

In any case, recognition of a "therapeutic opportunity window" or "therapeutic time window" in relation to the timing of the ischemic episode, the temporal course of the mechanisms of brain damage and/or repair, and the exerting of actions of presumptive pharmacological or non pharmacological neuroprotective agents, has been a relevant aspect in the approach to neuroprotection in experimental models of global cerebral ischemia (Pulsinelli et al., 1997; Barone & Feuerstein, 1999). In these, the beginning and the extent of this therapeutic window can be expected to be different according to the actions of neuroprotective procedures against immediate or late cellular mechanisms of brain damage, or in favor of later long-lasting cerebral processes of repair and plasticity.

Thus optimal neuroprotective effectiveness may require a schedule of drug administration in which drug actions are coincident with the therapeutic opportunity window, that have to be established for different drugs according to their specific mechanisms of action and pharmacokinetic characteristics. In this sense, counteracting of immediate cell mechanisms of neuronal damage may require the administration of neuroprotective drugs before the ischemic episode, though its administration has to be continued afterwards for variable periods. By contrast, drug-promoting repair or plasticity processes admit the starting of neuroprotective treatment hours or days after ischemia.

Accordingly, designs of neuroprotective studies in experimental animals in supporting proposals of neuroprotection for patients exposed to global cerebral ischemia due to cardiorespiratory arrest, should take in account that this clinical condition usually occurs unexpectedly, and requires cardiorespiratory resuscitation maneuvers; thus neuroprotection procedures have to be installed soon, but after the ischemic episode. Experimental designs of neuroprotection studies assessing neuroprotective procedures against late neuronal damage processes or promoting neuronal repair and plasticity, favoring functional preservation and recovery, may lead supporting to a wideness of the therapeutic opportunity window, for neuroprotection in human beings.

4.2.1 Prophylactic neuroprotection

Transient global cerebral ischemia can occur during certain clinical situations which can either be anticipated, occur during intraoperative emergencies, or even induced, like extracorporeal circulation for cardiac surgery. Under these conditions, prophylactic neuroprotection as that provided by intraoperative hypothermia and pharmacological

neuroprotection are possible alternatives to prevent or reduce the risk of ischemic neuronal damage (Savitz & Fisher, 2007; Weigl et al, 2005). This has stimulated designing of experimental studies on prophylactic neuroprotection to assess the effectiveness of several agents and their clinical potential. Some neuroprotective agents have proven to be more effective when applied before the ischemic insult than when given later in time, in particular those agents affecting the early cellular phenomena induced by ischemia, such as calcium channel blockers, GABAergic and anti-excitotoxic agents, as well as antioxidant drugs (Weigl et al, 2005). Pharmacological treatments (antihypertensive, antidiabetic, antithrombotic, antiatherogenic drugs) effective in modifying in the long term the risk for cardiac arrest or cardiac infarct which may result in global cerebral ischemia or in severe hypoperfusion have also been proposed as prophylactic neuroprotection procedures (Savitz & Fisher, 2007).

5. Conclusion

Though an increasing number of drugs have proven to be effective neuroprotective agents in experimental models of global cerebral ischemia, data supporting proposals for their clinical use have not been enough to influence clinical management and outcome of patients exposed to global cerebral ischemia in clinical trials. However, after its evaluation in animal models of global cerebral ischemia, special interest has been paid to carry out clinical trials with a non-pharmacological procedure, hypothermia, as a part of the intensive care of patients after a cardiorespiratory arrest. Nevertheless, the wide perspectives to gain information on neuroprotection through experimental designs including animal models of global cerebral ischemia are maintained to date, despite the tendency to preferentially conduct studies on rodents; in particular if differences between experimental animals and human beings are taken into account, and attention is paid to reproduce those components mainly accounting for brain damage after global cerebral ischemia.

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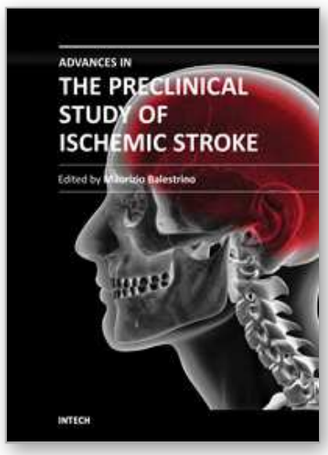

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This book reports innovations in the preclinical study of stroke, including - novel tools and findings in animal models of stroke, - novel biochemical mechanisms through which ischemic damage may be both generated and limited, - novel pathways to neuroprotection. Although hypothermia has been so far the sole "neuroprotection" treatment that has survived the translation from preclinical to clinical studies, progress in both preclinical studies and in the design of clinical trials will hopefully provide more and better treatments for ischemic stroke. This book aims at providing the preclinical scientist with innovative knowledge and tools to investigate novel mechanisms of, and treatments for, ischemic brain damage.

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University Campus STeP Ri
Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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