Mechanisms of secondary degeneration in the central nervous system during acute neural disorders and white matter damage

J.S. Guimarães [a], M.A.M. Freire [a], R.R. Lima [b], R.D. Souza-Rodrigues [b], A.M.R. Costa [b], C.D. dos Santos [b], C.W. Picanço-Diniz [c], W. Gomes-Leal [b]

MECHANISMS OF SECONDARY DEGENERATION IN THE CENTRAL NERVOUS SYSTEM DURING ACUTE NEURAL DISORDERS AND WHITE MATTER DAMAGE

Summary. Introduction. *Acute neurodegenerative diseases, including stroke and traumatic brain and spinal cord injury, possess an elevated worldwide incidence. Two distinct lesive patterns can be identified after these destructive events: primary damage, an early consequence of the primary pathological event, and secondary neural degeneration (SND), a group of pathological events inducing late degeneration in cells not or even only partially affected by the primary damage. This pathological mechanism is an important contributing factor for functional deficits and target for therapeutic approaches. Several factors are involved on the SND etiology, including excitotoxicity, inflammation, and oxidative stress.* Aim. *To review the main mechanisms underlying the SND occurring after acute neural disorders.* Development. *The more recent findings about the eliciting processes of SND degeneration are discussed, as well as their significance to degeneration of white matter tracts.* Conclusions. *The characterization of the events underlying SND is of fundamental importance for the development of new therapeutic approaches effective enough to decrease the functional deficits, contributing to the improvement of the quality of life of people suffering neurological diseases. These therapeutic approaches must be validated in experimental models of both brain and spinal cord diseases, which effectively simulate human neural disorders protecting both gray and white matters for a better neuroprotective efficacy. [REV NEUROL 2009; 48: 304-10]*

Key words. *Acute cerebral damage. Excitotoxicity. Inflammation. Neurodegeneration. Neuroprotection. White matter.*

INTRODUCTION

During acute neural disorders, such as lesions of the central nervous system (CNS) and stroke, both gray and white matters are affected, causing intense neural degeneration and subsequent major functional deficits [1]. Nevertheless, for a long time most studies focused only in the gray matter, neglecting the white matter [2]. Recently, however, it has been noticed that white matter lesions are extremely important event for the genesis of functional deficits and a fundamental factor behind the prognosis of neurological diseases in human CNS [3].

In this review, we present the main mechanisms involved in the pathophysiology of acute neural disorders. Then we discuss the most recent findings on processes responsible for the degeneration of the white matter in CNS diseases.

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[a] Laboratory of Cellular Neurobiology. International Institute for Neurosciences of Natal Edmond and Lily Safra (IINN-ELS). Natal, RN. [b] Laboratory of Neuroprotection and Experimental Neuroregeneration. [c] Laboratory of Functional Neuroanatomy. Institute of Biological Sciences. Federal University of Pará. Belém, PA, Brazil.

Corresponding author: Walace Gomes Leal, PhD. Laboratory of Neuroprotection and Experimental Neuroregeneration. Institute of Biological Sciences. Federal University of Pará. 66075-900 Belém, PA, Brazil. Fax: +55 91 3201-7891. E-mail: freire@natalneuro.org.br

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EPIDEMIOLOGY OF ACUTE NEURONAL DISORDERS

Acute neurodegenerative disorders have high rates of occurrence in several regions of the world [4,5] and are the third most common cause of death in Europe and the United States (USA), leaving behind both cardiovascular diseases and cancer [4,5].

Head trauma accounts for more than 85% of all cases of fatal head injury with ischemic brain injury as a consequence [6]. In the USA, epidemiological studies estimate that between 28 and 55 million people have already suffered some kind of trauma in the brain or the spinal cord.

About two million new cases are reported every year, with 75,000 leading to death and a similar number of cases with permanent functional deficits [4,5]. In the United Kingdom, the most common causes of acute brain injuries include automobile accidents (36-48%), violence (5-29%), falls (17-21%) and recreational activities (7-16%) [5,7,8]. One in every 300,000 households has at least one member with a permanent functional deficit due to head trauma [4,5].

Automobile accidents are the main cause of death among people aged below 35 years in the USA [4,5]. Seventy percent of new cases are related to traumatic brain injury [4,7]. The rate of brain injuries and transient or persistent post-concussional syndromes is around 370 per 100,000, at least three times greater than schizophrenia [4,5]. The USA spends about 7 billion dollars annually on treatment for brain trauma patients [9].

A number of experimental models of neurodegenerative diseases have been developed and some of the main mechanisms responsible for secondary neural degeneration (SND) following the primary pathological event have been established [10]. Considering the high incidence of acute and chronic neuropathologic conditions around the world, studies on the pathological mecha-

nisms underlying these events are of extreme importance to develop new therapeutic approaches [11,12]. Some drugs originating from this research effort have already been released for human use or are undergoing testing [13]. Among the possible factors responsible for cell death in acute pathological conditions, excitotoxic and inflammatory mechanisms remain central concepts and are potential targets for therapeutic intervention [12].

Accordingly, understanding the inflammatory and excitotoxic mechanisms underlying both acute and chronic pathological conditions is crucial for the development of new therapeutic approaches. In the subsequent topics, the pathophysiology of acute neural disorders will be addressed. After, the consequences of the pathological events on the tracts of white matter of the CNS will be discussed.

MECHANISMS OF SND

The SND consists of destructive events that can affect cells that were not or were only partially affected by the initial injury [14]. The primary neuronal injury initiates a process of degeneration and cell death with the release of chemical mediators to the extracellular environment that, acting on the neighboring cells initially spared by the primary insult, promote a further cell loss [14]. It has been described that even after the interruption of the stimulus that triggered the primary neuronal damage, additional injury of neurons may occur whereas these harmful substances persist in extracellular matrix. The degree of secondary neuronal damage is proportional to the extension of the initial injury, and the more intense and lasting the primary insult, more intense will be the release of mediators of secondary neuronal injury. These events occur simultaneously, so that at some point the same region possesses cells degenerating through the primary neuronal degeneration, by the secondary injury and also neuronal cells still intact, spared from the stimulus aggressor [15].

As described above, the neurons and their axons that were not or were only partially affected by the primary lesion may degenerate later if not safeguarded by therapeutic intervention. In acute neurodegenerative diseases, a primary lesion in the gray matter could spread and undermine the white matter, or vice-versa, inducing axonal injury and significantly increasing the functional deficit [16].

Several factors are involved in the pathophysiology of SND after acute neural disorders [17]. Between these factors, excitotoxicity, inflammation and oxidative stress have considerable importance to the tissue loss [18-20].

Excitotoxic cell death in acute neurodegenerative diseases

Glutamate is the main excitatory neurotransmitter of the mammalian CNS, and is present in concentrations of about milimolar in gray matter [17]. The post-synaptic response, as mediated by glutamate, occurs through the pharmacological action of inotropic and metabotropic receptors with distinct features. The metabotropic receptors are coupled to a system involving the participation of G proteins, which work through the release of second messengers, which activate the mobilization of calcium channels in the membrane of the cell [17]. The inotropic glutamatergic receptors are divided into three types according to their selective agonists: AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), NMDA (N-methyl-D-aspartate) and kainate (kainic acid). Each is an ion channel activated by glutamate, and may be permeable to sodium, potassium and calcium ions [17].

Glutamatergic neurons comprise about 80% of the total population of neurons in the cerebral cortex [21], so that this aminoacid has a key role in the physiology of the CNS. Their concentration, both extracellularly and in the synaptic cleft, is strictly controlled by mechanisms involving enzymes and transporters in glutamatergic neurons and glial cells [22,23]. In some pathological conditions, such as the status epilepticus, ischemia, traumatic injury of the brain and spinal cord and metal intoxication [17,18,20,24], these mechanisms are ineffective in maintaining physiological concentrations of glutamate in neural tissue. Accordingly, the concentrations of this neurotransmitter can be elevate several times in relation to normal physiological conditions, inducing cell death by excitotoxicity [12,18,19].

At the end of 1950's, emerged the first evidences that glutamate can play a neurotoxic role. These confirmations were revised and expanded by Olney, which confirmed the neurotoxicity of this aminoacid [25]. Excitotoxicity was originally the term used to refer to the ability of glutamate and its agonists to mediate neuronal death [25]. However, the different subtypes of receptors related to glutamate excitotoxicity do not participate in the same way of this event, with NMDA receptors being activated more rapidly during neuronal death than both AMPA and kainate receptors [18].

The systemic release of glutamate in young and adult animals cause acute swelling in both dendrites and cell body around 30 minutes, which is preceded by degeneration of intracellular organelles and picnosis. In the final phase of this process necrosis and phagocytosis of cellular debris by macrophages are observed [18]. Although glial cells are classically considered not affected, this fact does not seem to be true, since tumefaction and glial activation were recently reported during excitotoxic injury [26]. Oligodendrocytes are especially vulnerable to excitotoxicity mediated by non-NMDA receptors [27].

The high concentration of extracellular glutamate, usually after trauma or ischemic injury in the CNS, results in a high activation of inotropic glutamatergic receptors and, consequently, dysfunction of the sodium/potassium pump with an influx of sodium and chloride ions resulting in an increased uptake of water, which leads to an increase in the volume of cell body. Subsequently, the influx of calcium can trigger a secondary increase of its intracellular concentration. This influx or the release of ionic intracellular store can elevate their cellular level, thus exceeding the capacity of their regulatory mechanisms. These events can cause metabolic impairment, with consequent activation of various enzymes as proteases, lipases, phosphatases and endonucleases directly affecting the cellular structure and inducing the formation of free radicals that can mediate cell death [12,28,29] (Figure).

The experimental injection of glutamatergic agonists such as NMDA induces conspicuous neuronal degeneration in both brain and spinal cord [1,16]. The acute neuronal death is followed by inflammatory events, including recruitment of macrophages and glial activation [1,16], similar to events observed during acute nerve injury in humans [30].

Later, studies using antagonists of glutamatergic receptors for induction of neuroprotection in experimental models of neurological disorders showed its effectiveness as a neuroprotective agent in animal experimentation [12]. However, this approach was ineffective for human neural disorders [31]. The reasons for this include a low penetration by blood-brain barrier, inadequate protection of the white matter and impairment of normal neu-

ronal functions mediated by glutamatergic receptors [31,32]. This last point indicates that blocking these receptors may be beneficial in a temporal window, but very damaging in another [32]. Moreover, studies suggest that the blocking of other membrane receptors, including ion channels volume and pH-dependents, sodium and calcium pumps and channels not selective for calcium, can lead to potential therapeutic approaches [33].

As stated above, there seem to be two excitotoxic components: first, an acute component dependent of sodium and chloride, characterized by an immediate neuronal swelling, and a second component characterized by elevated levels of calcium, leading to the neuronal degeneration [33].

Oxidative stress and neurodegenerative diseases

The oxidative stress is one of principal pathological attributes during ischemia and inflammation [34], being one of the possible causes for conditions such as stroke, spinal cord injury, brain trauma and multiple sclerosis. The oxidative stress results from the generation of a large amount of derivatives of reactive oxygen species (ROS) during the pathological condition, which may induce degradation of proteins, lipids and nucleic acids [35], resulting in cell death by necrosis or apoptosis (Figure).

When amount of ROS exceed their normal levels, it can contribute to an indiscriminate impairment of structural and functional integrity of cells, and modification of cellular DNA, proteins and lipids [36,37]. However, cells have a variety of anti-oxidant mechanisms of defense and repair against the action of ROS produced during the anaerobic metabolism of the brain. In some circumstances, however, these systems fail, leading to oxidative stress where the production of oxidizing ROS suppresses the body's defenses because a dysfunction in balancing the production of pro-oxidants and free radicals. The oxidative stress is gradually increased during the anaerobic respiration in a framework of ischemia and reperfusion [34,38].

In acute neural disorders, the microglial activation induce an increased production of free radicals by the excessive activation of the enzyme NADPH oxidase [39,40]. It was demonstrated that abovementioned enzyme induces damage to neurons in experimental models of Parkinson's [41] and Alzheimer's diseases [42] and also in other types of dementia [42]. Their blockade of is a promising therapeutic approach for several diseases of CNS [39,40].

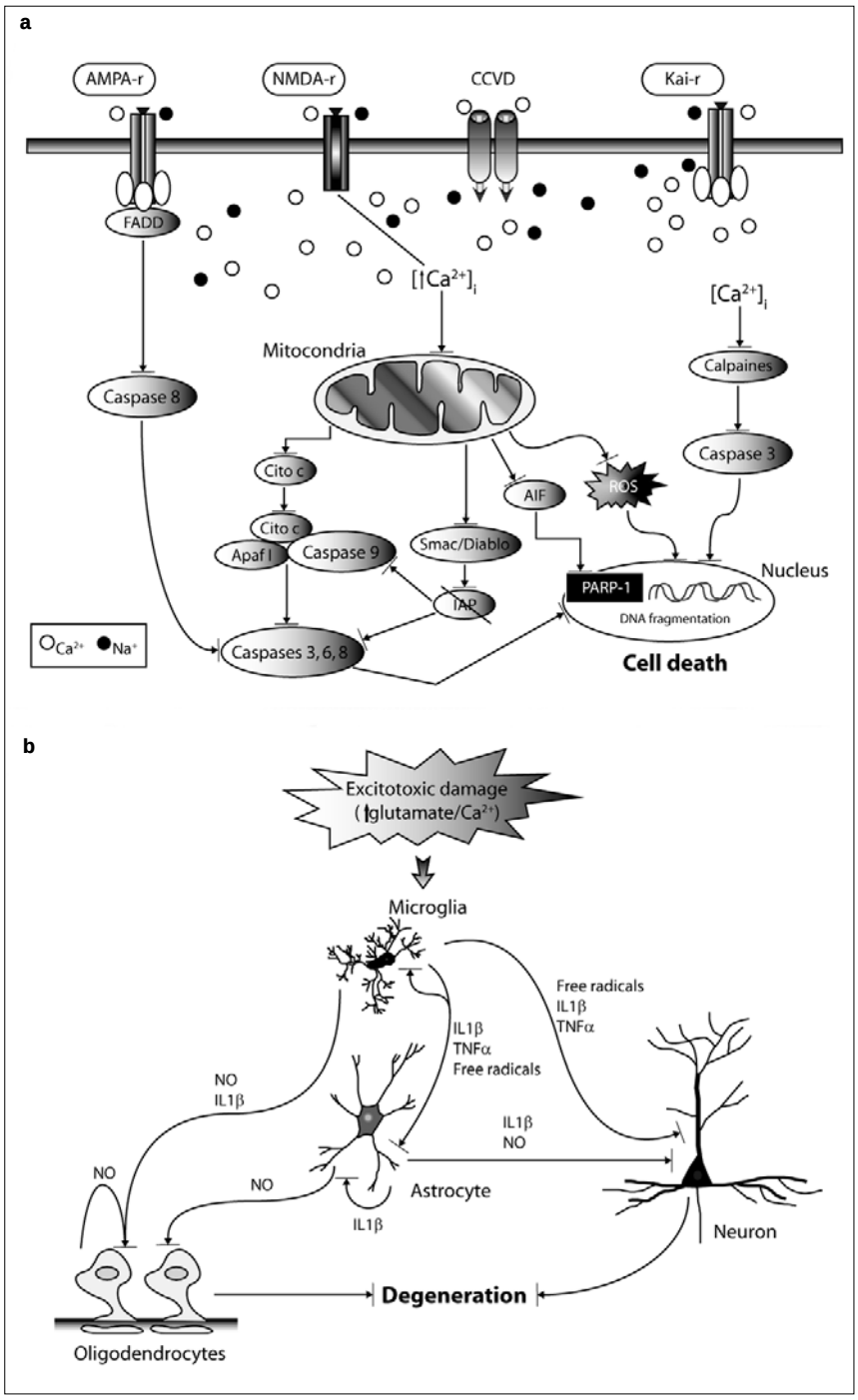

Figure. Cellular and molecular mechanisms of secondary degeneration caused by excitotoxicity and inflammatory response. a) The activation of AMPA (AMPA-r) and kainato (Kai-r) receptors generates a influx of sodium (Na^+) and calcium (Ca^{2+}) ions, with subsequent depolarization of the cell membrane and activation of voltage-dependent calcium channels (CCVD), contributing to the increased influx of this ion. Its consequent intracellular increase induces an amplified production of reactive oxygen species (ROS) by mitochondria, highly detrimental to the cell. Additionally, the mitochondria release cytochrome c (Cyto c) that, interacting with the apoptotic protease activating factor (APAF I), activate caspases which ultimately lead to cell death by apoptosis. Others apoptotic mediators include the apoptosis-inducing factor (AIF), which activates the poly (ADP-ribose) polymerase-1 (PARP-1) in the cell nucleus, the enzyme Smac/Diablo that, by blocking the action of inhibitors of apoptosis protein (IAP) increases the activity of caspases, and calpaines, calcium-dependent proteolytic enzymes. All these events result in fragmentation of the genetic material of the cell, thereby characterizing cell death by apoptosis. b) Increased levels of extracellular glutamate induced astrocytic and microglial activation, releasing several highly reactive chemical species such as free radicals, interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and nitric oxide (NO), which act directly in both neurons and glial cells, such as oligodendrocytes, inducing their degeneration. Schemes based on references [12,17,27,36-38,43-45,47]. FADD: Fas-associated protein with death domain.

The mechanisms responsible for the induction of oxidative stress after the release of excessive glutamate seem to involve two phases: an initial reduction of the xanthine oxidase enzyme and a late stage, with the production of free radicals, closely related to mitochondrial dysfunction [34]. The release of cytochrome C can also induce mitochondrial injury [43], and this event may be the final destination of the biochemical cascade responsible for apoptotic cell death mediated by the activation of glutamatergic receptors [44], as well as liberation/activation of other apoptotic inducers, such as Smac/Diablo mitochondrial enzyme, which acts blocking the inhibitors of apoptosis protein (IAPs) [45].

Inflammatory response in neurodegenerative diseases

The inflammatory response was firstly described by the Egyptians, but it was the Roman Cornelius Celsius who first defined this event by its characteristic features (heat, redness, swelling and pain, commonly present in inflamed tissues) [46].

Inflammation is the first response of the immune system to invasion of pathogens, mediating the protection of the tissue to these noxious agents and promoting healing, being generally beneficial to the organism, as limiting the survival and proliferation of destructive agents, promoting tissue repair and recovery and keeping the energetic levels needed for survival tissue [47,48]. However, a prolonged and exacerbated inflammatory response mediated by pro-inflammatory cytokines potentially cytotoxic such as interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), nitric oxide (NO) and cyclooxygenase 2 (COOX-2), can be highly harmful in both peripheral and nervous tissue [47].

The CNS is known as an immune privileged site. In general a stimulus equivalent in the parenchyma of peripheral tissues leads to a very subtle inflammatory response in nervous parenchyma [49,50]. Part of this immune privilege is associated with junctions of cerebral vasculature (blood-brain barrier), responsible for limiting the entry of large molecules and circulating cells in the neural parenchyma [50].

Evidences show that the inflammatory response may be involved in mechanisms responsible for the exacerbation of the SND in a number of neurodegenerative conditions such as cerebral ischemia, brain trauma and spinal cord injury, characterized by a substantial cell loss associated with severe functional deficits [1,50].

The involvement of the inflammatory response in many neurodegenerative diseases has been investigated by means of appropriate experimental models. These studies characterized the process of recruitment and activation of inflammatory cells (leukocytes and microglia) as well as the increased expression of transcription factors that coordinate the inflammatory response [47,48].

During the acute inflammatory response in the CNS there is the recruitment of neutrophils and macrophages to the site of injury. The microglia (resident macrophages of the CNS) has an important role during this process. After the injury the endothelial cells express adhesion molecules as P-selectines and E-selectines [51,52], which interact with receptors found in the membrane of neutrophils, adhere to the endothelium, cross the vascular wall and penetrate in the nervous parenchyma [53].

After the infiltration of the neutrophils, the monocytes migrate to the injured nerve region, where chemokines are synthesized by the cells located in this region and guide the migration of inflammatory cells from the bloodstream to the injured region [53,54]. The microglia then responds quickly to the injury, retracts their extensions and assumes an ameboid-like form. These cells are important phagocytes to the elimination of debris and release of a large number of pro-inflammatory mediators [55,56].

Despite its important phagocytic function, it is believed that microglial cells contribute to the phenomenon of SND in several pathological conditions, including injury of the spinal cord, ischemia and neurodegenerative diseases in both *in vivo* and *in vitro* models [53,55]. In these pathological disorders, the microglial cells can synthesize and release substances potentially harmful such as NO, free radicals, proteolytic enzymes, TNF-α and IL-1β [57]. It has been reported that during brain ischemia or excitotoxic injury, microglial cells release NO and IL-1β, which could contribute to the process of SDN [38,58] (Figure).

Similar to microglia, the macrophages seem to contribute to neuroregeneration in some experimental conditions [59,60]. After mechanical injury in the striatum of rats, an accumulation of macrophages and microglial activation was reported, with a growth of striatal dopaminergic fibers after injury and a significant expression of brain-derived growth factors by microglial cells [59], supporting the hypothesis that neurotrophic factors could be involved with neuroregenerative processes such as axonal regeneration.

The contribution of the inflammatory response and, in some cases, specific inflammatory mediators, has been associated to many chronic neurodegenerative diseases such as infections (meningitis, cerebral malaria virus and human immunodeficiency virus) as well as multiple sclerosis, Alzheimer's and Parkinson's diseases [61-63]. Studies show that a chronic inflammatory response has devastating consequences in the cellular environment and therefore is possible to speculate that this phenomenon may have a crucial role in the course of these diseases [61,62]. Thus, it is believed that the cellular components of the inflammatory response may contribute greatly to increase the area of secondary injury in acute and chronic neurodegenerative conditions.

White matter degeneration and diseases of CNS

In humans the white matter corresponds to approximately 50% of the total brain volume. Consequently, lesions in such region contribute significantly to the deficits seen in altered states [27].

The tracts of white matter of the CNS have the important function of transport neural signals from the spinal cord to the brain and vice-versa. In classical studies of experimental neuropathology, the pathological changes of these tracts were neglected [2]. However, new approaches suggest that in various neural disorders, including brain and spinal cord trauma, stroke, cerebral malaria, multiple sclerosis and amyotrophic lateral sclerosis, both the death of glial cells and the direct lesion of white matter tracts could be the main cause of subsequent functional deficits during the phenomenon of SND [3,64].

An important factor that supports this hypothesis is the significant functional deficit observed in the CNS after ischemic and traumatic injuries resulting in white matter dysfunction instead of gray matter dysfunction [65]. The harmful effects of a primary pathological alteration in the CNS (for example, anoxia or trauma) are exacerbated during the SND, which is the increase of the area of injury to adjacent regions or even distant from the site of primary lesion [66]. During this phenomenon,

besides the inflammatory mechanisms and neurotoxicity mediated by glutamate, ischemia post-traumatic, metabolic and ionic imbalance, generation of free radicals, and other factors seem to contribute to cell death [18,53].

It is thought that the functional deficit generated after traumatic injury of the brain and spinal cord, stroke and other acute and chronic pathological conditions may be caused mainly by the breakdown of white matter tracts, glial cells and myelin covering the axonal cylinder [27,67]. In both the spinal cord and brain, changes in the cytoskeleton of oligodendrocytes were described in both ischemic and excitotoxic experimental models [68-71], revealing a clear link between mechanisms excitotoxic and/or inflammatory and collapse of the white matter [27,67]. The ineffectiveness of clinical studies to develop efficient therapeutic agents for diseases of the CNS may be due, in large part, to the inability of these agents to protect the white matter [13].

The acute spinal cord injury in humans is an important pathological condition that causes permanent functional deficits in the affected individuals, which are mainly due to impairment of tracts of the white matter [72]. This impairment occur by compression of fractured vertebrae that can cause crushing of the spinal cord parenchyma [72]. In humans, massive lesions of the white matter of the spinal cord can induce permanent paraplegia in case of traumatic accidents. The injury involves several segments and is characterized by secondary expansion of necrotic cavities [72]. Intense inflammatory response followed by axonal injury and late degeneration of myelin and oligodendrocytes are observed [1,16], suggesting that the secondary degeneration of the white matter can be a consequence of inflammatory events [1,16]. Similarly, mechanisms related to the excessive formation of free radicals and inflammatory processes could be involved in the expansion of primary injury after acute spinal cord lesion [52]. In ischemic cases, the involvement of myelin, bodies of oligodendrocytes and axons are histopathological events of great importance that contribute greatly to the functional deficits [70,73,74].

The molecular mechanisms that ultimately lead to damage of the white matter seem involve excitotoxicity mediated by AMPA/kainate receptors, reversal of the activity of ATPases carriers of glutamate found the myelin, concomitant to the influx of sodium and calcium. Furthermore, the synthesis of reactive chemical species such as NO seems to contribute effectively in the pathophysiology of axonal injury in acute spinal cord trauma [75].

Until the beginning of the present decade it was believed in the non-existence of NMDA receptors in the white matter [71,76]. The alterations in this region, observed in experimental models, were attributed to the non-specific activation of non-NMDA receptors (AMPA and kainate) by glutamate released from neurons or glial cells undergoing degeneration in the gray matter or even other sources in the white matter itself [71,76].

In the former years it was investigated the use of antagonists of glutamatergic receptors for neuroprotection [66]. However, despite the effectiveness of these antagonists in experimental studies, clinical trials in humans showed the ineffectiveness of these compounds, mainly because of non-protection of the white substance, in addition to the blocking of the physiological roles of glutamatergic receptors [13,77]. As pointed out previously, numerous studies have suggested that the excessive activation of non-NMDA receptors (AMPA/kainate) would be important for the mechanisms that occur in harmful white matter during acute neural disorders [67,71]. In these studies, blocking of these receptors was efficient in protecting the white matter [67,71], suggesting the lack of a significant amount of the NMDA receptors in this region of the CNS [67,71], Nevertheless, the discovery of the presence of these receptors on oligodendrocytes [20,27,78,79], which can be activated during tissue injury [27], suggests an active role in the mechanisms of the NMDA lesion of the white substance, being possible, thus, the assessment of the degree of neuroprotection induced by non-competitive antagonists of these receptors in the abovementioned region [80,81].

Memantine is a low-affinity blocker of NMDA receptors [81], acting as a inhibitor of the activation of these receptors without excessive interference in their physiological activity, thus minimizing the collateral effects of this procedure [80,81]. Drugs such as memantine effectively protect the white substance in experimental models of neurological diseases and can be used in clinical trials in humans in the near future [81]. These studies open a new field of investigation, in which the selective blockade of NMDA-type glutamatergic receptors become a promising therapeutic approach for the protection of the white matter, minimizing the functional deficits in human neural disorders [80,81]. In addition, adult neurogenesis also appears as a potential candidate to reduce the deficits related to neurodegenerative disorders in the nervous system [82,83].

CONCLUSIONS

The pathophysiology of CNS diseases is extremely complex, but histopathological events including excitotoxicity, inflammation and oxidative stress certainly have an essential role in the secondary neuronal degeneration. A more complete understanding of these events is vital to the delineation of effective neuroprotective and neuroregenerative approaches to be applied in human neural disorders. Also, the protection of the different compartments of the CNS to the reduction of functional deficits underlying these neural disorders is critical. Accordingly, the protection of the white matter tracts of the CNS is extremely important, considering that the late degeneration of cell bodies of oligodendrocytes, the myelin sheath and axons is crucial to the genesis of functional deficits during neural disorders.

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MECANISMOS DE DEGENERACIÓN SECUNDARIA EN EL SISTEMA NERVIOSO CENTRAL DURANTE LOS TRASTORNOS NEURONALES AGUDOS Y EL DAÑO EN LA SUSTANCIA BLANCA

Resumen. Introducción. *Las enfermedades neurodegenerativas, incluyendo los accidentes cerebrovasculares, los traumatismos cerebrales o las lesiones de la médula espinal, tienen una elevada incidencia en todo el mundo. Se pueden identificar dos patrones lesivos claros tras estos episodios destructivos: un daño primario, consecuencia temprana del episodio patológico primario, y una degeneración neuronal secundaria (DNS), un grupo de episodios patológicos que inducen la degeneración tardía en células que no están afectadas por el daño primario o que sólo lo están parcialmente. Este mecanismo patológico es un importante factor que contribuye a los déficit funcionales y es el objetivo de enfoques terapéuticos. Hay varios factores implicados en la etiología de la DNS, incluyendo la excitotoxicidad, la inflamación y el estrés oxidativo.* Objetivo. *Revisar los principales mecanismos que subyacen en la DNS tras los trastornos neuronales agudos.* Desarrollo. *Se tratan los hallazgos más recientes sobre el proceso desencadenante de la DNS, así como su importancia para la degeneración de las vías de la sustancia blanca.* Conclusiones. *La caracterización de los episodios que subyacen en la DNS es de gran importancia para el desarrollo de nuevos enfoques terapéuticos suficientemente eficaces para disminuir los déficit funcionales y contribuir a la mejora de la calidad de vida de quienes padecen enfermedades neurológicas. Para una mejor eficacia neuroprotectora de la sustancia gris y de la sustancia blanca, estos enfoques terapéuticos deben validarse en modelos experimentales, tanto de enfermedades cerebrales como de la médula espinal, que simulen eficazmente los trastornos neuronales. [REV NEUROL 2009; 48: 304-10]*
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