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REVIEW ARTICLE

Mitochondrial dysfunction associated with nitric oxide pathways in glutamate neurotoxicity

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Abstract Multiple mechanisms underlying glutamate-induced neurotoxicity have recently been discussed. Likewise, a clear deregulation of the mitochondrial respiratory mechanism has been described in patients with neurodegeneration, oxidative stress, and inflammation. This article highlights nitric oxide, an atypical neurotransmitter synthesized and released on demand by the post-synaptic neurons, and has many important implications for nerve cell survival and differentiation. Consequently, synaptogenesis, synapse elimination, and neurotransmitter release, are nitric oxide-modulated. Interesting, an emergent role of nitric oxide pathways has been discussed as regards neurotoxicity from glutamate-induced apoptosis. These findings suggest that nitric oxide pathways modulation could prevent oxidative damage to neurons through apoptosis inhibition. This review aims to highlight the emergent aspects of nitric oxide-mediated signaling in the brain, and how they can be related to neurotoxicity, as well as the development of neurodegenerative diseases development.

PALABRAS CLAVE
Glutamato;
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Enfermedades neurodegenerativas;
Mitocondria;
Óxido nítrico;
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Apoptosis

Disfunción mitocondrial asociada a las vías del óxido nítrico en la neurotoxicidad por glutamato

Resumen Recientemente se han evaluado múltiples mecanismos que subyacen a la neurotoxicidad inducida por el glutamato. En este sentido, pacientes con neurodegeneración presentan disfunción mitocondrial, estrés oxidativo e inflamación. Cabe destacar que el óxido nítrico, un neurotransmisor atípico sintetizado y liberado según demanda por las neuronas postsinápticas, ejerce también la regulación de la apoptosis modulando la sinaptogénesis, la eliminación de sinapsis y la liberación de neurotransmisores. El papel emergente de las vías de óxido nítrico asociado a la apoptosis se ha discutido en la neurotoxicidad inducida por glutamato. Estos

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hallazgos muestran que la modulación de las vías de óxido nítrico podrían prevenir el daño oxidativo neuronal mediante la inhibición de la apoptosis. La presente revisión pretende destacar los aspectos emergentes de la señalización mediada por óxido nítrico en el cerebro, y la forma en que se puede relacionar con la neurotoxicidad, así como con el desarrollo de enfermedades neurodegenerativas.

In the middle of the last century, Dr. Awapara discovered the gamma aminobutyric acid (GABA), which is also usually an inhibitory neurotransmitter. GABA acts like a brake to the excitatory neurotransmitters that lead to anxiety. Thus, people with too little GABA tend to suffer from anxiety disorders. On the other hand, glutamate (discovered by Dr. Ikeda in 1907) is an excitatory relative of GABA. It is the most common neurotransmitter in the central nervous system and especially important in regards to memory. Of interest, glutamate is actually toxic to neurons, and an excess can kill them.[1] Sometimes brain damage or a stroke will lead to a glutamate excess and end with many more brain cells dying than from the original trauma. Many believe it may also be responsible for quite a variety of diseases of the nervous system, and are looking for the ways to minimize its effects. Glutamate was discovered by Dr. Ikeda of Tokay Imperial University in 1907, and however, it took decades for Dr. Usherwood to identify glutamate in locusts as a neurotransmitter.

Recently, multiples mechanisms underlying glutamate-induced neurotoxicity have been proposed. In this regard, current evidence highlights decoupling in the mitochondrial respiratory chain[2,3]; and this is consistent since it is known that glutamate transmission is strongly dependent on calcium homeostasis and on mitochondrial function.[4] Moreover, apoptosis is a regulated process inherent to the normal cellular brain development and/or maintenance, nevertheless a clear deregulation of the mitochondrial respiratory mechanism has been described in patients with neurodegeneration associated to an increase of the oxidative stress.[5–7] In this sense, several hypotheses have been proposed for neurotoxicity. These suggest mitochondrial dysfunctions and oxidative stress linked to glutamate-mediated excitotoxicity.[8,9] Accordingly, glutamate excitotoxicity, oxidative stress, and mitochondrial dysfunctions are common features leading to neuronal death in cerebral ischemia, traumatic brain injury, Parkinson's disease, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis.[10] In addition, growing set of observations points to mitochondrial dysfunction, oxidative damage and chronic inflammation as common pathognomonic signs of a number of neurodegenerative diseases.[11] However, mitochondrial disease may be a primary event in neurodegeneration, contributing to oxidative stress and apoptosis, or it may be caused by other cellular processes.

Particularly relevant for neurodegenerative processes is the relationship between mitochondria and nitric oxide (NO). NO, a common but short living product of nitrogen metabolism is now understood to participate as a regulatory factor in a diverse array of physiological functions, from the control of vascular resistance or acting as a neurotransmitter to mediating inflammatory processes.[12] Regulation of cell number is a crucial property of multicellular organisms. Every moment billions of cells die to ensure the functionality of the whole organism. Apoptosis is essential to normal development as well as physiological cell turnover. The excess and/or defect can be manifested across different kind of pathologies. NO is a factor involved in apoptosis modulation but it has produced controversies. In this sense, principal mechanisms for apoptosis modulation are cytoprotective stress protein, cGMP dependent protein kinase, caspase activity and cytochrome C release. The accumulated data indicate that physiologically relevant levels of NO contribute to apoptosis balance. Decision for a cell to undergo apoptosis is the result of a shift in the balance between the antiapoptotic and proapoptotic forces within a cell.[13] Thus, in an original study from Sorokina et al., they demonstrate the ability for NO to oxidize unsaturated fatty acids and the ability of serum albumin to bind them after their hydrolytic removal, and suggested that the serum albumin-induced potentiation of glutamate neurotoxicity resulted from exacerbation of the toxic effects of NO and other trace radicals on the neuronal membranes.[14] In addition, NO alone or in cooperation with superoxide anion and peroxynitrite is emerging as a predominant effector of neurodegeneration.[10] These and other more recent studies have proposed novel neuroprotective strategies with selective NO neuronal modulators. These findings suggest that NO pathways modulation could prevent oxidative damage to neurons by apoptosis inhibition. Moreover, growing evidence suggests that mitochondrial dysfunction linked to apoptosis is the key responsible in neurodegenerative diseases.[15,16] Given the fact that mitochondria participate in diverse cellular processes, including energetics, metabolism, and death, the consequences of mitochondrial dysfunction in neuronal cells are inevitable.

Finally, the etiology of main neurodegenerative diseases is still unknown, but increasing evidences suggest that glutamate and mitochondria are two prominent players in the oxidative stress process that underlie these illnesses.[17] Moreover, of particular interest to present knowledge, an emergent role of NO pathways linked to mitochondrial dysfunction has been discussed in the neurotoxicity from glutamate-induced apoptosis.

Nitric oxide in the central nervous system: a key player

NO, an ubiquitous gaseous signaling molecule, participates in the regulation of a variety of physiological and patho-

logical processes. Since it was first identified to play an important role in relaxation of blood vessels,[18] NO has been demonstrated to regulate many biological processes,[19–23] especially in the central nervous system (CNS).[24] Three types of enzymes produce NO in humans, one of these, the neuronal type is found almost exclusively in the nervous system. The original evidence of NO synthesis in the CNS was the finding that N-methyl-D-aspartate (NMDA) receptor agonists caused the release of a substance similar to endothelium derived relaxing factor[25]; and later this was followed by the demonstration of neuronal nitric oxide synthase (nNOS) in rat brain.[26]

NO is a non-typical neurotransmitter, which maintains the activities of neural cells and regulates the normal functions of brain. Promote the transfer of nerve signals from one neuron to another, maintaining the synaptic strength. Also, NO is a unique regulator on neurogenesis and synaptogenesis, producing the positive or negative effects upon different signal pathways or cellular origins and locations.[27]

In 1990, Dr. Bredt and collaborators, describe localization of nNOS indicating a neural role for NO.[28] They demonstrated nNOS in the brain exclusively associated with discrete neuronal populations, such as, in the neural innervation of the posterior pituitary, in autonomic nerve fibers in the retina, in cell bodies and nerve fibers in the myenteric plexus of the intestine, in adrenal medulla, and in vascular endothelial cells. Therefore, these transcendental findings provide the first conclusive evidence for a strong association of NO with neurons. In addition, several observations suggested that the Ca_2^+-dependent postsynaptic release of NO may be important in the formation and function of the vertebrate nervous system.

NO release is critically related to synaptic plasticity, control of cerebral blood flow, and the establishment and activity-dependent refinement of axonal projections during the later stages of development.[29]

At the present time, it is well known that NO participates in the regulation of a variety of physiological and pathological processes. Generally, low concentrations of NO are neuroprotective and mediate physiological signaling whereas higher concentrations mediate neuroinflammatory actions and are neurotoxic.

In relation to neurotoxic effects, some recent studies have implicated NO as a critical regulator of neuroinflammation, thus suggesting a possible role in the pathophysiology of major depressive disorder. Also, NO has long been considered part of the neurotoxic insult caused by neuroinflammation in the Alzheimer's brain. However, prior to the appearance of cognitive symptoms, is changing that perception. Therefore, this has highlighted a compensatory, neuroprotective role for NO that protects synapses by increasing neuronal excitability. Here, a potential mechanism for augmentation of excitability by NO *via* modulation of voltage-gated potassium channel activity has been suggested.[30] In addition, a low production of NO is linked to the pathogenesis of schizophrenia. NO donors might be a promising class of compounds for the treatment of schizophrenia. Moreover, current analysis shows that both NO donors and NOS inhibitors are involved in object recognition memory and suggests that NO might be a promising target for cognition impairments.[31,32] In this context, an interesting pharmacological application supporting evidence for the neuroprotective actions of D-arginine (NO donor) against neurotoxicity induced by high levels of glucocorticoids in the CNS has been recently discussed. This might be a novel way of neutralizing the neurotoxic effects of glucocorticoids without compromising their positive peripheral actions.[33] But, the potential neurotoxicity and the slight therapeutic window of NO donors would add a note of caution.

Nitric oxide linked to neurotoxicity from glutamate: mitochondrial emerging role

Glutamate is one of the 20 amino acids forming part of proteins. It is critical for cell function and is not an essential nutrient because in human can be synthesized from other compounds. It is the classic excitatory neurotransmitter in the human cortex. Its role as a neurotransmitter is mediated by the stimulation of specific receptors, called glutamate receptors, which are classified into ionotropic (ion channel) and metabotropic receptors (seven transmembrane G protein coupled domains). All neurons contain glutamate, but only a few use it as a neurotransmitter. Glutamate is potentially excitotoxic. Whereas a variety of neurotransmitters could potentially trigger excitotoxic cell injury, glutamate is thought to be the primary contributor because of its potent effect on increasing intracellular calcium through ionotropic receptors[34]; therefore a complex machinery to regulate levels is active. In this regard, and of special interest, the central role played by NO in the CNS has been emphasized in the current literature.

In CNS, the NO can originate at least from four different sources: the endothelium of cerebral vessels, the immunostimulated microglia and astrocytes, the nonadrenergic noncholinergic nerve, and the glutamate neuron.[35] To highlight, the highest stimulus for the release of NO is the activation of NMDA receptors by glutamate. Also, the release of NO can also be elicited by non-NMDA receptors for glutamate, as well as receptors for acetylcholine, angiotensin, bradykinin, serotonin (5-hydroxytryptamine; 5-HT), neurotensin and endothelin.[36]

An original report by Dawson et al., established that NO mediates the neurotoxicity of glutamate.[37] The authors proposed free radical formation linked to neurotoxicity, and NO is a reactive free radical. According to this, a growing body of evidence suggests involvement of oxidative stress, inflammation and apoptosis in neurodegenerative diseases.[38–41] Moreover, apoptosis is a regulated process inherent to the normal cellular brain development and/or maintenance, nevertheless a clear deregulation of the mitochondrial respiratory mechanism has been described in patients with neurodegeneration associated to an increase of the oxidative stress.[42–44]

Toxicity mediated by NO, has been controversial. In this sense, Dr. Kiedrowski suggested that neuroprotective properties of a NO donor as sodium nitroprusside (SNP) on glutamate- and NMDA-induced neurotoxicity are not due to the release of NO and activation of guanylate cyclase, but are determined by the ferrocyanide portion of the SNP molecule.[45] It was shown that NO afford protection from NMDA receptor-mediated neurotoxicity. This pathway for NO regulation of physiological function is not *via* cGMP,

but instead involves reactions with membrane-bound thiol groups on the NMDA receptor-channel complex.[46]

NO can react with superoxide to yield peroxynitrate, which is extremely reactive.[47] In models of macrophage-mediated cytotoxicity NO can complex with the iron–sulfur center of enzymes to inactivate them.[48] Because several of these enzymes are in the mitochondrial electron-transport complex, NO can inhibit mitochondrial respiration, diminishing the ability of the cells to deal with oxidative stress. Specifically, high concentrations of NO irreversibly inhibit complexes I, II, III, IV, and V in the mitochondrial respiratory chain, whereas physiological levels of NO reversibly reduce cytochrome oxidase.[49] Also, further evidence was found in a study on manganese neurotoxicity. Manganese is sequestered in mitochondria where it inhibits oxidative phosphorylation. The authors discusses that exposure to manganese results in important changes including: decreased uptake of glutamate; increased densities of binding sites for the ''peripheral-type'' benzodiazepine receptor, a class of receptor localized to mitochondria of astrocytes and involved in oxidative metabolism and mitochondrial proliferation; increased uptake of L-arginine, a precursor of NO, together with increased expression of the inducible form of NOS (iNOS). Accordingly, potential consequences include failure of energy metabolism, production of reactive oxygen species (ROS), and increased extracellular glutamate concentration with excitotoxicity effects.[50]

The mechanisms of neurotoxicity involve activation of NMDA receptors by glutamate, production of NO by nNOS and iNOS, oxidative injury to DNA, and activation of the DNA damage-sensing enzyme poly (ADP-ribose) polymerase (PARP). In this sense, the translocation of a mitochondrial protein apoptosis inducing factor (AIF) from mitochondria to the nucleus depends on PARP activation and plays an important role in excitotoxicity-induced cell death.[51] In addition, the accumulation of calcium into mitochondria may play a key role as a trigger to mitochondrial pathology. Calcium overload in neurons, the neurotoxicity of glutamate depends on mitochondrial calcium uptake, but the toxicity to mitochondria also requires the generation of NO. The calcium increase mediated by NMDA receptor activation is thus associated with NO, and the combination leads to the collapse of mitochondrial membrane potential followed by cell death.[52]

It's clear that, glutamate neurotoxicity is mediated, at least in part, by NO and mitochondrial damage. However, recently it has been postulated a new finding closely related. These reports indicate that heat shock protein 70 (Hsp70) upregulation may provide protection in depression by down-regulation of iNOS protein expression through suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation.[53] This was validated by Liu et al., who used an *in vitro* spinal cord injury model induced by glutamate treatment. Here, allicin (an organosulfur compound obtained from garlic) treatment significantly attenuated glutamate-induced lactate dehydrogenase (LDH) release, loss of cell viability and apoptotic neuronal death. Allicin decreased the expression of iNOS following glutamate exposure. Moreover, allicin treatment significantly increased the expression of Hsp70.[54]

Heat shock proteins (HSP) are a shock induced family of proteins, whose most prominent members are a group of molecules dedicated to maintaining the function of other proteins. Interestingly, after being exposed to heat shock typical proinflammatory agonists modify the heat shock-induced transcriptional program and expression of HSP genes, suggesting a complex reciprocal regulation between the inflammatory pathway and that of the heat shock response. The specific task of Hsp70, the most widespread and highly conserved HSP, is to protect against inflammation through multiple mechanisms. Hsp70 modulates inflammatory response, as well as down-regulates the nuclear factor kappa-light chain-enhancer of activated B cells. Also, a decreased expression of renal Hsp70 may contribute to activate the toll-like receptor 4-initiating inflammatory signal pathway. In addition, several studies have revealed that Hsp70 is involved in the regulation of Angiotensin II, a peptide with proinflammatory activity. Increased inflammatory response is generated by nicotinamide adenine dinucleotide phosphate oxidase (NADPH), following activation by Angiotensin II. Also, Hsp70 protects the epithelium by modulation of NADPH, a fundamental step in the pro-inflammatory mechanism.[55]

Inflammation is present in many diseases such as: diabetes, obesity, metabolic syndrome, impaired glucose tolerance, hypertension, cardiac, and CNS disease.[56,57] Inflammation is connected to mitochondrial dysfunction, overproduction of oxidants, and an over-activation of the renin-angiotensin system linked to the NADPH oxidase activity.[58] In addition, NO is also associated with inflammation linked to mitochondrial dysfunction. Moreover, and as mentioned above, reduced NO release induces Hsp70 expression,[54] mediating beneficial effects against oxidative stress injury, inflammation and apoptosis.[56,59] In this sense, glutamate induces the expression of Hsp70 genes linked to apoptosis or necrosis.[60] Later, Hsp70 was suggested as molecular markers of neurotoxicity.[61] According, some chaperones such as the members of the Hsp70 family also modulate polyglutamine (polyQ) aggregation and suppress its toxicity. These findings suggested that an imbalance between the neuronal chaperone capacity and the production of potentially dangerous polyQ proteins may trigger the onset of polyQ disease.[62] The formation of insoluble protein aggregates in neurons is a hallmark of neurodegenerative diseases caused by proteins with expanded polyQ repeats. In addition, the more frequent amyloid-related neurodegenerative diseases are caused by a gain of toxic function of misfolded proteins. Toxicity in these disorders may result from an imbalance between normal chaperone capacity and production of dangerous protein species. Increased chaperone expression can suppress the neurotoxicity of these molecules, suggesting possible therapeutic strategies.[63] Moreover, the effects of the Hsp70 were investigated in tau oligomers and tau toxicity linked to neurodegenerative disease. The authors illustrated that Hsp70 preferentially binds to tau oligomers over filaments and prevents anterograde fast axonal transport inhibition observed with a mixture of both forms of aggregated tau.[64] All this evidence strengthens the idea of a reduced NO release linked to induces Hsp70 expression, can mediated beneficial effects against oxidative stress injury, inflammation and apoptosis, during neurodegenerative and neurotoxicity diseases.[65] Robust evidence suggests that abnormalities in NO signaling may constitute a trait-marker related to neuroinflam-

mation, which could be explored for novel therapeutic targets.[66]

Finally, the etiology of main neurodegenerative diseases is still unknown, but increasing evidences suggest that glutamate and mitochondria are two key players in the oxidative stress process that underlie these illnesses. Moreover, of particular interest to present knowledge, an emergent role of NO pathways linked to mitochondrial dysfunction has been discussed in the neurotoxicity from glutamate-induced apoptosis. Taken together, evidences suggest that NO pathways modulation could prevent oxidative damage to neurons by apoptosis inhibition. The discussion remains open on emergent aspects of nitric oxide-mediated signaling in the brain, and how they can be related to neurotoxicity as well as the neurodegenerative diseases development.

Ethical responsibilities

Protection of human and animal subjects. The authors state that for this investigation have not been performed experiments on humans or animals.

Confidentiality of data. The authors declare that this article does not appear patients.

Right to privacy and informed consent. The authors declare that this article does not appear patient data.

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Conflict of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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