AMPAergic mechanisms linked to cerebral ischemia

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Brain ischemia is the most common cause of invalidity in adults and consequently of death throughout the world. This phenomenon occurs when blood flow is reduced or interrupted in the various brain districts leading to oxygen and glucose deprivation (OGD), which by triggering an intricate succession of biochemical plus molecular events such as an increased production of oxidized and misfolded proteins together with the breakdown of cellular integrity lead to cell death. Despite the lack of information on the triggering mechanisms of ischemic insults, numerous studies are pointing to excitotoxic glutamatergic receptor (GluR) neuronal signaling processes as key mediators of these events. Indeed, from cultured neurons of OGD-related global cerebral ischemia, it seems that this protocol causes a rapid internalization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) thereby suggesting these receptor subtypes as critical components of neuronal death. In particular it seems that OGD-dependent neuronal ischemia occurs via GluR2-sites in which a switching from GluR2-containing Ca²⁺-impermeable receptors to GluR2-lacking Ca²⁺-permeable subtypes constitutes an important step. Interestingly attention regarding excitotoxicity-related ischemic events, aside being largely directed to the over activation of AMPARs, appears to be also focused on the activation of the caspase factors through the translocation of the pro-apoptotic B cell lymphoma 2-associated X protein (Bax) to the mitochondria. Although molecular brain mechanisms capable of repairing part of the neuronal damages and to restore the morpho-functional organization during ischemic episodes are well known, this disorder continues to attract much attention especially due to its elevated mortality feature. In this review we analyzed the role played by GluR2 AMPAR subunit in the pathological processes that lead to neurodegenerative diseases with great attention being paid to the assembly of the major synaptic AMPARs together with cellular events that feasibly account for ischemic brain damages. In this context, knowledge of the different molecular mechanisms operating under these conditions may surely provide helpful indications regarding the identification of new therapeutic targets for treating cerebral ischemia.

Keywords: AMPAR; glutamate; ischemia

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Introduction

Ischemic stroke is a worldwide invalidating illness affecting millions of people every year [1] and is characterized by alterations of the morpho-functional homeostasis especially at the synaptic level, as shown by the typical neurodegenerative events in this pathology [2]. The importance of understanding the mechanisms underlying this process lies in the fact that the majority of patients affected by ischemic insults manifest irreversible events, which in the worst cases make disability, including motor dysfunction, post-stroke dementia and depression thus reducing the
quality of life. The progress of ischemic damages is determined by several factors including the duration of the ischemic episode and the properties of the affected cells [3-4]. An interruption in cerebral blood flow, which limits oxygen and glucose availability and induces energy depletion, leads to a disturbance in ionic gradients, and thereby a collapse of the membrane potential of neuronal cells, thus causing brain damages that become irreversible if the blood flow is not restored immediately [5-6]. Moreover, ischemic damages are significantly increased in response to reperfusion properties that characterize many pathological conditions such as stroke, hemorrhagic shock and organ transplantation [7]. Among the main factors of risk, non-modifiable factors such as age plus sex together with modifiable factors such as hypotension and progressive hypertension, which lead to fluctuations in the degree of cerebral oxygenation prevail [8] in conditions such as diabetes, hyperlipidemia, atrial fibrillation, smoking and obesity [9]. These risk factors interact with each other in a multiple manner and not simply in an additive fashion with the consequent increase in the risk of mortality.

The progression of ischemic damages and its consequent irreversibility are related to the activation of biochemical processes causing neuronal dysfunction and finally cell death. The increased release of glutamate (Glu) and the consequent formation of Glu receptors (GluRs) after hypoxia-ischemia activate this excitotoxic cascade [10]. Indeed, Glu is the principal excitatory neurotransmitter acting in the central nervous system (CNS), and once synthesized it is accumulated in vesicles and subsequently released in the synaptic cleft where it binds to specific postsynaptic receptors of neuronal and glial processes, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), N-methyl-D-aspartate receptors (NMDARs) and kainate receptors [11-12]. At the cellular level, NMDARs and AMPARs are not only confined to the postsynaptic density-associated membrane, but a significant amount of them are also localized around the persynaptic membranes and the intracellular light membranes, which are recognized as extrasynaptic receptor and intracellular receptor pools, respectively. In response to changes in synaptic activities, as well as during an ischemic condition, both type of receptors are rapidly transferred among the different neuronal pools leading to a variation in Ca$^{2+}$ membrane permeability [13]. Considerable evidences support the role of GluR2-lacking Ca$^{2+}$-permeable AMPARs in hypoxia-ischemia-induced neuronal death, as exhibited by molecular and functional features accounting for increased expression of such AMPAR subtypes thereby predicting increased neuronal vulnerability to extracellular Glu [14-15]. This feature was particularly conspicuous following the evaluation of Ca$^{2+}$-permeable AMPAR knockdowns, in which also in the absence of an ischemic bout there was an increase of neuronal death in some major brain sites such as the hippocampus pyramidal CA1/CA3 fields [16].

Modification and modulation of AMPARs during ischemic injuries

It has been widely accepted that NMDARs are the primary class of GluR that on the one hand are capable of modulating a variety of processes and above all evoking excitotoxic cell death through receptor-gated ion channel via the activation of reactive oxygen species (ROS) [17-19]. Indeed at date ample evidences suggest that Ca$^{2+}$-permeable AMPARs heavily operate during synaptic plasticity phenomena. They tend to play a pivotal role on memory development plus learning abilities as well as and more importantly during the internalization of GluR2-containing AMPARs promoting ischemic-related neurodegenerative syndromes [20-21-22-23-24-25] as pointed out by the reduction of Glu transportation in experimentally-induced diabetes leading to altered motor performances [26].

Structurally, NMDARs are neuroreceptors commonly composed of two NR1 plus two NR2 subunits, of which there are four types (NR2A-D) by which strongly depend the gating and ligand-binding plus channel properties [27-28-29]. In the case of kainate receptors five different genes (Grik1-5) encode the various subunits, which are classified into two distinct groups based on their capacity to form functional homeric receptors [29]. The principal subunits, GluK1, GluK2 and GluK3, form functional membrane-localized neuroreceptors, while GluK4 and GluK5 subunits are usually defined as the “high-affinity” or “auxiliary” subunits, in relation to both their nanomolar affinity for the marine toxin kainic acid, as well as for their inability to assemble into functional receptors [29]. AMPARs are tetrameric receptors composed of GluR1-4 subunits which, aside being codified by distinct genes are diversely distributed throughout the entire CNS. Due to GluR2 being the most widespread subunit (99% of cases in the edited form), it appears that most AMPARs are highly permeable to Na$^+$ and little to Ca$^{2+}$ [30], however, in the cases of cerebral ischemia there are considerable evidences that support the role of GluR2 lacking Ca$^{2+}$-permeable AMPARs, which are tightly linked to hypoxia-induced ischemia neuronal death [14-31]. At the same time excitatory postsynaptic currents in some post-ischemic brain areas like the hippocampal CA1 neuronal fields exhibit an enhanced Ca$^{2+}$-dependent response that is tightly linked to Ca$^{2+}$-permeable AMPARs and these events appear to implicate such a molecular channel condition in the pathogenesis of ischemia-related cerebral death [32-33]. This is due to the fact that almost all mature forms of GluR2 subunits are edited through a reaction...
catalyzed by the enzyme adenosine deaminase, that replaced in the subunit pre-mRNA glutamine codon with an arginine codon introducing a positive charge in the pore thus preventing the spreading of divalent cations and consequently diminishing the probability of activating Ca<sup>2+</sup>-mediated neurotoxic pathways thereby prolonging the decay kinetics of a synaptic current. Contextually, the reduced expression of GluR2 subunit accounting for the cytosolic Ca<sup>2+</sup> overload favors a cascade of deleterious events such as generation of ROS plus the degradation of cellular lipids, proteins and DNA via activation of phospholipases, proteases and nuclease, as well as increasing mitochondrial injuries that lead to neuronal death. It is particularly interesting that the initiation of mitochondrial apoptosis depends on changes of equilibrium between anti-apoptotic B cell lymphoma 2 family, indicated as Bcl-2, as well as on the translocation of Bcl-2 associated X protein (Bax) to mitochondria. After transient ischemia, Bax levels are dramatically increased thus disrupting the mitochondrial apoptosis depends on changes of equilibrium between anti-apoptotic B cell lymphoma 2 family, indicated as Bcl-2, as well as on the translocation of Bcl-2 associated X protein (Bax) to mitochondria. After transient ischemia, Bax levels are dramatically increased thus disrupting the more favorable Bcl-2 aggregation, which are indispensable for basal neuronal functions and hence leading to transient ischemic death. On the other hand, brain areas that are enriched in AMPARs lacking GluR2 are highly permeable to Ca<sup>2+</sup>, while other areas like the cerebellar satellite cells are characterized by Ca<sup>2+</sup>-impermeable AMPARs, which are activated by potassium channels. These events propose new scenarios since the activation of such a specific channel tends to decrease activity duration and by reducing the expression of GluR2-containing receptors, tend to suggest a molecular condition that very well displays therapeutic bearings against the onset of ischemic disorders.

The brain areas, which show the most vulnerability to ischemia, such as neocortex and hippocampus, are particularly rich in excitatory NMDARs and AMPARs. The subunit composition of AMPARs constitutes not only a crucial factor affecting the Ca<sup>2+</sup>-permeability but also for the modulation of receptors trafficking. At date several studies have begun to correlate many forms of synaptic plasticity and adaptive responses to stressful conditions with synaptic variations of specific AMPARs subunits. In particular, AMPARs containing GluR1, GluR3 and GluR4 subunits are Ca<sup>2+</sup>-permeable, while GluR2-containing receptors result impermeable to Ca<sup>2+</sup>. As pointed out above, GluR1 and GluR2 are retained the main AMPAR subunits that play a pivotal role on the conduction of fast excitatory synaptic transmission during neuronal developmental processes and which aside being involved with neuronal maturation activities inflammatory plus painful conditions together with epilepsy states, occupy the main center stage during the different ischemic states. Studies on an in vitro model of ischemic neuronal injury showed that GluR1, as well as GluR4, are cleaved in apoptotic hippocampal cell cultures, since GluR1 is a caspase-3 preferred substrate, the major form of neuronal caspase, thus suggesting its involvement on the impairment of Glu transport in the extracellular accumulation of Glu and consequently cell death. Indeed, most AMPARs localized throughout the CNS exist as heteromers containing GluR2 that are not able to conduct Ca<sup>2+</sup>. However, AMPARs may participate in an indirect fashion to neurotoxic pathways causing membrane depolarization thus removing Mg<sup>2+</sup>-dependent block of NMDAR due to its activation favoring GluR2-containing AMPARs internalization and hence facilitating Ca<sup>2+</sup> influx. Moreover, recent studies have shown that the surface expression of GluR2-containing AMPARs is down-regulated after ischemic injuries with a consequent increase in AMPAR-mediated Ca<sup>2+</sup> influx. In addition, GluR2-lacking receptors (consisting of GluR1, GluR3 or GluR4) are per se permeable to divalent Ca<sup>2+</sup> and Zn<sup>2+</sup>, and are strongly involved with in vivo Glu excitotoxicity events that consequently lead to global ischemia.

Another important factor operating during the exacerbation of neurodegenerative processes after hypoxia/cerebral ischemia is the neuromodulator adenosine, a ubiquitous purine nucleoside released from neurons and glial cells that plays a putative role in both physiological and pathological conditions. In particular, recent studies have pointed to the inhibition of NMDAR-mediated currents via the activation of adenosine A1 receptors as a crucial molecule leading to substantial synaptic depression during such a pathological condition. Indeed, it has been found that adenosine A1 receptors-induced persistent synaptic depression, involving clathrin-mediated GluR2 and GluR1 internalization, thus leading to hippocampal neurodegenerative phenomena after an ischemic insult.

**Molecular mechanisms of AMPARs operating during ischemia**

It is widely known that hippocampal CA1 pyramidal neurons normally expressing GluR2, show a protein down-regulation 72h after ischemia, as exhibited by a great reduction in GluR2 immunolabeling throughout both somata and dendritic processes of these pyramidal neurons. Interestingly, it seems that the suppression of this highly vulnerable ischemic-linked AMPAR subunit (GluR2) of CA1 neurons, occurred via activation of the repressor element-1 silencing transcription factor (REST). Such a molecular regulatory event was supported by the reduction of REST expression, accounting for augmented neuronal survival 72h after oxygen and glucose deprivation (OGD). Accordingly, blockade of AMPAergic currents, via the enhancement of GluR2 expression was suggested as a
protective procedure aimed to assure neuronal survival and tolerance against seizure susceptibility in some cerebral areas of hibernating rodents like the Syrian hamster [67] as well as the aestivating fish such as the lungfish *Proopterus annectens* [72].

Apart the modulation of GluR2 expression, the number of functional AMPARs on cell surface is also correlated with targeting and trafficking processes of their subunits as well as internalization and degradation of receptors at the synaptic level. It has been largely stated, even throughout this review, that immediately after ischemic injury the internalization of GluR2-containing AMPARs from synaptic membranes are induced by clathrin-dependent endocytosis thus favoring the distribution of synaptic GluR2-lacking AMPARs via soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-dependent exocytosis [21]. In a similar manner, also OGD exposure of hippocampal neurons promotes the redistribution of AMPARs together with the internalization of GluR2-containing receptors together with those of synaptic derivation supply AMPARs lacking this subunit [21]. Consistent to such evidences it has been also reported that agonist stimulation of AMPARs provoked internalization of GluR2 via a GluR2/glyceraldehyde-3-phosphate dehydrogenase (GAPDH) coupling-dependent process [73]. Indeed, among the several proteins regulating AMPAR activity differently, GAPDH a multifunctional protein also involved in apoptotic events, has been demonstrated to bind the N-terminal domain of GluR2 and this interaction seems to contribute to AMPAR-induced neuronal death. Accordingly, activation of AMPARs causes GluR2/GAPDH co-internalization as a complex regulating excitotoxicity processes while breakage of such an interaction prevents not only complex internalization but more importantly AMPAR-dependent cell death [74]. During the various moments of AMPAR trafficking events, not only during pathological conditions but also during plasticity processes, the protein interacting with C kinase-1 (PICK1) has shown to modulate receptor membrane levels by reducing AMPAR recycling and/or by favoring receptor internalization [64]. Interestingly the interaction of GluR2 with PICK1, as well as with other intracellular scaffolding proteins is known to be important for NMDAR-induced long term depression, that resulted to be strongly impaired in knockout mice lacking these proteins [64]. PICK1-GluR2 interaction was indicated as a mechanism that restricts GluR2 content of AMPARs modifying Ca\(^{2+}\) permeability [75]. Indeed PICK1 overexpression in CA1 neurons has been shown to cause a change in AMPARs subunit composition and consequently leading to inwardly rectifying AMPAR excitatory postsynaptic currents via reduced GluR2 at the surface [76]. In particular, during a brief OGD, redistribution of AMPARs at synapses and the subsequent switch in AMPAR subunits composition requires protein kinase C activation, disassembly of GluR2 from AMPAR-binding protein and conjugation with PICK1 [21].

Likewise to NMDARs, activation of AMPARs has also been shown to cause postsynaptic nitric oxide (NO) production via the activation of both enzyme neuronal NO synthase [77] and Ca\(^{2+}\)-dependent calpain [78]. During pathological conditions, the exacerbate production of NO and ROS can lead to the formation of peroxynitrite, a reactive agent involved with excitotoxic pathways after stroke [79]. However, contrary to NMDARs, AMPARs stimulation might promote neuroprotection through the transcription factor cyclic-AMP response element (CREB)-binding protein (CREB) plus brain-derived neurotrophic factor (BDNF) activity [80]. Indeed, CREB phosphorylation and activation have been shown to be important for the survival of neurons [81] very likely via the promotion of GluR2 activity [80]. In this context, the activation of CREB turns out to be a critical step for the expression of GluR2 gene in cortical neurons [82] and this may turn out to be responsible for the inhibition of GluR2-gated injurious signals in vulnerable neurons as pointed out by stress responses accounting for CREB-dependent up-regulation of the stress-related element BDNF [83].

**Role of neuroprotective factors during cerebral ischemia**

As previously reported, the hippocampal cells maintained in cultures respond to OGD with a quick internalization of GluR2 subtypes, thus favoring a switch from GluR2-containing Ca\(^{2+}\)-impermeable receptors to GluR2-lacking Ca\(^{2+}\)-permeable subtypes [15]. The increase of intracellular Ca\(^{2+}\) causes a cascade of events (proteases/endonucleases activation and production of free radicals that shatter cell membranes) leading to cell death through the induction of apoptosis [84]. On the basis of such observations, it is possible to say that the maintenance of the synaptic exposure of Ca\(^{2+}\)-impermeable AMPARs may play a protective activity against cerebral ischemia/reperfusion injuries [67-85]. This ability resulted to be particularly evident in the brain of hibernating mammals that are able to tolerate severe hypoxia conditions [86], very probably via the up-regulation of GluR2 that being responsible for low intracellular Ca\(^{2+}\) levels is consequently responsible for the greater resistance to ischemia-induced neuronal damages [67-87]. Additionally, the enhanced expression of Bcl-2, during the hypertensive arousal state of hibernation underlies a surviving capacity of some neurons in a pro-oxidative and pro-apoptotic environment [88]. Parallel to this capacity, also the persistent neuronal production in some adult brain areas constitutes a potential capacity for self-repairing processes following ischemic cerebral attack [89]. Indeed, after...
ischemia, neuronal proliferation was up-regulated several fold, and rapidly half of post-ischemic precursors develop neuronal phenotype in some hippocampal fields [85], that have shown to be the more ischemia-susceptible limbic areas [90].

From other recent findings it appears that discrete populations of neurons such as those of hippocampal neuronal fields exhibit different susceptibility levels to OGD and hence activate distinct neurocellular mechanisms in response to ischemic injury, while they result to be absent in cortical neurons [15]. Such a feature underlies the absence of GluR2 internalization in cortical neurons thus favoring their relatively low vulnerability to ischemia [91]. Moreover it appears that the positive modulation of GluR2 expression may be a result of the action of neurotranspheric factors including BDNF that can stimulate GluR2 expression acting on its promoter thus mediating neuroprotective measures [92]. Indeed, in addition to its function as ion channel, AMPARs also may operate as signal transducers at the membrane level and their assembly with the Src family kinases, that have been suggested to act as a “core kinases” to integrate synaptic signalings to synaptic activities [13], might very well lead to the activation of the mitogen-activated protein kinase. This in turn may determine an increase of BDNF expression thus protecting neurons against Glu-dependent excitotoxic phenomena [93].

**Potential targets (and future perspectives) for the treatment of ischemia**

At date, there are several molecular mechanisms proposed as causes, and consequently as pharmacological targets, for treatment of neurological disorders deriving from ischemic injuries. In all cases it largely seems that the main prevention of AMPAR-mediated excitotoxicity is the reduction at different levels of GluR2 internalization processes. This activity can be regulated at different levels, of which most of them are all triggered by an intricate series of biochemical reactions mediated by excitotoxic Gluergic signaling during cerebral ischemia, such as inflammatory responses, an increased production of misfolded and oxidized proteins as well as the disruption of cellular morphology [94-95]. Notably, the inactivation of protein degradation pathways, together with the exacerbate production of altered peptides and subsequent up-regulation of ubiquitin-conjugated proteins favor the accumulation of ubiquitin aggregates leading to neuronal cell death. This process involves above all the catalytic ubiquitin-proteasome machinery known as UPS, which is essential for the marking of various cellular proteins destined to be degraded and so is able to control not only basic cellular mechanisms but above all neuronal survival [95].

Other factors involved in GluR2 internalization process are the newly identified transmembrane AMPAR regulatory proteins (TARPs). This family of proteins includes several members, and namely γ-3, -4, -5, -7, -8 [96, 97], varying in their influence on AMPAR characteristics and manifesting different, although partially overlapping, distribution patterns throughout the CNS. Native AMPARs are thought to be composed of one to four TARPs together with their core pore-forming subunits; however, it is commonly accepted that only one type of TARP is expressed within a specific AMPAR complex [98-99]. TARP assembling influences various fundamental aspects of AMPAR activities thus modifying the neuronal trafficking abilities of GluR2-containing AMPARs. In particular it has been shown that TARPs are engaged in the subunit-specific trafficking of AMPARs, which by modulating the expression of specific AMPAR complexes [99] together with augmented single channel conductance and impaired block of GluR2-lacking AMPARs by endogenous intracellular polyamines tend to increment the molecular complexity operating during stress-related neuronal disorders [98].

In a similar manner, even peptides able to break down the assembled complex GluR2-PICK1 during an ischemic phenomenon [67] avoid the depression of transmission, suggesting a PICK1-dependent internalization of AMPARs following OGD and this may represents a potential novel mechanism for the reduction of excitotoxicity and for the promotion of neuroprotection [100]. It is also known that the neurodegenerative effects promoted by the internalization of GluR2 during transient global ischemia occur principally via its interaction with GAPDH. Indeed previous studies, regarding the onset of neurotoxicity processes mediated by Ca2+ NDMAR-gated ion channels in transient forebrain ischemia, have pointed to AMPAR as a key element liable for hippocampal neuronal loss very likely through an agonist-facilitated interaction between GluR2 and the interfering peptide of GAPDH, and namely GluR2NT1-3-2 [73]. During such a pathological state it has been shown that the administration of the above interfering peptide is capable of interrupting the assembly of GluR2-GAPDH and hence decrease infarct volume plus the neurological score [74]. The identification of such a discovery provides us with the opportunity to gain further insights dealing with the application of GluR2 interacting with GAPDH as a novel therapeutic target that specifically block AMPAR-mediated ischemic stroke as well as rescuing neurons from AMPAR-mediated cell death in hippocampal neuronal fields exposed to OGD [73-74]. At the same time even the proimmunocytokine tumor necrosis factor α (TNF-α) tends to play a pivotal role on the distribution of postsynaptic GluRs, however, at date the specific role exerted by TNF-α in mediating GluR expression, trafficking, and functions still
remains unclear. Recent works have demonstrated that TNF receptor type 1 (TNFR1) related reduction of neuronal expression and synaptic localization of the AMPAR GluR1 subunit, appear to safely prevent neuronal AMPAR-mediated excitotoxicity [101]. Besides the role exerted by TNFR1, also the concomitant activation of metabotropic GluR1 (mGluR1) and adenosine A3 receptor (ADORA3), together with an increase of intracellular Ca²⁺ level, tend to be requested for the elimination of surface AMPARs. So, the antagonization of mGluR1 and the ADORA3 could play a pivotal role in the reduction of AMPAR protein internalization after an ischemic insult [100]. Finally, other studies have reported that post-conditioning with propofol after ischemic/reperfusion of which constitute crucial steps of ischemia-induced up-regulation of Ca²⁺-impermeable GluR2 thus contributing to long-term neuroprotection [102].

In conclusion the controlled expression of Ca²⁺-permeable AMPARs, which represent key factors for the precise temporal regulation of neurosignaling pathways is largely required for the prevention of neuronal excitotoxicity deriving from an exacerbated AMPAR-gated Ca²⁺ influx, from the accumulation of Zn²⁺, apoptosis and autophagy, all of which constitute crucial steps of ischemia-induced neuronal death [103]. Evidences deriving from this study provide helpful indications concerning neuronal Ca²⁺-impermeable AMPAR strategies as a novel neuroprotective measure against perinatal hypoxic-ischemic insults. Surprisingly, the growing interests toward the role of GluR2 during ischemic insults are beginning to define not only its pivotal role in the pathogenesis of ischemic neurological disturbance, but also its interaction with other major factors such as Bcl-2 thus assuring a neuroprotective role against such neurodegenerative disorders. Despite the many lines of thought have proposed this type of AMPAergic subunit throughout the different biological events of ischemia, it can now be accepted that the reduction of GluR2 internalization processes leading to diminished Ca²⁺ influx tend to favor neuroprotective measures against ischemic insults. On the basis of the above considerations, it is tempting to suggest PICK1 together with GluR2 containing AMPARs as valuable neuronal elements capable of modifying the overall function of recycling compartments and by improving AMPAR trafficking processes may turn out to be a vital neuroprotective factor against ischemic disorders.

Conflict of interests

All authors declare that this original paper has not been published previously as well as not having any conflict of interests.

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