Neuropharmacology xxx (2017) 1–11

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Neurotransmitters in the mediation of cerebral ischemic injury

Diana Mayor [a, b], Michael Tymianski [a, b, c, *]

[a] Division of Fundamental Neurobiology, Krembil Institute, University Health Network, Toronto, Ontario, M5T 2S8, Canada
[b] Department of Physiology, University of Toronto, Toronto, Ontario, M5S 1A8, Canada
[c] Department of Neurosurgery, University of Toronto, Toronto, Ontario, M5G 1LG, Canada

ARTICLE INFO

Article history:
Received 7 August 2017
Received in revised form
28 November 2017
Accepted 30 November 2017
Available online xxx

Keywords:
Glutamate
Excitotoxicity
NMDA receptor
Neuronal cell death
Gamma AminoButyric Acid
Calcium

ABSTRACT

Under physiological conditions, neurotransmitters shape neuronal networks and control several cellular and synaptic functions. In the mammalian central nervous system (CNS), excitatory and inhibitory neurotransmission are mediated in large part by glutamate and gamma-aminobutyric acid (GABA), which are excitatory and inhibitory neurotransmitters, respectively. Glutamate and GABA also play crucial roles in neurological disorders such as cerebral ischemia. Glutamate in particular causes excitotoxicity, known as one of the hallmark mechanisms in the pathophysiology of cerebral ischemic injury for more than thirty years. Excitotoxicity occurs due to excessive glutamate release leading to overactivation of postsynaptic glutamate receptors, which evokes a downstream cascade that eventually leads to neuronal dysfunction and degeneration. Also, a reduction in GABA receptor response after ischemia impedes these inhibitory effectors from attenuating excitotoxicity and thereby further enabling the excitotoxic insult. This review focuses on the mechanisms by which glutamate and GABA mediate excitotoxicity and ischemic injury.

Contents

1. Introduction 00
2. Glutamate, a major excitatory neurotransmitter 00
3. Glutamate receptors 00
4. NMDA receptors 00
5. AMPA and kainate receptors 00
6. Metabotropic glutamate receptors 00
7. Glutamate levels during ischemia 00
8. Glutamate induced excitotoxicity 00
9. Nitric oxide: a complicated linked between NMDARs and PSD-95 00
10. The role of glutamate in free radical production 00
11. The major inhibitory neurotransmitter: γ-Aminobutyric acid (GABA) 00
12. GABA receptors 00
13. Mediation of excitotoxicity by GABA 00
14. Conclusion and perspectives 00
References 00

1. Introduction

Insults to the human central nervous system (CNS) occur more frequently than expected and can cause devastating, irreversible damage to patients. Acute ischemic stroke (AIS) has a considerable

* Corresponding author. Krembil Research Institute, Toronto Western Hospital, 8KD-406, 60 Leonard Avenue, M5T 2S8, Toronto, Ontario, Canada.
E-mail address: mike.tymianski@uhn.ca (M. Tymianski).

https://doi.org/10.1016/j.neuropharm.2017.11.050
0028-3908/

health and socioeconomic impact. In fact, Stroke is the fifth leading cause of death in the USA (Mozaffarian et al., 2016). According to the world health organization it is the number two cause of death and the leading and growing cause of acquired neurological disability worldwide (Mozaffarian et al., 2016, 2015).

The brain is the most metabolically active organ in the human body. It has the highest demand for oxygen and glucose and depends greatly on oxidative phosphorylation for energy production (Aarts and Tymianski, 2005; Caplan and Liebeskind, 2016). A focal reduction of cerebral blood flow, such as that occurring in AIS, restricts the delivery of oxygen and glucose to neurons and impairs the maintenance of ionic gradients across cell membranes (Caplan and Liebeskind, 2016). Under conditions of ischemia (blood flow levels below 50 mL/100 g per minute) protein synthesis is inhibited (Markus, 2004). Below 30 mL/100 g per minute, cellular metabolism is impaired, and the cerebral metabolic rate of oxygen begins to fall. (Kunimatsu et al., 1999; Markus, 2004). This represents the earliest ischemic/hypoxic perturbation synaptic function that affects the neocortical circuit manifest as an increase in spontaneous excitatory and inhibitory postsynaptic currents (sPSCs)(Fleidervish et al., 2001). Ischemia/hypoxia has a biphasic effect on the extracellular concentration of glutamate, the major excitatory neurotransmitter in the CNS. The first phase is a rapid presynaptic membrane depolarization, with a Ca^{+2} dependent glutamate release from the neurotransmitter pool due to the anoxic depolarisations (Allen et al., 2004; Kunimatsu et al., 1999; Rossi et al., 2000). After the first peak, glutamate concentration decreased rapidly due to the neurotransmitter reuptake by surrounding glia (Kunimatsu et al., 1999). However, persistent ischemia/anoxia leads to energy failure in glia, resulting in a reversal of the glutamate transport (Szatkowski and Attwell, 1994) which leads to a second increase in glutamate concentration (Kunimatsu et al., 1999). Additionally, a consequence of hypoxia or ischemia on brain tissue is “anoxic spreading depolarization” (ASD), a synchronized wave that propagates through the tissue leading to the loss of transmembrane ion gradients (Revah et al., 2016) increase brain impedance (Aiba et al., 2012; Aiba and Shuttleworth, 2012; Ayad et al., 1994) and the silencing of the electrical activity (Somjen, 2001). ASD's occurs after the ATP pool is greatly exhausted and is associated with the second phase of glutamate release. The deleterious of ASD's take several minutes to start and almost 30 min before the cell death occurs (Ayad et al., 1994; Heiss and Rosner, 1983; Memezawa et al., 1992; Nozari et al., 2010).

The overall pathophysiology of AIS involves an imbalance during the ischemic insult between brain metabolic capacity on one hand and oxygen and glucose delivery and distribution on the other, which eventually leads to a complex combination of processes such as excitotoxicity, propagation of the ischemic insult, inflammation, necrosis and apoptosis, all of which contribute to the same end point of cell death. Following acute insults, neurons may die within minutes to hours by several excitotoxic mechanisms (Bartus et al., 1995; Chan, 1994; Kihara et al., 1994; Saunders et al., 1995; Tominaga et al., 1993). A significant electrophysiological consequence of acute ischemic insult is ASD, which is synchronously associated with the changes in glutamate concentration (Fabricius et al., 1993; Iijima et al., 1999; Van Harreveld, 1959; Van Harreveld and Fifková, 1970; Van Harreveld and Kooiman, 1965). Several studies have shown the occurrence of spreading depolarization in patients with malignant ischemic stroke. ASDs were detected over peri-infact tissue and were associated with both hyperemic and hypoemic hemodynamic responses (Dohmen et al., 2008; Woitzik et al., 2013). Glutamate signalling is intrinsic to the ASD mechanism; the rise in extracellular glutamate concentrations is synchronous with ASDs in both the ischemic core and penumbra and the administration of glutamate reuptake inhibitors prolongs both spreading depolarization latency and the glutamate increase in a dose-dependent manner (Dreier, 2011; Hinzman et al., 2015). It has been previously shown that peri-infarct anoxic depolarizations have cortical negative direct current (DC) shifts of approximately 20 mV (Lauritzen et al., 2011) and the expansion of the infarct size is correlated with the number of PIDs (Mies et al., 1993). The use of a non-competitive NMDAR antagonist such as ketamine in patients presenting with malignant hemispheric stroke has shown a reduced occurrence of isoelectric spreading depolarizations but this has not yet been translated to improved clinical outcomes (Hertle et al., 2012; Revah et al., 2016; Sakowitz et al., 2009).

2. Glutamate, a major excitatory neurotransmitter

Glutamate is the primary excitatory neurotransmitter in the CNS. This neurotransmitter has a critical role in synaptic transmission, organization, and plasticity, as well as in neuronal migration in health and disease (Meldrum, 2000; Wang and Qin, 2010). In addition to its important physiological functions in the CNS, glutamate also plays a key role in the pathophysiology of many disorders such as epilepsy, neurodegenerative disorders and stroke (Derouiche, 2003; Kostandy, 2012).

During brain ischemia, there is an excessive release of glutamate into the extracellular space. Ischemia-induced glutamate peak concentrations measured during the ischemic/hypoxic insult are dependent on the tissue region that is sampled (Nakamura et al., 2005), the maximal concentrations range from 6 μM in the ischemic core (Hinzman et al., 2015) to 213 μM in the striatum (Kohno et al., 1998). Glutamate has a distinct biphasic release profile during ischemia; the highest concentrations are detected in the later phase of glutamate release (Kohno et al., 1998; Soria et al., 2014).

3. Glutamate receptors

Glutamate acts primarily though postsynaptic glutamate receptors, which comprise four main pharmacologically and functionally separate cell-membrane receptors groups, the NMDA (N-methyl D-aspartate), AMPA (A-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), kainic acid (KA) and metabotropic receptors. NMDA, AMPA and KA receptors are associated with ion channels that allow the flow of ions, with particular permeability to calcium, sodium, and potassium ions. Metabotropic receptors are coupled to GTP-binding proteins that trigger downstream signalling pathways that culminate among other things, with a mobilization of Ca^{2+} from internal stores (Arundine and Tymianski, 2003; Lai et al., 2014; Sattler and Tymianski, 2000).

4. NMDA receptors

Of the four groups of glutamate receptors, NMDA receptors (NMDARs) have received the greatest amount of attention through numerous studies. NMDARs are key participants in the cellular processes triggered by cerebral ischemia that cause neuronal cell death. NMDARs are heteromers composed of four of seven existing categories of NMDAR subunits: The glycine-binding N-methyl-D-aspartate receptor 1 (GluN1) subunit, four GluN2 (A-D) subunits and two GluN3 (A-B) subunits. Each one of these is composed of an extracellular amino-N-terminal domain, four trans-membrane domains, and an intracellular C-terminal tail (Hollmann, 1994). The conventional NMDAR is a heterotetramer containing 2 obligatory GluN1 and two GluN2 subunits (Kohr, 2006; Sun et al., 2015) and when activated allows the influx of calcium. Excessive activation of glutamate receptors and the consequent overload of intracellular calcium is one of the excitotoxic triggers that leads to cell

Please cite this article in press as: Mayor, D., Tymianski, M., Neurotransmitters in the mediation of cerebral ischemic injury, Neuropharmacology (2017), https://doi.org/10.1016/j.neuropharm.2017.11.050