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REVIEW PAPER

Caffeine and Its Neuroprotective Role in Ischemic Events: A Mechanism Dependent on Adenosine Receptors

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Abstract

Ischemia is characterized by a transient, insufficient, or permanent interruption of blood flow to a tissue, which leads to an inadequate glucose and oxygen supply. The nervous tissue is highly active, and it closely depends on glucose and oxygen to satisfy its metabolic demand. Therefore, ischemic conditions promote cell death and lead to a secondary wave of cell damage that progressively spreads to the neighborhood areas, called penumbra. Brain ischemia is one of the main causes of deaths and summed with retinal ischemia comprises one of the principal reasons of disability. Although several studies have been performed to investigate the mechanisms of damage to find protective/preventive interventions, an effective treatment does not exist yet. Adenosine is a well-described neuromodulator in the central nervous system (CNS), and acts through four subtypes of G-protein-coupled receptors. Adenosine receptors, especially A_1 and A_{2A} receptors, are the main targets of caffeine in daily consumption doses. Accordingly, caffeine has been greatly studied in the context of CNS pathologies. In fact, adenosine system, as well as caffeine, is involved in neuroprotection effects in different pathological situations. Therefore, the present review focuses on the role of adenosine/caffeine in CNS, brain and retina, ischemic events.

Keywords Brain · Retina · Ischemia · Adenosine receptors · Caffeine · Neuroprotection

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Abbreviations

AC	Adenylyl cyclase
AMD	Age-related macular disease
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
COX-2	Cyclooxygenase 2
CREB	CAMP-response element binding protein
Cyt C	Cytochrome c
DALYs	Disability-adjusted life years
DM	Diabetes mellitus
DR	Diabetic retinopathy
EAAT	Excitatory amino acid transporter
FasL	First apoptosis signal ligand
GDNF	Glial cell-derived neurotrophic factor
GSH	Glutathione
Gsk3β	Glycogen synthase kinase 3 beta
HI	Hypoxia–ischemia
HIE	Hypoxic-ischemic encephalopathy
IL-10	Interleukin 10
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
IOP	Intraocular pressure
LDH	Lactate dehydrogenase

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MCAO	Middle cerebral artery occlusion
NGF	Nerve growth factor
NICUs	Neonatal intensive care units
NO	Nitric oxide
NOS	Nitric oxide synthase
Nrf2	Nuclear factor erythroid 2-related factor 2
OGD	Oxygen glucose deprivation
OIR	Oxygen-induced retinopathy
OTH	Ocular hypertension
PKA	Protein kinase A
PKC	Protein kinase C
POAG	Primary open-angle glaucoma
ROP	Retinopathy of prematurity
ROS	Reactive oxidative species
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TIA	Transient ischemic attack
TNF-α	Tumor necrosis factor-alpha
tPA	Tissue-type plasminogen activator
VEGF	Vascular endothelial growth factor
VGCC	Voltage-gated calcium channels

Introduction

Hypoxia–ischemia (HI) is characterized by a local or systemic, transient or permanent, interruption of blood flow, and oxygen supply, leading to an inability to meet cellular energy demands. When the CNS is affected, the cell death caused by ischemia provokes brain injury and neurological disabilities. This pathological condition can affect both developing and mature CNS, with long-term consequences and few preventive/therapeutic interventions. In addition, all the main retinopathies that cause blindness in the world, such as age-related macular disease (AMD), glaucoma, and diabetic retinopathy (Bourne et al. 2017), display an ischemic component at some point of the disease, resulting in a worsening of visual impairment. So, ischemia is also a main problem in the ophthalmology field.

Since there is no effective treatment for ischemia, and concerning its negative outcomes, the importance to understand the mechanisms of cell death and possible neuroprotective interventions becomes evident. Ischemia induces several alterations in cellular physiology, starting with a decrease in ATP production, that affects all ATP-dependent cellular functions, followed by the release of neurotransmitters, such as glutamate, leading to excitotoxicity and cell death (Nicholls et al. 1987; Lipton 1999; Reid et al. 2003; Kostandy 2012; Mayor and Tymianski 2018). Moreover, there is also an increase in the extracellular availability of adenosine, both from ATP hydrolysis and by reversal of adenosine transporters (Melani et al. 2014b; Pedata et al. 2016). A number of studies have demonstrated a role for adenosine receptors in hypoxic and ischemic conditions. Adenosine receptors are G protein-coupled receptors named A_1 and A_3, which classically inhibit adenylyl cyclase (AC) by activating Gi protein, while A_{2A} and A_{2B} increase AC activity through Gs/Golf (Borea et al. 2018). A_1 and A_{2A} are the most abundant adenosine receptors in the CNS, and several studies have shown their involvement in cell protection mechanisms. These receptors are non-selectively inhibited by low–moderate concentrations of caffeine that can be achieved by daily doses of coffee (Fredholm et al. 2017). Caffeine is considered a mild stimulant to the CNS, and it can also be found in several other sources of foods and drinks consumed worldwide by the majority of adults (Heckman et al. 2010; Mitchell et al. 2014). Therefore, the present review will focus on studies that shed light into caffeine, as well as adenosine, as a promising therapeutic tool for ischemia. Moreover, it also brings data from epidemiology, health system costs, the mechanisms involved in ischemia-induced cell death, available treatments, and the present challenges. However, it is important to note that there is a robust amount of data on the roles of adenosine and caffeine on neurophysiology and neuroprotection, apart from ischemic context, that goes beyond the proposal of this review, but it is essentially connected to the subject and can be satisfactorily appreciated by some fulfilling readings (Cunha 2005, 2016; Costenla et al. 2010; Gomes et al. 2011; Dos Santos-Rodrigues et al. 2015; Kolahdouzan and Hamadeh 2017; Liu et al. 2019; Lopes et al. 2019).

Epidemiology of Ischemic Events

Adult Stroke

Among neurological diseases, stroke accounts for the largest proportion of deaths (67.3%), disability-adjusted life years (DALYs—47.3%), and it is the third overall leading cause of death worldwide after heart disease and cancer (Moskowitz et al. 2010; GBD 2017; Lallukka et al. 2018).

Stroke is classified into two main categories: ischemic, when blood flow is interrupted by a clot/thrombus, accounting for 87% of the cases; or hemorrhagic, when there is a rupture of a blood vessel resulting in leakage to adjacent tissue (Ovbiagele and Nguyen-huynh 2011; Bejot et al. 2016; Lee et al. 2018). As the nervous tissue has a high energy demand, the oxygen and substrate deprivation lead to irreversible damage detectable within minutes. Thus, it results in brain damage and neurological disabilities that can be reflected in impaired behaviors associated with memory, learning and locomotion (Janardhan and Qureshi 2004; Li et al. 2013; Lee et al. 2018).

There are several risk factors associated with the incidence of stroke, with hypertension being the most prevalent among modifiable ones, linked to 35% of the cases. Other risk factors include smoking, obesity, poor diet, sedentary lifestyle, diabetes mellitus, high alcohol consumption, psychosocial factors, cardiac cause, and ratio of apolipoprotein B and apolipoprotein A_1 (O'Donnell et al. 2010; Soler and Ruiz 2010; Bejot et al. 2016). Many of these are considerably easy to overcome, so preventive strategies should be used to reduce the risk and the cost of treatment. Non-modifiable factors connected to the pathology are as follows: age, as the incidence increases with aging (Wolf et al. 1992; Rosamond et al. 2008; Romero et al. 2008); gender, overall stroke incidence is lower in women, even though these numbers change when incidence and mortality are analyzed at older ages (Rothwell et al. 2005; Löfmark and Hammarström 2007; Reeves et al. 2008); genetics/heredity; and ethnicity (Soler and Ruiz 2010).

The economic burden of the disease is extremely relevant, as patients may need permanent care depending on the severity of the stroke (Table 1). In 40% of the cases, patients acquire moderate to severe impairment and need special care, while 10% need constant care in long-term care facilities (Rajsic et al. 2019). Table 1 also summarizes the current ischemic stroke treatment, which is based on two fronts approved by the United States Food and Drug Administration, along with its limitations.

Perinatal Hypoxia–Ischemia

Concerning prenatal developmental, HI may occur due to a mechanical process, placental insufficiency, prolonged labor or folds in umbilical cord (De Haan et al. 2006; Martinez-Biarge et al. 2012), besides events of preeclampsia and maternal bleeding (Paolo 2012). There are also other risk factors, such as anemia, hypotension, multiple births, smoking, and drug abuse (Pundik et al. 2006). Pre- and perinatal lesions alter CNS development, causing different outcomes according to the kind of insult, the developmental period, the intensity, and the affected area. HI events, in addition to causing newborns to die, are also the main triggering factor for encephalopathy (Kurinczuk et al. 2010) and permanent brain damage in children (Johnston et al. 2009; Volpe 2012). Perinatal hypoxic-ischemic encephalopathy (HIE) affects 1–3 of every 1000 babies born at term (Yang and Lai 2011). Of these children, 15–20% die in the postnatal period, characterizing HIE as one of the most significant causes of neonatal mortality. Of those who survive, 25% develop permanent neurophysiological consequences (Vannucci 2000; Chen et al. 2009). In spite of the advances in neonatal medicine, the proportion of infants diagnosed with neurological deficits after suffering perinatal insults remains stable (McIntyre et al. 2013).

In premature (or underweight) newborns, the numbers are even more alarming, since the incidence of perinatal asphyxia corresponds to around 60%, and 20–50% of the babies who have undergone HI events exhibit deficits later, such as difficulty in concentration, cognitive delay (Filloux et al. 1996; Gross et al. 2005), visual, motor and perceptual disorders, hyperactivity (Vannucci 2000; Perlman 2006) and, in even more severe cases, epilepsy and cerebral palsy (Nelson et al. 2003).

Cognitive damage, although strongly associated with neuromotor deficits, can be seen in children who have suffered HIE, in the presence or absence of motor impairments (Van Handel et al. 2007; Schreglmann et al. 2020). These sequelae can mark the school phase due to learning delays (Robertson and Perlman 2006) and the impairments may persist throughout adolescence, with an intense reduction in episodic memory (Gadian 2000), poor performance in executive functions, and visual and verbal memory (Mañeru et al. 2001).

Neonatal care represents a major burden for health systems around the world. Considering neonatal intensive care units (NICUs) in the US, there is an estimative of 77.9 admissions per 1000 live births in the period between 2007 and 2012 (Harrison and Goodman 2015). The damage caused by HIE is associated with high morbidity and mortality, which requires the highest level NICU care and interventions. In this context, HIE newborns have been considered to be part of a small group of patients who consume the major amount of NICU expenses (Bayne 2018). Information for expenditures and limitations of treatment for perinatal ischemia is summarized in Table 1.

In order to obtain therapies for the prevention of mortality and treatment of disabilities, the exploration of certain key factors involved in these damages is essential. Studies in animal models have revealed potential candidates for therapeutic intervention based on mechanisms anti-excitotoxicity, anti-oxidation, anti-inflammation, and anti-apoptosis (Greco et al. 2020).

Retinopathies with Ischemic Components

Ischemia may be considered a key factor in the pathophysiology of visual diseases, including retinopathies. Retina has been classified as one of the most energetically demanding tissues, being even more metabolically active than the brain (Ames 1992; Yu and Cringle 2001; Wong-Riley 2010). The acute or chronic occlusion of retinal microvasculature may impair retinal perfusion causing permanent visual loss, such as verified in glaucoma, DR, and AMD (Schmidt et al. 2008; Kaur et al. 2008; Szabadfi et al. 2010).

Table 1 Cost, treatment/limitations for stroke and perinatal ischemia

Condition	Cost	Treatment	Treatment limitations
Stroke	US: $140.000/patient/lifetime (Johnson et al. 2016); $11.145/patient/1st year (Mozaffarian et al. 2015; Rajsic et al. 2019); US economic burden estimated to be $240.7 billion by 2030 (Ovbiagele et al. 2013); Europe: € 27 billion/year (formal care), € 11.1 billion/year (informal care) (Gustavsson et al. 2011; Rajsic et al. 2019); Brazil: $2.315–35.092/patient (Safanelli et al. 2019; Vieira et al. 2019)	Intravenously administered recombinant-tPA) (Marko et al. 2020; Vermeij et al. 2018; Wardlaw et al. 2014)	Narrow safety window, blood pressure has to be ≤ 180/110 mmHg, with or without antihypertensive treatment; must show no evidence of bleeding in the brain or bleeding diathesis (Zivin 2009); Shows ineffective results in 10% for carotid occlusion or 30% for MCAO (Derex and Cho 2017)
		Intra-arterial thrombectomy (ITA) (Goyal et al. 2016; Vermeij et al. 2018)	More invasive, risk of vessel trauma and distal embolization; Effectiveness depends on circulation return within 6 h; Recommended for proximal anterior circulation (Derex and Cho 2017; Furlan et al. 2005; Goyal et al. 2016)
		Cell therapy (Stilley et al. 2004; Rabinovich et al. 2005; Kondziolka et al. 2005; Honmou et al. 2011; Bhasin et al. 2013; Jiang et al. 2013; Lemmens and Steinberg 2013; Hao et al. 2014)	Ongoing clinical trials. Still need further experiments and results in order to understand its benefits and possible side effects
Perinatal Ischemia	US: $50.000 for survivors of hypothermia treatment (Massaro et al. 2016); $900.000/lifetime for those who develop cerebral palsy (Eunson 2015)	Therapeutic hypothermia (Simbruner et al. 2010; Higgins et al. 2011)	Risk of mortality and neurological outcomes persist in 50% of the neonates affected by HI (Edwards et al. 2010; Jacobs et al. 2013); Lower efficacy for newborns who suffered serious insults (Higgins et al. 2011); Benefits may be limited to those born at term or late preterm (Perlman 2006; Rees et al. 2011; Jacobs et al. 2013); Treatment should be started within 6 h after birth (Higgins et al. 2011; Jacobs et al. 2013)

Glaucoma

Glaucoma is an optic neuropathy whose main clinical sign is the increase in intraocular pressure (IOP) and the main outcome is progressive and irreversible visual loss. It is estimated to affect more than 60 million people worldwide (Quigley and Broman 2006) and this number is expected to increase to 111.8 million in 2040 (Tham et al. 2014). It is classified as a prevalent neurodegenerative disease (Jiang et al. 2020) and the most important cause of irreversible blindness (Tham et al. 2014).

Glaucoma has been considered a multifactorial disease with genetic and environmental components, with aging being the most important risk factor (Doucette et al. 2015). Although its pathophysiology has not been completely defined so far, some mechanisms are proposed to explain the causes underlying retinal ganglion cell death and optic nerve damage (Doucette et al. 2015). Ischemic conditions may be created by an increase in IOP which exerts pressure on retinal vasculature (Harris et al. 2001; Osborne et al. 2001). Besides, glutamate excitotoxicity (Casson 2006), oxidative stress (Ko et al. 2005; Tezel 2006; Gericke et al. 2019), and inflammation (Fontaine et al. 2002; Wong et al. 2015; Gericke et al. 2019) have also a role in glaucoma pathogeny.

As current available interventions to treat glaucoma have several limitations, the development of new therapeutic agents is of great relevance concerning the economic burden represented by glaucoma treatment (Table 2).

Diabetic Retinopathy

Considering people in working age, DR is the leading cause of vision loss and blindness (Ding and Wong 2012; Yau et al. 2012). In general, one-third of the patients with DM may present DR (Nam Han Cho et al. 2017), being more prevalent among patients with type 1 DM (Tarr et al. 2012). For the next years, the number of people affected by DR is expected to dramatically increase, which reflects the high incidence of DM, obesity, and also population aging (Saaddine et al. 2008; Ting et al. 2016).

Retinal damage derived from chronic hyperglycemia in DM is complex, but the central event is attributed to oxidative stress (Brownlee 2001; Arden and Sivaprasad 2011; Mendonca et al. 2020). Hyperglycemia-induced alterations cause endothelial cell dysfunction, breakdown of blood–retinal barrier and increase in vascular permeability, leading to edema (Zhang et al. 2014; Stitt et al. 2016). Moreover, the production of trophic factors is reduced, which is associated with capillary degeneration (Brownlee 2001; Arden and Sivaprasad 2011). As a result, the tissue responds to ischemic-induced signaling, triggering events of neovascularization and generating an abnormal retinal vasculature, which characterizes the proliferative stage of the disease (Al-Shabrawey et al. 2013). Furthermore, the present view of DR involves neuroinflammation (Karlstetter et al. 2015; Yu et al. 2015), neurodegeneration (Kadłubowska et al. 2016; Simó et al. 2018), and excitotoxicity (Kokona et al. 2016; Ola et al. 2019) events that may precede vascular alterations.

The impacts of DR on visual function represent a relevant challenge in public health, especially concerning care expenditures and treatments (Table 2). Besides the expenses directly related to healthcare, a significant economic impact of DR is linked to the insertion or permanency of these subjects in the job market (Rein et al. 2006). Thus, further studies are needed to develop new effective therapeutic treatments.

Age-Related Macular Degeneration

AMD is a progressive degenerative disease that primarily impairs the central retina and leads to irreversible vision loss. It is currently considered a major cause of blindness in elderly people (Smith et al. 2001), affecting 170 million people in the world (Pennington and DeAngelis 2016). Studies project that the number of patients diagnosed with AMD may expand to 288 million by 2040 (Wong et al. 2014). The high number of cases is directly attributed to the increase in life expectancy, particularly in developed countries.

AMD consists of a multifactorial disease whose etiology comprises genetic and environmental elements. A series of genes have already been identified (Al-Zamil and Yassin 2017) as well as lifestyle risk factors, such as light exposure (Chalam et al. 2011), diet (Chapman et al. 2019), and tobacco smoking (Smith et al. 2001).

The disease can also be classified into two types: dry and wet AMD, although specific pharmacological options are only available for the treatment of wet AMD (Supuran 2019) (Table 2), but there are no preventive strategies or cure (Hernández-Zimbrón et al. 2018). The burden related to AMD is highly underestimated (Brown et al. 2005); however, it is clear that vision loss negatively affects not only one's health but also their contribution and interaction with others and consequently impacts society (Table 2).

Mechanisms of Cell Death Provoked by Ischemia

The development of new, and efficient, treatment depends on the profound understanding of cell death phenomenon during the time of ischemia itself and reperfusion period (Dirnagl et al. 1999). Ischemia refers to a pathological lack of blood supply to a given tissue, so its maintenance is drastically impaired (Fig. 1). When tissue perfusion is low, cells are deprived of oxygen and metabolic substrates, and

Table 2 Cost, treatment/limitations for the three most prevalent causes of vision loss

Condition	Cost	Treatment	Limitations
Glaucoma	US: $8157/patient/year (no vision loss) up to $18.670 (with vision impairment) (Feldman et al., 2020); Europe: €969/person/year (Traverso et al. 2005)	Topic beta-blockers (Mantravadi and Vadhar 2015; Foundation 2017) Cholinergic, alpha-adrenergic, carbonic anhydrase inhibitors (Mantravadi and Vadhar 2015; Foundation 2017) Prostaglandin analogs (Mantravadi and Vadhar 2015; Foundation 2017) Laser therapy (Garg and Gazzard 2018) Surgical procedures (Razeghinejad and Spaeth 2011; Aref et al. 2017)	All treatments target IOP, although it is estimated that half of glaucoma patients do not have an increase in IOP (Shields 2008); Direct medical costs as medication, laser and surgical interventions can not be afforded by a significant part of the population, especially in developing countries (Zhao et al. 2018)
Diabetic retinopathy	US: $493 million (medical costs in 2004) (Rein et al. 2006) Sweden: €433/patient/year (Heintz et al. 2010); Germany: €671–2933/patient/year (Kähm et al. 2018)	Laser photocoagulation (Stewart 2016) Intravitreal injections of anti-VEGF (Stewart 2016) Control of glycemia diet or medication (Stewart 2016) Candidates for the treatment of DR: aldose reductase inhibitors, anti-inflammatory drugs, carbonic anhydrase inhibitors, fenofibrate, hyaluronidase, PKCβ1/2 inhibitors, and renin-angiotensin system blockers (Tarr et al. 2012; Ebneter and Zinkernagel 2016)	Target an advanced stage of the disease, uncomfortable administration, high costs, long-term side effects, and ultimately do not cure the disease (Al-Shabrawey et al. 2013; Wong et al. 2016); Clinical studies with pharmacological candidates are still inconclusive or were discontinued due to side effects
Age-related macular degeneration	US: $7.133/patient/year (direct medical costs); $30.000/patient/year (additional indirect costs) (Brown et al. 2016)	Intravitreal injection of agents that indirectly block VEGF actions (Amoaku et al. 2015; Khanna et al. 2019); Corticosteroid implants as an adjunctive therapy (Campochiaro et al. 2012; Bailey et al. 2017; Vakalis et al. 2015; Bonfiglio et al. 2017) Combination of anti-VEGF, corticosteroids and photodynamic therapy with the use of verteporfin (Kawczyk-Krupka et al. 2015)	Anti-VEGF drugs have been less beneficial than expected (Schlottmann et al. 2017); Corticosteroid treatment increases risk for cataract and ocular hypertension (Kuppermann et al. 2015; Rezar-Dreindl et al. 2017)

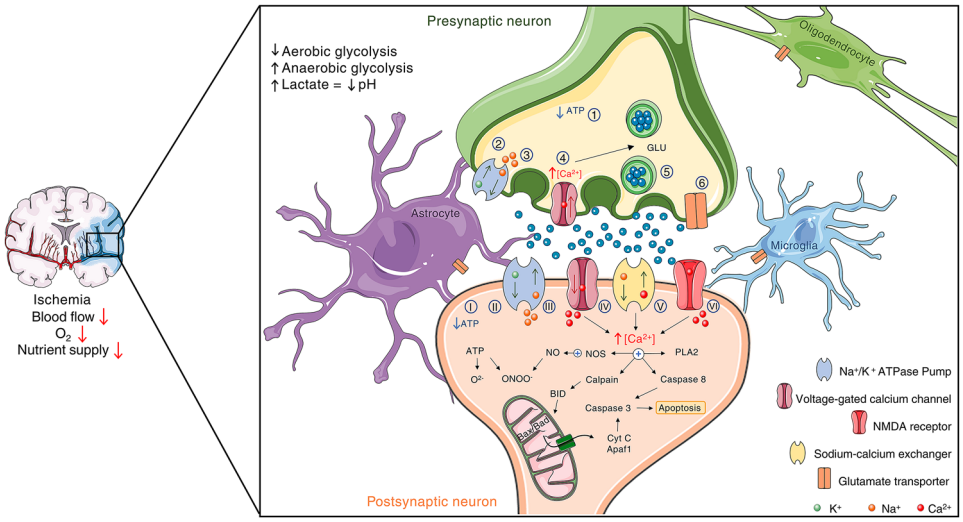

Fig. 1 Deleterious effects of ischemia on presynaptic and postsynaptic neurons. The interruption or reduction of blood flow is associated with the decrease of O_2 levels and nutrient supply. Neurons respond to these effects by decreasing aerobic glycolysis, while increasing anaerobic glycolytic process, leading to the accumulation of lactate and to a pH reduction. As ATP levels decrease (1 and I), the failure of Na^+/K^+/ATP pumps may occur (2 and II), which cause electrolyte imbalance (3 and III), depolarization and opening of Ca^{2+} voltage-dependent membrane channels (4 and IV). In the presynaptic neuron, these alterations increase neurotransmitter release, especially glutamate (5). The reversal of EAAT transporters contributes to the increase in glutamate availability in the synaptic cleft as well (6). ATP deficiency also impacts neurons by generating reactive oxygen/nitrogen species (e.g., superoxide and peroxynitrite). The depolarization mediated by intracellular sodium increase (III) stimulates voltage-gated Ca^{2+} channel (IV). Intracellular Ca^{2+} level is also elevated through the reversal of Na^+/Ca^{2+} exchanger (V). Ca^{2+} overload also affects the postsynaptic neuron as a result of NMDA receptor hyperactivation (VI), triggering glutamate excitotoxicity. Thus, intracellular Ca^{2+} accumulation leads to the activation of different death pathways such as the one mediated by NOS, Calpain, Caspase, and phospholipase A2 (PLA2). It is important to note that other pathways contributing to cell death are not described in the scheme for summarization purposes. For the clarity of the scheme Bax/Bad are show in mitochondria matrix

excretes begin to accumulate (Osborne et al. 2004; Kalogeris et al. 2016). Once a tissue becomes ischemic, a metabolic dysfunction is triggered. There is a decrease in glycolysis and oxidative phosphorylation, reducing ATP production, which, in turn, leads to failure in ionic pumps and ionic imbalance (Lipton 1999; Kalogeris et al. 2016). Reduction in sodium–potassium pump activity decreases the removal of intracellular sodium, affecting membrane potential maintenance, and consequently depolarizing cell membrane. Another result of cytoplasmic sodium accumulation is the passive influx of chloride, which also attracts water into the cell, causing cell swelling, and eventually, cell lysis, accompanied by cell content extravasation (Edinger and Thompson 2004; Duprez et al. 2009; Galluzzi et al. 2012). This kind of acute death is known as necrotic cell death and occurs mainly at the core of the ischemic region. Voltage-gated calcium channels (VGCC) are activated by this depolarization, increasing cytoplasm calcium concentrations and triggering neurotransmitter release (Mayor and Tymianski 2018).

Excitotoxicity

Glutamate is the major excitatory neurotransmitter in the CNS, and during ischemic events, a massive glutamate release occurs mainly through two different modes. Initially, glutamate is released by exocytosis, a calcium-dependent mechanism, and then by reversal of the glutamate transporters, a calcium-independent mechanism (Nicholls et al. 1987; Reid et al. 2003; Kostandy 2012). Both ATP and glutamate are also released through hemichannels (Pedata et al. 2016). Independent of the mechanism of release, glutamate further depolarizes glutamate receptors-containing cells, creating a positive feedback (Verkhratsky and Shmigol 1996; De Flora et al. 1998). The depolarization also promotes the release of magnesium from NMDA receptors (Zeevalk and Nicklas 1992), making them even more responsive to glutamate, and further intensifying the depolarization, by sodium and calcium influx. Calcium entry through NMDA receptors, VGCC and sodium–calcium exchangers can trigger signaling pathways that promote cell death through apoptosis (Figs. 1 and 2). Caspase-8 and calpains mediate BH3-interacting domain death agonist cleavage, which translocates into mitochondria, where it interacts with another set of pro-apoptotic proteins, like Bax, Bak, and Bad. This signaling promotes changes in mitochondrial permeability, triggering the release of mitochondrial proteins like cytochrome c (Cyt C), contributing to apoptosome formation through interaction with apoptotic protease activating factor 1 (Apaf-1)

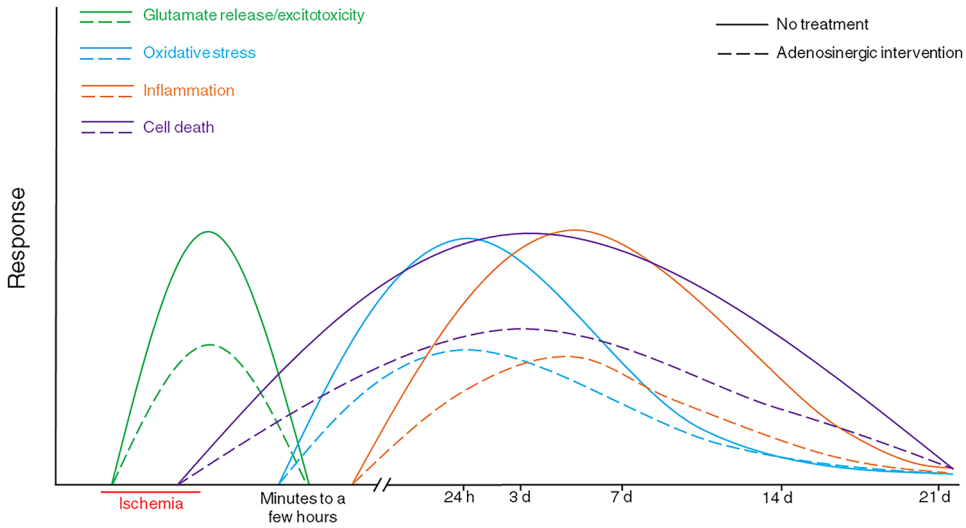

Fig. 2 Temporal profile of glutamate release/excitotoxicity (green), oxidative stress (blue), inflammation (orange), and cell death (purple) after ischemia induction. Glutamate release begins a few minutes after the onset of ischemia, reaching a peak within an hour if the noxious event lasts for that long. Extracellular glutamate content gradually decreases as soon as reperfusion takes place, and the time to restore basal levels is related to the severity of ischemia. Excitotoxic and necrotic cell death occurs rapidly at the ischemic core but programmed cell death and infarct volume are still ongoing for some days until it is not detectable anymore in weeks. At the onset of reperfusion, with the reestablishment of oxygen supply, reactive oxygen species production dramatically increases, reaching a peak close to 24 h after ischemia, when it starts to decline. Inflammation is the latest event, with microglial and macrophage activation, adhesion molecules expression, neutrophil infiltration, astroglial response, and cytokine release taking place within some hours after ischemia. Since inflammation is a multifactorial process, different phenomena occur in maximal intensity in a larger time window, with some events still rising up to 7 days, decreasing thereafter. The curves for non-treated conditions were based on data that explore the temporal pattern of mentioned parameters in the same study. The effect of adenosinergic intervention was based on data from studies mentioned throughout the text that explored at least one of the illustrated events in ischemia and demonstrated protective effects at one or more of the time periods shown

(Orrenius et al. 2015; Datta et al. 2020). The mechanism leads to effector caspase activation (e.g., caspase 3), leading to protein cleavage and DNA fragmentation, a hallmark of apoptosis (Fig. 1). Briefly, other apoptotic pathways are also provoked by ischemia, such as activation of death receptors by molecules, like tumor necrosis factor-alpha (TNF-α) and first apoptosis signal ligand (FasL). These induce apoptosis through the activation of procaspase-8, leading to executioner caspase-3 cleavage, which triggers cell signaling involving p53 translocation to nucleus and induces transcription of pro-apoptotic genes like Bax and Puma (Datta et al. 2020).

Oxidative Stress

Oxidative stress is another hallmark of an event of ischemia/reperfusion. Data suggest that reactive oxidative species (ROS) production begins at early reperfusion (Selakovic et al. 2011; Nakano et al. 2017; Godinho et al. 2018; Kapoor et al. 2019) (Fig. 2), when ATP is hydrolyzed to hypoxanthine, and ultimately converted to uric acid and superoxide ions in a calpain-dependent way. Superoxide ions can form hydroxyl radicals by Harber–Weiss reaction or interact with nitric oxide, induced by NMDA receptor activation during ischemia, generating peroxynitrite and nitrosyl radicals (Chan 1996; Love 1999; Osborne et al. 2004; Kostandy 2012). Furthermore, calcium interference on mitochondrial function causes an accumulation of free electrons, which will be accepted by the oxygen in the early phase of reperfusion, generating superoxide anions (Won et al. 2002). Regardless of the mechanism in which oxidative stress is generated, it triggers cell damage in the form of lipid peroxidation, DNA fragmentation or protein degradation (Czerska et al. 2015).

Inflammatory Contribution

Inflammation-induced cell death after ischemia is also a well-established late-component of the pathology (Stevens et al. 2002; Fang et al. 2006; Weston et al. 2007; Kriz and Lalancette-Hébert 2009; Moxon-Emre and Schlichter 2010; Perego et al. 2011; Shrivastava et al. 2013; Kawabori and Yenari 2015; Cotrina et al. 2017; Zhang et al. 2019; Kapoor et al. 2019) (Fig. 2). Within the lesion site, the expression of chemokines and adhesion molecules increases, recruiting immune cells from the bloodstream (e.g., T cells and macrophages). Local microglia are activated and secrete inflammatory mediators that can potentially worsen the tissue

damage in late phases of ischemia/reperfusion, increasing infarct size. TNF-α and interleukin 1 beta (IL-1β), important inflammatory mediators, are increased within ischemic lesion regions, contributing to cell death in the brain and retina. Corroborating these data, blockade of these inflammatory mediators reduces the magnitude of the damage (Stoll et al. 2002; Osborne et al. 2004; Kawabori and Yenari 2015).

Role of Adenosine in Ischemic Conditions

Adenosine is a nucleoside that functions as a neuromodulator in the CNS, regulating the release of neurotransmitters, synaptic plasticity, sleep–wake cycle, and cell death (Sheth et al. 2014). Adenosine acts through four types of G-protein-coupled receptors already cloned and classified into A_1, A_{2A}, A_{2B}, and A_3. The A_1 and A_3 receptors are classically coupled to Gi/o protein, inhibiting AC activity and the production of cAMP (Fig. 3a). On the other hand, A_{2A} and A_{2B} receptors are classically coupled to Gs/olf protein, activating AC and increasing cAMP levels, which will, in turn, act on a series of effector proteins (Sheth et al. 2014).

Data from different experimental approaches may raise doubts concerning adenosine affinity for its receptors. In the most common view, A_1 and A_{2A} are considered high-affinity receptors and A_{2B} and A_3 are low-affinity receptors (Beukers et al. 2000; Effendi et al. 2020; De Filippo et al. 2020). Indeed, the observation that adenosine could have high or low affinity for A_2 receptors led to the distinction of A_{2A} (high affinity) and A_{2B} (low affinity) receptors (Bruns et al. 1986). However, Fredholm and colleagues (Fredholm et al. 2011; Fredholm 2014) have reported the difficulty in measuring adenosine affinity and pointed out that a reliable method to estimate this information is to assess the potency of each receptor. This way, A_1, A_{2A}, and A_3 might be equipotent, while A_{2B} is supposed to require higher concentrations of adenosine to elicit the same response (Fredholm 2014). Interestingly, high amounts of adenosine are only released in pathological conditions, such as hypoxia, which also causes A_{2B} receptors upregulation (Vecchio et al. 2019).

Many studies in the literature describe the increase in extracellular adenosine availability during an ischemic event (Pedata et al. 1993; Frenguelli et al. 2007; Melani et al. 2012; Chu et al. 2013). The transient release of adenosine also increases during the period of cerebral ischemia and remains elevated during the reperfusion process (Ganesana and Jill Venton 2018). At the beginning of ischemia, adenosine arises from the hydrolysis of the released ATP and, later, cells release adenosine through their nucleoside transporters (Melani et al. 2012). Moreover, ischemia increases

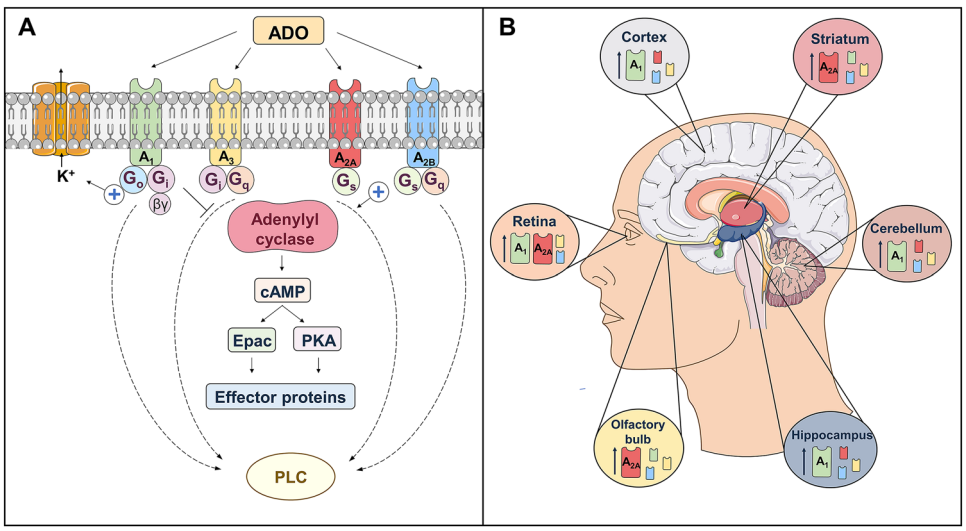

Fig. 3 Intracellular pathways coupled to adenosine receptors and CNS distribution. **a** There are four types of adenosine receptors named A_1, A_{2A}, A_{2B}, and A_3. The A_1 and A_3 receptors activate Gi/o protein, while A_{2A} and A_{2B} receptors are coupled to Gs/olf protein inhibiting and stimulating, respectively, adenylyl cyclase. Thus, adenosine receptors regulate cAMP levels, which impacts on protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac) activity. A series of other effector proteins may also be modulated. Moreover, adenosine receptors can stimulate the phospholipase C (PLC) pathway. A_1 receptors regulate PLC via beta/gamma complex (Biber et al. 1997; Dickenson and Hill 1998), whereas A_{2A} receptors act through Gq protein (Ribeiro et al. 2016; Socodato et al. 2011). Both A_{2B} and A_3 receptors can also stimulate PLC (Abbracchio et al. 1995; Kohno et al. 1996; Pilitsis and Kimelberg 1998). **b** The distribution of adenosine receptors varies dramatically within the CNS. High densities of A_1 receptors are expressed in the cortex, hippocampus, and cerebellum, while A_{2A} receptors are more abundant in the striatum and olfactory bulb. In contrast, A_3 and A_{2B} receptors are diffusely distributed in all brain regions in smaller amounts when compared to A_1 and A_{2A} receptors (Sheth et al. 2014). A_1, A_{2A}, A_{2B}, and A_3 receptors are also found in retinal cells, a structure that is part of the CNS, of different animals (Dos Santos-Rodrigues et al. 2015; Brito et al. 2016; Grillo et al. 2019; Portugal et al. 2021)

the expression of ecto-5´nucleotidase (CD73) in astrocytes, and induces its expression in microglia, enhancing extracellular adenosine formation (Braun et al. 1997). Within minutes, the concentration of adenosine in the extracellular medium reaches 1 mM, high enough to activate all P1-type receptors (adenosine receptors) (Melani et al. 2012), which are abundantly expressed in the CNS (Fig. 3b).

Interestingly, increased adenosine levels reduce neuronal damage and decrease the infarct area in rodent models of ischemia (Deleo et al. 1988; Dux et al. 1990; Lin and Phillis 1992; Mori et al. 1992; Park and Rudolphi 1994; Gidday et al. 1995; Matsumoto et al. 1996; Miller et al. 1996; Jiang et al. 1997; Newman et al. 1998; Tatlisumak et al. 1998; Kitagawa et al. 2002). Treatment with a daily dose of exogenous adenosine, initiated 24 h after cerebral ischemia and maintained for 7 days, contributes to decreased cell death and sensorimotor functional recovery in the CA1 area of hippocampus of rats (Seydyousefi et al. 2019). Accordingly, the knockout (KO) for ecto-5′nucleotidase (CD73) shows increase in ischemic damage (Petrovic-Djergovic et al. 2012). The signaling involved in adenosine protection in HI is still unclear, but the anti-apoptotic effect of adenosine in human umbilical vein endothelial cells (HUVECs) is reduced by the blockade of MAP kinase pathway (MEK/ERK1/2), nitric oxide synthase (NOS), and protein kinase A (PKA) (Feliu et al. 2019). Moreover, adenosinergic agents also represent a potential pathway for neuroprotection in immature neurons (Shalak and Perlman 2004; Perlman 2006).

Protective Role of Adenosine Through A_1 Receptor in Ischemia

The activation of A_1 receptors has been correlated with protective effects in ischemic situations both in mature and immature CNS (Melani et al. 2014b; Pedata et al. 2016) An important mechanism related to this effect refers to its capacity to regulate neuronal excitability by restricting calcium influx and, consequently, inhibiting the release of neurotransmitters, such as glutamate (Corradetti et al. 1984; Dunwiddie 1984; Andiné et al. 1990; Goda et al. 1998; Latini et al. 1999b; Sebastião et al. 2001; Tanaka et al. 2001; Marcoli et al. 2003; Arrigoni et al. 2005; Batti and O'Connor 2010). In fact, it has been shown that ischemia-induced synaptic depression is greatly inhibited in hippocampal slices of A_1 KO mouse, reinforcing the idea of protection through modulation of synaptic activity (Johansson et al. 2001; Kawamura et al. 2019). Indeed, treatment with A_1 receptor agonists (CPA or CHA) reduces lactate dehydrogenase (LDH) release induced by HI in cultures of cerebellar granule (Logan and Sweeney 1997), and hippocampal and cortex neurons (Daval and Nicolas 1994). In addition, A_1 receptors antagonist, DPCPX, could reverse this effect in granule cells (Logan and Sweeney 1997). A recent study has shown that the presence of CPA, an A_1 full agonist, or the partial agonists 2′-dCCPA and 3′-dCCPA, during the entire experimental procedure, in hippocampal slices, protects the neurons from oxygen glucose deprivation (OGD)-induced irreversible depression and increases cell viability of SH-SY5Y human neuroblastoma cells in culture after OGD (Martire et al. 2019). The same protective profile was observed in vitro, using primary cultures of neurons prepared from turtle brain homogenates subjected to anoxic condition (Milton et al. 2007). In this case, treatment with the selective A_1 receptor agonist, CCPA, prevents cell death and anoxia-induced ROS production, but A_1 antagonist (DPCPX) exacerbates the injury (Milton et al. 2007).

The cell signaling involved in A_1 receptor protection against ischemic death is also an important research field. In primary cortical neurons in culture, the increase in cell viability by treatment with paeoniflorin, before and during OGD, occurs via A_1 receptor activation and depends on Akt and ERK1/2 phosphorylation (Zhong et al. 2015). On the other hand, there is evidence that incubation with a high concentration of an A_1 receptor agonist (500 nM CPA) induces neuronal damage in the CA1 region of hippocampal slices, which is prevented by DPCPX (Stockwell et al. 2016). The authors suggest a mechanism of adenosine-induced persistent synaptic depression, which includes AMPA subunits internalization through dephosphorylation.

Similar effects are also found by using in vivo models of ischemia. In general, acute pre-treatment with A_1 agonists preserves the morphology of neurons, spatial memory, and learning capacity; increases neuron survival and neurological scores; and reduces mortality in gerbils (Héron et al. 1994; Von Lubitz et al. 1994a, 1996). Accordingly, in young A_1 KO mice (P10), larger infarct area has been reported after unilateral HI (Winerdal et al. 2016). Administration of A_1 agonist CCPA 24 h before middle cerebral artery occlusion (MCAO) protocol is also protective, reducing infarct area, TNF-α levels, and lipid peroxidation and increasing superoxide dismutase (SOD) and glutathione (GSH) levels (Hu et al. 2012). Administration of A_1 agonist CPA 1 h before ischemia also reduces lipid peroxidation when analyzed at 3 h and 3 days after ischemia (Sufianova et al. 2014). Atef et al. (2018) investigated the signaling activated by A_1 receptor in ischemia. The incubation of A_1 agonist CHA at the onset of reperfusion drastically diminishes pyknotic nuclei in hippocampal neurons induced by bilateral carotid occlusion. The receptor agonist promotes reduction of reactive microglia, glutamate, TNF-α, inducible NOS (iNOS), interleukin 6 (IL-6), Thiobarbituric acid reactive substances (TBARS), c-fos, Cyt C, and caspase-3, all increased by ischemia. Meanwhile, it increases interleukin 10 (IL-10) and nuclear factor erythroid 2-related factor 2 (Nrf2) and elicits better

performances in behavior tasks. Ischemia also increases phospho-ERK1/2 and diacylglycerol levels but those were further increased by CHA, which also potentiates the reduction in cAMP promoted by ischemia (Atef et al. 2018). A more recent study shows that pretreatment with A_1 agonist CCPA for 30 min reduces the brain infarction area after 90 min of MCAO, and this effect correlates to the increase in glycogen synthase kinase 3 beta (Gsk3b) phosphorylation (Geng et al. 2020). In another study, Cui et al. (2016) have shown that a blocker of dynamin-related protein 1 reduces stroke volume and improves neurological score of mice submitted to MCAO, depending on A_1 receptor, and involving increase in levels of extracellular adenosine through regulation of the ecto-5′ nucleotidase (CD39) expression in astrocytes via cAMP/PKA/cAMP-response element binding protein (CREB) phosphorylation. The protection afforded by electroacupuncture, which increases adenosine levels and reduces infarct volume in a model of MCAO also depends on A_1 receptor (Dai et al. 2017). Treatment with A_1 receptor agonists, soon after ischemia, is also effective in protecting neurons, improving neurological scores and reducing mortality (von Lubitz et al. 1988; von Lubitz and Marangos 1990). Accordingly, acute pre-treatment with A_1 antagonists CPX or 8-CPT significantly worsens the outcome and enhances neuronal destruction induced by global ischemia (Boissard et al. 1992; Von Lubitz et al. 1994a; Phillis 1995; Olsson et al. 2004).

However, while studies using an acute treatment with A_1 receptor antagonists show aggravation in ischemic damage, chronic treatment, previous to ischemia, has a protective effect. Exposure to A_1 antagonist CPX—1 mg/kg, i.p. for 15 days, up to 24 h before the ischemic event, reduces neuronal damage (Von Lubitz et al. 1994a). Such effect could be attributed to the fact that prolonged inhibition of a receptor induces its upregulation, a common neurochemical plasticity response observed in the CNS that also applies to A_1 receptor (Jacobson et al. 1996; Hettinger-Smith et al. 1996; Brito et al. 2012). Curiously, adult A_1 KO mice show no effect on cell death in hippocampus, cortex, and striatum after a 12-min global ischemia followed by 4 days of reperfusion, raising the question if compensatory mechanisms could be active in animals lacking A_1 receptor, which predominantly seem to promote the survival of the CNS cells in ischemic conditions (Olsson et al. 2004).

Thus, A_1 receptor consists of an interesting target of studies in the context of ischemic damage. Its essential effect represented by the reduction of neuronal excitability has proven to be beneficial in mature and immature brain lesions. Despite that, it is important to highlight that chronic treatments with A_1 antagonists may trigger compensatory mechanisms as receptor upregulation, which may be relevant as a protective strategy.

The Modulatory Effect of A_{2A} Receptors in Ischemic Conditions

Classically, A_1 and A_{2A} adenosine receptors elicit opposite intracellular responses. Accordingly, many studies demonstrate that A_{2A} receptor antagonism, as well as A_1 activation, is protective against ischemic damage. A_{2A} selective antagonist, administered just before ischemia, protects hippocampal neurons in a global prosencephalic ischemia model (Phillis 1995; Von Lubitz et al. 1995). Similarly, treatment with an A_{2A} selective antagonist (ZM241385) before ischemia reduces neuronal damage in hippocampal cells and improves animal performance in Morris water maze (Higashi et al. 2002). The beneficial effect provided by blockade of A_{2A} receptors in ischemic events is reinforced by studies showing that A_{2A} receptor KO protects from cerebral ischemic damage (Chen et al. 1999; Gui et al. 2009). When administered after the ischemic event (which in fact has greater clinical relevance), an A_{2A} antagonist also has protective effects. The use of SCH58261 after the ischemic event reduces neuronal damage in neonate and adult rats (Bona et al. 1997; Monopoli et al. 1998; Melani et al. 2003, 2006b). In newborn piglets, the A_{2A} inhibition-induced protection involves an increase in Na^+/K^+ ATPase pump activity, and prevention of the ischemia-induced phosphorylation of NMDA receptor subunit GluN1 at ser897 and of dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP32) at thr34. The protection also includes the reduction in ischemia-induced nitrative and oxidative stress (Yang et al. 2013). Mohamed and collaborators (Mohamed et al. 2016) have analyzed in more detail the intracellular pathways triggered by A_{2A} antagonism in ischemia. Intrahippocampal injections at the end of a 45-min ischemic event decrease protein levels of phospho-ERK (p-ERK), NFκB, TNF-α, IL-6, iNOS, caspase-3, Cyt C, p-CREB, and c-fos, all increased by ischemia/reperfusion (Mohamed et al. 2016). Moreover, the authors report a decrease in glutamate and TBARS, alongside increases in IL-10 and nuclear Nrf2 with the antagonist treatment. However, exposure to A_{2A} receptor antagonist (CSC), 2 h after stroke onset, has no protective effect in lesion volume, which could be due to the time window of effectiveness or dose (Fronz et al. 2014). Furthermore, prolonged use of SCH58261, starting 5 min and twice/day after tMCAO, does not change infarct volume when analyzed 7 days later, suggesting a time window of apparent protection that remains to be fully understood (Melani et al. 2015). Finally, A_{2A} receptor KO in younger (P7) rats intensifies the damage, caused by the occlusion of the left common carotid, and the performance in behavioral tests, such as rotarod (Ådén et al. 2003), which raises the question whether the effect of A_{2A} receptor blockade depends on the maturity of the tissue and/or differentiation of specific features during development to achieve neuroprotection.

To understand the role of adenosine A_{2A} receptor in ischemia-induced cell death, experiments with agonists have also been performed. In the gerbil, A_{2A} agonist (APEC), administered systemically and chronically for 13 days before the ischemic insult, has beneficial effects on the survival of hippocampal neurons and animals (Von Lubitz et al. 1995). Systemic administration of A_{2A} agonist ATL-146e or CGS 21680, just before reperfusion onset, protects from motor dysfunction and cell viability in spinal cord ischemia–reperfusion and infarct size, oxidative stress, and memory impairment in global cerebral ischemia, respectively (Reece et al. 2006; Grewal et al. 2019). The treatment with low doses (0.01–0.1 mg/kg i.p.) of this same agonist for seven days (and twice a day), after transient cerebral ischemia, decreases gliosis, the infarct area in the cortex, but not in the striatum, as well as the myelin disorganization in the striatum (Melani et al. 2014a). The possible explanation for the apparent contradiction (activation of A_{2A} receptor and protection) is the modulation of functions in non-neuronal cells-glial, endothelial, and immune cells that leads to several benefic effects (described in the next topic).

The data show an important neuroprotective function triggered by the inhibition/absence of A_{2A} receptors in neurons in different models of cerebral ischemia. Interestingly, in some cases, the protective action can also be achieved after ischemia, which makes A_{2A} receptor inhibition a promising tool in both prevention and treatment. In addition, the time frame of pharmacological intervention is crucial for the protective effect, as well as the period of development. In any case, the evidence mostly places the inhibition of A_{2A} receptors as a common denominator of neuroprotection.

Protective Mechanisms Through A_1 and A_{2A} Receptors Related to Glial and Other Cells

The protective effect of A_{2A} receptors inhibition can also be attributed to the regulation of synaptic transmission and glutamate release (Cunha et al. 1994; Latini et al. 1999a; Melani et al. 2003; Pugliese et al. 2009; Lopes et al. 2011; Maraula et al. 2013; Effendi et al. 2020). This effect seems to occur through modulation of A_1 receptor activity, at least in the hippocampus (Lopes et al. 2002). It is known that glial cells play an important role in the regulation of glutamate availability and excitotoxicity. Interestingly, in astrocytes, A_{2A} receptors inhibit glutamate uptake by excitatory amino acid transporter (EAAT)-2 while stimulating EAAT-2-independent release via PKA activation (Nishizaki et al. 2002). Acute (30 min) or chronic (24 h) activation of the A_{2A} receptor with CGS 21680 reduces D-aspartate uptake in astrocyte cultures, probably by decrease of glutamate transporters EAAT1 and EAAT2 mRNA expression (Matos et al. 2012). Cultures of rat astrocytes subjected to OGD for 150 min show great cell death after 24 h of reoxygenation. Death is inhibited by guanosine through a mechanism that depends on the activation of the A_1 receptor and the MAPK and protein kinase C (PKC) pathway. Activation of these pathways prevents the OGD-promoted reduction of EAAT2 glutamate transporters in the membrane, restoring glutamate uptake and, consequently, restricting cell death (Dal-Cim et al. 2019). This evidence is in agreement with the increase in the amount of EAAT2 by overexpression of A_1 receptors in astrocytes (Wu et al. 2011; Hou et al. 2020). Recently, it has been demonstrated in mouse astrocyte cultures subjected to OGD that the formation of A_1–A_{2A} heterodimers reduces the expression of EAAT2 through the transcription factor YY1 and repression of PPARγ transcription. Interestingly, the effect is blocked by the pharmacological activation or inhibition of the A_1 and A_{2A} receptor, respectively (Hou et al. 2020). Thus, A_{2A} receptors activation reduces the ability of glial cells to decrease glutamate availability, which could be harmful in ischemic events. In agreement, there is an increase in the expression of EAAT2 in astrocytes genetically devoid of A_{2A} receptors (Matos et al. 2015; Hou et al. 2020). In addition, A_{2A} receptor inhibition reduces reactive astrogliosis in slices of hippocampal rats submitted to OGD (Pugliese et al. 2009). It remains to be evaluated whether reactive astrogliosis depends on the modulation of glutamate transporters. New evidence points out that the astrocytic Lrp4 protein contributes to cell death induced by photothrombosis, ischemic stroke, and OGD, since Lrp4 KO animals exhibit lower cell death when compared to controls (Ye et al. 2018). The authors demonstrated that the absence of the protein reduces reactive astrogliosis and increases the release of ATP and astrocytic adenosine in ischemic conditions, which contributes to the reduction of neuronal death through activation of the P2X7 and A_{2A} receptors (Ye et al. 2018). In fact, astrocytes are a considerable source of adenosine release in ischemic conditions (Martín et al. 2007; Takahashi et al. 2010).

Ischemia, ATP and glutamate per se can also induce microglial activation (Pforte et al. 2005; Davalos et al. 2005; Melani et al. 2006a; Lai et al. 2011). Furthermore, A_{2A} receptor, stimulated by adenosine released during ischemia, activates microglia (Orr et al. 2009). Reactive microglia releases high concentrations of glutamate (Takeuchi et al. 2006; Socodato et al. 2015) and ATP (Imura et al. 2013), contributing to a positive feedback loop of microglial activation and enhancing excitotoxicity. Accordingly, glutamate release after ischemia can be attenuated by treatment with A_{2A} antagonist (SCH 58261) in vivo and in rat and human cortex slices (Marcoli et al. 2003, 2004; Melani et al. 2003). Furthermore, A_{2A} antagonism prevents the ischemia-promoted increase in p-p38 and TNF-α in microglia and in p-JNK in oligodendrocytes, which would lead to a disorganization of myelin (Melani et al. 2006b, 2009; Mohamed et al. 2016). Another interesting point is that NGF plays a neuroprotective role in cerebral ischemia. Astrocytes, together with

microglia, are the main responsible for NGF secretion, which is stimulated by A_1 and A_{2A} receptors, respectively (Heese et al. 1997; Ciccarelli et al. 1999; Liu et al. 2019). The relation of NGF production/secretion and A_1 or A_{2A} receptors in ischemic events is still unclear. The activation of A_{2A} receptor is also related to the production and release of neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) (Gomes et al. 2006, 2013; Tebano et al. 2008; Sebastião and Ribeiro 2009; Jeon et al. 2011; Vaz et al. 2015), which could help maintain/restore function and neuronal integrity. However, the release of these neurotrophic factors may not compensate for several other malefic alterations triggered by A_{2A} receptor activation during ischemia. Activation of A_{2A} receptor in microglial cells also induces cyclooxygenase 2 (COX-2) content, and prostaglandin E2 release (Fiebich et al. 1996), nuclear translocation of hypoxia inducible factor (HIF-1α) and transcription activation of vascular endothelial growth factor (VEGF) and iNOS (Merighi et al. 2015).

Besides glial cells, other cell types can contribute to protection induced by A_{2A} inhibition. The specific inactivation of A_{2A} receptors in endothelial cells have recently shown to be beneficial in a model of embolic MCAO. The cell-specific knockout decreases infarct volume and improves neurological outcome (Zhou et al. 2019). Furthermore, the KO shows reduced protein levels of adhesion molecules, such as VCAM and ICAM, neutrophil and monocytes infiltration, reduced blood–brain barrier leakage, and consequently reduced edema. The mechanism seems to involve less activation of the NLRP3 inflammasome in the endothelial KO. Taken together, these data indicate that a plethora of changes triggered by A_{2A} receptor inhibition during or soon after ischemia result in CNS protection.

Furthermore, the best window for treatment with A_{2A} receptor inhibitors, and therefore, the outcome efficiency after ischemia, can be challenging due to the action in non-neuronal cells. The activation of A_{2A} receptor in immune cells could contribute to the protection after ischemia/reperfusion, as it reduces infiltration of those cells into the ischemic site, and release of inflammation signal, which aggravates injury (Haskó et al. 2008; Antonioli et al. 2014; Melani et al. 2014a). Studies indicate that adenosine, by activating A_{2A}, A_{2B}, and A_3 receptors, restrains the production of macrophage pro-inflammatory mediators, such as TNFα, IL-6, IL-12, NO, and macrophage inflammatory protein (MIP)-1α (Antonioli et al. 2019). In vitro, human dermal microvascular endothelial cells (HDMECs) and rabbit DMECs show less apoptotic levels after hypoxia when treated with A_{2A} agonist (CGS-21680) before the onset of hypoxia and again before reoxygenation (Cao et al. 2017, 2019). Thus, these results show that A_{2A} receptors may also account for protection by preserving the vascular integrity and can hinder the best protocol of treatment with the A_{2A} inhibitors.

Beneficial Effects of A_{2B} Receptors in Ischemia

The role of A_{2B} receptors has been less explored but, interestingly, due to the low affinity for adenosine and the relative paucity in the brain, A_{2B} receptors appear to be activated, and may be biologically operative, mainly under noxious situations, such as hypoxic or ischemic conditions, when adenosine levels increase (Koeppen et al. 2011; Popoli and Pepponi 2012). In the stratum radiatum of the CA1, the A_{2B} receptor is found in non-astrocytic cells, and the number and labelling density increase after cerebral ischemic preconditioning (Zhou et al. 2004). In A_{2B} KO mice, basal levels of TNF-α and adhesion molecules, such as ICAM-1, P-selectin, and E-selectin, are increased (Yang et al. 2006). In addition, A_{2B} receptors demonstrate an important function in endothelial cells to control vascular leakage and neutrophil infiltration induced by hypoxia in several organs (Eckle et al. 2008). However, in the brain, although the genetic absence of A_{2B} receptors in bone marrow increases vascular permeability, A_{2B} receptor agonist or antagonist treatment has no effect (Eckle et al. 2008). Additionally, hypoxia upregulates A_{2B} receptors, together with HIF-1α and IL-6, in primary microglial cells (Merighi et al. 2017). Interestingly, the role of A_{2B} receptors in tissue-type plasminogen activator (tPA) treatment, one of the frontlines to treat stroke in humans, was recently evaluated. An inconvenient side effect of tissue-type plasminogen activator is the possibility to induce hemorrhagic transformation. Treatment with an A_{2B} agonist (BAY 60-6583) after ischemia reduces infarct volume in the presence or not of tPA and counteracts the blood–brain barrier damage induced by tPA (Li et al. 2017). These data could open the possibility to include A_{2B} agonists as adjuvants in tPA treatment after stroke.

A_{2B} receptors were also studied in the context of protection mediated by propofol in ischemia. This anesthetic could reduce microglial proliferation, and the levels of nitric oxide, TNF-α, and IL-1β, all increased by transient MCAO. An A_{2B} antagonist (MRS agar) blocks the beneficial effects of propofol, suggesting an interesting protective effect of propofol in ischemia through A_{2B} activation (Yu et al. 2019). Docosahexaenoic acid protects hippocampal slices from OGD-promoted cell death through A_{2B} receptors activation (Molz et al. 2015). In the same model, A_{2B} antagonists (MRS1754 or PSB603) delay OGD-induced anoxic depolarization, restoring field excitatory postsynaptic potentials (fEPSPs), decreasing the apoptotic marker cytochrome c, and improving neuronal survival (Fusco et al. 2018).

Therefore, different from A_1 and A_{2A} receptors, which are widely distributed in the CNS, A_{2B} receptors may play a restricted role in adverse conditions, such as ischemia. As a consequence, A_{2B} antagonists may elicit the protection of ischemic neurons. Moreover, as A_{2B} modulation may impact blood circulation, pharmacological strategies based on this receptor should benefit the scheme of pharmacological intervention in cases of stroke.

The Action of A_3 Receptors in Ischemic Events

The A_3 receptors also appear to be involved in the process of cell survival and death, depending on the level of receptor activation and pathophysiological conditions, such as the ischemic process (Abbracchio and Cattabeni 1999; Borea et al. 2009). Pretreatment with a selective A_3 agonist (Cl-IB-MECA) increases cell viability of primary cortical cultures exposed to OGD, as well as attenuates ischemia-induced TUNEL labeling and cerebral infarct volume, and increases locomotor activity (Chen et al. 2006). Treatment with IB-MECA after ischemia reduces infarct size, reactive gliosis, and microglia infiltration when evaluated 7 days later (Von Lubitz et al. 2001). The reduction of microglial infiltration by IB-MECA after ischemic events may depend on direct inhibition of chemotaxis and down-regulation of Rho GTPases (Choi et al. 2011). In agreement, KO for the A_3 receptor exhibits greater ischemic (Chen et al. 2006) or hypoxic damage (Fedorova et al. 2003). In vitro studies with hippocampal slices, prepared from young rats (P12–P16), submitted to 15-min OGD, result in depression of fEPSPs that was persistent only at CA3 region, but not at CA1, and application of A_3 receptor antagonist (VUF5574 or MRS1191) prevented the persistent depression (Dennis et al. 2011). The authors suggest that A_3 activation can partially contribute to OGD-induced AMPA receptors internalization in the CA3 region, potentially protecting it from following excitotoxicity. In hippocampus slices from adult rats, A_3 antagonists prevent sustained depression induced by OGD at CA1 region (Pugliese et al. 2007). Moreover, in a model of global ischemia of the anterior brain in the gerbil, chronic administration of IB-MECA (100 µg/kg i.p. daily for 10 days before ischemia), reduces neuron loss in the hippocampus (Von Lubitz et al. 1994b). In human astrocytoma cells, low concentration of Cl-IB-MECA reduces hypoxia-induced apoptosis, as well as cell death is exacerbated in A_3 KO astrocytes (Björklund et al. 2008).

Although, high concentrations of adenosine or 2-Cl-IB-MECA seem to be toxic to oligodendrocyte cultures prepared from optic nerve, by causing ROS production, mitochondrial membrane depolarization and caspase dependent cell death, which are blocked by MRS 1220, an A_3 receptor antagonist (González-Fernández et al. 2014). Furthermore, MRS 1220 reduces OGD-induced cell death in isolated optic nerve, also restoring myelin basic protein levels.

The evidence strengthens the idea that A_3 receptor activation triggers a protective mechanism in ischemic events, similar to A_1 receptor stimulation. The neuroprotective effect seems to depend directly on the activation of the receptor in neuronal cells; however, an indirect effect via other cell types cannot be ruled out.

Role of Adenosine Receptors in Ischemic Retina

In the mature retina, A_{2A} receptor inhibition or A_1 receptor activation has also beneficial effects in ischemic conditions. The increased availability of adenosine, using an adenosine deaminase blocker, or an A_1 receptor agonist, both applied just before ischemia, preserves the tissue integrity, and the electrical activity impaired by ischemia (Larsen and Osborne 1996). Interestingly, A_1 receptors blockade also impairs the histological protective effect provided retinal ischemic preconditioning (Sakamoto et al., 2004). In addition, the A_{2A} inhibition protects both structure and tissue functionality after ischemic events of 5, 30, or 60 min, whereas A_1 blockade does not exert the same effect (Li et al. 1999). In a model of ischemia induced by increased IOP and reperfusion for 7 days, the A_{2A} antagonist KW6002 also reduces the inflammatory response and the apoptotic levels in the rat retina (Boia et al. 2017). In the same model, an A_{2A} antagonist (SCH 58261) reduces microglial reactivity, IL-1β levels, and TUNEL staining (Madeira et al. 2016a). Intriguingly, selective A_{2A} activation before ischemia alleviates the thinning of the inner retina (Konno et al. 2006).

In both in vitro and in vivo models of the retina, A_3 receptor selective agonist provides protection against excitotoxic stimuli and ischemia–reperfusion injury, increasing the survival of retinal cells, including ganglion cells (Galvao et al. 2015). This protective effect could occur through receptor desensitization (Pugliese et al. 2007).

Caffeine as a Possible Neuroprotector in Ischemia

Caffeine and Coffee Consumption

Caffeine (1,3,7-trimethylxanthine) is an alkaloid that belongs to the class of xanthines, being the most consumed psychostimulant in the world. The worldwide consumption of caffeine occurs through different sources, such as coffee, teas, chocolates, soft drinks, energy drinks, and medicines (Heckman et al. 2010; Yoon and Danesh-Meyer 2019). However, the main source of this stimulant in Western society is through the consumption of coffee, where its concentration can vary between 40 to 180 mg/150 mL. In Western countries, the daily intake of caffeine reaches 70–80% of the population (Heckman et al. 2010; Mitchell et al. 2014), increases with age, and the consumption, considering all sources, can vary from 135 to 213 mg/day (Drewnowski and Rehm 2016). Brazil is the second largest consumer of coffee in the world, and the consumption of caffeine by adults, from all sources, can reach 300 mg/day (Heckman et al. 2010; Sousa and Da Costa 2015).

Molecular Mechanisms and Caffeine Metabolism

The biological effects triggered by caffeine concentration reached by average daily consumption are related to its

antagonism of adenosine receptors, more specifically A_1 and A_{2A} receptors (Rivera-Oliver and Díaz-Ríos 2014). Besides adenosine, other molecular targets can be modulated by caffeine only at high/toxic concentrations, which are unlikely to be reached in humans by any form of normal use of caffeine-containing beverages. Comparing to the concentration range that selectively inhibits adenosine receptors, caffeine can inhibit phosphodiesterase (in a ten times higher concentration), $GABA_A$ receptors (40 times higher), and mobilize calcium from intracellular stores (100 times higher) probably by its action on ryanodine receptors (Fredholm 1979; Fredholm et al. 1999; Gupta et al. 2018). Thus, the vast majority of the effects described in animal models and human studies using caffeine are exclusively related to inhibition of adenosine receptors (see Box 1 for information about caffeine dose translation).

Box 1: How to Translate Caffeine Dose from Animal Models to Humans

Several studies have been researching the role of caffeine in different pathologies using animal models. Concerning that, it is important to bear in mind that caffeine dose cannot be directly compared between animals and humans because of the difference in the body surface area (BSA). Reagan-Shaw et al. (2007) call the attention to the usage of appropriate normalizations to extrapolate animal dose to humans. The Food and Drug Administration (FDA) recommends the usage of a factor (Km) to convert animal dose to human equivalent dose (HED) using the following formula:

$$\text{Human equivalent dose (mg/kg)} = \text{animal dose(mg/kg)multiplied by } \frac{\text{animal Km}}{\text{human Km.}}$$

For example, the treatment of a mouse with 30 mg/kg of caffeine corresponds to a HED of 2.43 mg/kg, since the values of Km for adult human (with 60 kg) and mouse (Table 1) are, respectively, 37 and 3 (Reagan-Shaw et al. 2007). Therefore, for an adult with 60 kg it corresponds to 146 mg of caffeine, which is a low dose for humans. However, the Km for rats is 6, so a 30 mg/kg treatment corresponds to a HED of 4.86 or 292 mg of caffeine, a higher HED. The HED obtained in the rat, but not in the mouse example is in the range considered, by The American College of Obstetricians and Gynecologists, unsafe for pregnant women. Therefore, researchers must be careful about which dose they should choose depending on the consumption range they may plan to stimulate in humans.

After ingestion, caffeine is rapidly and completely (99%) absorbed by the gastrointestinal tract in humans, reaching a plasma peak between 15 and 120 min. For doses of 5–8 mg/kg, the plasma caffeine concentration can vary between 8 and 10 mg/L (Arnaud 1993). Due to its hydrophobic profile, caffeine is able to cross all biological barriers, such as hemato-intestinal, hemato-placental, blood–brain barrier, and blood–retinal barrier (Arnaud 1993; Cappelletti et al. 2015). The half-life of caffeine in humans varies between 2.5 and 4.5 h for doses less than 10 mg/kg (Fredholm et al. 1999). Caffeine metabolism occurs in the liver and is carried out mainly by the cytochrome P450 1A2 enzyme system (CYP1A2), even though xanthine oxidase and acetyltransferase 2 (NAT-2) also contribute to this function (Nehlig 2018). However, the functionality of CYP1A2 is reduced in different animals, neonates and premature babies, which dramatically increases the half-life of caffeine in these individuals (Arnaud 1993; Fredholm et al. 1999; Nehlig 2018). Thus, metabolic rate is another important factor that influences caffeine effect in animal models. For doses lower than 10 mg/kg, the half-life of caffeine ranges from 0.7 to 1.2 h in rats and mice, 1–4 h in rabbits, 3–5 h in monkeys (Bonati et al. 1984; Arnaud 1993; Xu et al. 2010).

The metabolism of caffeine that occurs in the liver produces, among other components, three dimethylxanthines: paraxanthine, theobromine, and theophylline. Among the three, paraxanthine is produced in a greater proportion (84%), followed by theobromine (12%) and theophylline (4%) (Cappelletti et al. 2015). These metabolites have physiological actions (Ribeiro and Sebastião 2010). Interestingly, it has been observed that after chronic caffeine consumption, the concentration of theophylline in the brain of mice seems to remain higher than their own peripheral concentrations, higher than the concentrations of other metabolites and higher than the concentration of caffeine itself. These findings suggest that caffeine metabolism in the CNS may be different (Johansson et al. 1996), which could impact the outcome of treatment with caffeine. Therefore, more studies aiming to understand the role of these metabolites in ischemic events could help reach an efficient protocol of therapy.

Implications of Caffeine Exposure During Development

Caffeine and its metabolites can accumulate during pregnancy since clearance and excretion are reduced due to decreased CYP1A2 activity (Stavric 1988; Nehlig 2018). The ability of caffeine to freely cross the placental barrier,

coupled to the fact that its metabolism is immature during embryonic and postnatal development, can lead to a high concentration of this compound in the body of these fetuses/neonates and compromise the correct development of different systems. In fact, there are a number of studies that relate the administration of high doses of caffeine during embryonic development in animal models with teratogenic effects (Tye et al. 1993; Sahir et al. 2000; Momoi et al. 2008; Li et al. 2012; Ma et al. 2012, 2014; Tan et al. 2012; Xu et al. 2012). In humans, epidemiological surveys have shown an increased risk of low birth weight (Momoi et al. 2008; Sengpiel et al. 2013), fetal growth restriction (Klebanoff et al. 2002; Bracken et al. 2003; Bakker et al. 2010) and miscarriage as caffeine intake increases. In some cases even the consumption of one cup of coffee (100 mg caffeine) per day increases the risk (Konje and Cade 2008; Weng et al. 2008; Bakker et al. 2010; Chen et al. 2014; Li et al. 2015; Rhee et al. 2015). However, The American College of Obstetricians and Gynecologists states that less than 200 mg per day of caffeine consumption does not appear to be a major contributing factor in miscarriage or preterm birth, whereas for fetal growth restriction it is undetermined (Counseling 2019). In addition, caffeine is used in the treatment of apnea of prematurity, which decreases the risks of patent ductus arteriosus, brain injury, retinopathy of prematurity (ROP), and postnatal steroid use (Abdel-Hady 2015; Kua and Lee 2017; Kumar and Lipshultz 2019). Nevertheless, the best therapeutic window, dose, and duration of therapy remain to be determined (Abdel-Hady 2015; Kumar and Lipshultz 2019).

Apnea of Prematurity and Caffeine

Clinical Aspects of the Apnea of Prematurity

An apneic episode is characterized by respiratory failure that lasts more than fifteen seconds and it is accompanied by hypoxia, bradycardia, cyanosis, or pallor. It is one of the most common diagnoses in the NICU and requests the attention of the medical community. Its occurrence is inversely proportional to gestational age, and it can be classified as central, obstructive, or mixed (Martin and Wilson 2012; Eichenwald 2016). The understanding of the pathogenesis of the apnea of prematurity has revealed central (e.g., decreased central chemosensitivity, hypoxic ventilatory depression) and peripheral (e.g., dysregulation of carotid body activity, excessive bradycardic response) mechanisms involved in these events and it has guided the search for therapeutic interventions not only to increase survival but also to avoid long-term consequences that may include neurodevelopmental disorders (Martin and Wilson 2012). Usually, these children request air supply to survive, and exposure to higher oxygen tension can lead to ROP. In premature children, the exposure to high oxygen tension, compared to in uterus conditions, inhibits retinal normal vessel growth, creating avascular/ischemic zones (Schmidt et al. 2007; Liegl et al. 2016; Hartnett 2017). As the newborn develops, tissue metabolic demand increases, triggering signaling pathways to promote neovascularization, and consequently, formation of disorganized and nonfunctional vessels. ROP is a leading cause of infant blindness worldwide (Gilbert 2008; Blencowe et al. 2013; Quimson 2015; Bashinsky 2017), and the treatment for the disease includes photocoagulation and use of VEGF inhibitors (Liegl et al. 2016).

Therapeutic Agents and Caffeine Function

The procedures to treat apnea include options, such as nasal continuous positive airway pressure (NCPAP), which reduces frequency and severity of apnea by decreasing the risk of obstructive apnea; blood transfusion in the attempt to reduce apnea by increasing respiratory drive, oxygen carrying capacity, and tissue oxygenation, a short-lived method linked to anemia occurrence; and the xanthine therapy, which is the standard method, normally by using caffeine citrate due to its longer half-life (Eichenwald 2016).

Xanthines exhibit respiratory effects as they improve ventilation and increase carbon dioxide sensitivity by blockade of adenosine receptors. Although caffeine had been used for thirty years, the first study evaluating the long-term efficacy and safety of caffeine therapy for apnea of prematurity was developed by Schmidt and colleagues and published in 2007 (Schmidt et al. 2007). Previously, this group has demonstrated that caffeine reduces the incidence of bronchopulmonary dysplasia (Schmidt et al. 2006). Then, Schmidt and co-authors (2007) have observed that, at eighteen to twenty-one months old, caffeine significantly enhances the rate of survival without developing neurological problems (Schmidt et al. 2007). They show a reduction in the severity of eye disease, cerebral palsy, and cognitive delay, as well as a better psychomotor development in the caffeine-treated group. The authors discuss that these results could be achieved because treatment with caffeine reduces important variables: time with respiratory support, the need of postnatal corticosteroids, the surgery to close a patent ductus arteriosus, and the rate of bronchopulmonary dysplasia. However, the strongest intermediate variable is the reduced time for any positive airway pressure, because it can compromise the lungs, which in turn can evolve into a bronchopulmonary dysplasia, a risk factor for the development of neurological issues (Schmidt et al. 2007). Therefore, caffeine levels higher than 7.9 mg/kg

body weight per day have been reported as being safe and effective in apnea of prematurity treatment in neonates born before 28 weeks of gestation (Francart et al. 2013).

Caffeine and Retinopathy of Prematurity

Caffeine treatment for infants with apnea of prematurity also reduces severity of ROP. As an ischemic retinopathy, adenosine is also released as a consequence of ischemia, and the role of the nucleoside has been investigated in animal models of ROP, described as oxygen-induced retinopathy (OIR). Genetic inactivation of A_{2A} or treatment with an antagonist of the receptor, KW6002, reduces vaso-obliteration induced by OIR and inhibits irregular retinal angiogenesis both in young and adult animals (Liu Xiao-Ling et al. 2010; Zhou et al. 2018). KO of A_1 receptor also has positive effects on vaso-obliteration in a OIR model, reducing normal vessel growth, even though it does not reduce neovascularization into the vitreous (Zhang et al. 2015). Zhang et al. (2017) have also evaluated the effect of caffeine (1 g/L) through nursing mothers, in OIR model (from P7–P12), during different time windows: P0–7 (pre-treatment), P0–17 (continuous treatment), P7–12 (hyperoxic phase), and P12–17 (hypoxic phase). Caffeine exposure reduces vaso-obliteration and creation of avascular zones when treatment occurs during the entire period, or even restricted to hyperoxic phase. Furthermore, neovascularization is reduced by treating during any time window except for pre-treatment. Importantly, caffeine treatment does not interfere in normal postnatal vascular development (Zhang et al. 2017). Further analyzes show that the effect of caffeine (the decrease of avascular zones) at P12 is totally dependent on A_{2A}, while the effect on avascular zones and neovascularization at P17 is only partially correlated to the receptor. In accordance, caffeine (10 mg/kg i.p.), as a single application 15 min before protocol of hyperoxia (80% oxygen) for 24 or 48 h, reduces oxidative stress markers, like lipid peroxidation, heme oxygenase-1 (HO-1), and H_2O_2 formation, and reduces gene expression of Nrf2, glutamate-cysteine ligase and increases gene expression of SOD3 in brain homogenates (Endesfelder et al. 2017). Additionally, the authors observe reduction of inflammatory markers such as iNOS, IL-1β, TNF-1α, and interferon gamma, a reduction of apoptotic mediators, like nuclear poly (ADP ribose) polymerase 1 (PARP-1), apoptosis inducing factor (AIF) and caspase-3, and a reduction of the matrix metalloproteinase 2 activity, which could contribute to neurotoxicity and inflammation. Caffeine citrate (20 mg/kg i.p. at P0 and maintenance doses of 5 mg/kg/day from P1–13) and ketorolac (COX inhibitor; topical ocular administration once a day from P5–7) reduce severe OIR performed from P0–14 and analyzed at P14, or 7 days later (enabling recovery) (Aranda et al. 2016). Therefore, the data obtained by animal model studies corroborate the idea of caffeine as a good therapeutic tool to reduce retinal damage in ROP. Most recently, it was shown that treatment with caffeine (30 mg/kg, single in ovo injection, 48 h before ischemia) protects chick embryo retinal cells in an ex vivo model of acute ischemia (OGD). The protective effect is dependent on CREB phosphorylation and BDNF signaling. Such effect could be mimicked by DPCPX, an antagonist of adenosine A_1 receptors, indicating the presumably mechanism of action for caffeine (Pereira-Figueiredo et al. 2020). It is important to note that other pharmacological interventions have also been investigated as potential treatment for ROP, such as Omega-3 fatty acid, insulin-like growth factor 1 inducers, vitamin A, cyclooxygenase inhibitors, inositol, and propranolol (Beharry et al. 2016; Aranda et al. 2019).

Caffeine in the Immature Ischemic Brain

Caffeine Dose and Neuroprotection

Studies in animal models have also been positively correlating low–moderate doses of caffeine treatment with cell survival in the immature brain, exposed to ischemic events in different developmental windows. A protective effect for caffeine is achieved in a close time window, at least less than 6 h, after ischemia. Interestingly, even a single injection of caffeine (5 mg/kg i.p.), directly after HI, also reduces infarct zone and cerebral atrophy in rats submitted to ischemia at P10 and analyzed at P24 (Winerdal et al. 2017). Cognitive function also seems to be affected by a single dose of caffeine (10 mg/kg i.p.) after induction of ischemia at P7, and evaluated months later, as a better performance was observed in Morris water maze at P90–95 rats (Alexander et al. 2013). Treatment of P7 rats with caffeine citrate (20 mg/kg/day i.p) just before ischemia, and during the following 3 days, reduces TUNEL staining in hippocampus and parietal cortex analyzed at P11 (Kilicdag et al. 2014). Using a similar protocol of treatment, caffeine citrate (20 mg/kg i.p.), given just after ischemia and 24 h later, also restores standard behavior, besides cortical and hippocampal volume, in adult rats submitted to ischemia at P6 (Potter et al. 2018). Recently, Di Martino and colleagues have shown that a single dose of caffeine (5 mg/kg i.p.) right after HI in rats at P10 reduces global damage score, apoptotic cell number, microglial activation, and inflammatory gene expression. The protection did not occur if caffeine was administered at 6, 12, or 24 h after HI (Di Martino et al. 2020). Therefore, the available data from animal models indicate a protective role for low–moderate doses of

caffeine when administered in a close time window, at least less than 6 h after ischemia.

Beneficial outcomes with caffeine treatment in the drinking water of dams are also observed. Low dose of caffeine (0.3 g/L in the drinking water of the dams), from P0 to P21, reduces brain damage induced by HI performed at P7, and evaluated by brain weight at P21 (Bona et al. 1995). On the other hand, a high dose of caffeine (0.8 g/L) has no protective effect (Bona et al. 1995).

White Matter Brain Injury

Few studies explore the caffeine protective effects in the white matter of the ischemic immature brain. Caffeine exposure (0.3 g/L in drinking water through the dam) as soon as P2–P12 reduces periventricular white matter injury (PWMI) induced by chronic hypoxia (P3–P12) (Back et al. 2006). PWMI is known to affect very low birth weight infants, and it is the leading cause of neurological disability in survivors of prematurity (Volpe 2003; Ferriero 2004). Accordingly, treatment of P7 rats with caffeine citrate (20 mg/kg/day i.p) just before ischemia, and during the following 3 days, decreases white matter damage in subcortical regions (Fa-Lin et al. 2015).

Effect of Caffeine in the Adult Brain and Retina in Ischemic Conditions

Brain Ischemia and Role of Caffeine

The preventive/therapeutic potential of caffeine for ischemia has also been investigated in CNS of adult animals. It has been reported a correlation between coffee consumption and lower risks of stroke (Lopez-Garcia et al. 2009; Larsson et al. 2011; Kim et al. 2012; Liebeskind et al. 2016). The correlation is not direct to caffeine, and the potential of other coffee compounds cannot be ruled out (Cossenza 2018). Even though, evidence using adult animal models corroborates the idea that the main chemical agent involved in this protection is caffeine. Exposure to caffeine in water (0.2%) for 4 weeks before a 5-min bilateral occlusion in adult gerbils, evaluating 7 days after ischemia, reduces loss of pyramidal cells in the CA1 region of the hippocampus (Rudolphi et al. 1989). Resonance images and histopathological analysis of adult rodents reveal differences between chronic (three times a day by gavage, 20 mg/kg per dose for the first week, and 30 mg/kg per dose in the third week, last dose at 24 h before ischemia) and acute (10 mg/kg i.v. 30 min before ischemia) effects of caffeine on ischemic neuronal injury of rats subjected to forebrain ischemia. While chronic treatment reduces neuronal injury, acute treatment has no effect (Sutherland et al. 1991).

Caffeine Effect in Ischemic Retinopathies

Interesting data concerning ischemia in the mature retina are also reported. Recently, the effect of caffeine (100 μM) was evaluated in an in vitro model of diabetic macular edema, the major cause of vision loss in diabetic retinopathy. The xanthine reduces permeability, induced by hyperglycemia/hypoxia, in monolayer culture of human retinal pigment epithelial cells (ARPE-19) by restoring tight junctions and reducing apoptotic rates (Maugeri et al. 2017). Treatment with caffeine in drinking water (1 g/L) for 2 weeks, before the ischemia induction until the end of the experiment, reduces apoptotic levels and pro-inflammatory cytokines when analyzed 7 days after the transient IOP raise, even though exacerbates 48 h after IOP (Boia et al. 2017). Using photocoagulation of trabecular meshwork of limbal veins to produce ocular hypertension (OTH), to mimic glaucoma symptoms, the same group, using the same treatment protocol, shows that caffeine could diminish inflammation and ganglion cell loss 7 days, but not 3 days, after OTH (Madeira et al. 2016b). In humans, a 20-year follow-up involving 121.172 people found no association between caffeinated coffee consumption and the risk of developing primary open-angle glaucoma (POAG). However, for those with family history of glaucoma and high IOP, the association seems to exist, as coffee drinkers show higher chances of developing the pathology (Kang et al. 2008). But, the risk may not be due to caffeine's effects on IOP, since ocular application of the compound does not contribute to elevate IOP in a small five patients study with POAG/OTH (Chandra et al. 2011). However, it does show an acute IOP-elevating effect in a study with seventeen healthy patients (Redondo et al. 2020). It seems that this acute effect is dependent on the level of routine consumption, being more expressive in low caffeine consumers as demonstrated in a study involving forty patients (Vera et al. 2019). The positive association of caffeinated coffee consumption and risk of exfoliation glaucoma or exfoliation glaucoma suspect, compared to abstainers, is also reported in another follow-up involving more than 120.000 people for more than twenty years (Pasquale et al. 2012), as for higher IOP in coffee consumers with open-angle glaucoma in a smaller study involving 3654 patients (Chandrasekaran et al. 2005).

Concluding Remarks

Ischemia provokes cell death in developing and mature CNS, promoting neurological disabilities and ophthalmological deficits. The neural damage occurs as a consequence of energy deficit and ionic imbalance, which leads

to excitotoxicity, oxidative stress, and inflammation. Several studies have been investigating the protective potential of adenosine receptors since the concentration of adenosine increases soon after the ischemic event. Taken together, the data from adult CNS indicate that adenosine release during ischemia is protective mainly via activation of A_1 receptors. Even the upregulation of A_1 receptors, previous to an ischemic event, reduces the tissue damage, possibly by increasing the availability of receptors to be activated by released adenosine during ischemia (Rudolphi et al. 1989; Von Lubitz et al. 1994a). The main protective mechanism mediated by A_1 receptor seems to be the inhibition of neurotransmitter release, especially glutamate, attenuating the ischemia-induced excitotoxicity. A few studies focus on the signaling pathways involved in the beneficial role of A_1 receptors. The stimulation of A_1 receptors reduces oxidative stress, TNFα production, and increases phosphorylation of ERK and GSK3β (Fig. 4).

There is a substantial amount of data indicating that A_{2A} receptor inhibition is also protective in ischemic CNS. The absence of A_{2A} (KO) in adults renders a greater resistance against ischemia-provoked cell death (Chen et al. 1999; Gui et al. 2009). The main protective mechanism provided by the inhibition of A_{2A} receptors seems to be the modulation of synaptic transmission. In addition, it has been described that the blockade of A_{2A} receptors also promotes the modulation of glutamate availability by astrocytes, the control of inflammatory signals in microglia, as well as the maintenance of myelin organization, empowering the protective outcome (Fig. 4). The protection could also involve endothelial cells since the absence of A_{2A} receptors in these cells renders several protective changes in the context of ischemia (Zhou et al. 2019). A few studies have focused on the signaling pathways that support this beneficial role. Moreover, the inhibition of A_{2A} receptors diminishes p-ERK, NFκB, TNF-α, IL-6, iNOS, caspase-3, Cyt C, p-JNK, p-p38, p-CREB,

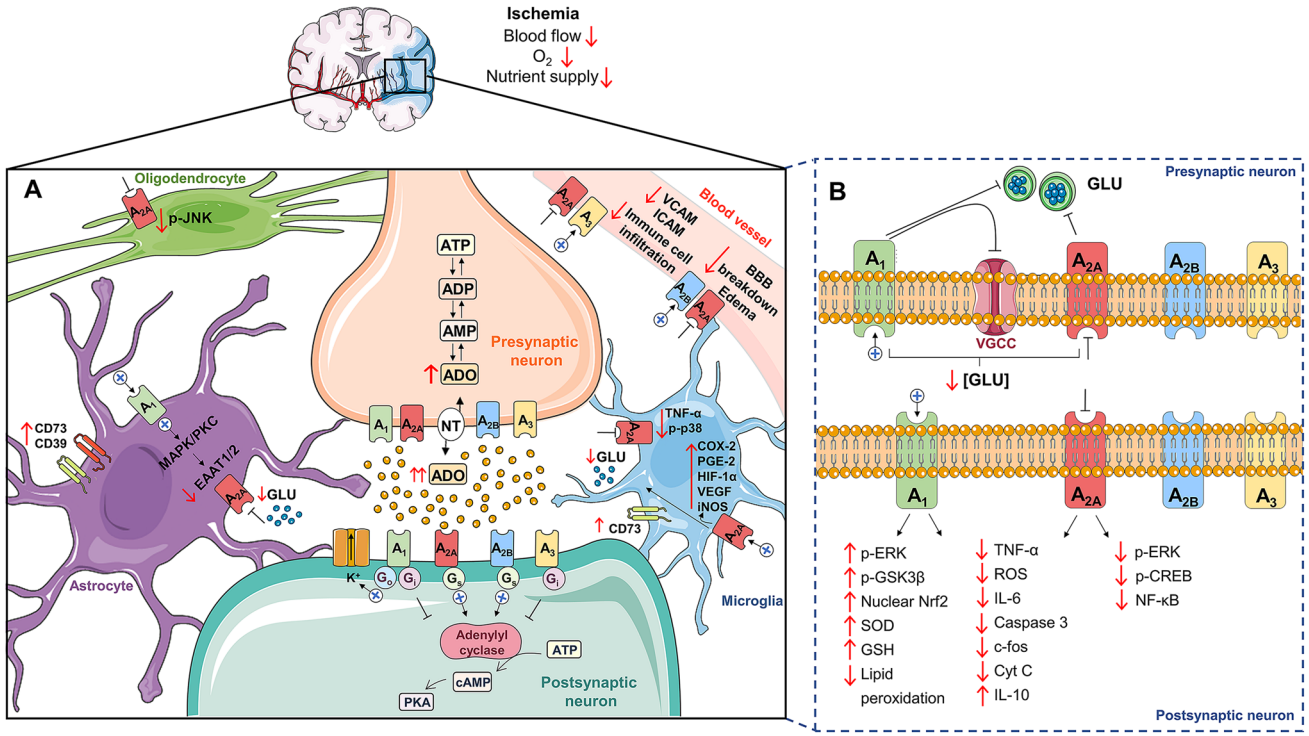

Fig. 4 Effects of adenosine receptor modulation in ischemic events. **a** The increase of extracellular adenosine availability during ischemia allows the activation of all adenosine receptors in different cell types. In astrocytes, stimulation (positive symbol, +) of A_1 receptors (green), or inhibition (—┤) of A_{2A} receptors (red), reduces EAAT1/2 exacerbating the augment in extracellular glutamate and contributing to excitotoxicity. Astrocytes and microglia experience an increase in CD39 and CD73 content in ischemic events. In the case of A_1 receptors, the regulation of EAATs occurs through MAPK/PKC pathway. The activation of microglial A_{2A} receptors induces intracellular pathways related to an inflammatory response. Furthermore, in endothelial cells, A_{2B} (purple) and A_3 (yellow) receptors stimulation, or A_{2A} receptor inhibition, reduces VCAM/ICAM content, immune cells infiltration, BBB breakdown, and edema. The inhibition of A_{2A} receptors in oligodendrocyte and microglia cells reduces, respectively, p-JNK and p-p38 as well as TNF-α. Canonical pathway is represented in postsynaptic neuron. The right panel depicts the pre- and postsynaptic terminals and the effect of adenosine receptors agonists or antagonists during ischemia. **b** The activation of presynaptic A_1 receptors decreases glutamate release through a direct mechanism or through the inhibition of voltage-gated Ca^{2+} channels (VGCC). Antagonists of A_{2A} presynaptic receptors also inhibit glutamate release. In the postsynaptic neurons, A_1 agonism or A_{2A} antagonism triggers multiple intracellular pathways promoting antioxidant and anti-inflammatory responses, decreasing oxidative stress and cell death

c-fos, and ROS, all increased by ischemia/reperfusion (Fig. 4). Finally, it seems that the effect can also depend on the CNS area since activation of A_{2A} can reduce damage induced by ischemia specifically in the spinal cord and cortex (Reece et al. 2006; Melani et al. 2014a).

Although there are fewer data concerning A_{2B} and A_3 receptors effect, the stimulation of these scarce receptors has been associated with a protective outcome acting on different types of cells, endothelial, microglia, and neurons (Fig. 4). Nonetheless, in vivo intervention with A_3 receptor agonists could be challenging due to a hypotensive response.

It is relevant to highlight that most of the studies using selective pharmacological tools to modulate adenosine system in ischemia were performed in adult animals. A few available data from adenosine role in the immature context points to a different protective mechanism from adults. For instance, the absence of A_1 receptors (KO) can prevent hypoxia-induced ventriculomegaly, a distinctive trace of periventricular leukomalacia, commonly associated with brain damage in premature infants (Turner et al. 2003); treatment with adenosine A_1 agonist, after HI, does not feature neuroprotective results (Åden et al. 2001); and A_{2A} KO aggravates neuronal damage in immature brain after HI (Åden et al. 2003). What is the source for this different response? The signaling underlying cell survival, in developing or mature neurons, can differ in crucial aspects, especially involving calcium transients and NMDA receptor activity (Cunha 2005). These differences probably account for the existence of some conflicting data about the role of adenosine receptors in brain ischemia. In addition, some studies show that the coupling to G protein/intracellular pathways of A_{2A} receptors may change during development. Socodato and colleagues have shown that A_{2A} receptor activation leads to cell death through coupling to PLC-protein kinase C in a narrow window of an early period of retinal development (Socodato et al. 2011). Although A_1 receptor expression/content is upregulated by A_{2A} receptor (Pereira et al. 2010; Brito et al. 2012), which could explain the findings, the study discards this possibility by showing that A_1 receptor blockade has no effect. Therefore, the mechanisms involved in the different resistance to ischemia from immature to mature brain still represents a field to be explored.

Considering that the main molecular targets of caffeine, at least in a non-toxic dose, are A_1 and A_{2A} receptors, together with the great amount of data correlating the adenosine system with neuroprotection, many studies have been investigating the potential of caffeine to alleviate ischemic damage. Since caffeine has been used in the apnea of prematurity for more than thirty years, due to its bronchodilator effect, the majority of studies have explored the outcome in the immature CNS. A considerable number of studies show that low–moderate doses of caffeine attenuate the ischemia-induced injury in immature CNS, indicating that the inhibition of A_{2A} receptor could be more efficient to save CNS cells than stimulation of $A_1/A_{2B}/A_3$ receptors by released adenosine or selective agonists. It is not well established the reason why the blockade of A_{2A} prevails when compared to activation of A_1 receptor by adenosine released during ischemia. It probably involves different neurochemical aspects, such as adenosine/caffeine metabolization, strict control of extracellular adenosine availability, control of A_1 by A_{2A} receptor in heterodimers, and upregulation/downregulation after treatment, among others. Besides that, due to the activity of A_{2A} receptors in different cell types during ischemia, caffeine could target not only neurons but almost every other CNS cell type (endothelial, microglial, astrocytes, and oligodendrocytes), perhaps resulting in a stronger prosurvival outcome (Fig. 4). Despite all that, the therapeutic time window of caffeine administration seems to be narrow and close to the ischemic event. Accordingly, a single exposure to caffeine soon after ischemia reduces infarct area and ameliorates cognitive function evaluated later in the adult.

The data from mature retina studies indicate that pretreatment with A_1 agonist or post-treatment with A_{2A} antagonists reduces the damage provoked by ischemia. Using animal models of glaucoma, caffeine exposure, before ischemia and for additional two weeks, decreases ischemic injury. However, caffeine treatment in a later period can worsen ischemic deterioration. The analysis of the possible correlation of human consumption and glaucoma in studies that include a higher number of subjects, evaluating longer periods, show positive correlation of coffee drinkers with the (a) chance to develop the pathology in those with family history of glaucoma and high intraocular pressure; (b) higher intraocular pressure in open-angle glaucoma patients; and (c) risk of exfoliation glaucoma, even though no association of coffee consumption with the risk of developing POAG was found.

Finally, in the mature brain, there are only two studies with animal models demonstrating that chronic, but not acute, caffeine treatment reduces the damage promoted by ischemia (Rudolphi et al. 1989; Sutherland et al. 1991). More intriguingly, one of these studies suggests that the effect depends on the upregulation of A_1 receptor, even though it was not tested (Rudolphi et al. 1989). Thus, despite the great number of studies in immature CNS, it is still unclear whether caffeine protects the mature brain from ischemia and the gap of information is even wider concerning the signaling pathways involved. Even in the immature CNS, the cellular mechanisms involved in the protective role of caffeine have not been largely explored. Although different experimental paradigms strengthen the neuroprotective role of caffeine in the context of CNS ischemia, further studies are still required to successfully translate the current knowledge to human therapies.

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Declarations

Conflict of interest All authors declare that they have no conflict of interests.

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