Oxidative Stress and Regeneration

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Abbreviations

ACM – astrocyte-conditioned medium ; AD – Alzheimer's disease; AHPs – adult hippocampal progenitor cells; APOE – apolipoprotein E; ATP – adenosine triphosphate; Aβ – amyloid-β; BBB – blood-brain barrier; BDNF – brain-derived neurotrophic factor; C4ST – chondroitin 4-O-sulfotransferases; C6ST – chondroitin 6-O-sulfotransferases; CIRI – cerebral ischemia/reperfusion injury; CNS – Central nervous system; CS-GAG – chondroitin sulfate glycosaminoglycan; CSPG – chondroitin sulfate proteoglycans; Cys – cysteine; ECM – extracellular matrix; ERK1/2 – extracellular signal-regulated protein kinase; GABA – γ-aminobutyric acid; GFAP – glial fibrillary acidic protein; GPXs – glutathione peroxidases; GSH – glutathione; 4-HNE – 4-hydroxynonenal; IL-1β – interleukin-1beta; IL-6 – interleukin-6; iNOS – Inducible NOS; iPSCs – induction of pluripotent stem cells; JNK – c-jun N-terminal kinase; KEAP1 – Kelch-like ECH-associated protein 1; MAPK – mitogen-activated protein kinase; MCAO – middle cerebral artery occlusion; MCAOR – middle cerebral artery occlusion and reperfusion; mTOR – mammalian target of rapamycin; NADPH – nicotinamide adenine dinucleotide phosphate; NF-κB – nuclear factor-κB; NGF – nerve growth factor; NICD – Notch intracellular domain; NLRP3 – NOD-like receptor P3; NMDA – N-methyl-d-aspartate; nNOS – neuronal nitric oxide synthetase; NO – nitric oxide; NOX – NADPH oxidases; NPC – neuronal stem/progenitor cells; NRF2 – nuclear factor erythroid 2 (NF-E2)-related factor 2; NSPC – Neural stem/progenitor cells; Parp3 – Poly(ADP-ribose polymerase-3; PI3K – phosphatidylinositol 3-kinase; PN – perineuronal nets; PPARδ – peroxisome proliferator-activated receptor δ; PTEN – phosphatase and tensin homolog; ROCK – Rho-kinase; ROS – reactive oxygen species; SOD – Superoxide dismutase; SPARC – cysteine-rich acid secreted protein; TBI – traumatic brain/spinal cord injury; TGFβ – transforming growth factor β; TNFα – tumor necrosis factor alpha; TSP – Thrombospondin

Highlights

- Oxidative stress can have both negative and beneficial effects in regeneration
- The effects of oxidative stress in neuroregeneration are not well understood
- 4-HNE is pathogenic factor of neurodegeneration and traumatic brain damage
- 4-HNE may also positive effects, which have yet to be revealed

Abstract

Regeneration is the process of replacing/restoring a damaged cell/tissue/organ to its full function and is limited respecting complexity of specific organ structures and the level of differentiation of the cells. Unlike physiological cell turnover, this tissue replacement form is activated upon pathological stimuli such as injury and/or disease that usually involves inflammatory response. To which extent will tissue repair itself depends on many factors and involves different mechanisms. Oxidative stress is one of them, either acute, as in case of traumatic brin injury or chronic, as in case of neurodegeneration, oxidative stress within brain involves lipid peroxidation, which generates reactive aldehydes, such as 4-hydroxynonenal (4-HNE). While 4-HNE is certainly neurotoxic and causes disruption of the blood brain barrier in case of severe injuries, it is also physiologically produced by glial cells, especially astrocytes, but its physiological roles within CNS are not understood. Because 4-HNE can regulate the response of the other cells in the body to stress, enhance their antioxidant capacities, proliferation and differentiation, we could assume that it may also have some beneficial role for neuroregeneration. Therefore, future studies on the relevance of 4-HNE for the interaction between neuronal cells, notably stem cells and reactive astrocytes might reveal novel options to better monitor and treat consequences or brain injuries, neurodegeneration and regeneration.

Keywords: oxidative stress; neuroregeneration; traumatic brain injury; insult; 4-hydroxynonenal; penumbra; astrocytes; neuronal stem cells; redox signaling; neurodegeneration

1. Introduction

During lifetime human body constantly replaces older cells with new ones to preserve tissue homeostasis. It is estimated that the rate is about 4 million cells/s, and almost 90% of them are bone marrow-originated blood cells [1]. This turnover of cells is highly cell/tissue-specific and depends mostly on adult stem cells and the age of person. Similarly, regeneration also requires adult stem cells to restore full tissue function. Unlike physiological cell turnover, this tissue replacement form is activated upon pathological stimuli such as injury and/or disease that usually involves inflammatory response [2]. Not all tissues will completely regenerate, if not scar formation (fibrosis) with diminished tissue function occurs instead. To which extent will tissue repair itself depends on many factors and involves different mechanisms. Oxidative stress is one of them, and its role in the context of regeneration, focusing on neuroregeneration, will be further overviewed herein.

2. Oxidative stress and redox signaling

Oxidative stress commonly implies an imbalance between prooxidants and antioxidants in favor of the former, while updated definition describes it also as an imbalance in a redox steady-state [3]. The advancement of more sophisticated analytical techniques, together with multidisciplinary research models and scientific approaches have shifted our perception of oxidative stress from only detrimental to a more complex one, distinguishing oxidative distress (bad stress) from oxidative eustress (good stress) [4]. Overwhelming accumulation of reactive oxygen species (ROS) leading to diverse disorders represents distress, while levels of ROS necessary for physiological redox signaling important for proper cellular/tissue/organism functioning represent eustress [4]. Superoxide anions, hydrogen peroxide and hydroxyl radicals are the most common representatives of ROS, but there are others also. Both, intracellular and extracellular sources contribute to the generation of ROS. Intracellular sources include NADPH (nicotinamide adenine dinucleotide phosphate) oxidases (NOX), mitochondria, cytochrome P450, endoplasmic reticulum, lysosomes, peroxisomes, and others, while extracellular sources are ionizing radiation, ultraviolet light, and xenobiotics [5,6].

Redox signaling involves reversible oxidation or adduct formation of specific cysteine (Cys) residue(s) on a target protein. In the context of redox signaling, ROS might be perceived as tools that a cell produces upon a certain cue, because of their signaling ability to transfer a received message in a cell-fate decision within the cell or in the neighboring ones [6]. Therefore, ROS are involved in defining whether a cell will proliferate or differentiate, will it activate autophagy or apoptosis. These regulatory roles of ROS are intertwined with the metabolism and antioxidative mechanisms in dependence to the ROS produced and the proximity of their targets thus being highly cell/tissue-specific. Due to its relative stability and the ability to pass biomembranes through pore-forming channels called peroxiporins [7], hydrogen peroxide is considered as main redox signaling molecule. Its main route of formation includes NOXs and mitochondria, depending upon metabolic demands [8]. Another ROS, produced by mitochondria and NOX, important in redox signaling is superoxide anion, which has more limited signaling abilities in comparison to hydrogen peroxide. This fine-tuning of ROS levels is balanced with the cellular antioxidant mechanisms. Superoxide dismutases (SODs) are the main enzymes catalyzing the conversion of superoxide anion to hydrogen peroxide, while catalase and glutathione peroxidases (GPXs) further reduce hydrogen peroxide to water. Coupled oxidation of

glutathione (GSH) to glutathione disulfide is required for the GPX conversion [9]. The presence of iron or copper leads to the conversion of hydrogen peroxide to hydroxyl radical, which is recognized as the most reactive and damaging ROS with no known signaling ability. Only recently, Prasad and colleagues have suggested the importance of hydroxyl radical in the differentiation of a pro-monocytic cell line U937. However, they did not offer the underlining mechanism nor could they exclude that other ROS formed upon phorbol 12-myristate 13-acetate treatment are responsible or are accompanying to the observed effect [10].

ROS possess diverse signaling abilities modulating a broad range of transcriptional factors and proteins, such as Kelch-like ECH-associated protein 1 (KEAP1), hypoxia-inducible factor, AMP-activated protein kinase, nuclear factor-κB (NF-κB), and others (see [11,12]) thus affecting a broad range of signaling pathways involved in the metabolic response, inflammatory response, DNA repair, growth promotion or differentiation, apoptosis, autophagy. The main pathway responsible for modulating ROS levels is nuclear factor erythroid 2 (NF-E2)-related factor 2 (NRF2)/KEAP1 signaling pathway. By modifying the specific Cys residues on KEAP1, ROS alter its repression of NRF2 and subsequent proteasomal degradation, leading to NRF2 translocation to the nucleus and its transcriptional activation of numerous cytoprotective and metabolic genes [13]. Not only ROS, mainly hydrogen peroxide, but other molecules contribute to redox signaling as well. Such an example are peroxiredoxins, thioredoxins, and glutaredoxins that were previously perceived just as antioxidants [14], and major bioactive product of polyunsaturated fatty acids peroxidation, the reactive aldehyde 4-hydroxy-2-nonenal (4-HNE)[15].

The term oxidative stress is often associated not only with ROS but also with its secondary messengers such as 4-HNE and other reactive aldehydes that are occurring during lipid peroxidation [16]. 4-HNE is the most studied of them, due to its numerous biological activities and high biomedical relevance. It is the α,β-unsaturated aldehyde derived from ω-6 polyunsaturated fatty acids, mainly arachidonic acid and linoleic acid. Its three functional groups, C1 carbonyl group, C2 = C3 double bond, and C4 hydroxyl group, are making 4-HNE highly potent electrophile, prone to interact with diverse proteins, lipids, and nucleic acids [17,18]. Current research recognizes its growth modulating abilities [19] and its involvement in diverse stress-associated disorders [20] such as neurodegenerative disorders and diseases [21] [22], atherosclerosis [23], different types of cancer [24] including brain tumors [25]. Thus, 4-HNE is also considered a bioactive marker of various pathophysiological processes [26]. It regulates cellular processes ranging from cell proliferation to cell death in a concentration- and cell/tissue-dependent manner by affecting different signaling pathways such as NRF2/KEAP1, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), NF-κB, transforming growth factor β (TGFβ) signaling and others [17,27–29]. For example, 4-HNE binds to KEAP1 thus initiating NRF2 dissociation from its repressor, leading to its translocation to the nucleus and subsequent antioxidant transcriptional expression of glutathione S-transferase A4, aldoketone reductase 1C1, and heme oxygenase-1 [17,30]. 4-HNE can also induce senescence by activating peroxisome proliferator-activated receptor δ (PPARδ) in a thioredoxin-interacting protein-dependent manner [31].

2.1. Oxidative stress and central nervous system (CNS)

The central nervous system (CNS), in particular brain, needs a lot of energy (in a form of adenosine triphosphate (ATP)) and oxygen for its function, thus being dependent on redox signaling.

Yet, it also contains high levels of iron and polyunsaturated fatty acids, lower antioxidative protection what makes it highly susceptible to oxidative damage when the redox balance is disrupted [32].

A tight connection between metabolism, ROS induction and normal brain function implies ROS signaling influences on neuronal development, regulation of its functional polarization, connectivity, and plasticity [33–35]. For example, in the immature hippocampus, the ATP-induced ROS from astrocytes control γ-aminobutyric acid (GABA) release toward CA3 principal cells thus providing proper wiring of the hippocampal network [36]. Both NOX and mitochondria are important sources for ROS signaling. NOX-generated ROS regulates stemness and proliferation of neural progenitor cells (specifically NOX2) through PI3K/AKT signaling [37] and axonal pathfinding and regeneration through the modulation of the Hedgehog pathway [38], while knocking out NOX2 leads to reduced neurogenesis [39]. Astrocytes not only control neuronal metabolism but also, through induction of mitochondrial ROS, oversee redox balance in neurons [40]. Yet, disturbances in the balancing of ROS levels could lead to diverse unfavorable CNS disorders. In a majority of cases, it is difficult to assess whether ROS are causative factors or merely a consequence of pathological changes. In a case of sporadic Alzheimer's disease (AD), Birnbaum and colleagues have shown that increased ROS levels, due to the aberrant mitochondrial function, are integral pathogenic component in the early stages of the disease development, preceding the appearance of amyloid β and tau protein (characteristic markers of the AD) [41].

Lipid peroxidation in the brain is mostly related to ferroptosis (an iron and lipid peroxidation-dependent cell death) [32] leading to neurodegenerative diseases. For example, NOX4 was shown that, by promoting oxidative stress, induces generation of the lipid peroxidation end-products, 4-HNE and malondialdehyde, eventually regulating the ferroptosis-dependent cytotoxicity of astrocytes in AD. The increase of NOX4 is accompanied by impairment of mitochondrial metabolism [42]. Therefore, lipid peroxidation and its end-products, such as 4-HNE, are mainly perceived as contributors to the development of diverse pathologies, such as AD and Parkinson's disease (reviewed in [20]), while its possible physiological roles for the CNS are currently not known. As mentioned, 4-HNE affects cellular processes from proliferation to cell death in a concentration-dependent and a cell/tissue-specific manner, therefore it might play important roles also for the CNS, which should be explored. It regulates transcriptional factors, such as NRF2, activating protein-1 (AP-1), NF-κB, and PPAR, and activates stress-response signaling pathways as well [43]. By regulating NRF2 activation, 4-HNE can also modulate the ROS levels in a feedback loop.

Whether lipid peroxidation has a beneficial physiological role in CNS, or is it mainly activated as a mechanism of oxidative stress related to cell death and neurodegeneration still needs to be elucidated. Possible involvement of 4-HNE in physiology and neuroregeneration is not certain. One may ask if any specific end-product of lipid peroxidation could be generated depending upon certain physiological needs, if yes, which one and what might be the underlying mechanism(s)? Supporting their hypothetic physiological role, lipid peroxidation and hydrogen peroxide signaling were recently revealed as important regulators of the retina development and in maintaining homeostasis of the mature retina in a zebrafish model [44]. The 9-hydroxystearic acid was shown to be involved in this hydrogen peroxide downstream fine-tuning of neuronal differentiation. The mechanism involves the inhibition of the histone deacetylase 1 and the activation of the Notch and Wnt pathways. 4-HNE was also shown to be involved in this fine regulation [44], which is important for synaptogenesis during the development of CNS and for neuronal function in the mature brain as a pathway through which astrocytes could regulate adult neurogenesis. The Wnt/β-catenin signaling pathway depends on the

cytoplasmic level of free β-catenin. In vitro adult hippocampal progenitor cells (AHPs) were stimulated by Wnt/β to differentiate into neurons [45]. The astrocytes of adult human hippocampus express Wnt-3, while for cocultures of AHPs with astrocytes neuronal differentiation could be reduced by Wnt inhibitors [46]. Opposite to that, pro-neuronal genes Nurr-1, Pitx-3, Ngn-2 and NeuroD1 were found to enhance neurogenesis through Wnt/β signaling pathway [45], while age-dependent decline of Wnt3/3a protein in rat astrocytes is accompanied by decrease in proneuronal gene Neuro D1 [47]. In cell cultures derived from ischemic murine brain inhibition of Wnt pathway resulted in redistribution of K+ and Na+ channels and increase of immunoreactive cells to Doublecortin, glial fibrillary acidic protein (GFAP) and proliferating cell nuclear antigen [48,49]. The Wnt-1 levels increased in penumbra over 1-6 hours in middle cerebral artery occlusion (MCAO) rat model, and β-catenin levels increased in endothelial cells within 3 hours [50,51]. Notch is the major signaling pathway, acting through four transmembrane receptors in regulation of proliferation and differentiation of CNS and has important role in promoting reactive astrocyte functions in brain injury. Jagged-2 and Delta1-4 are cell surface proteins which activate Notch receptor promoting proteolytic cleavage by γ-secretase of the Notch intracellular domain (NICD) [52,53]. Reactive astrocyte around infarct area expresses NICD-1, but inhibition of Notch signaling after administration inhibitors of γ-secretase decrease number of proliferating astrocyte [54].

3. Regeneration

Regenerative capacity and the onset of regeneration varies among different species, being in negative relation to the degree of evolution of the species. Hence, hydra can regenerate a whole organism from just a tiny body piece [53], amphibia and some reptiles can regenerate tails and/or limbs, while regenerative capabilities of humans are highly restricted and decline with age [54]. Regeneration is the process of replacing/restoring a damaged cell/tissue/organ to its full function and is limited respecting complexity of its structures and the level of differentiation of the cells. Therefore, not every tissue will heal completely. The majority will form a scar, sometimes with compromised tissue/organ function.

There are several overlapping processes involved in tissue healing, including hemostasis, inflammation, proliferative phase that potentiates repair and remodeling phase. Adult stem/progenitor cells are important in this process. Their contribution in maintaining normal tissue homeostasis does not instantly replicate their regenerative capabilities. For example, peripheral nerves, although being more quiescent than CNS, are highly regenerative in comparison to CNS due to inducing dedifferentiation/redifferentiation processes with no need for an additional stem cell population [57]. ROS are regulating diverse signaling pathways important in the maintenance of adult stem cells, induction of pluripotent stem cells (iPSCs), and tissue regeneration [58].

While iPSCs are considered as promising approach in tissue healing and regeneration, such as in preventing cognitive dysfunction in post-traumatic stress disorder [59], sometimes tissue defects/damages are too great demanding use of advanced biomaterials to assist the healing process. Although they are biocompatible, meaning they do no induce host response, during healing both cells and biomaterials produce ROS as their route of communication [60]. Thus ROS and 4-HNE were shown to be activated as a growth-promoting signal in osteoblast-like cells in bioactive glasses skeletal-defect therapy [6,61,62], while 4-HNE also induced neuronal outgrowth on carbon nanotubes [63].

4. Neuroregeneration after CNS injury

Acute CNS injuries include traumatic brain/spinal cord injury (TBI) and stroke. TBI may be classified as: 1. primary or immediate injuries caused by direct physical injury at the time of trauma, and 2. secondary injuries as an indirect result of an insult. A common feature of ischemic stroke, that accounts for 87% of strokes [64], is cerebral ischemia/reperfusion injury (CIRI). CIRI is accompanied by various processes, including blood-brain barrier (BBB) disruption, inflammation, mitochondrial dysfunction, oxidative stress and apoptosis.

4.1. Astrogliosis and oxidative stress – a hallmark of CNS lesions

Consequences of injury depend on severity, location and properties of injury. The CNS insults trigger multicellular responses, the three stage process, involving CNS intrinsic neural and non-neural cells as well as blood borne non-neuronal cells, such are leukocytes and other bone marrow-derived cells [65]. The first phase occurs immediately after CNS injury and is marked by the local parenchymal cell death, BBB leak, infiltration of leukocytes, inflammation and debris removal. During inflammation, activated leukocytes generate excessive amounts of ROS impairing redox balance and modulating cellular signaling pathways [20,66]. Both mild and severe CNS injury induce oxidative stress that promotes astrocyte adaptation preconditioning them to a subsequent stress [67]. Although ROS are needed for normal physiology of the brain including neurogenesis, the excessive ROS will have adverse effects [25]. High content of iron in the brain may further contribute to elevated ROS [68] and support ferroptosis after CNS injury [69]. The second phase of CNS injury includes cell proliferation and tissue replacement while tissue remodeling is part of the third phase [65]. The most abundant cell type in the mammalian CNS are astrocytes, that play critical roles in numerous physiological and pathological processes and are pivotal responders to CNS insult. Following an insult, individual astrocytes will have different responses and are thus classified to: i) static astrocytes that retain initial morphology, ii) astrocytes that become reactive and hypertrophy, ii) astrocytes that proliferate [70]. Astrogliosis, a hallmark of CNS lesions, is a defense mechanism in which tissue damage triggers polarization and activation of astrocytes. Depending on the severity of injury, reactive astrocytes release ROS, various pro-/anti-inflammatory cytokines, chemokines as well as intermediate filaments, such is GFAP [71]. Oxidative stress in the microenvironment upregulates GFAP expression and induces ROS generation by astrocytes [72]. In addition, excessive ROS promote neuronal death in part via N-methyl-d-aspartate (NMDA) receptor [73]. Namely, following CNS trauma, cAMP Response Element-Binding Protein activation is decreased while NMDA receptor activation is increased, thus impairing Ca^{2+} homeostasis via increased Ca^{2+} influx consequently leading to mitochondrial dysfunction and further ROS production [74]. We have recently demonstrated that mitochondrial ROS are responsible for neuronal excitability and that treatment with mitochondrial antioxidants was able to prevent Ca^{2+} overload and neuronal death [75]. Activation of NMDA receptors does not only affect the neurons where they are activated, but also by inducing activation of NOX2 it contributes to extracellular release of ROS and propagation of excitotoxic injury of neighboring neurons and astrocytes [76]. Sustained production of ROS/RNS in chronic astrogliosis will have detrimental effects on neurons [77]. Complementary to that peroxidation of lipids leads to excessive 4-HNE endogenously that mediates different neurotoxic effects [78]. The role of microenvironmental

oxidative stress on inflammatory response mediated by astrocytes, reactive astrogliosis and glial scar formation has been recently reviewed [77]. The extent of astrocyte reactivity ranges from mild to extent astrogliosis. Severe injuries are marked with pronounced proliferation and hypertrophy of astrocytes that ultimately lead to overlap of astrocytic domains and scar formation around the injury epicenter. This process where parenchyma is disrupted is irreversible leaving the scar tissue and the surrounding area dysfunctional [79,80]. On the contrary, consequences of mild astrogliosis may be reversed [80]. A recent study on transgenic animals using loss-of-function models to prevent astrocyte scar formation demonstrated that prevention of astrocytic scar formation results in the lack of spontaneous axonal regrowth after spinal cord injury and it does not lead to reduced chondroitin sulfate proteoglycans (CSPG) level after injury [81]. The CSPG's neuroprotective action against ROS in perineuronal nets will be described below. The same study also showed that targeted removal of scar formed after injury does not stimulate axonal regeneration, but rather affects tissue integrity, which is opposite to initial assumption that astrocyte scar formation may actually aid axonal regeneration. Still, the underlying mechanisms remain to be elucidated.

4.2. Astrocytes as regulators of brain redox homeostasis

Astrocytes are among the key regulators of redox balance in the brain, and alteration in redox level may impair their function. The master regulator of the cellular response to excessive ROS is Nrf2 [13], which was found to be 1600-fold more expressed in astrocytes if compared with neurons of an adult brain [82]. This huge difference in *Nrf2* is likely to be a consequence of developmental epigenetic *Nrf2* repression, as neuronal maturation dependent pathways are redox sensitive [83]. In the state of oxidative stress in order for neurons to cope with elevated ROS, astrocytes ensure the "GSH building blocks" for neurons. Hence, in response to H_2O_2, the astrocytic multidrug resistance protein 1 mediates export of GSH to extracellular space [84] where it is cleaved to CysGly by gamma glutamyl transpeptidase that serves as precursor for neuronal GSH synthesis. Neuronal aminopeptidase N hydrolases CysGly to Cys and Gly that are then used by neurons as substrates for GSH synthesis [85]. It is therefore evident that the neuron-astrocyte cooperation is vital part of neuroprotection from oxidative damage [86].

4.3. Purinergic signaling in brain

The CNS injury-evoked release of ATP and adenosine from damaged cells into extracellular space is sensed by astrocytes via purinergic signaling [87]. The amount of ATP and adenosine in the microenvironment correlates with the severity of injury. Purinergic signaling of ATP via P2X receptors triggers rapid synaptic responses, while P2Y triggers slow synaptic responses [88]. Adenosine triggers purinergic signaling via P1 receptors and mediates proliferation of microglia [89], while activation of P2Y receptors has been implicated in the regeneration of nerves and glial cells after CNS injury [90]. High levels of extracellular ATP activate P2X receptors, among which is P2X7 receptor that promotes microglia activation and proliferation [91] whereas it inhibits amyloid-β (Aβ) phagocytosis by microglia [92]. The P2X7 receptor activation on microglia promotes ROS production via NOX, interacts with NOD-like receptor P3 (NLRP3) allowing NLRP3 inflammasome activation, and stimulates release of proinflammatory cytokines, thus modulating the clearance of debris by microglia and can lead to decay of adjacent neurons [93–95].

4.4. Chondroitin sulfate proteoglycans (CSPGs)

Reactive astrocytes induce marked changes of the extracellular matrix (ECM) composition. Cellular components of scar tissue express CSPGs, that are considered the major inhibitors of axonal regeneration. CSPGs are also the major component of perineuronal nets (PN), an extracellular matrix surrounding neuronal cells, and are responsible for its high negative charge. CSPGs are composed of core protein and covalently linked chondroitin sulfate glycosaminoglycan (CS-GAG) chains [96]. The CS-GAG chains were suggested to be the critical determinant responsible for the inhibitory action of CSPGs, as their removal promoted axonal regeneration and functional recovery after CNS injury. Degradation of CS-GAG with chondroitinase-ABC, in an animal mode, attenuated CS-GAG inhibitory effect in CNS injury and enabled axon regeneration [97]. Recent studies have suggested that depending on the sulphation of CS-GAG chains expressed, they may govern the permissiveness of ECM for axonal regeneration. Indeed, sulphation patterns modulate extracellular signal transduction, for example acting as molecular recognition elements for growth factors [98]. The chondroitin backbone may be modified by chondroitin 4- and/or 6-O-sulfotransferases (C4ST / C6ST) with sulphate at positions 4 or 6, respectively, creating a sulphation pattern that may bear the functional information [99]. CS-4-sulfation of astrocytic CSPGs (CS-A motif) and additional CS-A sulphation at the 6-O position (CS-E motif) are associated with negative influence on axonal regeneration [100], with CS-E sulphation motif having the highest affinity towards PTPσ and potent inhibitory effect of neurite outgrowth [101]. Opposite to that, CS-6-sulfation only (CS-C motif) is associated with positive influence on axonal regeneration [102]. In addition, an adequate amount of CS-C was also suggested to be critical for neuroplasticity and can improve memory impairment in the aged brain [103]. Moreover, modification by sulphation is implicated in the neuronal cell protection against oxytosis and ferroptosis [104]. This could be attributed to Gibbs-Donnan effect, by which highly negatively charged PNs control ion mobility and act as “anionic shield” for anionic ROS [105,106]. PNs may also maintain ion homeostasis in neuronal microenvironment by scavenging and binding iron ions. Alterations in PNs negative charge, by removal of a part of negatively charged molecules, results in the loss of PN neuroprotective properties rendering neurons susceptible to iron-induced oxidative stress [107].

4.5. Kinases in neuroregeneration

The pathophysiological outcome of CNS trauma induced oxidative stress is complex, as in response to elevated ROS a plethora of signaling pathways is activated. Among those pathways, PI3K, Rho-kinase (ROCK), and MAPKs have been demonstrated to be involved in neuroregeneration. The involvement of redox signaling and kinases in neuroregeneration is shown on Figure 1.

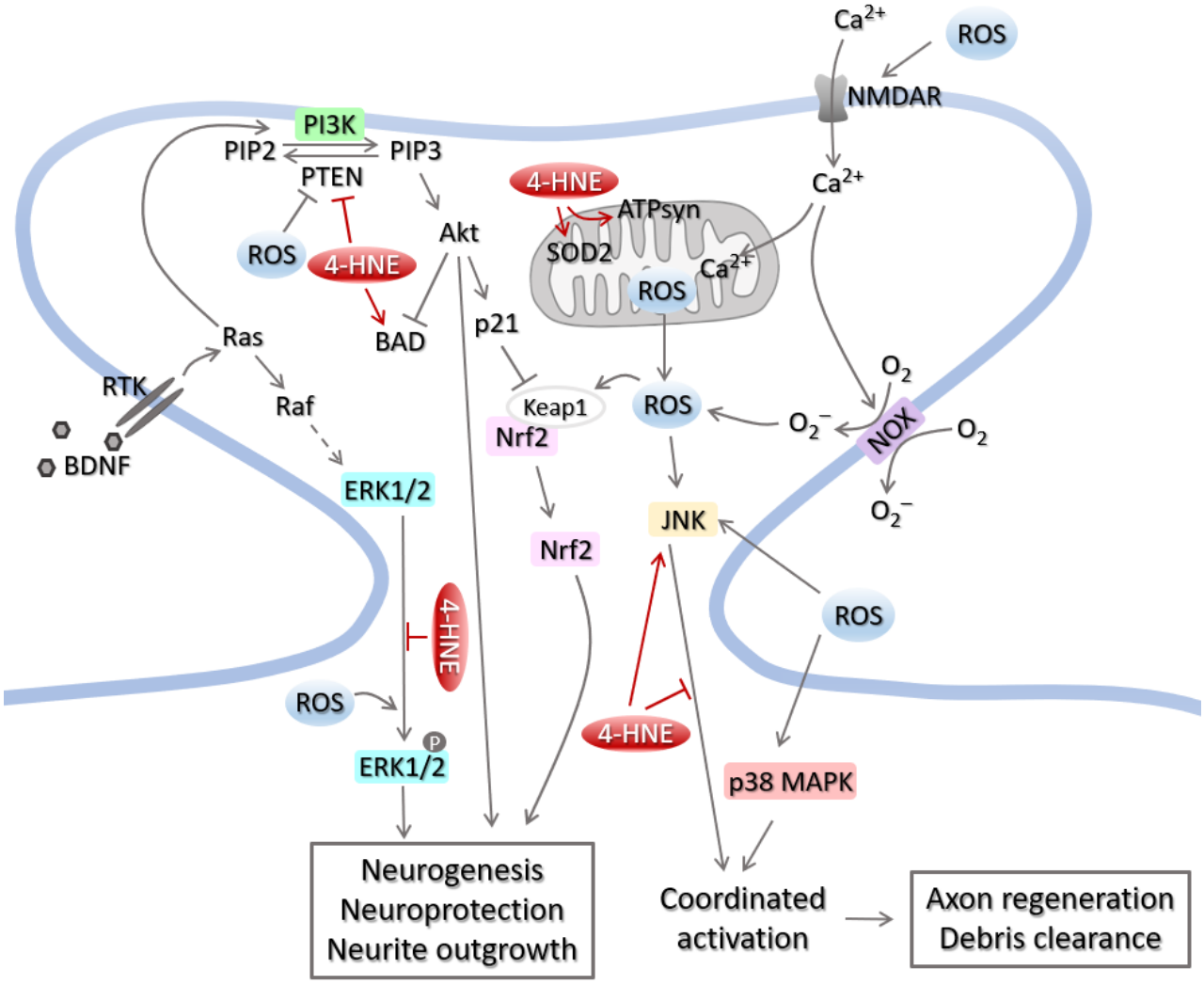

Figure 1. ROS-mediated cellular signaling in neuroregeneration. The CNS injury-induced ROS activate NMDAR leading to calcium influx, which further contributes to intracellular ROS accumulation by the action of NOX. Intracellular ROS inactivates PTEN, causing accumulation of PIP3 that guides Akt to the plasma membrane promoting Akt activation and neurogenesis. In addition, Akt activates p21 that disrupts interaction between Nrf2 and its repressor Keap1 promoting Nrf2 stability, consequent detoxification of excessive ROS and neuroprotection. Binding of BDNF, upregulated in CNS injury, to RTK activates ERK1/2 signaling pathway. Site specific oxidation of ERK cysteine results in its activation. All the above events promote neurogenesis, neuroprotection and neurite outgrowth. Finally, ROS induce both JNK and p38 MAPK, whose coordinated action is essential for debris clearance and axon regeneration. However, high level of oxidative stress triggers peroxidation of lipids and formation of 4-HNE that may exhibit effects that are detrimental for neuroregeneration. (BDNF – brain-derived neurotrophic factor; ERK1/2 – extracellular signal-regulated protein kinase; 4-HNE – 4-hydroxy-2-nonenal; JNK – c-jun N-terminal kinase; MAPK – mitogen-activated protein kinases; NMDAR – N-methyl-d-aspartate receptor; NOX – NADPH oxidase; Nrf2 – nuclear factor erythroid 2 like 2; PI3K – phosphatidylinositol 3-kinase; PIP2 – phosphatidylinositol (4,5)-bisphosphate; PIP3 – phosphatidylinositol 3,4,5-trisphosphate; PTEN – phosphatase and tensin homolog; RTK – receptor tyrosine kinase)

Low levels of oxidative stress trigger pro-survival signals by stimulating phosphorylation of extracellular signal-regulated protein kinase (ERK1/2) and Akt/PKB. Furthermore, neurotrophins, such is brain-derived neurotrophic factor (BDNF) and neurotrophin-3, have high affinity towards receptor tyrosine kinase that when activated engage signal transduction pathways, including ERK and PI3K, supporting neuronal survival and neurite outgrowth [108]. On the other hand, during intense oxidative stress pro-apoptotic signals via activation of c-jun N-terminal kinase (JNK) dominate with subsequent phosphorylation of c-Jun leading to neuronal cell death [73]. In addition, at high levels of oxidative stress, 4-HNE downregulates thioredoxin, SOD2, Bcl2 and leads to reduced amount of phosphorylated ERK1/2 in cortical neurons [78]. As mentioned before, due to its three functional groups 4-HNE can bind to macromolecules altering their structure and function [18,109,110], including modification of ATP synthase or SOD2 that will trigger uncontrolled ROS generation and mitochondrial dysfunction thus promoting neurodegeneration [20]. Production of 4-HNE following CNS trauma may support transport of tumor necrosis factor α (TNF-α) across the BBB [111], while TNF-α promotes ROS generation oxidizing JNK-inactivating phosphatases consequently resulting in their inhibition and sustained JNK activation [112]. A recent study, identified the mammalian sterile 20-like kinase-1 as a key regulator of neuronal cell death via JNK/caspase-3 signaling [113], while JNK activation may be inhibited by increased α-synuclein expression [114]. However, JNK activation and upregulated activating transcription factor 3 may induce expression of the heat shock protein 27 thus inhibiting JNK-induced apoptosis of neuronal cells [115]. Hence, an emerging body of evidence suggests that JNK has dual role being essential for neuroregeneration. Namely, coordinated activation of MAPK pathways, JNK and p38, seems to be required for axon regeneration [116], while activation of JNK pathway is also critical for CED-1 mediated regeneration of axons and removal of axon debris [117].

The PI3K/Akt pathway is essential for the survival of both neurons and neuronal stem/progenitor cells (NPC) as well as for neurogenesis. NPCs are multipotent and reside in different regions of adult brain enabling neurogenesis throughout life [118,119]. Activated PI3K phosphorylates PIP2 to PIP3, whose accumulation guides Akt to the plasma membrane promoting Akt activation and neurogenesis. However, PIP3 is also a substrate for phosphatase and tensin homolog (PTEN), which inhibits downstream signal transduction. PTEN is redox sensitive, and upon oxidation by ROS is reversibly inactivated enabling neurogenesis [120].

NOX are pivotal contributors to basal ROS generation in neurons. The most abundant NOX isoforms in the brain are NOX2 and NOX4 depending on the region of the brain [121]. Inactivation of NOX2 down-regulates H_2O_2 and consequently leads to decrease in proliferation of NPC in the hippocampus of adult brain [39]. In addition, NOX4 mediated generation of ROS is induced by angiotensin II and detrimental for NPCs proliferation in cerebellum [122]. NOX4-induced ROS are fine-tuned by Poly(ADP-ribose) polymerase-3 (Parp3) that motors astrocyte differentiation [123]. In response to cerebral hypoxia-ischemia in striatum, Parp3 is upregulated in NPCs. Inactivation of Parp3 results in increased ROS production by NOX4, and alters activity of mTOR complex 2 required for Akt activation during NPC differentiation to astrocytes [123]. Elevated ROS in experimental stroke model were reduced by miR-130a, that also targets PTEN and promotes PI3K/Akt signaling exerting neuroprotective effects [124]. NOX-dependent signaling was also suggested to have an important role on NPCs proliferation induced by BDNF [37].

The CIRI-induced BBB disruption involves activation of ROCK, increased prooxidant NOX activity and altered intercellular junctions. Besides, scar components and repulsive various myelin-derived axon growth inhibitors in a CNS injury activate ROCK signaling preventing neuroregeneration [125,126]. Inhibition of Rho-kinase was found to ameliorate those effects [127,128] and could represent a potential target to promote functional recovery and neuroregeneration after CNS injury.

4.6. Neurodegenerative properties of steroids

Some steroids could have neuroregenerative properties. Thus, inflammation, apoptosis and oxidative stress, after TBI and stroke, can be reduced by progesterone and progesterone metabolites, which also promote formation of new myelin sheaths [129]. The neuroprotective progesterone mechanisms include down-regulation of axonal growth inhibitor Nogo-A and GFAP, while it up-regulates growth-associated protein-43 in the cortex after TBI [130]. Neuroprotection by steroids could also be attributed, at least in part, to the blockade of nitric oxide synthesis and consequent oxidative damage via reduction of neuronal NADPH-diaphorase/nitric oxide synthase [131]. Still, the underlying mechanisms remain to be fully elucidated.

5. Penumbra

Among stress- and age-associated diseases, which are the dominating chronic diseases of the modern mankind, stroke has prominent position as the leading cause of death worldwide [132]. Ischemic stroke is composed of core with neuronal necrosis and surrounding penumbra (Latin: paene=almost; umbra =shadow), where functionality of some neurons is transiently changed [133,134]. Some of these neurons could recover well over extended time, while the other will eventually appear to be irreversibly damaged. Interruption of the blood flow or its decrease for about 20%, together with reduced ATP level to 50-70% of the basal values in penumbra results in ionic disequilibrium, swelling, accumulation of ROS, glutamate and calcium [135]. Within hours after interruption of blood flow damaged tissue is affected by inflammation making penumbra into an area of mixed reparation, vasculogenesis, neurogenesis and apoptosis [133,134].

According to Grčević, similarly to penumbra in stroke, in case of primary TBI lesions at the epicenter of injury comprise irreversibly damaged tissue, while peri-pericentric area of "traumatic penumbra" has only moderate presence of irreversibly disrupted axons presented as "retraction bulbs" [136]. Within such traumatic penumbra, the recovery of integrity of brain tissue, its structures and functions may take place.

Both in ischemic and in traumatic brain injuries the onset of edema, thrombolysis and reperfusion, occurring within penumbra zone, may influence reversibility of a damage sustained or the development of secondary brain injury after the primary insult [136–139].

Free radicals are produced soon after ischemia and contribute to cell death or recovery within the penumbra mostly according to the ischemia/reperfusion type of injury. The cascade of events after brain injury includes not only the damage core and penumbra, but also brain/CNS and entire organism, involving neurons, glial cells, stem cells originating from brain and from blood, inflammatory cells, blood vessels and stroma. The molecular pathophysiology of this post-traumatic cascade on molecular level depends on oxidative stress and its homeostasis. Patients, especially smokers, with stroke comorbidities such as diabetes mellitus, hypertension, obesity and atherosclerosis have already

persistent, chronic oxidative stress with lowered endogenous antioxidant defense. Thus, hydrogen peroxide stimulates NF-κB, which induces the transcription of SOD genes that could eventually catalyze the dismutation of superoxide into hydrogen peroxide [140]. Catalase or GPX decompose further hydrogen peroxide into water and oxygen unless it reacts with nitric oxide (NO), which is in penumbra generated mostly by neuronal nitric oxide synthetase (nNOS) [141], together with inducible NOS (iNOS) producing high concentrations of NO in case of ischemic penumbra [142]. High concentrations of superoxide and NO in condition of low pH in stroke core result in production of peroxynitrite that spreads the damage further. Within one hour of MCAO and reperfusion (MCAOR), cytosolic SOD1 and nNOS increase in penumbra, mitochondrial SOD2 follows three hours after occlusion, followed by nitrotyrosine, marker of peroxynitrite production, four hours after occlusion [142], which can inactivate SOD [143]. In later phase, 24 hours after MCAOR, Nrf2 plays important role in brain defense against oxidative stress. However, the Nrf2 is upregulated in neurons, astrocytes and microglia only in ischemic penumbra, but not in the core of insult [144,145].

Free radicals break the BBB in an early and in late phase of blood flow interruption (ischemia/hypoxia), which is followed by reperfusion and activation of microglia in penumbra. Three hours after reperfusion matrix metallopeptidase 9 causes degradation of extracellular matrix and basal lamina around blood vessels [146–148]. Approximately 4 hours after reperfusion microglia is associated with endothelial cells, after 24 hours these cells are colocalized with chemokine CX3CL1, involved in microglia migration, and claudin 5, the tight-junction protein of BBB [149]. During inflammation that occurs 24 hours after injury, delayed production of free radicals by the inflammatory reactions to tissue damage in penumbra contributes to disintegration of blood vessels and the break of BBB with consequential cerebral edema. Latest at that time neutrophils invade BBB and infiltrate penumbra [149]. After 72 hours the activity of microglia declines while monocytes migrate from blood to penumbra [150].

Astrocytes are specialized glial cells important for nutrition, potassium homeostasis, synaptogenesis, neurogenesis and BBB regulation. Reactive astrocytes contribute to modulation of neuroinflammatory and neurorepair processes in brain injuries and infections. It was found that in vitro increase of interleukin-1beta (IL-1β) in primary astrocyte cultures induced expression of proinflammatory genes including iNOS and TNFα, which, together with IL-1β, IFN-γ and C1q activate astrocytic proliferation [151,152]. On the contrary, TGFβ1 inhibits expression of astrocytic MHC class II, and astrocytic production of TNFα, thus preventing reactive astrocytes to form glial scar after injury [153,154]. Activated astrocytes also release GSH which acts as free radicals scavenger [155,156]. Glutamyltranspeptidase γ, present on the surface of astrocytes, hydrolyses extracellular GSH producing cysteine and glycine, which are the source for GSH synthesis in neurons [155,156]. Activated astrocytes release glutamine, which is also source for synthesis of neuronal GSH [157]. The IL-1β can induce production of nerve growth factor (NGF) by astrocytes in vivo and in vitro [158]. In astrocytic cell cultures the IL-1β also induced production of ciliary neurotrophic factor and interleukin-6 (IL-6) genes [158,159], thus indicating that reactive astrocytes could rescue, repair and recovery neurons in penumbra, through expression of CNFT and NGF that enhance growth of the new cells. However, majority of astrocytes in adult brain are not neurogenic [160].

Major sources of cells able to differentiate into new astrocytes and/or neurons in the adult brain are subgranular zone of dentate gyrus and subventricular zone of lateral ventricles. Neural stem/progenitor cells (NSPC) of the dentatal gyrus look like GFAP-immunoreactive cells that can upon

a stimulus, including ischemic brain infarction, differentiate into neurons or astrocyte [161,162]. The NSPC outside neurogenic regions are positive to neuronal/glial antigen 2 and are neurogenic, at least in vitro [163].

Hippocampal astrocytes and microglia release BDNF, which is considered to act as the main factor of neuronal maturation and synaptic plasticity [164,165]. Abrineurin or BDNF is a member of neurotrophins, which regulate synaptogenesis [164,165]. Pro-BDNF is released by neurons, it accumulates in astrocytes and is further converted to mature BDNF, which is secreted by astrocyte through phosphorylated NMDA channels, GABA receptors and neuronal tropomyosin receptor kinase B, important for memory retention through maintenance of long-term potentiation of synapse [166]. In ischemic stroke BDNF was found increased in reactive astrocytes one day after MCAO [167] and also later on for eight days after infarction [168]. In different experimental models, BDNF released from astrocytes was found to be associated with recovery of synapses and vestibular synaptogenesis [169], with spine density and with dendritic growth in transgenic mice model of AD [166].

Synaptic plasticity is dynamically changing in dependence on requests for neuronal circuits, comprising formation of functional synapses and elimination of uncompetitive synapses [170]. Astrocytes have critical role in neurorepair process and building of new neural network with functional synapses [171]. They can adhere and sense several synapses in coordination with neighboring astrocytes. Association of synapses with astrocyte is dynamic process modulated by neuronal activity [172], while neurotransmitters released from neurons activate signaling pathways in astrocytes, which modulate synaptic behavior. Hence, after TBI reactive astrocytes can assist in restoration of synapses [173]. To fulfil such a demanding function astrocytes produce and utilize several potent factors.

Neurogenic transcription factor NeuroD1 can reprogram reactive astrocyte in functional neurons both in TBI and in mouse model of AD [174]. Moreover, NeuroD1 can mediate in vitro astrocyte to neuron conversion from a glial scar into neural tissue [175] and efficient astrocyte to neurons conversion in spinal cord injury thus generating functionally mature neurons of dorsal horn integrated into spinal cord circuitry [176].

Thrombospondin (TSP) secreted by astrocytes is matrix protein associated with brain tissue repair and synaptogenesis in vitro and in vivo. Hence, purified TSP increased number of synapses in cultured neurons if compared with astrocyte-conditioned medium (ACM) or removal of ACM [177]. In the TSP1/2 double knockout mice exhibit lack of synaptic density and axonal germination when compared to the wild-type animals [178]. Protoplasmic astrocytes in gray mater express TSP1 and TSP2, while fibrous astrocytes and astrocytes from subventricular zone express TSP4. The TSP1 is upregulated in peri-infarction zone within 3 days, while the increase of TSP2 is observed one week later. Astrocytic signal transducer and transcription-3 activator regulates formation of perineuronal astrocytic process and re-expression of TSP2, which is responsible for astrocyte mediated recovery from excitatory synapses after axotomy in adult mice model [173].

The cysteine-rich acid secreted protein (SPARC) and hevin are expressed by astrocytes of superior colliculus and are important for formation, maturation and plasticity of excitatory synapses. Hevin-induced synaptogenesis in cultured rat retinal ganglion cells was found to act as positive, while SPARC acts as negative regulator of synaptogenesis. Thus, hevin-negative mice showed fewer synapses, whereas SPARC-null mice have increased synaptogenesis in superior colliculus [179]. The levels of both SPARC and hevin after the end of CNS development are reduced, but their levels increase in reactive astrocyte and in microglia, after injury and stroke [180–182]. While hevin itself

has synaptogenic effects, it may also support connection between presynaptic receptor neurexin and postsynaptic receptor neuroligin within their synaptogenic actions [45].

Agrin is atrocytic-derived synaptogenic promotor, which was found increased after hippocampal TBI, inducing synaptogenesis by acting through reactive astrocytes that are in contact with the synaptic terminals in penumbra [183]. Therefore, agrin can play important role in neuronal repair and synaptogenesis, as induced by exercise after stroke in rat model [175].

Among synaptogenic factors of particular relevance for oxidative stress is cholesterol-bound apolipoprotein E (APOE), which acts as synaptogenic molecule promoting synthesis and maturation of synaptic vesicles and was found to increase presynaptic differentiation in retinal ganglion cells, at least in vitro [184,185]. Cholesterol depletion can inhibit synaptogenesis and interfere with formation of synaptic vesicle curvature [186]. On the other hand, application of the cholesterol-binding sigma-1 receptor agonist two days after MCAO decreased infarct size and enhance recovery, due to increased export of cholesterol to neurons via the sigma-1 receptors of astrocytes [187]. Similar effects on synaptogenesis were obtained in mice model 24 hours after MCAO and administration of liver X receptor agonist GW3965 of high-density lipoproteins [188]. It seems that APOE genotype is important for the overall homeostasis of CNS. Namely, APOE4 is major genetic risk factor for AD and is associated with cognitive decline due to aging and with poorer outcome after TBI and stroke [189,190]. The APOE4 brain endothelial cells produce less apolipoprotein E (apoE), if compared to APOE3 and have altered expression of metabolic and inflammatory genes. Autocrine signaling of apoE in brain endothelial cells is important cellular mechanism how APOE regulates neurovascular function [191]. Hence, APOE4 brain endothelial cells express higher chemokine levels and immune cell adhesion, higher markers of mitochondrial activity and higher levels of superoxide, but with lover levels of antioxidants related to hem and GSH, eventually causing oxidative protein modifications and LPO [191]. Paracellular permeability and inflammation are also higher in APOE4 brain endothelial cells cultures and even more after high dose lipopolysaccharide treatment, but could be prevented by nuclear receptor Rev-Erg agonist, SR9009 [191].

After TBI damaged endothelial cells upregulate cell adhesion molecules and generate ROS, which together with pro-inflammatory mediators contribute to endothelial damage and damage of BBB [192]. Hence, conjugates of catalase linked to anti-intercellular adhesion molecule 1 antibodies minimize effect of OS on BBB and improves recovery in TBI [192]. On the other side, lipid peroxidation, notably 4-HNE, increases permeability of the BBB, and was highly pronounced in damaged brain tissues after TBI [19,193,194], as well as in case of primary or metastatic brain tumors [25]. Therefore, it is not surprising that 4-HNE is abundant in penumbra, as presented by Figure 2.

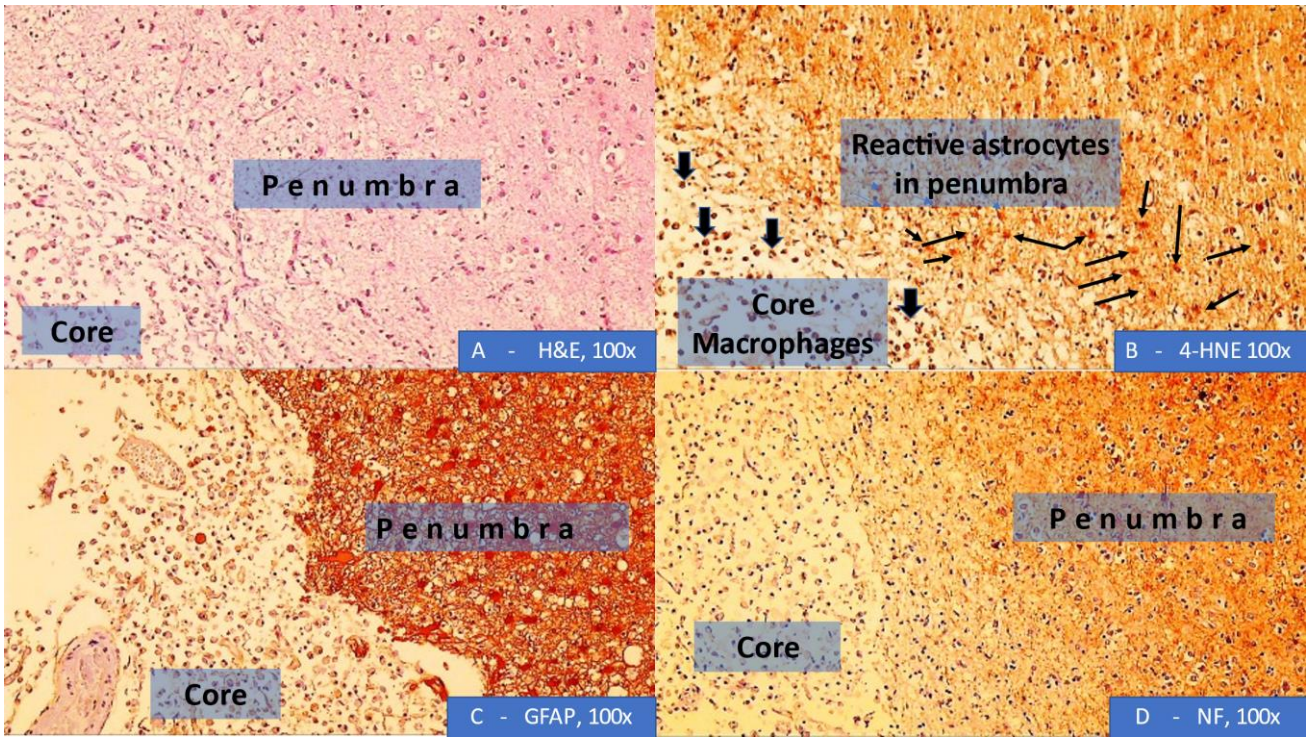

Figure 2. Immunohistochemical appearance of 4-HNE-protein adducts and respective biomarkers of glial and neuronal cells in the autopsy tissue sample of human subacute cerebral infarction (insult). Core of subacute ischemic cerebral infarction and adjacent penumbra are visible on hematoxylin-eosin staining slide (A). Immunohistochemical positivity for 4-HNE-histidine adducts staining is prominent in foamy macrophages in the infarction core and in reactive astrocytes of penumbra are indicated by arrows (B). Numerous GFAP-positive reactive astrocytes can be seen in penumbra (C), together with neurofilament-positive cells (NF) within penumbra remote from the core of infarction (D).

As can be seen, the core of ischemic cerebral infarction is presented by partly disintegrated, edematous tissue losing integrity under decay. However, the adjacent penumbra shows integrity, containing numerous neuronal (NF positive) and glial cells that could be the source of neuroregeneration. It should be noticed that the core of insult contains 4-HNE positive foamy macrophages that apparently tend to phagocyte the debris containing lipids. The reactive astrocytes could be seen as GFAP-positive cells, while neuronal cells are neurofilament-positive and present only in penumbra, indicating neuroregenerative capacity. The abundance of 4-HNE in penumbra is considered to be merely consequence of insult and/or TBI causing tissue damage and oxidative stress, which might be the source and mediator of the secondary tissue damage based on oxidative stress [195].

Consequently, treatments reducing 4-HNE in penumbra could be beneficial for recovery, as in case of s-nitrosoglutathione or aldehyde dehydrogenase [196-198]. However, 4-HNE is known not only as cytotoxic but also as hormetic and growth regulating factor, so we cannot entirely rule out some of its beneficial effects for neuroregeneration, too [17-20, 60-63, 199-202].

6. Conclusion and future perspectives

Complexity of CNS and in particular brain is associated with limited capacity for (neuro)regeneration, while high levels of lipids, demands for oxygen, restricted space of the rigid anatomical surrounding and extremely high level of differentiation of the cells, both neuronal and glial, make CNS susceptible to oxidative stress. Either acute, as in case of TBI or chronic, as in case of neurodegeneration, brain suffers from oxidative stress involving lipid peroxidation, which generates reactive aldehydes, among which 4-HNE is accused to be the notorious one. However, while 4-HNE is certainly neurotoxic and causes disruption of the BBB in case of severe injuries, shock, sepsis or hypovolemia, it is also physiologically produced by glial cells, especially astrocytes, but its physiological roles within CNS are not understood. Because 4-HNE can regulate the response of the other cells in the body to stress, enhance their antioxidant capacities, proliferation and differentiation, we could assume that it may also have some beneficial role for neuroregeneration. Therefore, future studies on the relevance of 4-HNE for the interaction between neuronal cells, notably stem cells and supportive astrocytes might reveal novel options to better monitor and treat consequences or brain injuries and neurodegeneration.

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