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Alteration of Neuron-Glia Interactions in Neurodegeneration: Molecular Biomarkers and Therapeutic Strategy

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1. Introduction

Accumulating evidence suggests that alterations of neuron-astroglia interactions are associated with development of neurodegenerative diseases (Barres, 2008; Ricci et al., 2009; Verkhratsky et al., 2010). Astrocytes contribute to a variety of functions of neurons, including synapse formation and plasticity, energetic and redox metabolism, and synaptic homeostasis of neurotransmitters and ions (Bolton & Eroglu, 2009; Nimmerjahn, 2009; Salmina, 2009; Verkhratsky, 2010; Wang & Bordey, 2008). It is well known that astrocytes play important role in supporting energy production in neurons. Astrocytes produce lactate which is actively taken up by active neurons. They utilize lactate as an alternative energy fuel. In turn, neuronal activation results in glutamate-stimulated glycolysis in astroglial cells. Thus, neuron-astrocyte metabolic coupling provides tight interactions between the activated neuronal cells consuming lactate and lactate-producing astrocytes. Remodeling of astrocytes is required for adequate synapse turnover in the brain, and astrocytes or the closely related radial glial cells possess all the attributes of a neural stem cells, thereby playing a key role in neurogenesis (Steindler & Laywell, 2003; Theodosis et al., 2006).

Functional relationship between neurons, glial cells, and vascular cells within so-called neurovascular unit is very important in the context of pathogenesis of neurodegenerative disorders. A major function of the neurovascular unit is to regulate the transport and diffusion properties of brain capillary endothelial cells that compose the brain-blood barrier. Astrocytes exhibit anatomic relationships with cerebral arterioles and neurons. In the brain parenchyma, the extensive ensheatment of cerebral arterioles by astrocytic end-feet far exceeds any direct neural contacts with those perfusion-regulating microvessels. That unique arrangement permits astrocytes to transduce signals arising from activated neurons and to transmit that information to the cerebral microcirculation. Alteration of these processes may play a particularly significant role in the pathogenesis of neurodegenerative diseases. The early and mid-term stages of neurodegenerative processes are associated with generalised atrophy of astroglia, whereas the later stages are characterized with an

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astrogliosis and microglial activation linked to neuropathological lesions such as senile plaques (Rodriguez & Verkhratsky, 2010).

Acute neurodegeneration is encountered during and following stroke, transient cardiac arrest, brain trauma, insulin-induced hypoglycemia and status epilepticus. All these severe clinical conditions are characterized by neuronal calcium overload, aberrant cell signaling, generation of free radicals and elevation of cellular free fatty acids, conditions that favor activation of the mitochondrial permeability transition pore (mtPTP) (Friberg & Wieloch, 2002).

Pathological cascade leading to clinical manifestations of chronic neurodegeneration (i.e. Parkinson's disease, Alzheimer's disease, Hungtington's disease) includes progressive loss of functional synapses, irreversible damage and loss of neurons, neurotoxicity, and excessive activation of astroglial (reactive astrogliosis) and microglial (neuroinflammation) cells. Neurodegeneration is associated with axonal and synapse degeneration which is triggered by mechanical, metabolic, infectious, toxic, hereditary and inflammatory stimuli. Several signaling pathways are implicated in axonal and synapse degeneration, but identification of an integrative mechanism for these self-destructive processes has remained elusive. Also, neurodegenerative events are known to be associated with alterations in cell-cell interactions, gene expression, dynamics of neuronal networks, development of oxidative stress, accumulation of lipid and protein oxidation products, production of fatty acids metabolites with biological activity, mitochondrial dysfunction, impairment of multiple signaling pathways, activation of programmed cell death (Salmina, 2009).

In general, the link between the character of astroglial activation and neuronal damage or repair in neurodegeneration is well established (Theodosis et al., 2008). The current conception includes impairment of astroglia-assisted synapse formation and plasticity, synapse elimination, neurogenesis, function of neural circuits, and functioning of the blood-brain barrier; dysregulation of gliovascular control and cerebral blood flow, alterations of neuronal metabolism, astrocyte-dependent augmentation of oxidative stress due to impaired antioxidant activity, stimulation of neuroinflammatory response, potentiation of excitotoxic insult, mitochondrial and glycolytic failure, impairment of glial calcium homeostasis, pathology of neurovascular unit, reactive astrogliosis accompanied by scar formation and initiation of brain repair (Bambrick et al., 2004; Barres, 2008; Buffo et al., 2008; L'Episcopo et al., 2010; Ricci, et al., 2009; Sofroniew, 2009; Stevens, 2008; Verkhratsky, et al., 2010; Verkhratsky et al., 1998).

Recent achievements in deciphering cell and molecular mechanisms of acute and chronic neurodegeneration suggest new prospective biomarkers and therapeutic targets for modulation of neuron-glia interactions. In this chapter, we will focus on several aspects of metabolism of nicotinamide adenine dinucleotide (NAD^+) in neurons and astrocytes as a critical factor in neurodegeneration-associated cell damage.

2. Neuronal and glial NAD^+-generating and NAD^+-converting enzymes in neurodegeneration

Few decades ago, the actions of NAD^+ have been extended from being an oxidoreductase cofactor for single enzymatic activities to acting as substrate for a wide range of proteins. These include NAD^+-converting enzymes, and transcription factors that affect a large array of cellular functions. Through these effects, NAD^+ provides a direct link between the cellular redox status and the control of signaling and transcriptional events (Houtkooper et al., 2010). Cellular bioenergetic homeostasis requires production and delivery of energy-rich

phosphoryls and NAD^+. In cytosol, NAD^+ and NADH mediate glycolysis acting as co-factors for rate-limiting glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase, participate in lactate-pyruvate conversions, and affect mitochondrial oxidative phosphorylation. Also, NAD^+ serves as a substrate for NAD^+-converting enzymes (ADP-ribosyltransferases, poly(ADP-ribosyl)polymerase and ADP-ribosyl cyclase).

Synthesis of NAD^+ *in vivo* and *de novo* is possible by means of 4 pathways: 1) from nicotinic acid (niacin); 2) from nicotinamide (vitamin PP); 3) from tryptophan; 4) from aspartate (in plants only). Recently, a biosynthesis pathway which uses nicotinamide riboside as a precursor has been described. For the synthesis of NAD^+ from L-tryptophan, the indole ring should undergo transformation into the pyridine ring, and finally quinolinate is formed. Quinolinic acid undergoes further transformations resulting in NAD^+ formation. Indoleamine 2,3-dioxygenase (expressed in various tissues) and tryptophan 2,3-dioxygenase (expressed in liver) catalyze the formation of N-formylkynurenine in the reaction representing the first rate-limiting step in this pathway. Indoleamine 2,3-dioxygenase is a unique enzyme in that it can utilize as the substrate, in place of oxygen, the superoxide anion radical, thus acting as a radical scavenger. The second rate-limiting step in this pathway is represented by the reaction catalyzing by quinolinate phosphoribosyltransferase responsible for the conversion of quinolinic acid and 5-phospho-α-D-ribose 1-diphosphate to nicotinate mononucleotide, pyrophosphate and CO_2 (Magni et al., 2004).

Enzymes responsible for producing neuroactive compounds in the kynurenine pathway are preferentially localized in astrocytes and microglia. Astrocytes are well equipped with enzymes for kynurenine metabolism, i.e indoleamine 2,3-dioxygenase is highly expressed in these cells (Suh et al., 2007), thus raising the possibility that generation of the neuroactive compounds may play significant role in neuron-glial cell interactions (Ying, 2006). Interestingly, tryptophan and kynurenine stimulate expression of nerve growth factor in astrocytes (Dong-Ruyl et al., 1998), while interferon-gamma hyperactivates indoleamine 2,3-dioxygenase resulting in elevated production of kynunerines (i.e. quinolinic and picolinic acids) and stimulation of iNOS in human aged brain and vascular cognitive impairment (Oxenkrug, 2007). In general, kynurenine pathway is up-regulated in Alzheimer's disease brain, i.e. in hippocampus, where indoleamine 2,3-dioxygenase and quinolinic acid immunoreactivity was detected in astrocytes, microglia and neurons, with highest expression in glial cells in the perimeter of senile plaques. Quinolinic acid immunoreactivity was also present in granular deposits within the neuronal soma of cortex, and looks to label neurofibrillary tangles (Guillemin et al., 2005). Dysfunction of quinolinate metabolism in the human brain has been postulated to be involved in the pathogenesis of Alzheimer's disease ("quinolinate hypothesis") (Fukuoka et al., 2002). At the same time, it was suggested that astrocytes alone are neuroprotective by minimizing quinolinic acid production and maximizing synthesis of kynurenic acid (due to absence of kynurenine hydroxylase), but in the presence of macrophages and/or microglia, astrocytes become indirectly neurotoxic by the production of high concentrations of kynurenine that can be secondary metabolized by neighboring cells to quinolinic acid (Guillemin et al., 2001).

Mononucleotide adenylyltransferase (NMNAT) is a central enzyme in NAD^+ biosynthesis, catalyzing the condensation of nicotinamide mononucleotide or nicotinic acid mononucleotide with the AMP moiety of ATP to form NAD^+. NMNAT-1 has nuclear localization, and was proposed to have functional relations with poly (ADP-ribosyl) polymerase (PARP) in prevention of NAD^+ depletion during PARP over-activation. NMNAT-2 isoform has cytoplasmic localization, and is very prone to oxidation due to

presence of nine cysteines versus four cysteines present in NMNAT-1. NMNAT-3 presents in cytoplasm and mitochondria, has much lower enzymatic activity comparing with NMNAT-1 and NMNAT-2 (Raffaelli et al., 2002). Extracelullar nucleotides (*e.g.* NAD^+ and NMN) undergo extracellular degradation resulting in the formation of permeable precursors which are further converted to NAD^+ in mitochondria due to activity of NMNAT3 localized to the mitochondrial matrix (Nikiforov et al., 2011). Interestingly enough, in genomewide screen for late-onset Alzheimer's disease, SNP of the NMNAT-3 gene was found, thus suggesting involvement of NAD^+ synthesizing pathways in pathogenesis of this neurodegenerative disorder (Liu et al., 2007)].

Recently, a role for mitochondrial permeability transition, and mitochondrial dysfunction, in development of axonal degeneration has been proposed. Axonal degeneration has been shown to be regulated by proapoptotic proteins (i.e. caspases 3 and 6) and/or NAD^+-sensitive pathways (Schoenmann et al., 2010). Since these degenerative processes can cause permanent loss of function, they represent a focus for neuroprotective strategies (Barrientos et al., 2011). Functioning of NMNAT as a chaperone acting through a proteasome-mediated pathway was found (Zhai et al., 2008), thus suggesting novel aspects in regulation of NAD^+ homeostasis under the conditions of cellular stress. Overexpression of NMNAT in the mitochondrial matrix resulted in suppression of axonal degeneration seen in neurodenegeration (Sasaki & Milbrandt, 2010; Sasaki et al., 2009; Yahata et al., 2009). In amyloid-treated cells, NMNAT-sensitive program is uniquely involved in axonal, but not cell body, degeneration (Vohra et al., 2010). Axonal degeneration can be slowed by the addition of extracellular NAD^+ (Billington et al., 2008).

Nicotinamide N-methyltransferase (NNMT) methylates pyridines, in particular nicotinamide, to N-methyl nicotinamide which is further used for synthesis of NAD(P) and NAD(P)H. Increased activity of NNMT leads to cellular nicotinamide deficiency. It was demonstrated that elevated levels of NNMT result in reduced Complex I activity in idiopathic Parkinson's disease (IPD) in two ways: (1) reduction in the levels of nicotinamide available for nicotinamide adenine dinucleotide synthesis; and (2) increased methylation of compounds such as tetrahydroisoquinolines and β-carbolines, which are potent Complex I inhibitors. Expression of NNMT is increased in Parkinson's disease which may ultimately lead to neurodegeneration via a reduction in Complex I activity (Parsons et al., 2003). A.C.Williams has proposed that elevated activity of NNMT may be responsible for dopaminergic toxicity of N-methylated pyridines (i.e. MPP^+) and for depletion of NAD^+ in the cells (Williams et al., 2005).

Apart from the pathways of NAD^+ synthesis *de novo*, there are some reactions for the regeneration of NAD^+ from molecules formed during its functioning and catabolism (reduced pyridine nucleotides (NADH, ADP-ribose, nicotinamide, $NAAD^+$). It should be noted that re-synthesis of NAD^+ from ADP-ribose and nicotinamide requires as many as four molecules of ATP, therefore being energetically unfavorable (Di Lisa & Ziegler, 2001). Regeneration of NAD^+ from NADH may be achieved through the activity of following enzymes and processes: 1) specific NADH flavin dehydrogenase acting in the respiratory chain; 2) transhydrogenase of the outer mitochondrial membrane; 3) specific NADH oxidases; 4) malate-aspartate shuttle. Regeneration of NAD^+ is very important not only for the economic using of cellular pool of pyridine nucleotides, but also for their effective intracellular redistribution at the appropriate moment under physiological and pathological conditions. Murine glial cells have been shown to synthesize NAD^+ from quinolinic acid,

however, the pathway for NAD^+ regeneration from nicotinic acid is a preferred route for NAD^+ biosynthesis (Grant & Kapoor, 1998).

Among all the NAD^+-converting enzymes, poly(ADP-ribosyl) polymerase (PARP) and ADP-ribosyl cyclase attract the main attention in terms of neurodegenerative disorders (Kauppinen & Swanson, 2007). Poly(ADP-ribosyl) polymerase functions as DNA damage sensor and signaling molecule binding to single- and double-stranded DNA breaks. Upon binding to damaged DNA PARP forms homodimers and catalyzes the cleavage of NAD^+ into ADP-ribose and nicotinamide. ADP-ribose is then used to synthesize the branched polymer attached to nuclear (or mitochondrial) acceptor proteins. Variety of acceptor proteins has been described (histones, DNA repair enzymes, topoisomerases, transcription factors, DNA-dependent protein kinase, lamin B, p53), but the most efficient acceptor appears to be the enzyme itself (Ziegler, 2000).

There is a growing number of evidences on involvement of PARP and PARP-mediated depletion of intracellular NAD^+ in the acute and chronic injury of cells (ischemia/reperfusion, endothelial dysfunction, genotoxicity, inflammation, traumatic injury) (Oliver et al., 1999). In respect to the CNS, NAD^+ depletion and mitochondrial permeability transition were shown to be sequential and necessary steps in PARP-1 overactivation-dependent cell death in astrocytes (Alano et al., 2004). Increased poly(ADP-ribosylation) of nuclear proteins was demonstrated in neurons in Alzheimer's disease (Love et al., 1999). Intra-mitochondrial PARP contributes to NAD^+ depletion and cell death induced by oxidative stress in neurons (Du et al., 2003). Increased poly ADP-ribosylation of nuclear proteins in Alzheimer's disease has been detected, and double immunolabelling for poly(ADP-ribose) and markers of neuronal, astrocytic and microglial differentiation showed many of the cells containing poly(ADP-ribose) to be neurons, while few of the cells were astrocytes, and no poly(ADP-ribose) accumulation was found in microglia (Kauppinen & Swanson, 2007; Love, et al., 1999). Moreover, it was shown that β-amyloid affected cholinergic receptor-mediated signal transduction to PARP, probably, through free radical evoked inhibition of inositol-3-phosphate formation in the hippocampal cells (Adamczyk et al., 2005). Glutamate neurotransmission involving NMDA receptors and neuronal nitric oxide synthase activity in part mediates neuronal DNA strand breaks and PARP activation. These events are especially important for neurons since astrocytes able to maintain higher levels of NAD^+ comparing with neurons (Pieper et al., 2000), and much higher concentrations of oxidants are required for killing astrocytes (Ying et al., 2002). It should be taken into the consideration that excessive PARP activation leads to impairment of glycolysis in affected cells, thereby impaired glycolytic flux is involved into PARP-mediated neuronal and astroglial cell death. Since astrocyte-produced lactate is a major endogenous energy substrate used by neurons in brain, NAD^+ depletion caused by excessive PARP activation in neurons would result in alteration of lactate-pyruvate conversion thus affecting the efficacy of oxidative metabolism in neurons and astrocyte-neuronal lactate shuttle mechanism. In addition, neurological metabolic coupling implies subcellular compartmentation of pyruvate and monocarboxylate recycling through the plasma membrane of both neurons and glial cells, subcellular compartmentation of pyruvate allows neurons and astrocytes to select between glucose and lactate as alternative substrates depending of the concentrations and the operation of a redox switch (Cerdan et al., 2006). Pyruvate compartmentation results in effective transcellular coupling between the cytosolic NAD^+/NADH redox states of neuronal and glial cells, therefore, impairment of this

mechanism due to PARP hyperactivation in neurons could directly affect restoring the basal redox state in astrocytes.

Another class of enzymes utilizing NAD^+ is represented by the CD38 family (EC 3.2.2.5, EC 3.2.2.6). Two ligands of CD38 – the substrate ligand NAD^+ acting either extracellularly or intracellularly, and the non-substrate ligand CD31 expressed in endothelial cells – have important functions in brain cells under (patho)physiological conditions (Higashida et al., 2001a; Higashida et al., 2007; Salmina et al., 2010a; Salmina et al., 2006b). CD38 possesses the capability to catalyze different reactions, such as the hydrolysis of NAD^+ and cADPR to ADP-ribose, and the cyclization of NAD^+ and nicotinamine guanine dinucleotide (NGD^+) to cADPR and cGDPR, respectively. The physiological meaning of the latter reaction is still unclear, but biological activity of cADPR is well defined in many cell types (Deaglio et al., 2008; Malavasi et al., 2008a). ADP-ribosyl cyclase attributable to CD38 was detected in the central nervous system where its activity and expression showed developmental changes. ADP-ribosyl cyclase synthesizes Ca^{2+} mobilizing messengers by cyclizing NAD^+ to produce cyclic ADP-ribose (cADPR) acting through activation/modulation of ryanodine receptor channels involving FKBP12.6. In addition, cADPR was also shown to affect some potassium currents and thereby could be involved in synaptic activity. In murine brain, CD38 was found in both neurons and glial cells, showed predominant intracellular location, and was enriched in neuronal perikarya. In human brain, CD38 immunoreactivity was demonstrated in neurons, astrocytes, and microglial cells. In rat astrocytes, ADP-ribosyl cyclase has been reported to have both intracellular and extracellular actions. Co-culture of astrocytes with neurons resulted in significantly increased expression of astrocytic CD38 both on the plasma membrane and cytosol, and this effect was attributed to neuron-released glutamate action on astrocytes (Bruzzone et al., 2004). It is known that astrocytic response to neuronal activity can be most readily detected by observing changes in the intracellular Ca^{2+} concentrations mediated via calcium flux trough the plasma membrane calcium channels or calcium release from intracellular stores. Subtype-specific coupling with ADP-ribosyl cyclase of various neurotransmitter receptors confirms the involvement of this enzyme in signal transduction in neuronal and glial cells. The expression of CD38 is regulated by various substances (cytokines, retinoic acid), while enzymatic activity of ADP-ribosyl cyclase/CD38 is controlled by the structure of the catalytic center, the integrity of the sulfhydryl cysteine residues in this center, the intracellular levels of ATP and NADH, intracellular localization of the enzyme (plasma membrane, mitochondrial membrane, nuclear membrane, and cytosol), conformational plasticity, ligands (NAD^+, CD31), and capacity to form dimers in a membrane for effective transport of reaction product.

In the cells of the CNS, ADP-ribosyl cyclase is expressed in different cell compartments (the nucleus, cytosol, and mitochondria), including the plasma membrane; however, the mechanisms that control translocation of the enzyme molecules, role of intracellular localization in the realization of enzymatic activity, and the mechanisms of directed transport of the enzyme to different cell compartments are unclear (Higashida et al., 2001; Salmina et al., 2008). Proposal exists that CD38 is a regulator of cellular NAD^+ levels under physiological conditions, while PARP is the key factor determining intracellular NAD^+ levels when significant DNA damage occurs (Ying et al., 2005).

A key role of CD38 in regulation of NAD^+ homeostasis in cells has been suggested (Aksoy et al., 2006). Thereby, CD38 may contribute to regulation of activity of SIRT proteins or TRPM (transient receptor potential) channels. SIRT1 promotes survival and stress tolerance in brain

cells. SIRT expressed in neuronal and astroglial cells requires NAD^+ as an essential cofactor for their deacetylase activity, thus providing direct link between the metabolic and transcriptional response (Cohen et al., 2009; Kwon & Ott, 2008), while TRPM2 channels are expressed predominantly in neurons and microglia and are activated by cyclic ADP-ribose or by NAD^+ (Togashi et al., 2006).

It is known that astrocytic response to neuronal activity can be most readily detected by observing changes in the intracellular Ca^{2+} concentrations mediated via calcium flux through the plasma membrane calcium channels or calcium release from intracellular stores. Products of enzymatic activity of CD38 – cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate ($NAADP^+$) – work as potent Ca^{2+} mobilizing second messengers acting at ryanodine receptors (Higashida, et al., 2001a). Immunocytochemical studies revealed association of altered Ca^{2+} regulation in astrocytes (i.e. calcineurin up-regulation) with their activation in aging or Alzheimer's disease models (Norris et al., 2005). Functional ryanodine receptors are required for astrocyte migration that is important component of regenerative process in the brain (Matyash et al., 2002). Therefore, expression and functional activity of CD38 in astrocytes and/or neurons, and ectocellular action of cADPR and $NAADP^+$ on astrocytes resulting in Ca^{2+} signaling (Heidemann et al., 2005; Pawlikowska et al., 1996) would have physiological and pathophysiological meaning as a mechanism of Ca^{2+} signaling involved in neuron-astroglia cell interactions. Alterations in ryanodine receptor binding and function are very early events in the pathogenesis of Alzheimer's disease (Kelliher et al., 1999) while Aβ increases ryanodine receptors expression and function in cortical neurons (Supnet et al., 2006). Taking into account importance of neuronal calcium mishandling in the development of Alzheimer's disease (Verkhratsky, et al., 1998), one can suggest involvement of cADPR-associated signaling pathways in observed ryanodine receptor dysfunction.

Figure 1 summarizes data on NAD^+-generating and NAD^+-converting pathways in mammalian cells.

3. Astroglial CD38 and Cx43 in neuron-glia metabolic coupling

Glial cells can communicate with each other by means of Ca^{2+} waves, and any perturbation of astrocytic intracellular concentration can propagate to other adjacent astrocytes through gap junction formed by connexins (Cx). Astroglial calcium signaling can be linked to synaptic transduction between neurons and neuronal-astroglial metabolic coupling (Allegrini et al., 2009). Cx43-formed gap junctions extensively couple neurons with glia (Nagy et al., 2004), and astrocytes represent the largest gap junction-coupled cellular network within the brain (Nakase & Naus, 2004). In the adult brain, Cx43 levels vary according to the developmental stage and brain region: Cx43 is expressed from early in development and further its expression increases.Cx43 is believed to be mediator of intercellular communication and operator between processes originating from a single astrocyte. In astrocytes, connexons are activated at metabolic inhibition, pro-inflammatory microenvironment, brain injury. Cx43 contributes to paracrine pathways in astroglial cells by regulating Ca^{2+} waves and uptake and release of glutamate, ATP, glucose, and glutathione (Giaume et al., 2010).

Astroglial cells express connexin-based gap junction channels and hemichannels that allow passage of molecules between the cytoplasm and extracellular cells or between the cells

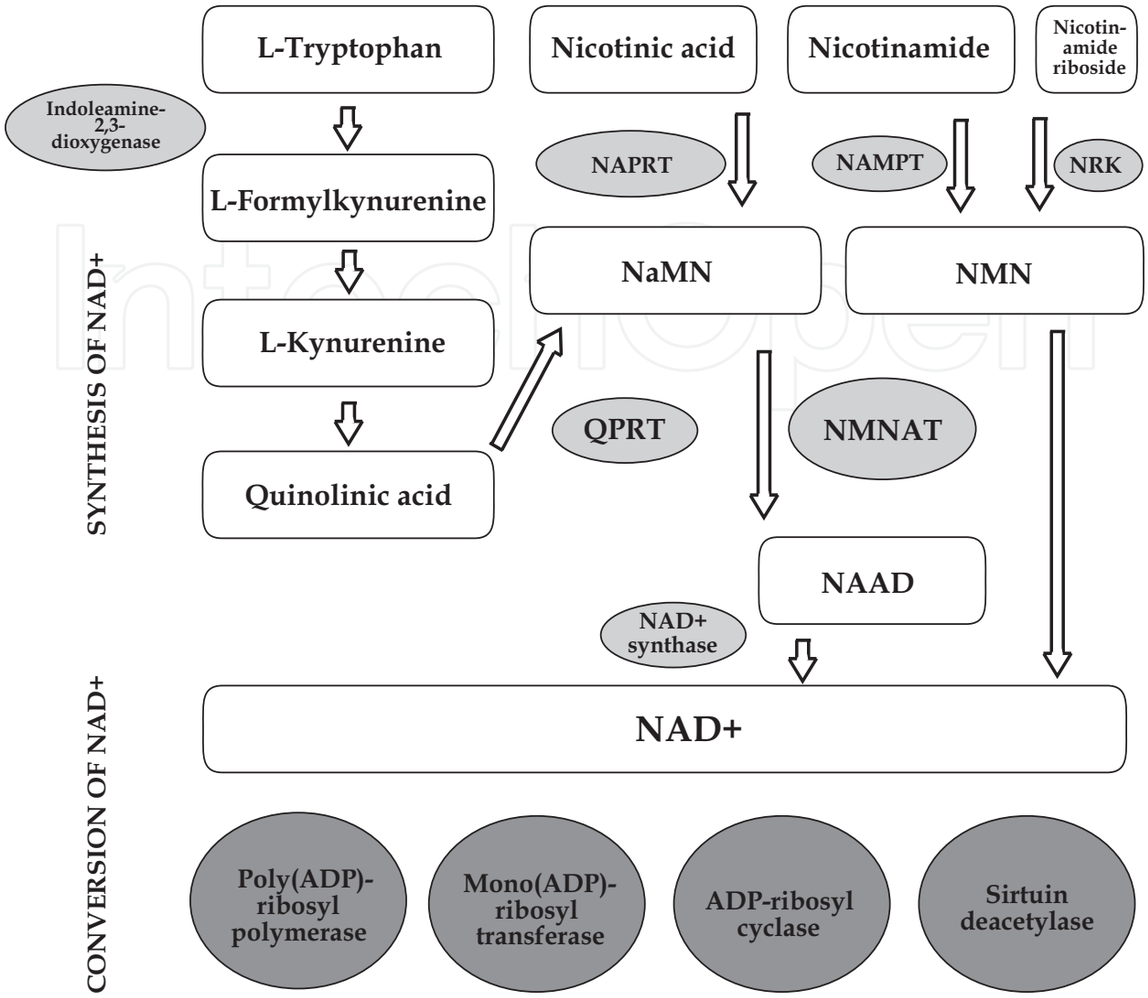


Fig. 1. Metabolism of NAD^+ in mammalian cells. Abbreviations used: NAPRT – nicotinic acid phosphoribosyltransferase, NAMPT – nicotinamide phosphoribosyltransferase, NRK – nicotinamide riboside kinase, NaMN – nicotinic acid mononucleotide, NMN – nicotinamide mononucleotide, QPRT – quinolinate phosphoribosyltransferase, NMNAT – nicotinamide mononucleotide adenylyltransferase, NAAD – nicotinic acid adenine dinucleotide, NAD^+ - nicotinamide dinucleotide

(Contreras et al., 2004). Synapse-glial interactions in the developing, adult and injured brain are very important for brain plasticity. Distinct phases of synapse development depend on assistance from glial cells (Pfrieger, 2010). Astrocytic hemichannels consisted of connexin 43 mediate release of glutamate and other amino acids (Ye et al., 2003). Gap junction channels allow the coordination of intrinsic or elicited metabolic and/or electrical responses of cells in a heterogenous population, and regulate poroliferative activity of astroglial cells. Astrocytes with a radial glia–like morphology in the subgranular zone of the dentate gyrus are considered as stem cells which give rise to neurons within different regions of the adult brain. Radial glia-like cells express GFAP, nestin, and Cx43. The latter contribute to controlling proliferation and differentiation of these cells since no other mechanisms (i.e. glutamatergic) have been detected in radial glia-like cells (Kunze, 2009).

Two primary hypotheses of gap junction coupling in the CNS are the following: (1) generalized coupling occurs between neurons and glia, with some connexins expressed in both neurons and glia, and (2) intercellular junctional coupling is restricted to specific coupling partners, with different connexins expressed in each cell type. The most important question is a role of connexon in mediating communication between different cell types in the brain (Rash et al., 2001). It is well-known that intercellular calcium signaling between different types of glial cells (astrocytes and oligodendocytes) is mediated by Cx43 (Parys et al., 2010). Several connexin proteins have been identified at gap junctions between neuronal and astroglial cells. Moreover, expression of Cx43 but at much lower levels comparing to astrocytes has been detected in oligodendrocytes, Schwann cells and neurons (Nagy, et al., 2004). However, astrocytes are still considered as connexin-dependent signaling cells (Saez, 2008). Expression of Cx43 is closely related to the role of astrocytes in coordinating the neuronal signals and local blood flow (neurovascular coupling).

In the CNS, expression and activity of Cx43 are modulated by cytokines, NO. Recently, novel protein interacting with Cx43 in astrocytes has been identified – brain-derived integrating factor-1 (BDIF-1) which is probably involved in regulating of astroglial activity (Ito et al., 2011). Pharmacological modulation of Cx43 can be achieved by various compounds (Dhein et al., 2002). T. Nakase et al. (Nakase & Naus, 2004) reported that the activation of astrocytes associated with an increase in the expression and activity of connexin 43 protects neurons from ischemia-induced damage. It should be noted that Cx43 can provide NAD^+ to the ectodomain of CD38. In fibroblasts, Cx43 hemichannels mediate release of NAD^+ to the extracellular medium, presumably allowing cytoplasmic NAD^+ to reach the active site of ADP-ribosyl cyclase/CD38 located at the extracellular part of plasma membrane (Franco et al., 2001). The same mechanism could work in astrocytes (Verderio et al., 2001) since glutamate-induced CD38 overexpression in astrocytes was observed in the model of neuronal-astroglial cell coupling. Functional cross-talk between Cx43 hemichannels and CD38 may be triggered by elevation of intracellular Ca^{2+} concentrations or by binding of a ligand to Cx43 or CD38. De Flora et al. (De Flora et al., 2004) suggested that extra phosphorylation of Cx43 induced by Ca^{2+} rise decreases the open-state probability of connexons, thereby downregulating NAD^+ transport across them and resulting in lower access of NAD^+ to the active site of CD38 and decreasing cADPR generation and limiting of Ca^{2+} levels inside the cell. Thus, autocrine and paracrine Ca^{2+} signaling is mediated by Cx43-CD38 system. Whether or not such system is operating in astrocytes in the context of neuronal-astroglial coupling remains to be elucidated. This mechanism is very important, because it helps to prevent NAD^+ loss from cells, depletion of intracellular NAD^+ due to elevated CD38 activity, and cADPR overproduction leading to calcium accumulation to toxic levels (Salmina et al., 2009a).

CD38 and Cx43 also may serve as transporters of nucleotides (NAD(H), cADPR, and $NAADP^+$) into the cell from the extracellular space (Billington, et al., 2008), thus contributing to maintaining NAD^+ homeostasis within the cell. NAD^+ itself can enter astrocytes via gap junction-mediated pathway (Ying, et al., 2005).

What are the possible roles for Cx43 hemichannes in neurodegenerative processes? Elevated expression of Cx43 in reactive astrocytes may reflect: 1) extensive buffering of neurotoxic substances by activated astroglial cells required for protecting the neurons from cell death (i.e. inhibition of gap junctions with octanol abolishes the ability of Aβ to enhance the velocity and extent of propagation of astroglial calcium waves (Orellana et al., 2009));

2) propagating Ca^{2+} waves between communicating astrocytes and/or individual processes of a single cell; 3) active proliferation and migration of Cx43-immunopositive progenitor cells to the site of neurodegeneration; 4) activation of autocrine and paracrine signaling in astrocytes and adjacent neurons; 5) action of stimuli (prooxidant and proinflammatory) able to increase Cx43 expression. In neurodegenerative diseases and ischemia, reactive astrocytes have increased levels of Cx43, and changes in Cx43 expression are dependent on the proximity of the reactive astrocytes to the focus of neurodegeneration. In the site of injury, reactive astrocytes can lose their non-overlapping domains (Giaume, et al., 2010).

Functional hemichannels that have a role in glutamate homeostasis may significantly contribute to astrocyte-mediated regulation of neuronal activity. It is interesting that in the Alzheimer's type of neurodegeneration, elevated expression of Cx43 has been detected at β-amyloid plaques due to reactive astrogliosis (Mei et al., 2010). It was suggested that in Alzheimer's disease, increased Cx43 expression might represent an attempt to maintain tissue homeostasis by augmented intercellular communication via gap junction formation between astrocytic processes that invest senile plaques. In addition, one can propose that elevated expression of Cx43 hemichannels could result in massive release of glutamate from astrocytes into the extracellular space resulting in excitotoxic injury of neurons. Connexin 43 regulates astrocytic migration and proliferation in response to injury. Reactive astrocytes display up-regulation of the gap junction protein Cx43, and astroglial cells with depleted expression of Cx43 show diminished ability to migrate and to proliferate in the wound area of the brain (Homkajorn et al., 2010). Drebrin as an actin binding protein whose level is greatly decreased in brains of Alzheimer's patients was found to be a binding partner of the Cx43 COOH-terminal domain in astrocytes. In experimental model, depletion of drebrin in cells results in impaired cell-cell coupling, internalization of gap junctions, and targeting of Cx43 to a degradative pathway (Butkevich et al., 2004)]. It was suggested that increased Cx43 expression in a close vicinity to amyloid plaques might represent aberrant induction of Cx43 expression stimulated by excessive degradative pathway. In support of this hypothesis, increased expression of Cx43 was found to be induced by β-amyloid precursor protein (Hallaq & Killick, 2006)], thus suggesting direct effect of amyloid deposites on the mechanism of glutamate release from astroglial cells and neuron-astrocyte communication.

Recently, changes in expression and activity of Cx43 have been registered in rotenone-induced model of Parkinson's disease: enhancement of Cx43 protein levels in cells treated with rotenone (mitochondrial complex I inhibitor) resulted in increased efficacy of gap junctional intercellular communication (Kawasaki et al., 2009). However, some authors registered inhibited expression of astrocytic Cx43 and gap junction permeability in astrocytes in rotenone models of Parkinson's disease. Moreover, rotenone-induced dysfunction of astrocytic Cx43 can be reversed by opening mitochondrial ATP-sensitive potassium channels (iptakalim and diazoxide) resulting in prevention of astrocyte apoptosis (Zhang et al., 2010). Thus, we believe that Cx43-CD38 functional coupling in astrocytes significantly contribute to controlling energy homeostasis in astroglial and neuronal cells.

Opening of the mitochondrial permeability transition pore is known to play a role in cell death. Its opening has been shown to cause activation of NAD^+ glycohydrolase located in the outer mitochondrial membrane following by NAD^+ hydrolysis in cardiomyocytes at postischemic reperfusion (Di Lisa et al., 2001). Since mitochondrial NAD^+ glycohydrolase has been identified as ADP-ribosyl cyclase (Ziegler et al., 1997), NAD^+ released from mitochondrial matrix could be transformed into cADPR which promoting Ca^{2+} release from

intracellular stores. Thereby, amplification of initial rise in intracellular Ca^{2+} levels might be important in cell damage. It was reported that mitochondrial dysfucntion leads to postponed changes in CD38 expression (Mills et al., 1999). Thus, accumulating data suggest that ADP-ribosyl cyclase may affect mitochondrial functioning through various mechanisms.

Mitochondrial localization of Cx43 has been shown in cardiomyocytes, and the role for Cx43 as regulator of mitochondrial potassium uptake (Miro-Casas et al., 2009) or mitochondrial respiration (Boengler et al., 2008a) has been suggested. Stimulatory effect of Cx43 on mitochondrial KATP channels resulting in cytoprotectiion has been shown in cardiomyocytes (Rottlaender et al., 2010). It is intriguing to speculate that mitochondrial Cx43 contributes to regulation of respiration and potassium uptake in astroglial cells, thus providing adaptation of mitochondrial activity to altered microenvironment in activated astrocytes in the site of brain injury. It was proposed that Cx43 may directly regulate respiratory chain complex I activity and mitochondrial oxygen consumption: decrease in mitochondrial Cx43 levels reduced complex I activity (Boengler et al., 2008b).

Mitochondrial localization of CD38 is well documented. I. Balan et al. (Balan et al., 2010) detected NAD^+- glycohydrolase activity in isolated synaptosomes and also in intact brain mitochondria, confirming localization of CD38 also in outer mitochondrial membranes. Interestingly, the NAD^+- glycohydrolase activity appeared to be much higher in nonsynaptic mitochondria compared with mitochondria isolated from synaptosomes. Taken together, these data suggest that NAD^+ depletion can occur more rapidly in astrocytes following ischemic insult, compromising the ability of astrocytes to support neuronal functions. Interestingly, the NAD^+ catabolic activity is higher in brain regions that are vulnerable to ischemic insult, furthermore, the CD38 NAD^+ glycohydrolase activity is significantly increased in postischemic tissue, and the immunohistochemistry shows overexpression of this enzyme preferentially in neuroglial cells (Kristian et al., 2011; Salmina, et al., 2008; Salmina, et al., 2009a). Activation of CD38 can lead to rapid and almost complete tissue NAD^+ depletion (Balan, et al., 2010). A prolonged MPT results not only in dissipation of the mitochondrial electrochemical hydrogen ion gradient and swelling of mitochondria but also depletion of pyridine nucleotides from the matrix (Di Lisa & Ziegler, 2001), however, significant loss of matrix pyridine nucleotides can lead to inhibition of mitochondrial respiration but without irreversible damage to the respiratory complexes or mitochondrial membranes (Kristian, et al., 2011). It was proposed, that once the cellular CD38 enzymatic pool is saturated, cytosolic NAD^+ concentrations rise to a level that permits efflux into extracellular space where NAD^+ becomes to be the substrate for surface-expressed CD38 acting as autocrine or paracrine regulator of Ca^{2+} signaling.

Neurodegeneration is associated with altered energy metabolism in the brain; accumulation of glycolytic enzymes, such as enolase and glyceraldehyde 3-phosphate dehydrogenase, decrease in expression of voltage-dependent anion-selective channel protein-1 (VDAC-1), and decrease in expression of subunits of multiprotein enzyme complex NADH:ubiquinone oxidoreductase (complex I of the mitochondrial electron transport chain) have been registered in Alzheimer's disease (Butterfield et al., 2003)]. It is well known that astrocytes play important roles in supporting energy production in neurons. According to astrocyte-neuron lactate shuttle hypothesis, lactate is produced in an activity-dependent and glutamate-mediated manner by astrocytes and is then transferred to and used by active neurons (Pellerin et al., 1998). Neuronal activation results in uptake of glutamate by astrocytes leading to activation of glutamine synthetase and Na^+-K^+-ATPase, followed by

activation of anaerobic glycolysis in astrocytes, and release of lactate supporting the activity-related energy required for neurons (Magistretti, 2000)]. In general, astrocytes metabolize glucose mainly to lactate and release it into the extracellular medium, while neurons appear to have a kinetic preference for oxidizing lactate imported from the external medium over pyruvate/lactate produced in neurons by glycolysis (Itoh et al., 2003). However, neurons die more intensively than astrocytes even though the apparent dysfunction takes place in astrocytes. Glycolysis is high in astrocytes, so they need a way to maintain the adequate levels of NAD^+. Probably, astrocytes can sustain themselves adequately with glycolytic metabolism, not significantly affected by mitochondrial dysfunction, thereby being more resistant to oxidative stress and NAD^+ depletion.

4. CD38 expression in acute and chronic neurodegeneration

Very few data are available on CD38 expression in neurodegeneration. In different experimental models of acute and chronic neurodegeneration in rats (focal brain ischemia, rotenone model of Parkinson's disease, and perinatal hypoxic-ischemic brain injury), we found elevated expression of CD38 in neurons and astroglial cells in the acute period of brain injury (Salmina, et al., 2008; Salmina, et al., 2009a; Salmina et al., 2006a).

In the model of perinatal hypoxic-ischemic brain damage, we found that changes in CD38 expression and ADP-ribosyl cyclase activity in neuronal and glial cells attribute to alterations in intracellular NAD^+ level as well as to susceptibility of the cells to the action of apoptogenic stimuli; acute period of perinatal hypoxic/ischemic brain injury is characterized by reactive astrogliosis and elevation of CD38 expression, changes in CD38 and Cx43 expression in astrocytes serving as markers of neuron-glial interactions in perinatal CNS injury; ADP-ribosyl cyclase activity in neurons in response to stimulation of NMDA is changed after perinatal hypoxic-ischemic brain injury. It has been demonstrated that, in the immature brain, the impairment of intracellular calcium homeostasis is the leading mechanism of perinatal damage to both neuronal and glial cells (Vannucci et al., 2001). Based on our data, we can conclude that the mechanisms of maintenance of intracellular calcium homeostasis, which are under the control of ADP-ribosyl cyclase and Cx43, play a special role in responses of neurons and glia to hypoxic–ischemic damage.

We demonstrated that most of the cells that expressed Cx43 were CD38-immunopositive in acute neurodegeneration. Interestingly, in the 10-day-old rats subjected to cerebral damage, the number of Cx43 and CD38 coexpressing cells was several times higher as compared to GFAP and CD38 coexpressing cells, whereas the fractions of cells that expressed both GFAP and CD38 were similar in the control and experimental groups. These data suggest that other types of Cx43-containing cells, such as microglia, substantially contributed to the total elevation in CD38 expression after perinatal brain damage. Taking into account the data on the functional coupling of CD38 ADP-ribosyl cyclase activity and connexin 43, we studied the effects of a connexin blocker, glycyrrhetinic acid (GRA), on ADP-ribosyl cyclase activity in astrocytes isolated from brain tissue of control and experimental animals. We found that a 30-minute incubation of astrocytes with 5μM GRA resulted in decrease in ADP-rybosyl cyclase activity in these cells (Salmina, et al., 2009a).

In the model of focal brain ischemia in adult animals, we confirmed that CD38 could be considered as a marker of neuron-glia interactions disturbances caused by acute ischemic injury, and that modulation of ADP-ribosyl cyclase/CD38 expression and activity in the

brain significantly improved clinical manifestations of neurological dysfunction associated with ischemia-induced neurodegeneration (Salmina, et al., 2006a).

In patients with ischemic stroke, elevated expression of CD38 in peripheral blood leukocytes corresponds to formation of membrane-derived microparticles and progression of endothelial dysfunction due to CD38-CD31 interactions (Inzhutova et al., 2008; Salmina et al., 2010b). It is well known that astrocytes play important role in the formation, extent and configuration of the junctional complexes in the brain endothelium in a manner that astrocyte-induced enhanced tight junction communication is associated with the reduction of gap junctions. A major function of the neurovascular unit is to regulate the transport and diffusion properties of brain capillary endothelial cells that compose the brain-blood barrier (Banerjee & Bhat, 2007). Astrocytes exhibit anatomic relationships with cerebral arterioles and neurons. In the brain parenchyma, the extensive ensheatment of cerebral arterioles by astrocytic end-feet far exceeds any direct neural contacts with those perfusion-regulating microvessels. That unique arrangement permits astrocytes to transduce signals arising from activated neurons and to transmit that information to the cerebral microcirculation (Xu et al., 2008).

Coupling of NMDA receptors to ADP-ribosyl cyclase/CD38 in neuronal and glial cells, involvement of CD38 in neuronal-glial (Higashida et al., 2007a; Salmina, et al., 2009a) and leukocyte-endothelial interactions (Deaglio, et al., 2008; Inzhutova, et al., 2008; Malavasi et al., 2008) suggest new approach to treat endothelial dysfunction caused by various stimuli, i.e. by homocysteine (Boldyrev, 2010) in neurodegenerative processes.

As we mentioned above, in acute neurodegeneration, $CD38^+$-expressing cells were predominantly represented by $GFAP^+/Cx43^+$ cells of astroglial origin. We found that in neurons, elevated CD38 expression resulted in intracellular NAD^+ depletion and cell death, while in astrocytes high levels of CD38 expression relate to increased resistance to the action of apoptogenic stimuli, development of reactive gliosis, and changes in their glycolytic activity. Mitochondrial ADP-ribosyl cyclase activity was mainly induced by ischemic stimuli. Our data well fit the previous observations that intracellular NAD^+ levels regulate astroglial response to neuronal activation, NAD^+ released from astrocytes regulate apoptosis of neurons in postischemic period, and astrocytes are more resistant to hypoxia than neurons.

In the developing brain, direct correlation between the CD38 expression and apoptosis development in the given cell populations has been registered. We found stimulating effects of agonists of mGluRI, mGluRIII, suppressive effects of agonists of NMDAR on CD38 activity in premature injured brain cells. However, in the adult brain, reverse correlation between CD38 expression and apoptosis progression was observed. Under the pathophysiological conditions, development of cell death and ability of brain cells to maintain the levels of intracellular NAD^+ are determined by hypoxia/ischemia-induced disturbance in the dynamics of ADP-ribosyl cyclase activity in the brain cells. These data are in agreement with our report on the contribution of CD38 overexpression to development of plasma membrane blebbing in neuroblastoma x glioma NG108-15 hybrid cells (Egorova et al., 2000).

In the experimental model of Parkinson's disease, we found that loss of dopaminergic neurons via apoptosis was associated with elevation of expression and activity of ADP-ribosyl cyclase/CD38 in remaining tyrosine hydroxylase-immunopositive cells. Immunochemical studies with anti-CD38 antibodies indicated accumulation of CD38 antigen in the neurofibrillary tangles that occur in neuronal perikarya and proximal

dendrites in Alzheimer's disease (Otsuka et al., 1994). Literature data suggest that in Alzheimer's disease, accumulation of CD38 antigen in the neurofibrillary tangles, an association of altered Ca^{2+} regulation in astrocytes, alterations in ryanodine receptors binding and functions are detectable.

Dramatic rise in CD38 messenger RNA levels in IL-1β-activated astrocytes was reported in HIV-associated neurodegeneration and dementia: in astrocytes, pre-treatment with the cADPR-specific antagonist 8-Br-cADPR and CD38 siRNA transfection returned elevated $[Ca^{2+}]_i$ to baseline, thus confirming a CD38-cADPR specific response. These data have broader implications in other inflammatory diseases involving astrocyte activation and CD38 dysregulation (Banerjee et al., 2008).

We suggest that possible causes of elevation of CD38 expression in brain cells are the following: 1) changes in NAD^+ bioavailability (release from mitochondria into cytosol, cell death, connexin Cx43 activation); 2) redistribution of the enzyme in the cells; 3) cytokine-dependent (IL, TNF) changes in expression of gene encoding for CD38 in the sites of brain injury of neurodegeneration; 4) action of neuro- and gliotransmitters. Since CD38 expression in astrocytes is stimulated by glutamate release from neurons, we can suggest that CD38 is a marker of altered neuron-astrocyte interactions under the conditions of excitotoxic insult. Also, since mitochondrial complex I dysfunction causes elevation of CD38 expression, we suggest that CD38 is a marker of mitochondrial dysfunction in the context of neuron-glia metabolic coupling. Activity of Cx43 prevents NAD^+ depletion in CD38-overexpressing astrocytes and provides enough NAD^+ for glycolysis, thus making astrocytes more resistant to the action of stimuli causing neurodegeneration.

Therefore, we propose that expression of CD38 in neuronal and glial cells: 1) is regulated under (patho)physiological conditions; 2) is associated with various signal transduction pathways (i.e. GluR in neurons and Cx43 in astrocytes) whose activity is important for molecular pathogenesis of neurodegeneration; 3) reflects – specifically or non-specifically – mitochondrial dysfunction; 4) could be considered as a target for pharmacological correction of neurodegeneration. Deciphering of CD38-associated molecules/events in neuronal and glial populations would give us new biomarkers for diagnostics of neurodegeneration, while pharmacological manipulation of ADP-ribosyl cyclase activity in brain cells would provide new therapeutic opportunities for the treatment of neurodegenerative disorders.

5. Modulation of NAD^+ metabolism in glial cells as therapeutic approach in neurodegeneration

Manipulating the neuron-glial cell interactions associated with changes in NAD^+ levels represent one of the promising approaches to treatment of Alzheimer's disease (Braidy et al., 2008; Henricksen & Federoff, 2004). Pharmacological manipulation may be targeted to the modulation of intracellular NAD^+ metabolism with substances affecting activity of NAD^+-synthesizing and NAD^+-converting enzymes, modulators of NAD^+-dependent enzymes (i.e. sirtuins, glycolytic enzymes), regulators of tryptophan kynurenine metabolism, substrates of NAD^+ synthetic pathways, ligands and regulators of CD38 expression and activity, modulators of NAD^+ and cyclic ADP-ribose transport across the membrane (i.e. Cx43).

Metabolism of NAD^+ could be efficiently regulated by inhibitors of mono(ADP-ribosyl) transferase and poly-ADP-ribosyl polymerase activities. Pharmacological interventions aimed at inhibiting PARP activity have been shown to be efficient in prevention of PARP-mediated death of neurons and astrocytes (Ying, et al., 2002). Several studies have suggested

the therapeutic potential of sirtuins (NAD^+-dependent histone deacetylases consuming NAD^+) for Alzheimer's disease (Anekonda & Reddy, 2006). Inhibitors of kynurenine 3-hydroxylase can reduce the production of neurotoxic metabolites (Khan et al., 2007). It was reported that decreases in β-amyloid content in the brain can be achieved by governing cellular sirtuin activity (Qin et al., 2006). Improvement of cognitive functions was detected after treatment with oral stabilized NADH (Demarin et al., 2004), probably, due to ability of NADH to enter into astrocyets and block PARP-mediated astrocyte death (Zhu et al., 2005). However, efficacy of NADH to correction of cognitive dysfunction in dementia remains to be ambiguos (Rainer et al., 2000). Recently, CD38 was suggested as a new target for dementias including Alzheimer's disease (Chini et al., 2007). It is interesting enough that NAD^+ (and, probably, NADH) can be transported across the plasma membranes of astrocytes through connexin hemichannels (Verderio, et al., 2001) or purinergic receptors (Lu et al., 2007), thus suggesting new approach to manipulating its intracellular concentrations and metabolism.

Overexpression of NMNAT results in suppression of Wallerian degeneration in neurons, however, in Cd38-/- cells with higher levels of intracellular NAD^+ no difference in the axon degeneration patterns were registered. In general, increased NAD^+ synthesis is responsible for axonal protection (Yan et al., 2010). In vitro NNMT expression significantly decreased cell death which correlated with increased intracellular ATP content, ATP: ADP ratio, Complex I activity and a reduction in the degradation of the NDUFS3 subunit of Complex I. These effects were replicated by incubation of cells with 1-methylnicotinamide. In the context of pathogenesis of Parkinson's disease, it is important that both NNMT expression and 1-methylnicotinamide protected SH-SY5Y cells from the toxicity of the Complex I inhibitors MPP^+ and rotenone by reversing their effects upon ATP synthesis, ATP:ADP ratio, Complex I activity and the NDUFS3 subunit (Parsons et al., 2011). Overexpression of SIRT1 or its activation in neuronal and glial cells with resveratrol has been shown to protect the brain tissue from degeneration in Alzheimer's disease and Huntington's disease, and calorie restriction able to modulate SIRT activity is neuroprotective against Parkinson's disease and Alzheimer's disease (Outeiro et al., 2008). Modulation of TRPM channels which are abundantly expressed in the brain has neuroprotective activity in Parkinson's disease and Alzheimer's disease (Yamamoto et al., 2007). Protection of neurons from glutamate and β-amyloid toxicity was achieved by preloading neurons with creatine (Brewer & Wallimann, 2000) or by pyruvate (Massieu et al., 2001). The latter as well as another tricarboxilic acid cycle substrate – α-ketoglutarate - were also potent in preventing death of neurons and astrocytes caused by intracellular NAD^+ depletion (Ying, et al., 2002).

Experimental pharmacological intervention in the cADPR-signaling pathway are usually restricted to two targets, the cADPR-binding protein and the ADP-ribosyl cyclase (Guse, 2000). The agents used for such properties are: a) cADP-ribose and its analogues; b) modulators of ryanodine receptors activity such as caffeine, ryanodine, procaine, ruthenium red; c) ligands of FKBP. The usefulness of cADP-ribose as a pharmacological tool is limited by its rapid hydrolysis, therefore various cADPR analogues have been synthesized.

Among all inhibitors of NAD^+-consuming enzymes, nicotinamide attracts the biggest interest. Nicotinamide has several cellular functions in CNS and serves as an anxiolytic, increases brain choline concentrations and is endogenous ligand of benzodiazepine receptors (Maiese & Chong, 2003). Neuroprotective action of nicotinamide has been reported in neurons at oxidative stress even it may be attributed to changes in glycolysis, apoptotic machinery, MAP kinase activity etc. rather than inhibition of NAD^+

glycohydrolases. Age-dependent susceptibility of glial cells to the action of nicotinamide analogs has been reported (Krum, 1995). 6-aminonicotinamide as niacin antagonist produces neurotoxic activity by inducing inflammatory response of astroglial and microglial cells (Penkowa et al., 2003). But using of inhibitors of NAD^+ hydrolysis may have even unfavorable results: partial inhibition of poly-ADP-ribosylation with 5-iodo-6-amino-1,2-benzopyrone preserves NAD^+ and improves functional outcome after traumatic brain injury, whereas more complete inhibition impairs spatial memory acquisition independent of injury (Satchell et al., 2003). Therefore, cytoprotection with inhibitors of NAD^+-consuming enzymes might be concentration specific. We found that nicotinamide (500 mg/kg) reduced expression of CD38 in the brain cortex in the model of ischemia-induced acute neurodegeneration in adult rats in vivo and potentiate neurological dysfunction caused by ischemia, thereby further confirming ambiguity of nicotinamide action on neuronal and glial cells.

Retinoic acid (RA) is a potent inducer of CD38 in peripheral blood cells, and recently it was suggested that this compound can be used to 'rescue' cells exhibiting low CD38 synthesis and hence might be a novel therapeutic strategy in treatment of autism associated with impaired CD38 expression in neurosecretory cells (Ebstein et al., 2011). Cultured astrocytes express the key enzyme mRNAs of retinoic acid biosynthesis and actively produce retinoic acid acting at RA receptors (RAR). Synthesis of retinoic acid in astrocytes is provided by retinal dehydrogenase and alcohol dehydrogenase (Wagner et al., 2002). It was shown that blockage of retinoic acid signaling by the pan-RAR antagonist prevented glia-induced neuron formation by noncommitted stem cells, thus suggesting a role for retinoic acid in astroglia-induced neuronal differentiation (Kornyei et al., 2007). Retinoids control expression of wide spectrum of genes in neuronal and glial cells (Lane & Bailey, 2005).

We tested effect of all-trans retinoic acid in vivo (20 mg/kg with ethanol to suppress endogenous synthesis of retinoic acid) in rats with experimental model of perinatal ischemic-hypoxic acute neurodegeneration. We found that suppression of endogenous synthesis of retinoic acid with ethanol reduced expression of CD38 in the cortex, while retinoic acid itself partially restored the level of CD38 (Salmina et al., 2009b).

Retinoid and retinoid-associated signaling plays an essential role in normal neurodevelopment and appears to remain active in the adult CNS. Molecular factors involved in RA-mediated responses become up-regulated in the adult CNS as a consequence of injury or degeneration. Our data and recent findings of R. Ebstein et al. (Ebstein, et al., 2011) suggest that intervention that modulates RA-regulated CD38 may have therapeutic potential in CNS disorders. It is interesting that a prolonged regime of vitamin A deprivation in adult rats has been shown to cause a deposition of β-amyloid peptide in the forebrain, RA could regulate the expression of the tau protein, and in particular the level of phosphorylated forms of tau, as suggested by *in vitro* observations, vitamin A, as well as β-carotene and coenzyme Q10, have also been shown to dose-dependently inhibit the formation of α-synuclein fibrils *in vitro,* RA reduces the effect of β-amyloid, and thus inhibits the neurotoxic effect of activated microglia, by suppressing the production of these cytotoxic molecules (Malaspina & Michael Titus, 2008). Retinoid receptors are involved in the regulation of brain functions, and retinoic acid signaling defects may contribute to pathologies such as Parkinson's disease (Krezel et al., 1998). Whether or not these events are associated with NAD^+-converting activity of CD38 in neuronal and astroglial cells remains to be elucidated.

6. Concluding remarks and outstanding questions for further investigation

So far, several hypotheses have been suggested to explain pathogenesis of acute and chronic neurodegenration. Almost all of the proposed mechanisms include processes considered as gliopathy (Maragakis & Rothstein, 2006; Verkhratsky, 2010). Different molecules mark gliopathological changes, and CD38 expressed in astroglial cells should be considered as one of the markers of neuron-astrocyte metabolic coupling. Neuron-glia communication is responsible for establishment of vicious circles in the pathogenesis of neurodegeneration, therefore deciphering new molecular mechanisms of intercellular communication will provide us with new diagnostic and therapeutic strategies. To achieve this goal in the context of NAD^+-controlled neuronal-astroglial coupling, the following questions should be addressed:

1. Which glial- and neuronal-derived factors can affect NAD^+ metabolism in acute and chronic neurodegeneration? What is an integrative scheme for NAD^+ homeostatic mechanisms in neurons and astrocytes?
2. What is the role for CD38-Cx43 interactions in initiation and progression of mitochondrial dysfunction in neurodegeneration?
3. Which molecular mechanisms coupled to NAD^+ homeostasis in brain cells are involved in axonal degeneration and neuronal repair?
4. Which new biomarkers could be developed for early diagnostics of astroglial dysfunction in neurodegeneration? Which molecular targets in neurons and glial cells could be efficiently used for the appropriate treatment of neurodegeneration?

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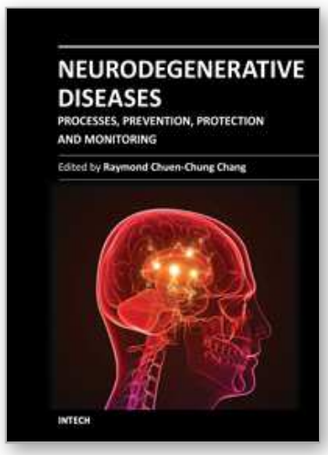
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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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