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REVIEW

NMDA Receptors in Immune Competent Cells

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Abstract—This review presents analysis of literature data indicating the presence of NMDA-type glutamate receptors in several types of immune competent cells such as thymocytes, lymphocytes, and neutrophils. The possible role of these receptors in the function of these cells is discussed. The interaction of the receptors with certain ligands circulating in the bloodstream and their role in modulation of immune function is described. It is suggested that homocysteine acts as modulator of these receptors, and its toxicity is largely explained by hyperactivation of the NMDA-type glutamate receptors.

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Glutamate ionotropic receptors of NMDA type, which play a unique role in neuronal function, draw specific attention because of their participation in mechanisms of recognition and memory. These receptors are widespread in the neuronal systems of both invertebrates and vertebrates. The receptor is a tetramer consisting of two heterodimers, the NR1 subunit and one of the species of NR2 subunits (NR2A, NR2B, NR2C, or NR2D) being the obligatory partners. Each subunit consists of an N-terminal domain, three transmembrane domains, one internal (channel-forming) loop, and an intracellular C-terminal domain. The N-terminal part contains ligand-binding sites, whereas the C-terminal domain has some sites for interaction with intracellular regulatory proteins. The NR2 subunits in invertebrate neurons have a much smaller C-terminal domain that contains no sites for regulatory proteins [1].

A glutamate-binding site is located on NR2 subunits, whereas NR1 contains binding site for glycine, which serves as a co-agonist of glutamate. Recently, the presence of another isoform of NMDA receptor has been shown; it contains an NR3 (instead of NR2) subunit also containing a glycine-binding site. This isoform is rather broadly represented in neuronal systems of different animals; it characteristically has lower penetration for calcium, and its function is not clear [2].

The subunits of NMDA receptor are coded by seven different genes, *NR1*, *NR2A-NR2D*, *NR3A*, and *NR3B*, and the product of *NR1* gene expression can undergo alternative splicing to form eight isoforms [3]. Different isoforms of NR2 subunit are expressed in cells of different type. NR2 defines the electrophysiological properties of the receptor. This suggests that formation of functionally active tetramer is a result of interaction of two preformed dimers, and which dimers are formed initially (homo- or heterodimers) is still unknown [4].

NMDA receptors play an important role in maturation of the central nervous system, generation of respiratory rhythm and locomotion, as well as in learning processes and neuronal plasticity. The latter property is tightly related to their ability to activate intracellular signal mechanisms involving mitogen activated protein kinases, MAPK [5]. MAPK regulate cellular response to a variety of extracellular signals (osmotic stress, heat shock, cytokines, mitogens, etc.) and affect cell division, differentiation, and apoptosis.

Recently data were published showing that final result of activation of intracellular components of the MAPK family depends of the strength and longevity of an extracellular signal. Activation of NMDA receptors clearly results in a short-term phosphorylation of components of the MAPK system, which provides for their transient activation. Such activation is an important factor of neu-

Abbreviations: HC, homocysteine; HCA, homocysteic acid; MPO, myeloperoxidase; NMDA, *N*-methyl-D-aspartate; ROS, reactive oxygen species.

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ronal viability and realization of long-term potentiation; however, long-term activation of the MAPK cascade has a proapoptotic effect [6]. This process disorders recognition of specific substrates by MAPK partners, which results in phosphorylation of proteins not restricted to this cascade and thus in violation of their function [7].

Various ligands for NMDA receptors can induce non-identical time profiles of MAPK cascade activation. Actually, glutamate and NMDA induce short-term phosphorylation (and thus activation) of the kinase system, whereas homocysteine results in long-term phosphorylation and disordering of the native mode of signal transduction stimulating cellular death [8, 9]. It is noteworthy that hyperactivation of NMDA receptors taking place under several pathological states of the central nervous system and resulting in so called "excitotoxicity" [10] is explained by disordering of normal signal transduction from outer cell membrane to the intracellular kinase cascade.

NMDA receptor subunits form in the neuronal membrane ionic channel penetrable for sodium and potassium as well as for calcium ions, which determines the specific role of these receptors in neuronal function. Entry of calcium into the cytoplasm, which occurs when receptors are activated, induces immediate activation of a variety of proteins associated with the receptors inside the cell. Among these are Ca^{2+}-calmodulin dependent protein kinases responsible for long-term potentiation, a process involved in long lasting neuronal memory formation [11].

Because glycine and glutamate sites are structurally similar, it is suggested that both ligands are important for receptor activation [3]. A structural analog of glutamate, homocysteine, which is a natural metabolite of methionine, is able to modulate NMDA receptor-associated effects of both glycine and glutamate. Under low glycine concentrations, corresponding to its normal levels (up to 10 μM), homocysteine serves as a partial antagonist at the glycine site and restricts receptor activation, thus demonstrating neuroprotective properties, whereas at higher concentrations (more than 100 μM) it shows toxic effect. When glycine is uploaded (typical for patients after stroke or brain trauma) even low concentrations of homocysteine (10-15 μM) have toxic effect on NMDA receptors [12].

In addition to the natural agonists of NMDA receptors (glutamate and glycine), there are some other modulators of NMDA receptors such as polyamines and Zn and Mg ions. Mg is located inside the channel structure of the receptor and prevents ion fluxes. For this reason, activation of NMDA receptor is possible only after depolarization of neuronal membrane by other means, for example after activation of other glutamate receptors (kainate- or AMPA-dependent ones).

Many articles have been published recently that describe expression of NMDA receptors in non-neuronal tissues of humans and other animals [13]. They were found in kidney, lungs, spleen, testis, and ovaries, although their role in these organs is still obscure [14, 15]. Functionally active NMDA receptors are present also in osteoclasts, where they participate in remodeling of bone tissue and osteogenesis [16]. In pancreas, activation of NMDA receptors increases membrane depolarization and concentration of ionized calcium within cells [17]. In rat lungs, activation of NMDA receptors results in edema, which can be prevented by specific blockers of the receptors [18]. In platelets, activation of NMDA receptors in thrombocytes inhibits thromboxane B2 synthesis and suppresses platelet aggregation, this effect being accompanied by increase in intracellular calcium concentration and elevation of cAMP levels [19, 20]. Platelets precursors, megakaryocytes, also express on their membrane NMDA receptors, which take part in proliferation of these cells in marrow; the receptors remain within the membrane after release of platelets into peripheral blood [21].

NMDA receptors were recently found in red blood cells; their function was found to be associated with regulation of calcium entry into the cells [22]. Hyperactivation of these receptors increases the risk of thrombosis, natural agonists of the receptors being homocysteine and homocysteic acid [22, 23].

Expression of NMDA receptors in immune competent cells (thymocytes, lymphocytes, and neutrophils) is suggested to have special importance. Accumulation and constant circulation in peripheral blood of agonists of glutamate receptors described for several pathological and boundary states of mammals (including humans) induce hyperactivation of these receptors and disrupt immune system function.

Thymocytes. The thymus is the organ where T-lymphocytes are matured from predecessor cells. As a result, a great variety of matured T-cells are formed that are able to recognize different antigens. In thymus, several reactions take place simultaneously: proliferation and differentiation of T-lymphocytes as well as selection of functionally competent cells, which is accompanied by death of a significant number of functionally defective cells. Early forerunners of T-lymphocytes from bone marrow enter into the cortical layer of the thymus and then migrate into the medullar layer where they meet thymic epithelial cells, macrophages, and dendritic cells. When entering the medullar region, thymocytes become matured (differentiated) and acquire step-by-step specific for matured T-cells membrane receptors and antigens. From stromal cells they received signals regulating the proliferative process, change in surface phenotype, and rearrangement of genes responsible for presentations of specific antigen-recognizing receptors [24].

NMDA receptors are supposedly involved in a definite step of thymocyte maturation. Glutamate receptors on the membrane of isolated thymocytes and thymic

stromal cells were first identified in 2000; the receptors were classified as metabotropic receptors of groups I and II [25]. These receptors were suggested to be involved in T-cell maturation via inositol trisphosphate turnover and cAMP synthesis.

Actually, it was found that in cultured thymic cells glutamate induces apoptosis affecting the Bcl-2/Bax ratio, which are antiapoptotic and proapoptotic protein regulators, correspondently [26]. This pointed out the possible participation of glutamate receptors in regulation of thymus function. Finally, NMDA receptors were identified within thymocyte membrane where their participation in Ca^{2+}-dependent stimulation of caspase-3 was demonstrated when these receptors were activated during direct contact of thymocytes with dendritic cells [27].

These facts suggest an ability of T-cells to express NMDA receptors and stress a necessity to elucidate their role in immune response of the organism.

Lymphocytes. These cells are a heterogeneous population in terms of their properties and functions. Several subpopulations of lymphocytes are distinguished.

T-Lymphocytes. Multiple sorts of T-cells with a variety of functions are known. Some are interacting with B-cells helping their multiplication, maturation, and antibody production. Others interact with mononuclear phagocytes favoring destruction of foreign microorganisms. All these cells are named helpers. The following subpopulation of T-cells destroys body cells infected by viruses or other pathogenic microorganisms multiplying intracellularly. These cells are named cytotoxic T-lymphocytes. Their action on other T-lymphocytes is realized via direct cell-to-cell contacts or by releasing soluble proteins, cytokines delivering a signal to other cells.

B-Lymphocytes. Each individual B-cell is genetically programmed for synthesis of an outer cell receptor that is specific to a particular antigen. After its recognition, B-cells start to multiply and to differentiate into plasmatic cells, which synthesize and release a large quantity of soluble receptor molecules, e.g. antibodies. These are high molecular weight glycoproteins displayed in blood and tissue fluids. Because of their identity with initial receptor molecules, these antibodies interact with antigen that primarily activated the B-cell.

Natural killers (NK) express neither T-cell nor B-cell antigen-binding receptors. Their function is direct cytotoxic action, which is concluded in recognition and destroying of malignant or infected cells. Different subpopulations of NK express immunoglobulins that regulate their cytotoxic activity [28].

Thus, lymphocytes contain a variety of functional markers that appear in the process of their maturation and functioning. The composition of proteins that are expressed on their membrane is rather changeable and depends on several factors of activation. Besides functionally addressed proteins recognizing foreign cells (particles), different receptors to humoral factors are also expressed on lymphocyte membrane, namely receptors to adenosine, serotonin, and glutamate are found that provide sensitivity of the cells to these compounds [29-36].

Information about the ability of lymphocytes to express NMDA receptors appeared not long ago. The first evidence for their existence was a description of binding of H^3-labeled glutamate with human lymphocyte membranes; it was characterized by high affinity (K_d = 0.24 μM) and specificity – glutamate could only be displaced by quisqualate that is an agonist of ionotropic glutamate receptors at low concentration [37].

Later it was shown that incubation of lymphocytes with glutamate can have functional consequences – glutamate increased the intracellular calcium levels and suppressed proliferation of lymphocytes stimulated by phytohemagglutinin. These effects were prevented by adding specific antagonists of NMDA receptors – D-AP5 or MK-801 [32].

Using several biochemical and molecular biological methods (PCR, flow cytometry, immunocytochemical staining), expression of ionotropic receptors of AMPA-type class [38], metabotropic group I glutamate receptors (mGlu1R and mGlu5R) [39], as well as mRNA for NR1 subunit of NMDA receptors [40] in human T-lymphocytes was demonstrated. Moreover, mRNA for NR2B subunit of NMDA receptors was also found in non-stimulated cells. In phytohemagglutinin-stimulated cells, in addition to mRNA for NR1 and NR2B synthesis, mRNA for NR2A and NR2D subunits was found [34].

Using immunocytochemical staining in a population of T-lymphocytes stimulated by phytohemagglutinin, a subpopulation of cells labeled with anti-NR1 antibodies was found. The share of these cells varied from 24.6 to 95% depending on time of stimulation. In intact cells (not activated) the share of labeled T-lymphocytes was only 5.6% [34, 41]. In addition, in *in vivo* experiments it was found that during development of inducible inflammation of spinal cord of rats, in the inflammatory area only those lymphocytes are infiltrated that contain on their membrane NMDA receptors [41]. Thus it was shown that expression of NMDA receptors on lymphocyte membrane is a regulated process, and the number of such lymphocytes can be changed by several factors.

Activation of NMDA receptors in mice [42, 43], rat [44], rabbit and human [35] lymphocytes stimulates accumulation of free radicals by such cells, which shows the functional role of NMDA receptors. It is interesting that only T-cells and NK respond to NMDA exposure by accumulation of free radicals, while B-cells do not participate in this process [35].

The specific structure of synapses in a neuronal system guarantees highly specific and effective interaction of neuromediator released from presynaptic area with subsequent receptor on the postsynaptic membrane. In peripheral blood there is no such selectivity in the interaction of ligands with the receptors. It is more probable that in the

bloodstream, along with specific ligands similar metabolites, structural analogs of the ligand can activate the same receptor. The question appears what the potential ligand for NMDA receptors in the bloodstream may be.

The most probable candidate on the role of such ligand is glutamate, but its concentration usually does not exceed 10-30 μM, which is too low for activation of the receptors. Recently it was found that structural analogs of glutamate, homocysteine (HC) and homocysteic acid (HCA), can specifically activate these receptors [45], similar to their effect on NMDA receptors in neuronal cells [46, 47].

HCA is a product of spontaneous oxidation of HC, and it has been suggested that it also can serve as an excitatory neurotransmitter stimulating NMDA receptors [48]. Neurotoxic effect of HCA can be blocked by selective antagonists of NMDA receptors [49, 50].

There are some evidences on a possible regulatory role of HC in lymphocyte survival, while contradictions exist in understanding of effect of HC on T-lymphocyte apoptosis. HC can serve as an agent stimulating activation and differentiation of T-cells. In some articles, however, an ability of HC to increase ConA-induced apoptosis and death of T-lymphocytes is described [51]. In other publications, HC was found to suppress ConA-induced apoptosis of T-cells [52, 53]. Moreover, it was found that HC stimulates apoptosis in non-stimulated (intact) cells [54]. It is probable that these contradictions are explained by differences in of experimental protocols. For example, even the HC concentrations used in the cited articles varied in the range of 0.1-1.0 mM.

It was found that HC is able to increase intracellular free radical levels in lymphocytes [52]. There is evidence that HC can increase the accumulation of interleukin-2, IFN-γ, TNF-α, and interleukin-10 by lymphocytes incubated with anti-CD-3 antibodies [54]. The mechanism of this effect was not studied. How HC affects these functions of the cells – because of interaction with specific membrane receptor or as a result of its penetration into the cell and direct interaction with intracellular enzyme systems – is still unknown. In agreement with some data, HC, when it accumulated by cells, can suppress some protein phosphatases, thus phosphorylation of cytoskeletal proteins is increased, cytoskeleton architecture is disordered, and this induces cell necrosis [55]. This effect was found to occur after long-term incubation (longer than 30 min).

Using inhibitory analysis, it was found that HC affects lymphocyte function by activation of NMDA receptors. Actually, HC induces Ca^{2+} entry into cells, which, in turn, stimulates reactive oxygen species (ROS) accumulation [44]. When lymphocytes are exposed to HC, activation of protein kinase C, NO synthase, and NADPH oxidase takes place. All these events result in accumulation of cytokines with no sign of cellular death [36]. Thus, it was demonstrated that NMDA receptors modulate immune function of lymphocytes. It is important that expression of the receptors is stimulated by oxidative stress when its regulation is necessary.

Neutrophils. Neutrophil segmentonuclear leukocytes form a predominant population of white blood cells. Under normal conditions, they are in the range of 47-72% of total blood leucocytes. Additionally 1-5% of the cells are functionally immature neutrophils [56].

After briefly circulating in the bloodstream (7-10 h), the neutrophils leave the vessels to migrate in tissues and organs in following a gradient of chemotactic factors (like leukotriene B4 and IL-8), where under normal conditions they are presented in very low quantities. After 3-5 days they undergo apoptotic transformation [57], while a small portion of the cells can differentiate into long-lived tissue macrophages [58].

In tissues, neutrophils serve as protectors destroying pathogenic bacteria and microorganisms. In some cases it has been noted that neutrophils are involved in antitumor immune response [59].

The protecting role of neutrophils develops in two different ways: by generating respiratory burst and accumulating ROS via activation of NADPH oxidase complex [60], or by release of proteins which provoke penetrability of the bacterial wall, like defensins, cathelicidins, acidic hydrolases, and proteases [61]. These proteins are accumulated in a variety of cytoplasmic granules and released into the outer space after neutrophil activation. Features of structure of nuclear chromatin, namely the inaccessibility of DNA promoter sites for factors of differentiation restrict the gene expression and *de novo* synthesis of macromolecules by matured neutrophils.

NADPH oxidase of outer cell membrane is an oligomeric complex containing proteins recruited from both membrane and cytoplasmic areas. In intact cells, NADPH oxidase is inactive because is in a disassembled state. Activation of neutrophil results in formation of NADPH oxidase complex and generation of superoxide radical anion ($O_2^{\cdot-}$). Also, in the cells the level of free arachidonic acid increases, which induces leukotriene synthesis [62].

Superoxide anion radical, which is formed by activated NADPH oxidase, in turn starts other enzyme systems working, namely superoxide dismutase and myeloperoxidase (MPO), whose concerted work accumulate hydrogen peroxide and hypochlorous anion, the latter being one of the most effective oxidants formed in biological systems. Hypochlorite interacts easily with sulfhydryl and thioester groups of proteins forming chloramines [63]. Interaction of hypochlorite with other compounds, particularly with nitrite, results in formation of strong nitrosylating agents and initiates lipid peroxidation [64]. Thus, neutrophils represent the unique group of cells generating a significant amount of ROS outside the cell. This feature, on one side, allows them to provide nonspecific immunity, and on the other side makes these

cells potentially dangerous for the organism because in the case of hyperproduction of ROS they injure the cells of the organism itself.

The two-stage concept of neutrophil activation is discussed in the literature. In agreement with this concept, "first wave" agents interfere with neutrophils and prepare them for the state when they are ready to interact with other group of metabolic agents directly activating the cells [65, 66]. The preliminary treatment of the cells resulting in the following activation is called "priming". Among known priming agents are cytokines, chemotactic factors, and metabolic regulators affecting several membrane-bound receptors like insulin [67, 68]. Moreover, agonists of glutamate receptors HC and NMDA can also serve as primers [69].

Neutrophils respond to the priming agent by two important changes: F-actin reorganization, which transforms the cell to begin adhesion, and beginning formation of active NADPH oxidase complex in the outer membrane. In this last process two key components of MAPK family are involved – ERK1/2 and p38; increase in intracellular calcium ions both entering from the intercellular space and releasing from intracellular compartments is also important [70, 71]. This last factor activates cytosolic Ca^{2+}-dependent enzymes like protein kinase C and tyrosine kinase, which together with MAP kinases participate in phosphorylation of components of NADPH oxidase.

The order of phosphorylation and translocation into the cell membrane of cytosolic proteins of NADPH oxidase depends on the nature of the priming agent and the mode of its action. It was shown that incubation of cells with HC decreases the amount of MAPK phosphatase 1, the enzyme responsible for dephosphorylation of both p38-MAPK and ERK1/2; at the same time, phosphorylation of these proteins is elevated [69].

Constant circulation of HC in the bloodstream can be a risk factor for the vital activity of neutrophils. It was found using a chemiluminescence approach that HC affects intact and activated neutrophils in a different manner: on the former it acts as a modest suppressor of free radical production, whereas on the latter (isolated from the inflammation area where neutrophils are concentrated because of pathogenic invasion) it provides a stimulating effect resulting in about 50% increase in ROS production [72].

It is known that in immune cells HC induces phosphorylation of MAP kinases regulating assembling of NADPH oxidase. One can suggest that an opposite effect of HC is related to other direction of its action on production of free radicals. In other words, HC can stimulate NADPH oxidase but inhibit MPO and/or neutralize hypochlorite anion. This suggestion can explain the decrease in radical levels after incubation of HC with intact cells activated *in vitro*. This is in agreement with the instantaneous character of HC action when it is added to a suspension of cells at the maximum of their activation *in vitro*.

The study of a commercially available MPO sample showed that HC totally neutralizes hypochlorite anion at as low concentrations as 1-10 μM, and further increase in its concentration inhibits MPO activity. At 500 μM HC, full inhibition of MPO occurs (E. A. Bryushkova and O. V. Tyulina, unpublished data).

The mechanism of stimulation of NADPH oxidase by HC is not known at present. Our data showed that neutrophils activated *in vivo* are also able to respond to exposure to 500 μM NMDA by increased ROS accumulation. The effect of both HC and NMDA is suppressed by a specific NMDA receptor blocker, MK-801 [72]. It is known that the effect of HC on both neurons and lymphocytes can be realized *via* ionotropic and metabotropic glutamate receptors [44, 46, 73]. Using immunofluorescence staining of neutrophils in the presence of antibodies for regulatory subunit of NMDA receptor, we have showed that activation of neutrophils *in vivo* results in expression of these receptors. Sensitivity of the effect of HC to the presence of MK-801 shows the functional activity of these receptors on the neutrophil membrane [72]. We have also measured the possible presence of metabotropic receptors in neutrophils using antibody analysis. No single group of metabotropic glutamate receptors in both intact and *in vitro*-activated cells was found.

It is known that activation of NMDA receptors can start both pro- and antiapoptotic cascades [7-9], thus one can suggest that expression of NMDA receptors in activated neutrophils has a regulatory role eliminating hyperactive and potentially dangerous neutrophils.

Recently in some independent experiments it was demonstrated that NMDA receptors of T-lymphocytes are involved in an intracellular signaling pathway including MAPK [74]. It was also found that information transfer from NMDA receptors to nuclear processes is associated with Ras activated kinases ERK1/2, p38, and SAPK/JNK. This can be considered as an independent indication of a common way for participation of NMDA receptors in intracellular signaling reactions in both neuronal and immune systems.

The presence of NMDA-type glutamate receptors in immune competent cells elucidates the basis for interaction between neuronal and immune systems. NMDA receptors in neurons are involved in long-term potentiation as a result of activation of intracellular MAPK complex that performs similar function both in lymphocytes and neutrophils – regulation of intracellular calcium and ROS levels and cytokine production. In both systems, not only trivial neuromediators/modulators but also metabolites, whose content changes with age or under pathologies, can play a regulatory role *via* these receptors. This gives a chance to develop additional abilities to regulate metabolism (or its adaptation) and to find a way for

restriction of the excitotoxic component of NMDA receptor function.

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