Various Pharmacological role of NMDA's receptors in the various Neuro-disorder and Peripheral organs

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***Abstract*- NMDA receptors are ionotropic receptors mediating glutamatergic neurotransmission and play a role in several basic functions in the central nervous system, from regulating neurodevelopment and synaptic plasticity, learning and memory formation, cognitive processes, rhythm generation necessary for locomotor activity and breathing, and excitotoxicity. Due to their complex involvement in the above processes, NMDA receptors have been established to play a role in the etiopathology of several neuropsychiatric disorders such as ischaemia and traumatic brain injury, neurodegenerative disorders, pain syndromes, addiction, affective disorders and such neurodevelopmental disorders as autism or schizophrenia. Besides, the receptors have also been found to present extensively in peripheral organs, such as lungs, kidneys, heart, and pancreas. Under various pathological conditions, peripheral NMDARs are upregulated and excessively activated, initiating calcium influx and intracellular calcium overloading. Subsequently, mitochondrial dysfunction, oxidative stress, and proinflammatory signalling pathway activation ultimately aggravate tissue damage and organ dysfunction. In addition, excessive activation of NMDARs also directly initiates mitochondrial apoptosis in many organs. Here, we discuss pathophysiological roles of NMDARs in cardiovascular system, lungs, kidneys, and pancreas.**

***Key words*- Arrhythmia, Diabetic Nephropathy, Huntington's Disease, Pancreatic Tumours.**

I.INTRODUCTION

Glutamate is a major excitatory neurotransmitter in the brain plays an important role in the signal conduction of nervous system excitatory neurotransmission, brain development, synaptic plasticity associated with memory formation, central sensitization during persistent pain, excitotoxicity, and neurodegenerative diseases in the CNS. NMDAR is important in various physiological activities in central nervous system (CNS) [1] and pathophysiological progression of neurodegenerative diseases such as Parkinson's disease [2], suggesting NMDAR as a therapeutic target in neurological diseases nervous NMDAR's structure, function, and distribution have been widely clarified. NMDAR's also present in peripheral tissues including heart, lung, kidney, retina, bone, and pancreas, in which NMDAR participates in bone apposition, wound healing, insulin secretion, and other physiological or pathophysiological processes [3]. This review describes on the possible role of NMDARs in the pathophysiological process of diseases in lungs, heart, kidneys, and pancreas, where the up-regulation and over-stimulation of the NMDARs contribute to either acute injury or chronic diseases [4]. Meanwhile, the possibility of peripheral NMDARs as a therapeutic target has also been discussed. NMDARs have different characteristics compared to other ligand-gated cationic channels, such as the capacity of simultaneously binding to co-agonists glutamate and glycine, voltage-dependent block of the channel by extracellular Mg2+ and has high permeability to Na+, Ca2+ and K+ ions [5].

II.The Structure of N-Methyl-D-Aspartate Receptor

N-methyl-D aspartate receptors (NMDARs) belong to the family of ionotropic glutamate receptors (iGluRs) and are ligand gated ion channels that assemble into tetrameric receptor complexes composed of glycine-binding GluN1 and GluN3 subunits (GluN3A-B) and glutamate-binding GluN2 subunits (GluN2A-D). In Central nervous system, the synaptic excitatory conduction is mainly mediated by the activation of glutamate receptors, which are classified into two major categories: the metabotropic glutamate receptors and the ionotropic glutamate receptors [6]. The latter one, playing the role of ligand-gated ion channels, can be divided into four subtypes according to their pharmacological properties: GluA (α-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid receptor, AMPAR), GluKkainate receptor), GluN (NMDAR), and GluD (δ). Among the four subtypes, the distinct characteristics of NMDARs from other ionotropic glutamate receptor subtypes are that NMDARs have permeabilities of Ca2+ (especially high), K+, and Na+, and such permeabilities may be blocked by Mg2+ in a voltage-dependent manner. Because of the pivotal role calcium ions play in the maintenance of physiological functions such as synaptic plasticity, insulin secretion, and cell death under pathological conditions, attention has been paid to NMDARs with high permeability of Ca2+ in both CNS and peripheral organs.

III.PHARMACOLOGY OF NMDA RECEPTORS:

Hyper- or hypofunction of NMDA receptors is involved in a range of neuropsychiatric conditions, and the NMDA receptor offers multiple sites of possible pharmacological action. Competitive agonists and antagonists bind to agonist binding sites (the glycine binding site on the NR1 subunit, and the glutamate binding site on the NR2 subunit). Allosteric modulators such as protons, zinc, polyamines or ifenprodil (noncompetitive antagonists) bind to the N-terminal domain of NR2 subunits. Pore blockers such as endogenous Mg++, memantine, ketamine, or MK-801 bind to sites in the channel pore. There are also possible intracellular target

sites for drug action including signalling molecules, such as kinases, phosphatases, scaffold proteins and other enzymes which are either the upstream modulators of NMDA function or downstream effectors of receptor activity [7]. Due to the complex subunit composition of the receptor, the pharmacology of NMDA receptors is very diverse and complicated. Although in the past two decades several broad-spectrum competitive antagonists and channel blockers have been developed, due to the complex functions of the NMDA receptors, molecules with a broad-spectrum effect on all subunit types are not likely to be clinically useful. Subunit selective pharmacological tools to distinguish between NMDA receptor subtypes are still limited. These would not only be useful in clinical therapy, but also as pharmacological tools for the better understanding of the distinct roles of NMDA receptor subtypes. We need to develop further selective agonists and antagonists of NMDA receptor subunits to gain further understanding of the role these subunits play in the central nervous system, and in turn give us the possibility of creating new, more selective, and specific tools for treating several neuropsychiatric disorders where NMDA receptors play a role in the etiology. Currently many substances available are selective for the NR2B subunit.

A. NMDAR's role in anxiety

Several direct and indirect studies in animals and humans involve the NMDARs crosstalk as a key interacting structure in a range of processes [8]. The NMDARs appear involved in anxiety. Several reports, show the anxiolytic activity of some of its competitive antagonists. Using site-directed mutagenesis in conjunction with homologous recombination to generate two mouse lines carrying point mutations in the glycine binding site of the NR1 subunit appears that a milder reduction in receptor glycine affinity results in a long-term potentiation (LTP) and spatial learning and alterations in anxiety-related behaviour, providing further evidence for the role of NMDARs activation in these processes. Furthermore, it has been proposed that NMDARs dependent LTP of limbic system circuits controlling defensive behaviour underlies stressor-induced lasting increases in anxiety-like behaviour (ALB). The findings of NMDARs are involved in initiation, but not in maintenance of neural changes mediating lasting increases in anxiety following severe stress.

B. NMDAR's role in depression

The principal cause of depression is largely unknown but many antidepressants have NMDARs channel blocking properties. In animal models of depression, NMDARs antagonist exerts positive effects in most cases. These animal studies have suggested that many antidepressant drugs show activity at the NMDARs and that antagonists have antidepressant profiles in preclinical models of depression. Seven subjects with major depression completed 2 test days that involved intravenous treatment with ketamine hydrochloride or saline solutions. Since it has been shown that increased pyramidal cell activity following NMDAR blockade is associated with reduced gamma-aminobutyric acid (GABA) release onto pyramidal neurons [9] and linked to several symptoms including cognitive process (core feature of this disease) of schizophrenia. The impairment of glutamatergic input in the GABAergic interneurons in the hippocampus results in a reduction of GABAergic control of pyramidal cell firing [10]. This condition underlies the development of symptoms of schizophrenia. Due to the high affinity NMDARs channel blockers, mimic both positive and negative symptoms of schizophrenia in humans suggests that this receptor plays a role in this disease [11,12]. The receptor antagonists are known to produce a syndrome-resembling schizophrenia, probably due to their blockade of NMDARs. The level of mRNA for the NMDAR subunits NR1 and NR2B was significantly different between groups; in several hippocampal subregions, the level of NR1-subunit mRNA was lower and the level of NR2B-subunit mRNA higher in schizophrenia. Because the NR1 subunit of the NMDAR is critical to full receptor activity, a reduction of NR1 subunit in hippocampus in schizophrenia suggests a functional impairment in glutamatergic transmission at the receptor, resulting in reduced glutamatergic transmission within and possibly efferent from the hippocampus in schizophrenia.

C.NMDAR's role in epilepsy

One of the first suggested therapeutic applications of NMDARs antagonist was in epilepsy [13,14]. Human cortical dysplasia (CD) is a frequent cause of medically intractable focal epilepsy. The neurotransmitter mechanisms of epileptogenicity in these lesions have been attributed to changes in various glutamate receptor subtypes. Increased NMDAR (NR) 2A/B co-assembled with NR1 subunits has been shown in focal epileptic CD. Epileptogenic significantly higher NR2A/B immunoreactivity in both the dysplastic stomata and all their dendritic processes. The calcium channel of the NMDARs has been implicated in the sustained depolarization phase of PDS and in epileptogenesis after kindling and is a main target for new antiglutamatergic drugs.

IV.DRUGS TARGETING NMDA RECEPTORS IN THE THERAPY OF NEUROLOGICAL DISORDERS

A. Alzheimer's Disease

Alzheimer's disease is hypothesized by the high levels of amyloid-β proteins reduce NMDA receptor excitatory postsynaptic potentials and thus inhibit synaptic plasticity. Investigation of brains indicate a selective loss of NR1, NR2A and NR2B subunits in affected brain areas in Alzheimer's disease [15,16] and decreased NMDA receptor localization at synaptic sites [17]. Currently memantine, a broad-spectrum low affinity NMDA receptor channel blocker is approved for the treatment of cognitive symptoms in Alzheimer's disease, and it is supposed to act by normalizing NMDA receptor activation in a way like Mg++ ions by improving signal/noise ratio. Neramexane is also an NMDA receptor open channel blocker with similar kinetics to memantine and therefore similar tolerability, being developed for Alzheimer's disease but not in clinical trials yet. Dimebon (latrepirdine) is in clinical trials for Alzheimer's disease and Huntington's disease, it's supposed action is blocking NMDA receptors maybe at the polyamine site, and originally developed as an antihistamine [18].

B. Parkinson's Disease

Broad spectrum NMDA receptor antagonists have been described to exhibit antiparkinsonian and anti-dyskinetic activity in several animal models, while amantadine, a low affinity NMDA receptor antagonist has anti-dyskinetic activity. Amantadine, a channel blocker was the first amino adamantane molecule for clinical use, originally developed for influenza-A related respiratory infection prophylaxis but later found to possess positive effects on extrapyramidal symptoms in Parkinson's disease and it may have positive

effects on levodopa induced dyskinesia, concerning its role in frontotemporal lobar degeneration [18]. Studies also indicate a role for selective NR2B antagonists in Parkinson's disease. Recently NR2B selective NMDA receptor antagonists show efficacy in preclinical Parkinson models with an improved adverse effect profile. Ifenprodil failed to show efficacy, but CP-101,606 shows anti-dyskinetic but not anti-parkinsonian effects, although only in doses that also cause dissociation and amnesia.

C. Huntington's Disease

Excitotoxicity mediated by extra synaptic NR2B subunit containing NMDA receptors plays a significant role in striatal neurodegeneration in Huntington's disease [19]. In Huntington's disease changes in NMDA receptor composition, function and changes also include altered neuronal responses to NMDA receptor activation, leading to altered synaptic function and increased susceptibility to NMDA receptor mediated excitotoxicity, indicating a key role for NMDA receptors in the etiopathology of Huntington's disease. [20] In Huntington's Disease mutant huntingtin proteins lead to an increase in NMDA receptor phosphorylation sensitizing the receptor to glutamate and thus promoting neuronal death [21]. Due to the role of NR2B subunit containing receptors in neurodegeneration, selective NR2B antagonists are a possible therapeutic approach to Huntington's disease. Such selective antagonists, however, as ifenprodil, RO-25,6981 and traxoprodil failed to show efficacy in a transgenic mouse model of Huntington's disease, although this may reflect characteristics of this animal model. Memantine and ifenprodil may be good candidates for human clinical trials.

D. Ischaemia

In cerebral ischaemia and traumatic brain injury NMDA receptors play a role in mediating excitotoxic neuronal cell damage. Broad spectrum NMDA receptor antagonists have been shown to be neuroprotective in animal models but did not show efficacy in clinical studies, probably due to side effects. NR2B selective antagonists may offer neuroprotective action with an acceptable side effect profile. However, despite its improved side effect profile, clinical studies did not demonstrate efficacy for traxoprodil (CP-101,606) in ischaemic stroke. MK-801 was effective in animal models in reducing neuronal damage probably because these agents fail to protect against other factors that play a role in neuronal death during ischaemia [22].

E. Schizophrenia

According to Carlsson's hypothesis in schizophrenia the basic nervous system failure is NMDA receptor dysfunction and there is an increasing recognition for the association between schizophrenia and glutamatergic dysfunction, which also effects pharmacotherapeutic approaches [23]. In schizophrenia several behavioural symptoms such as cognitive deficits, locomotor activity, increased psychomotor stereotypy and social withdrawal may be associated with NMDA receptor hypofunction. Schizophrenia symptoms can be modelled by such noncompetitive NMDA receptor antagonists as phencyclidine or ketamine. Atypical neuroleptic clozapine increases NMDA receptormediated excitatory currents in most prefrontal cortical neurons, however, haloperidol, a typical neuroleptic doesn't show this effect [23]. Altered NMDA receptor subunit expression, receptor localization and trafficking have been reported in schizophrenia and expressing significantly reduced levels of NR1subunits exhibit schizophrenia-like behavioural alterations that can be reversed by clozapine and haloperidol treatment. According to the glutamate hypofunction hypothesis of schizophrenia such pharmacological agents should be identified which enhance the activity of NMDA receptors. Glutamate agonists, however, lead to excitotoxic cell death. Approaches targeting the glycine binding site are more promising, Current efforts focus on enhancing glycine site occupancy and receptor tone by glycine agonists including glycine and D-serine [25]. Prevention of glycine reuptake is a further potential approach. Targeting modulatory sites with NMDA enhancers or positive allosteric modulators seems to be the most promising strategy.

F. Affective Disorders

Affective disorders have also been linked to NMDA receptor dysfunction, partly in line with the hypothesis that depression is linked to impaired neurogenesis, and the association of mood disorders with glutamatergic dysfunction is also supported by the successful treatment of both unipolar and bipolar depression with NMDA receptor antagonists [26]. Classical treatments for affective disorders such as lithium or sleep deprivation also induce changes in NMDA receptor functions. Broad spectrum NMDA receptors antagonists, such as ketamine, also possess anti-depressive properties, but cannot be used due to their intolerable side effects. NR2B subunit selective molecules, such as traxoprodil, however, show good antidepressant efficacy with treatment resistant depression.

G. Pain

NMDA receptor activation in peripheral terminals of primary sensory afferents by glutamate released during injury and inflammation causes pain-related behaviour, and peripheral administration of the noncompetitive agonist MK-801 has local anaesthetic like effects. In conditions of pain upregulation NMDA receptors appear to play a role in the enhanced responsiveness of nociceptive neurons in the dorsal horn of the spinal cord, where increased NR2B expression was also described, and NMDA receptors in the brain stem and NR2B containing cortical neurons are also important in chronic pain syndromes [27]. In models of neuropathic pain NMDA channel blockers memantine, ketamine and MK-801 attenuate hyperalgesia, the side effects are intolerable. Perzinfotel, a potent competitive NMDA antagonist showed efficacy in inflammatory and neuropathic pain models but its low bioavailability when administered orally limits its usability. There is, however, currently a search for a prodrug molecule with more advantageous pharmacokinetic properties. Such broad-spectrum NMDA receptor antagonists as ketamine and dextrometorphane are used off label for chronic neuropathic pain due to their good efficacy and despite their narrow therapeutic index. Since NR2B subunit containing receptors are present in pain relevant brain areas, NR2B selective molecules are promising candidates for effective analgesic drugs which do not produce adverse side effects. Ifenprodil, eliprodil and traxoprodil in antinociceptive doses show no psychotomimetic side effects or motor deficits. These molecules show efficacy in the treatment of acute and chronic inflammatory pain, neuropathic pain, and visceral pain without much behavioural side effects.

H. Alcohol Addiction

NMDA receptor antagonists are also potential tools for the clinical management of alcohol addiction, as they were reported to play a role in alcohol tolerance, dependence, craving, withdrawal, and relapse. Ethanol acutely inhibits NMDA function in several brain

areas; however, acute tolerance develops when sensitivity of NMDA receptors to ethanol inhibition is acutely decreased over a short period of time, and this may counteract the inhibitory effect of ethanol. Chronic ethanol exposure and withdrawal leads to the alteration of NMDA receptor function, leading to hyperactivation of the ion channel maybe as a result of an adaptation mechanism resulting in the increase in receptor outnumbers [28]. Alcohol reduces NMDA receptor mediated glutamatergic neurotransmission, and consequently excitatory activity in the central nervous system. Alcohol withdrawal causes neuronal hyperexcitability, in turn causing mesolimbic D2 receptors crave for alcohol. Thus, modulators of NMDA receptor function may be a promising clinical tool to treat alcoholism [29]. NMDA antagonists have been supposed to have potential clinical use also in the treatment of alcoholics. Ketamine in recovering alcoholics reduces psychosis, the worsening of cognitive function and dysphonic mood, while memantine reduces craving, which gives a possibility to use memantine in the treatment of alcohol addiction. Acamprosate, a taurine derivative currently used in the treatment of alcohol addiction to reduce craving acts at least partly *via* modulating NMDA receptor function as a weak agonist or partial co-agonist. Acamprosate substitutes for the effect of alcohol during abstinence periods, reducing neuronal hyperexcitability caused by alcohol withdrawal thus reducing distress of withdrawal and craving for alcohol.

V.N-Methyl-D-Aspartate Receptor and Pulmonary Pathologies

A. N-Methyl-D-Aspartate Receptor and Acute Lung Injury

Acute lung injury (ALI) is an acute clinical syndrome caused by various inflammatory response such as sepsis, ischemia and reperfusion, and traumatic injury [30]. The tight association between functional NMDARs and ALI has been revealed in a variety of studies. In ALI models induced by lipopolysaccharide (LPS), hypoxia, and ischemia-reperfusion (I/R), the NMDARs in lung tissues are overactivated, caused by increased release of endogenous glutamate, aggravated glutamate signalling [31], and prompted expression of NMDAR subunits NR1, NR2A, and NR2B. The direct over-activation of NMDARs with NMDA perfusion induced ALI with identical histological and biomolecular changes, while the protective effects of NMDAR blockade or antagonism against ALI induced by various insults supported that over-activated NMDARs indeed participated in ALI. Since the protective effects of NMDAR antagonism were timely consistent with the upregulation of NR2D subunit, NR2D was suggested to play an essential role in ALI. Mechanically, the implications of NMDARs on ALI involve several pathophysiological processes including oxidative stress accumulation, inflammation, and dysfunction of specific lung tissues and cells. In ALI models induced by bleomycin (BLM), heat or sepsis and in hyperoxia-induced new born animal ALI models, activated NMDARs elevated xanthine oxidase (XOD) activity, lipid peroxidation (MDA), stimulated c-Src activation in Toll-like receptor 2 (TLR2) signalling, modulated nitric oxide synthase (NOS) metabolism, and inhibited the removal of oxidative stress by down-regulating antioxidants including glutathione (GSH), sulfhydryl (SH), catalase (CAT), and superoxide dismutase (SOD), leading to accumulation of intracellular ROS, which may aggravate inflammation responses via activation of NF-κB. Besides, activated NMDARs also prompt pulmonary inflammation by down-regulating anti-inflammatory cytokines, stimulating neurogenic inflammatory responses in LPS-induced ALI animal models and prompting allergic inflammatory response in ovalbumin sensitized (OVA-sensitized) and challenged mice. Given the crucial role inflammation plays in ALI, activated NMDAR-mediated inflammatory responses partly via oxidative stress generation and neuropeptide regulation are in the progress of ALI. Overactivation of NMDARs in alveolar type II epithelial cells (AT II cells) reduced the production of pulmonary surfactants and down-regulated phosphatidylcholine cytidine transferase-α (CCT-α), the rate-limiting enzyme in generation of phosphatidylcholine. In ischemic/reperfusion injury models, blockade of NMDARs normalized the airway's muscle tone and pulmonary vessels [32]. In this way, activated NMDAR in specific lung tissues and cells take parts in ALI specifically.

B. N-Methyl-D-Aspartate Receptor and Chronic Lung Diseases

Over-activated NMDAR participates in several chronic lung diseases like hyperoxia-induced chronic lung disease, chronic obstructive pulmonary disease (COPD), and BLM-induced pulmonary fibrosis. In COPD mouse models and cigarette-treated (CS-treated) Raw264.7 cells, NR1 was upregulated, while hyperoxia also prompts NR2 expression. NMDA treatment of human fetal lung fibroblasts down-regulated NR2A, up-regulated NR2D, and caused lower, delayed but prolonged glutamate-induced influx of Ca2+, consistent with the subtype-specific effects of NMDARs [33]. In several chronic lung injury animal models and C Streated mouse macrophage cells, cystine/glutamate transporter protein xCTwas upregulated, prompting the release of endogenous glutamate. Mechanically, the implications of excessively activated NMDARs in chronic lung diseases employed multiple types of cells. For instance, enhanced NMDAR-mediated (especially NMDAR2D) cell proliferation, collagen deposition, and morphological transformation in fetal lung fibroblasts are crucial to hyperoxia-induced pulmonary fibrosis. The NMDAR activation inhibited both paracrine function and homing ability of bone marrow mesenchymal stem cells (BM-MSCs) by reducing paracrine factor hepatocyte growth factor (HGF) and stromal cell-derived factor/CX- C chemokine receptor type 4 (SDF/CXCR4) signalling axis. In addition, the over-activation of NMDARs in macrophages also prompted pro-inflammatory cytokine secretion via Ca2+-mediated phosphorylation of extracellular regulated protein kinases 1/2 (ERK1/2). In this way, abnormally activated NMDARs aggravate inflammatory responses, regulate the functions of fibroblasts and BM-MSCs, and contribute to chronic lung diseases like pulmonary fibrosis and COPD.

VI. N-Methyl-D-Aspartate Receptor and Cardiovascular Pathologies

A. N-Methyl-D-Aspartate Receptor and Arrhythmia

Cardiac NMDARs are tightly associated with arrhythmia. The acute or chronic activation of NMDARs with NMDA increased the incidence of arrhythmia like ventricular tachycardia (VT) and ventricular fibrillation (VF) in isolated rat hearts, normal rats, and rats with myocardial infarction (MI), myocardial necrotic injury (MNI), or nerve sprouting.[34]

Also, NMDARs were involved in VT, VF, and atrial fibrillation in MI rats treated with I/R injury or high dose monosodium L-glutamate. Blockade of the receptor improved reperfusion-induced VT, NMDA induced tachycardia, and sinus arrhythmia, leading

to bradycardia. NDMARs are up-regulated and excessively stimulated in several pathological conditions such as sympathetic nerve sprouting, MNI, and myocardial I/R injury, increasing the incidence of ventricular tachyarrhythmias. The overactivated NMDARs contributed to arrhythmia via multiple aspects including calcium overload, cardiovascular dynamics, cardiac electrical remodelling, and so on. In myocardial I/R injury, activated NMDAR caused intracellular calcium accumulation via inhibition of SERCA2a protein expression and sarcoplasmic reticulum (SR) Ca2+-ATPase activity to reduce Ca2+ uptake of mitochondria [35]. Overstimulation of cardiac NMDARs in rats or rhesus monkeys decreased parasympathetic outflow, heart rate variability (HRV), and therefore increased the incidence of ventricular arrhythmias after MI, which were attenuated by MK-801. Chronically activated NMDAR reduced major repolarization channel (such as Ito, f) proteins and induced cardiac electrical remodelling featured via increased cardiac excitability, prolonged cardiac repolarization, transmural dispersion of repolarization, and increased spatial dispersion of action potential duration (APD), increasing the susceptibility of arrhythmias. The loss of gap junction (downregulation of connexins and upgradation of metalloproteinase 9) is also involved in NMDAR-mediated arrhythmogenesis. In hyperhomocysteinemia (hHcy), homocysteine has been thought to excessively activate NMDAR, leading to decreased constitutive NO, production of inducible nitric oxide synthase/NO/oxidative stress (iNOS/NO/oxidative stress), and thus arrhythmogenesis.

B. N-Methyl-D-Aspartate Receptor and Cardiomyopathy

With NMDA or NMDAR antagonists, researchers have uncovered that overactivated NMDARs mediate cardiac remodelling, stress-induced cardiomyocyte injury, heart failure, and even cardiomyopathic sudden death in animal models with I/R, Mg2+ deficiency (MgD), or cardiomyopathy.[36] The negative effects of NMDARs on myocardium contractile function especially in animals with hHcy were also observed, although those did not present in thyroxine-induced (T4-induced) cardiac remodelling. Effects of activated NMDARs on cardiac myocyte injury and dysfunction are mostly exhibited via calcium-dependent pathways and NMDAR-related oxidative stress in cardiac myocytes injury. In MgD animals, NMDAR-mediated inflammation involves the neuropeptide substance P (SP) from dorsal root ganglion and systematic oxidative stress generation, while reactive oxygen species (ROS) and NO production are attributed more to excessively activated NMDAR-mediated intracellular calcium load, causing mitochondrial membrane potential ($\Delta\Psi m$) depolarization and mitochondrial dysfunction [37]. The increased mitochondrial ROS (mtROS) contributes to cell apoptosis via release of pro-apoptotic cytochrome c, generation of caspase- 3, and reduction of the Bcl-2/Bax ratio in cardiomyocytes. Meanwhile, the ROS-sensitive matrix metalloprotein- 9 (MMP-9) is up-regulated to activate cysteine protease calpain and translocation of connexin-43 (Cxs-43) into mitochondria, leading to mitochondrial permeability transition related (MPT-related) cardiomyocyte contractile dysfunction and mitophagy in hHcy. NMDAR-prompted lipid peroxidation is observed and related to neutrophil infiltration in isoproterenol-induced heart failure models. NMDAR-mediated calcium influx also upregulates protein kinases like anti-apoptotic protein kinase B (Akt) and ERK [38], I/R injury-related protein kinase C-δ/ε (PKC-δ/ε), forming protective feedback against NMDAR-induced cardiomyocyte apoptosis or mediating myocardial I/R injury, respectively. Cardiac NMDARs also serve as binding sites of HIV-1 envelope glycoprotein gp120, participating in gp120-induced cell autophagy, and thus HIV-1-related cardiomyopathy.

C. N-Methyl-D-Aspartate Receptor and Hypertension

Nervous NMDARs especially those in hypothalamus and nuclei tractus solitarii neurons are crucial in the regulation of systematic blood pressure (BP) [39]. In addition, the involvement of peripheral NMDARs in hypertension has been suggested since stimulation or inhibition of NMDARs peripherally exhibits distinct effects on BP. Activated peripheral NMDARs induce pressor responses dose-dependently partly via vascular neuronal nitric oxide synthase (nNOS)- derived NO generation and afterward ROS production [40] and are crucial in the pathogenesis of T4-induced systemic hypertension. Moderate ethanol inhibited the implications of NMDA on BP and heart rate, which is NOS independent and partly involves decreased ROS generation.

VII. N-Methyl-D-Aspartate Receptor and Renal Pathologies

A. N-Methyl-D-Aspartate Receptor and Acute Kidney Injury

Acute kidney injury (AKI) featured by significant decrease of renal function and accumulation of toxic metabolites includes endothelial dysfunction, microcirculation alteration, tubular injury, inflammation, and other pathophysiologic processes in kidney [41]. In gentamicin-induced AKI rats, NR1 and NR2C subunits in renal cortex were upregulated, and glomerular expression of NR1 and NR2Awas elevated in rats with hHcy . Chronic intake of monosodium glutamate (MSG) also upregulated NMDAR in both renal glomeruli and proximal tubular cells [42,43]. The acute and chronic overstimulation of NMDARs inhibited the expression of cell markers and induced mitochondrial apoptosis of podocytes, consistent with NMDAR-related aggravation of AKI in I/R models. In addition, blockade of NMDAR on different allosteric sites by antagonists (ketamine, magnesium sulfate, kynurenic acid, and MK-801) exhibited protective effects against renal injury induced by I/R injury, hHcy, gentamicin, or endotoxemia and improved tissue damage like glomerulosclerosis, renal hypoperfusion, and excretion dysfunction. Kynurenic acid acting on the glycine binding sites of NMDARs attenuated glycine-induced aggravation of I/R injury in AKI, and over-functioned NMDARs also take part in chronically MSG-induced pathophysiological alterations like increased glomerular filtration rate (GFR), tubular reabsorption, and oxidative renal damage. Mechanically, excessively activated NMDAR increased oxidative stress accumulation in various AKI animal models via promotion of ROS generation and inhibition of ROS scavenging SOD, CAT, and glutathione peroxidase (GSHPx) [44]. Activated NMDAR in podocytes increased production of NADPH oxidase-mediated ROS, triggering the mobilization of transient receptor potential canonical (TRPC) 6 channels and the downstream calcineurin activation, dephosphorylation, and translocation of nuclear factor of activated T cells (NFAT) and modulation of small GTPase (activation of Rho and inhibition of Rac activation), leading to cell marker loss and apoptosis. In hHcy rats or Hcys-treated rat mesangial cells, NMDAR-mediated Nox-dependent $O2^-$ production regulated enzyme systems MMPs/TIMPs to prompt ECM accumulation and thus glomerulosclerosis. In LPS-induced AKI, ROS accumulation and NF-κB activation upregulated NMDARs, forming a vicious circle to aggravate AKI. Besides, the activation of endothelin-endothelin receptor B nitric oxide pathway which contributed to

gentamicin nephrotoxicity might be mediated by up-regulated NMDARs. Thus, renal NMDARs are upregulated, overactivated by nephrotoxic insults, and prompt the progression of AKI via multiple oxidative stress-related pathways and enzyme systems.

B. N-Methyl-D-Aspartate Receptor and Diabetic Nephropathy

Diabetic nephropathy (DN) is a common complication of diabetes and the second reason causing end-stage renal disease (ERSD). The pathogenesis of DN is very complicated [45], and it is almost unavoidable for patients with DN to progress to ERSD, despite current therapeutic strategies. The obligatory NR1 subunit of NMDARs was observed to express highly in high-glucose-incubated (HG-incubated) podocytes, mesangial cells and glomerular cells, glomeruli and tubules of several animal models with diabetes, db/db mice, and kidney biopsies from patients with DN. In diabetic conditions, the upregulation of the receptor is MMP-dependent and inversely related to H2S production, with the involvement of classic PKC. The renal protective effects of NMDAR blockade or knockdown against diabetic nephropathy orHG-mediated cell damage in vivo or vitro shed light on the essential role ofNMDARs in the physiopathology of DN. These receptors contributed to HG-mediated cytoskeletal organization disruption, cell collapse, and increased bovine serum albumin (BSA) permeability by inhibiting the activation of cell division cycle 42 (Cdc42). NMDAR activation also reduced connexins like Cxs-40 and -43 which formed gap junctions.

VIII. N-Methyl-D-Aspartate Receptor and Pancreatic Insulin Cell Dysfunction

A. N-Methyl-D-Aspartate Receptor and Pancreatic β Cell Dysfunction

Diabetes caused by insulin deficiency or insulin-response failure (insulin resistance) is a metabolic disease group featured by chronic hyperglycemia. Overt diabetes occurs only when
insulin-secreting pancreatic β cells are unable to compensate insulin deficiency. In diabetic conditions such as high-glucose-incubated β cells or patients with diabetes, pancreatic NMDARs are over-stimulated by the excessive release of endogenous glutamate, which plays a vital role in hyperglycemia-mediated β cell dysfunction. The acute or chronic activation of NMDARs or combination with homocysteine significantly impaired β cell glucose-stimulated insulin secretion (GSIS) [46], while the blockade or genetic silence of NMDARs exhibited protective effects on insulin secretion from β cells against glucotoxicity [47]. Mechanically, NMDAR-mediated impairment of GSIS is caused by decreased cell depolarization involving ATP-sensitive K+ (KATP) channels, reduced expression of β cell function genes, and enhanced endoplasmic reticulum (ER) stress. In pancreatic islets, activated NMDARs cause extracellular Ca2+ influx, activate small-conductance calcium-activated potassium (SK) channels, and KATP channels via NO-cGMP or reduced ATP generation from calcium-overload mitochondria, promotes K+ outflow, inhibits voltage-dependent calcium channel-dependent Ca2+ influx, shortens the span of β cell depolarization and Ca2+ oscillation peak, and impairs GSIS finally [48]. HG-induced excessive activation of NMDARs inhibits the expression of β cell function genes such as insulin, Pdx-1, and MafA via NF-κB activation and C/EBP homoiogousprotein-dependent (CHOP) endoplasmic reticulum stress. Even though acute exposure to NMDA for 1 h did not induce observable apoptosis of β cells, chronic activation of NMDARs contributed to decreased cell viability and β cell loss or apoptosis in diabetic conditions, and dietary intake of MSG reduced pancreatic β cell mass of rats. Chronically excessive activation of NMDARs causes both intracellular and intramitochondrial calciumoverloading, which leads to loss of mitochondrial transmembrane potential (MTP), mtROS accumulation, dose-dependent decreases in mitochondrial ATP production, and oxidative phosphorylation levels, i.e., mitochondrial bioenergy dysfunction. Identical to events in nervous system, the mitochondrial malfunction and reduction in intracellular ATP pools prompted free radical generation and afterward cascades related to cell death. The overstimulation of NMDARs also initiates β cell apoptosis via mitochondrial apoptotic pathway, upregulating pro-apoptotic Bim and Bax, downregulating anti-apoptotic Bcl-2, and promoting cleavage of caspase-3. Besides, NMDAR-mediated ROS -κB activation, and inflammatory responses involving nucleotide binding oligomerization domain-like receptors (NLRP3) inflammasomes and pro-inflammatory cytokines such as TNF-α and IL-1β accelerated the β cell dysfunction and apoptosis process. In summary, in diabetic conditions, NMDARs, which are excessively activated by enhanced glutamate secretion, exert negative implications on both insulin secretion and viability of β cells, involving inhibited cell depolarization, endoplasmic reticulum stress generation, mitochondrial bioenergy dysfunction, and mitochondrial apoptotic pathway. Thereinto, massive calcium influx is tightly associated with the downstream signalling cascades, playing a predominant role in NMDAR-mediated glucotoxicity in β cells. Given the vital role excessively activated NMDARs play in β cell dysfunction and viability in diabetes, the potentiality of NMDAR antagonist like amantadine as a novel antidiabetic medication has been studied. Studies in diabetic animal models and clinical patients showed the protective effects of dextromethorphan (DXM) and its metabolite dextrorphan (DXO) against islet dysfunction and impaired glucose tolerance (without glucopenia side effects) via NMDAR antagonism. NMDAR antagonists were used in combination with other chemicals such as glucagon-like peptide-1 (GLP-1) analogues, dipeptidase-4 (DPP-4) inhibitors to achieve better curative effects. Besides, prenatal treatment with NMDAR antagonists decreased the susceptibility to diabetes induced by high-fat diets in rats with intrauterine growth constraints.

B. N-Methyl-D-Aspartate Receptor and Pancreatic Tumours

Pancreatic tumours are generally classified into two types according to their origins: pancreatic cancer originated from epithelium and pancreatic neuroendocrine tumours (PNET) originated from neuroendocrine pluripotent stem cells. The highly lethal pancreatic cancer, which is mainly originated from pancreatic intraepithelial neoplasia, is poorly diagnosed because of its special anatomical location and few standard biomarkers to predict risk. The expression of NMDAR2A was observed in pancreas adenocarcinoma cell lines including PaTu8988t and Panc-1, while NMDAR2B were detected in most pancreatic cancer cell lines (PanC-1, BXCPC3, and HPAC-1) and tumour samples from patients [49]. Blockade of NMDARs inhibited the tumour progression behaviours including cell proliferation and apoptosis, prompted cell necrosis in pancreas cancer cell lines. Inhibition of NMDAR2B with antibodies or ifenprodil reduced cell viability of pancreatic cancer cell lines and growth rate of human pancreatic tumour xenografts in nu/nu mice. Therefore, functional NMDARs, especially NMDAR2B, are vital to the viability and progression of pancreatic tumours via presumably calcium-mediated intracellular cascades [50]. VEGF and growth factor-mediated phosphorylation are also involved in

NMDAR-related modulation of biological behaviours of pancreatic cancer, and propofol, a common intravenous anaesthetic, exhibits antitumor effects by inhibition of VEGF expression and tumour migration via downregulation of NMDAR. Pancreatic neuroendocrine tumours (PNETs), which are originated from pancreatic islet cells, are referred as functional or non-functional according to whether the tumour secrets hormones and contributes to specific symptoms. The surface expression of NMDAR is positively associated with tumour size, and phosphorylation of NR2B is significantly increased at the periphery of PNET tumours, indicating the poor prognosis. A computational model involving release of glutamate, NMDAR activation, depolarization, and calcium influx predicted that glutamate released by autocrine and paracrine strongly activated NMDARs in pancreatic neuroendocrine tumour cells [52], which contributed to cell proliferation and tumour invasion of PNET (especially in late stage) via downstream MEK-MAPK and calmodulin kinase (CaMK) pathways [51]. The frequent cell necrosis in rapidly growing tumours releases excessive glutamate, contributing to activation of NMDARs in nearby tumour cells [53]. Modulation of NMDAR activation is also involved in its scaffold protein guanosine kinase binding protein (GKAP)-regulated tumour invasion of PNET cell lines via downstream effectors fragile X mental retardation protein/heat shock factor 1 (FMRP/HSF1). A genome-wide expression profile compiled from the NMDAR-GKAP signalling axis has been extracted and transcriptome features in tumours with limited NMDAR activation which show better prognosis in several cancer types [54].

IX. CONCLUSION

NMDA receptors are involved in various central nervous system physiological processes and consequentially also in the etiopathology of a diverse range of neuropsychiatric disorders; and offer several possible target sites for pharmacological intervention the clinical therapy of various neuropsychiatric conditions. Although broad spectrum NMDA receptor antagonists are prevented from clinical use due to their intolerable side effect profile, newer subunit selective agents offer valuable tools for the treatment of various diseases from neurodegenerative disorders, to pain, ischaemia, depression, alcohol addiction or neurodevelopmental disorders such as schizophrenia. We have an increasing knowledge about the role of NMDA receptors in disease etiopathology, and thus several specific theoretical targets for intervention. Translating scientific models into clinical practice, however, is still a challenge for the future. In the review, we discussed the participation of peripheral NMDARs in multiple pathologies of various organs like lungs, kidneys, heart, and pancreas. Despite the various physiological role, over activated NMDAR is essential to the progress of both acute organ injury and chronic diseases like diabetes and its complications, indicating the potentiality of novel therapeutic strategy to target the hyper functioned receptor.

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