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# *N*-methyl-D-aspartate (NMDA) and the regulation of mitogen-activated protein kinase (MAPK) signaling pathways: A revolving neurochemical axis for therapeutic intervention?

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**Abstract**

Excitatory synaptic transmission in the central nervous system (CNS) is mediated by the release of glutamate from presynaptic terminals onto postsynaptic channels gated by *N*-methyl-D-aspartate (NMDA) and non-NMDA (AMPA and KA) receptors. Extracellular signals control diverse neuronal functions and are responsible for mediating activity-dependent changes in synaptic strength and neuronal survival. Influx of extracellular calcium ($[Ca^{2+}]_e$) through the NMDA receptor (NMDAR) is required for neuronal activity to change the strength of many synapses. At the molecular level, the NMDAR interacts with signaling modules, which, like the mitogen-activated protein kinase (MAPK) superfamily, transduce excitatory signals across neurons. Recent burgeoning evidence points to the fact that MAPKs play a crucial role in regulating the neurochemistry of NMDARs, their physiologic and biochemical/biophysical properties, and their potential role in pathophysiology. It is the purpose of this review to discuss: (i) the MAPKs and their role in a plethora of cellular functions; (ii) the role of MAPKs in regulating the biochemistry and physiology of NMDA receptors; (iii) the kinetics of MAPK–NMDA interactions and their biologic and neurochemical properties; (iv) how cellular signaling

*Abbreviations:* AA, arachidonic acid; AIDS, acquired immunodeficiency syndrome; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APV, 2-amino-5-phosphonovalerate; 2-AP5, 2-amino-5-phosphonopentanoic acid; ATF, activating transcription factor; BAPTA-AM, 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid; BDNF, brain-derived neurotrophic factor; BSO, L-buthionine-(*S*,*R*)-sulfoximine; CaM, $Ca^{2+}$/calmodulin; CaMK, $Ca^{2+}$/calmodulin-dependent protein kinase; CAT, catalase; CEE, conjugated equine estrogens; CNS, central nervous system; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CPP, 3-[(*RS*)-2-carboxypiperazin-4-yl)]-propyl-1-phosphonate; CREB, cAMP responsive element binding protein; CS, conditioned stimulus; DA, dopamine; ECS, electroconvulsive shock; EGF, epidermal growth factor; ERK, extracellular receptor kinase; ERT, estrogen replacement therapy; ERT-kinase, EGF receptor threonine kinase; FGF, fibroblast growth factor; GAP, GTPase activating protein; γ-GCS, γ-glutamylcysteine synthetase; GDNF, glial cell line-derived neurotrophic factor; GEF, guanine nuclear exchange factor; GluR, glutamate receptor; GSH, glutathione; GSTp, glutathione *S*-transferase P*i*; HEK, human embryonic kidney; HFS, high-frequency stimulation; $H_2O_2$, hydrogen peroxide; IEG, immediate early gene; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS, insulin receptor-substrate; JIP, JNK-interacting protein; JNK, Jun N-terminal kinase; KA, kainic acid; LPS, lipopolysaccharide-endotoxin; LTD, long-term depression; LTM, long-term memory; LTP, long-term potentiaion; MAP, microtubule associated protein; MAPK, mitogen-activated protein kinase; MAPKK, MAP kinase kinase; MAPKKK, MAP kinase kinase kinase; MBP-kinase, myelin basic protein kinase; MCPG, α-methyl-4-carboxy-phenyl glycine; METH, methamphetamine; MF, mossy fiber; mGluR, metabotropic glutamate receptor; MI, metabolic inhibition; MKP, MAPK phosphatase; MLK, mixed lineage kinase; MSG, monosodium glutamate; NGF, nerve growth factor; NO, nitric oxide; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NMDA-EPSP, NMDA excitatory postsynaptic potential; NRC, NMDA receptor multi-protein complex; PAK, p21-activated kinase; PCP, phencyclidine; PDGF, platelet-derived growth factor; PI 3-kinase, phosphatidylinositol 3-kinase; PLA2, phospholipase A2; PKA, protein kinase A; PKC, protein kinase C; PPD, paired-pulse depression; PTK, protein tyrosine kinase; PTX, pertussis toxin; RGC, retinal ganglion cell; RNS, reactive nitrogen species; RSK-kinase, ribosomal S6 protein kinase; RTK, receptor tyrosine kinase; SAPK, stress-activated protein kinase; SD, succinate dehydrogenase; *S*-DHPG, (*S*)-dihydrophenylglycine; SH, Src homology; SIN-1, 3-morpholinosydnonimine; SNAP, *S*-nitroso-*N*-acetylpenicillamine; SNOC, *S*-nitrosocysteine; SOD, superoxide dismutase; SRF, serum response factor; STM, short-term memory; TBS, theta-burst; TCF, ternary complex factor; TEA, tetraethyl-ammonium chloride; TGF, transforming growth factor; TNF, tumor necrosis factor; VSCC, voltage-sensitive $Ca^{2+}$ channel; z-VAD-fmk, *N*-benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone

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pathways, related cofactors and intracellular conditions affect NMDA–MAPK interactions and (v) the role of NMDA–MAPK pathways in pathophysiology and the evolution of disease conditions. Given the versatility of the NMDA–MAPK interactions, the NMDA–MAPK axis will likely form a neurochemical target for therapeutic interventions.


*Keywords:* Biochemistry; Calcium; CNS; Glutamate; Kinase; MAPK; Neurochemistry; NMDA; Pathophysiology; Phosphorylation; Signaling

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