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INTERFACIAL DISSOCIATION OF THE NMDAR-TRPM4 COMPLEX: A TARGETED NEUROPROTECTIVE STRATEGY IN ACUTE AND CHRONIC EXCITOTOXICITY

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Glutamate-mediated excitotoxicity represents a convergent pathological mechanism underlying a wide spectrum of neurological disorders, ranging from acute insults such as ischemic stroke and traumatic brain injury to chronic neurodegenerative diseases including Alzheimer's and Huntington's disease. Central to this process is the overactivation of N-methyl-D-aspartate receptors (NMDARs), leading to excessive Ca^{2+} influx. However, therapeutic strategies based on global NMDAR antagonism have demonstrated limited clinical efficacy, largely due to a narrow therapeutic index and disruption of essential synaptic pro-survival signalling. Recent advances have highlighted the importance of signalling context and receptor microdomain localization, particularly the distinction between synaptic and extrasynaptic NMDAR populations. While synaptic NMDAR activation promotes neuronal survival via CREB-dependent transcription and brain-derived neurotrophic factor (BDNF) expression, extrasynaptic NMDARs preferentially engage cell death pathways, including CREB shutoff, mitochondrial dysfunction, and oxidative stress. Within this framework, the NMDAR-TRPM4 ion channel complex has emerged as a potentially critical mediator of excitotoxic signalling. TRPM4, a Ca^{2+}activated non-selective cation channel, does not itself conduct Ca^{2+} but may amplify excitotoxic injury by facilitating sustained Na^{+} influx, membrane depolarization, and bioenergetic compromise. This functional coupling has been proposed to bias downstream signalling toward calpain activation, mitochondrial permeability transition, and reactive oxygen species (ROS) generation, thereby promoting necrotic and apoptotic cell death.

A novel pharmacological strategy has therefore shifted toward interaction-selective modulation, targeting the protein-protein interface between NMDAR and TRPM4 rather than the receptor pore itself. Small-molecule interface inhibitors such as FP802 and its brain-penetrant derivative HZS60 have been reported in preclinical studies to selectively disrupt this pathological complex without significantly impairing physiological ion conduction or synaptic transmission (Ramirez et al., 2025). In contrast to conventional non-competitive antagonists such as Memantine, which broadly attenuate receptor activity, these agents may offer pathway-specific neuroprotection by preserving synaptic signalling while suppressing extrasynaptic death cascades (Lotti et al., 2026). Experimental models of ischemic injury suggest that HZS60 may reduce infarct volume and attenuate dendritic and mitochondrial damage (Sun et al., 2025), while studies in Huntington's disease models indicate a potential reversal of transcriptional repression of neuroprotective genes, including BDNF and INHBA (Oberländer et al., 2026). However, it is important to note that the current body of evidence remains largely preclinical, and the translational applicability of these findings to human disease is yet to be established. Furthermore, the long-term safety profile, potential off-target effects, and reproducibility across independent models require further investigation. While interaction-selective modulation represents a conceptual shift from global receptor inhibition toward spatially and mechanistically refined targeting, its clinical utility will ultimately depend on rigorous validation in large-scale studies. Nonetheless, this approach offers a promising direction in the ongoing effort to develop effective therapies for excitotoxic neurodegeneration.