N-Methyl-D-Aspartate Receptor Uncompetitive Antagonists and Depression, from Psychopharmacology and Pathology to Physiology: A Unifying Hypothesis for the Epigenetic Code of Neural Plasticity

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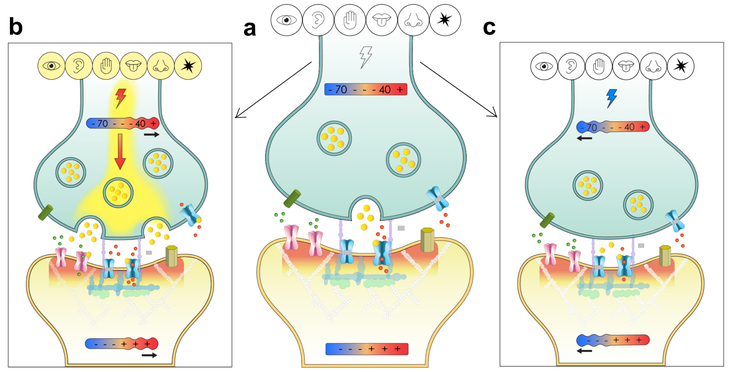
INTRODUCTION

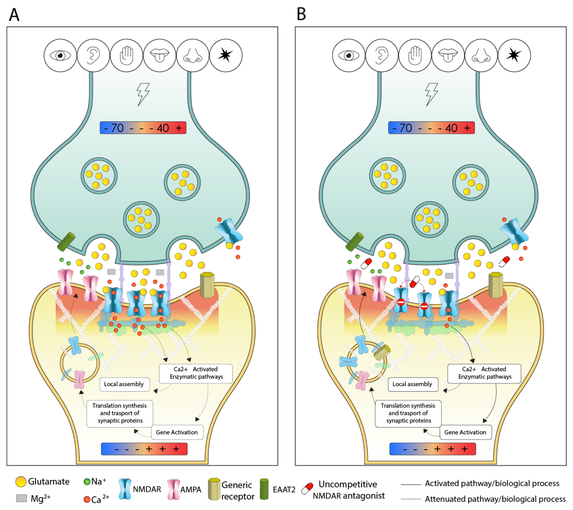
Uncompetitive NMDAR (N-methyl-D-aspartate receptor) antagonists restore impaired plasticity and reverse depressive-like phenotype in animal models of depression and relieve depression in humans. We integrated recent in silico, in-vitro, in-vivo, and human studies of uncompetitive NMDAR antagonists into the extensive knowledge on the role of NMDARs in neural plasticity. Uncompetitive NMDAR antagonists preferentially target NR2D subtypes because these subtypes are most sensitive subtype to activation by low concentrations of extracellular glutamate and pathological agonists. Hyperactivity of NR2D subtypes may underlie depression pathophysiology. We hypothesize that neural plasticity is epigenetically regulated by precise Ca2+ quanta entering cells via NMDARs. Stimuli reaching specialized receptor-cells change their membrane potential regulating extracellular glutamate release. Free glutamate binds glutamatergic receptors regulating NMDAR-mediated Ca2+ influx. Quanta of Ca2+ via NMDARs activate enzymatic pathways regulating synaptic protein homeostasis and synaptic receptors. Thereby, Ca2+ quanta via NMDARs control the balance between long-term potentiation and long-term depression. This NMDAR Ca2+ quantal hypothesis for the epigenetic code of neural plasticity integrates recent psychopharmacology findings into established physiological and pathological mechanisms of brain function.

Physiological stimulus-driven NMDAR-mediated Ca2+ regulated neural plasticity at resting and at phasic membrane potential.



The figure depicts a specialized receptor-cell -> first-order neuron synapse following depolarizing or hyper-polarizing stimuli. At resting membrane potential, subthreshold stimuli are reaching the receptor-cell (center figure, a) with tonic release of glutamate, activating a small fraction AMPARs and NMDARs, resulting in preferential NR2D graded postsynaptic influx of Ca2+ quanta. Tonic NMDAR-mediated graded Ca2+ influx (preferentially via NR2D subtypes) directs synaptic protein homeostasis. When depolarizing stimuli reach the receptor-cell (left figure, b), there is massive release of glutamate into the synaptic cleft. This release activates all postsynaptic ionotropic receptors, e.g., "fast" Na+ permeable AMPARs and "slow" Ca2+ permeable NMDARs. For completeness, we also show the response to stimuli resulting in receptor-cell hyperpolarization (right figure, c), e.g., visual stimuli reaching photoreceptors, with reduction in tonic release of glutamate. Reduced glutamate release leads to a graded reduction of NMDAR-mediated Ca2+ entry into the postsynaptic neuron.

The depressive phenotype, impaired neural plasticity and uncompetitive NMDAR antagonists: psychopharmacology of dysfunctional synapses in depression.



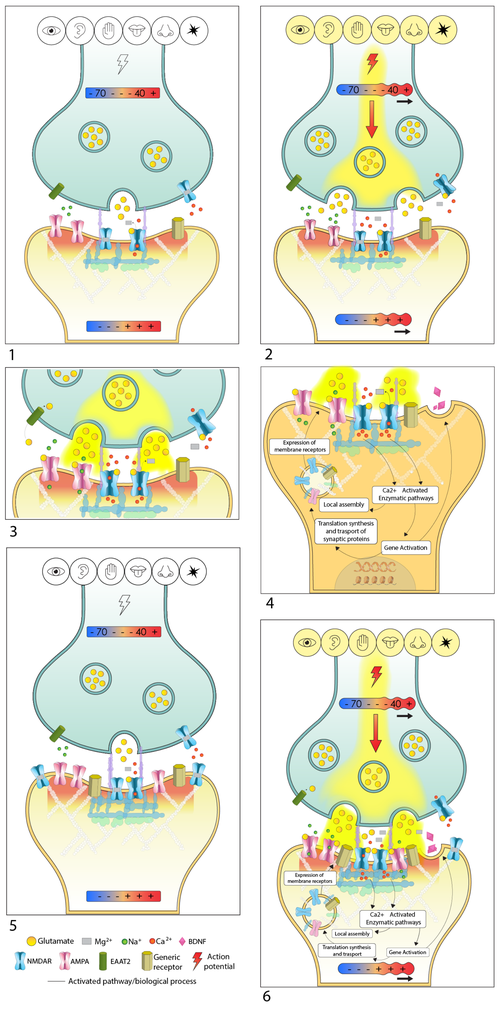
A) Receptor-cell -> first-order neuron synapse in patients with depression. At resting membrane potential, hyperactive postsynaptic NMDARs determine excessive Ca2+ influx, leading to chronic hyper-activation of CaMKIII-eEF2 signaling and downstream effectors causing unavailability of synaptic proteins in neurons part of neuronal circuits relevant to depression.

B) Low potency uncompetitive NMDAR antagonists preferentially block NR2D channels in the open conformation and free of Mg2+ during resting membrane potential. The decreased influx of NR2D-mediated Ca2+ restores synaptic protein homeostasis through down modulation of the CaMKIII-eEF2 pathway and re-activation of downstream effectors. Postsynaptic protein homeostasis enables physiological neural plasticity and determines resolution of the depressive phenotype. Solid lines represent activated pathways/biological processes; dashed lines indicate attenuated pathways/biological processes.

DISCLOSURES

All authors have received grants or other compensation from Relmada Therapeutics or from companies affiliated with Relmada Therapeutics. PM is inventor on patents related to esmethadone.

Stimulus-induced NMDAR-regulated Ca2+ quanta and hot spot neural plasticity.



1-6) receptor-cell -> first-order neuron synapsis.

1) Resting membrane potential: Stimuli reach the specialized receptor-cell and change its membrane potential, regulating the activity of presynaptic NMDARs. Based on frequency and intensity of incoming stimuli, graded Ca2+ quanta via presynaptic NMDARs instruct the receptor-cell on glutamate vesicle density. When presynaptic glutamate vesicles reach density threshold, one or more vesicles fused with the membrane of the receptor-cell and release glutamate. Free glutamate released at graded resting membrane potential activates a small percentage of glutamate receptors, including AMPARs and NMDARs at the hot spot of the first order neuron. Low nanomolar concentration of free glutamate preferentially activates NR2D subtypes.

2) Action potential: When depolarizing stimuli reach the receptor-cell, release of glutamate occurs from all vesicles juxtaposed to the membrane, leading to massive activation of hot spot postsynaptic glutamate receptors, including AMPARs and NMDARs.

3) Coincidental AMPAR-mediated depolarization ("fast" Na+ influx) causes Mg2+ release from open-conformation NMDARs, initiating NMDAR-regulated "slow" Ca2+ influx. Excitatory Amino Acid Transporters (EAATs) re-uptake free glutamate from the synaptic cleft, terminating the action potential.

4) NMDAR-regulated postsynaptic Ca2+ quanta activate enzymatic pathways leading to transcription of genes encoding synaptic proteins. Synthesized proteins are then transported (trafficking) to the synapse and undergo local assembly and expression at the synaptic membrane (receptor subunits and scaffolding proteins) or are released in the synaptic cleft (neurotrophic factors).

5) After depolarizing stimuli, EAAT activity restores resting membrane potential. Subthreshold stimuli at resting membrane potential again induce graded glutamate release, and graded activation of AMPARs and NMDARs, leading to preferential NR2D regulated postsynaptic Ca2+ influx, instructing synaptic protein homeostasis. Stimuli induce neural plasticity at the synaptic hot spot: the synaptic framework (type and density of receptors) and availability of synaptic proteins (receptor subunits, neurotrophic factors and scaffolding proteins) are regulated by incoming stimuli or lack of thereof (points 2-4).

6) Subsequent non-depolarizining or depolarizing stimuli will again trigger graded or massive glutamate release into the synaptic cleft, activating AMPARs and NMDARs, directing graded or massive NMDAR-mediated Ca2+ influx. Subsequent stimuli always find a modified receptor framework because of neural plasticity induced by incoming prior stimuli or lack of prior stimuli (LTP and PTD stimulus driven balance shaping the receptor framework).

CONCLUSIONS

This psychopharmacology driven NMDAR-mediated Ca2+ quanta hypothesis may advance our understanding of the physiological and evolutionary integration of stimuli into species-preserving neuronal circuits and may open new perspectives on the pathophysiology of neuropsychiatric conditions and their therapeutical management.

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