Translational Vignette

NMDA Receptors and Pain—Hopes for Novel Analgesics

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Glutamate is arguably the most important excitatory transmitter in the vertebrate central nervous system (CNS), and the cell surface receptors which mediate the effects of glutamate release can be found at most excitatory synapses throughout the CNS. These receptors are divided into the slow, G-protein coupled metabotropic receptors and the fast ligand-gated ion channels (ionotropic receptors). The latter class is again divided according to the agonists originally used to characterize them. AMPA receptors mediate the majority of fast excitatory neurotransmission, and kainate receptors are as yet little understood but are likely to be important. The NMDA receptor, named after the synthetic glutamate analogue and agonist N-methyl-D-aspartate, is perhaps the most interesting glutamate receptor in terms of physiology and pathology. These NMDA receptor channels have a very high calcium permeability and slow gating kinetics, such that their activation and the ensuing calcium influx is powerful enough to trigger long-term changes within and around that cell, such as resetting synaptic strength. The NMDA receptor generates plasticity in many systems such as memory, motor function, vision, and spinal sensory transmission. Excessive NMDA receptor activation and the huge calcium influx this causes is thought to be responsible for the excitotoxic neuronal death seen after cerebral ischemia and is also implicated as a final mechanism of neuronal death in many neurodegenerative diseases. Because it is a powerful switch, tight controls are placed on the NMDA receptor. Because several events must combine for its activation, the NMDA receptor is often described as a "coincidence detector." Apart from binding of glutamate, glycine is also needed as a co-agonist for channel opening to occur; the magnesium block of the channel that is present at resting membrane potentials must be relieved by membrane depolarization and modulatory sites for polyamines, protons, zinc, and redox agents are also located on the receptor complex (Fig. 1).

All of these events combine in the spinal cord under conditions of repeated afferent fiber stimulation to turn on the NMDA receptor switch and enhance the transmission of nociceptive information in pain pathways. This NMDA receptor-dependent windup underlies central hypersensitivity and the enhanced transmission of pain in both acute and chronic pain situations. Acute weak noxious stimuli are relayed through the spinal cord with little or no modulation and give a faithful report of the pain—a pathway which is predominantly AMPA receptor mediated. Continued and more intense stimulation and/or damage to tissue or nerve causes increased activity in primary afferents. The resultant peptide transmitter release...
Fig. 1. The regulation of the NMDA receptor, showing the receptor (NR1 plus NR2 subunits), the glycine co-agonist site, and the ion channel. The resting magnesium block of the channel is removed by a membrane depolarization, and activity of the ion channel is further regulated by polyamines, zinc, and protons. The sites of action of certain channel blockers are also shown.

causes cumulating excitatory postsynaptic potentials which summate sufficiently to relieve the magnesium block of the NMDA receptor channel: now the criteria for activation of the NMDA receptor are fulfilled, and glutamate can open the channel. The ensuing calcium influx leads to a hyperexcited state in the neuron, which then gives an increased response to any further stimuli arriving, a situation which lasts for several minutes. This process can be induced artificially in an in vivo rat model: after repeated electrical stimulation of C-fiber afferents in the hindpaw of the rat, enhanced responses are recorded from dorsal horn neurones while the intensity of the stimulus is kept the same. This windup is dependent on NMDA receptor activation (1). Thus, persistent afferent activity will induce and then maintain continued spinal NMDA activity and so hyperexcitability.

There is evidence for involvement of the NMDA receptor in inflammatory pain, neuropathic pain, allodynia, and ischemic pain—all processes where the faithful relationship between stimulus and response breaks down. In these persistent pain states, the NMDA receptor is vital both in establishing the heightened pain state and in maintaining this state when it has outlived its natural usefulness. Because the NMDA receptor is so critical to the plasticity of the system, it is a potential target for development of new analgesics.

The NMDA receptor is not restricted to spinal pain pathways, and it is not surprising that ubiquitous NMDA receptor antagonists such as the channel blocker ketamine and competitive antagonists are associated with a range of adverse effects including impairment of learning and memory, psychostimulation, and potential neurotoxic effects. There are several approaches to avoiding and lessening these side effects. Glycine site antagonists are associated with less side effects, while still being antinociceptive. Another approach is to target a particular receptor type by its subunit composition. The NMDA receptor is a hetero-oligomer composed of two different types of polypeptide subunits—NR1 and NR2—which come together to form an integral ion channel which gates sodium, potassium, and calcium. The stoichiometry of this interaction has been in contention for some time, and Laube et al. (2) recently presented evidence for a tetrameric structure for NMDA receptors: two NR1 and any combination of two NR2 subunits.

NR2 subunits do not form functional homomeric receptors in expression systems, but coexpression with NR1 generates channels with large whole cell currents which resemble native NMDA receptors (3). Combinations of NR2 subunits and NR1 splice variants give a wide diversity of receptor types, which differ in single channel properties, in sensitivity to glutamate and glycine-site antagonists and, for example, sensitivity to ifenprodil antagonism (4). Ifenprodil is
a noncompetitive NMDA-receptor antagonist, which is selective for receptors containing the NR2B subunit (5). It and similar compounds with this selectivity have low side effect profiles in vivo (6). Once the functional significance of these various receptor types is determined, then subunit selective drugs can be targeted to the relevant brain regions and receptor types, avoiding the side effects of ubiquitous block of this receptor.

Thus, a greater understanding of the composition of the NMDA receptor, arguably the most important central excitatory contributor to pain transmission, may lead to the development of useful clinical agents lacking the side effects of ketamine; drugs that may have a wide application for many types of pain.

References