

## **Summary**

**Tony Priestley**

### **Pharmacology and electrophysiology of excitatory amino acid receptors**

The ionotropic glutamate receptors are multimeric ligand-gated cation channels. Electrophysiological properties of each receptor class are ideally suited to specific signaling functions. AMPA- and kainate-activated receptors show rapid and extensive desensitization – key properties required for a high-fidelity frequency-coding modality. NMDA receptors mediate longer lasting postsynaptic responses and require coincident membrane depolarisation for full activation – characteristics which are more suited to an integrative function. There are a substantial number of high-affinity, selective ligands for each receptor class, including agonists, partial agonists, competitive, uncompetitive and non-competitive antagonists and allosteric modulators. The biophysical and pharmacological characteristics of recombinant glutamate receptors are influenced substantially by subunit composition. This review provides a molecular profile of the ionotropic glutamate receptor family illustrating how diversity of function has been attained and how this has been, and remains to be, exploited pharmacologically.

## **Summary**

**Michael Rigby, Robert P. Heavens, David Smith, Ruth O'Donnell, Ray G. Hill and Dalip J.S. Sirinathsinghji**

### **Distribution of NMDA receptors in brain and spinal cord**

All of the subunits (NR1-NR3) that form the heteromeric NMDA receptor complex show a heterogeneous distribution throughout the CNS, both brain and spinal cord. In the brain there is a fair consistency between species and between protein and mRNA distributions (with the possible exception of exon 5 of the NR1 mRNAs). The NR1 mRNA species are more heavily expressed than the NR2 but show a differential pattern of distribution. The NR2 series also show a differential pattern with NR2A being largely expressed throughout the brain, NR2B is more prominent in forebrain. NR2C and NR2D are more weakly expressed (apart from NR2C mRNA in the cerebellum). NR2C is weak in cortex and subcortical structures, but extremely heavy in the cerebellum. NR2D appears more restricted to thalamic regions but is likely to be expressed at low levels in cortex. Within the spinal cord the largest controversy has been over the distributions of the NR2 subunits. It is clear that the low levels of expression of these subunits, probably in conjunction with relatively lower neuronal densities in cord than brain, have confounded the issue. Overall a consensus is beginning to form that NR2A is distributed throughout all laminae, NR2B shows a propensity for the substantia gelatinosa, NR2D is uniformly distributed (like NR2A) and NR2C appears to be largely non-neuronal. The order they have been described in here also reflects a decreasing relative abundance.

It is hoped that as more selective antibodies become available it will be possible to colocalise various subunits together. Identification of relationship of different subunits with each other will be assisted by the increasing use of techniques, such as immunocytochemistry in conjunction with in situ hybridisation, and single cell PCR.

### **Summary**

**Michael J. Cumberbatch, Boris A. Chizh and P. Max Headley**

#### **Spinal nociceptive processing: NMDA receptors and modulation by neuropeptides**

Perceptions of the role of NMDA receptors in spinal nociceptive processing have changed somewhat over the last few years. Initially it was thought that NMDA receptors were only active following intense depolarisation and that they were specifically involved in mediating enhanced responses to noxious stimuli during inflammation or nerve injury. However, more recent evidence suggests that NMDA receptors may carry significant post-synaptic current from tonically released glutamate under resting conditions. This implies that, at the level of the spinal cord, activation of NMDA receptors alone may have relatively little contribution to acute or chronic nociceptive processing. There is increasing evidence that a gain in NMDA function may occur in parallel or as a result of activation of other neurotransmitter systems, such as the tachykinins. The combined release of other neurotransmitters with glutamate may result in the facilitation of NMDA receptor mediated events and may represent an important step in the pathophysiology of persistent pain.

### **Summary**

**Qing-Ping Ma and Clifford J. Woolf**

#### **The NMDA receptor, pain and central sensitization**

The capacity to feel pain in response to a noxious stimulus serves an important protective function, helping to protect the body from severe injury in the face of potentially damaging stimuli in the environment. The N-methyl-D-aspartate (NMDA) receptor appears to have a minimal role in the generation of this physiological nociceptive pain. Under pathological conditions, however, the pain threshold can be significantly reduced and the sensation of pain is generally enhanced. Pain hypersensitivity comprises two conditions: allodynia, a reduction in pain threshold so that normally innocuous stimuli cause pain, and hyperalgesia, enhanced pain sensation evoked by noxious stimuli. It is on these manifestations of hypersensitivity that the NMDA receptor may have a major contribution.

### **Summary**

**Stéphanie Le Guen, Victoria Chapman and Jean-Marie Besson**

#### **Some pharmacological aspects of NMDA-mediated nociceptive transmission in the rat spinal cord as revealed by c-fos immunocytochemistry**

In this chapter we have reviewed the contribution of fos technology in understanding NMDA receptor mediated events in the spinal cord dorsal horn. Many pathological conditions lead to amplification of nociceptive input in the spinal cord, partly due to central sensitization. Central sensitization involves a variety of transmitters and post-synaptic mechanisms implying notably activation of NMDA receptors by glutamate, and activation of the NK-1 tachykinin receptor by substance P and neurokinin A. Activation of these receptors allows an inrush of calcium through ligand and voltage-gated ion channels, which in turn stimulates protein kinase C activity and regulates the activation of immediate-early gene products leading to neuronal plasticity. One of these immediately-early genes is c-fos, largely used as an indirect marker of nociceptive processes in the dorsal horn of the spinal cord.

We report here several pieces of data showing the involvement of NMDA receptors in models of inflammatory pain, and the close co-operation between opioids agonists, substance P and NMDA receptors in nociceptive-mediated events and in the development of antinociceptive morphine tolerance in the rat spinal cord.

### **Summary**

**Anthony H. Dickenson and Fiona C. Taylor**

#### **Interaction of NMDA and other neurotransmitter receptor systems in modulation of nociception**

Activation of the NMDA receptor leads to a major excitatory drive in the dorsal horn of the spinal cord where wind-up and associated central hypersensitivity are induced following NMDA receptor activation. For this to occur, high intensity C-fibre or noxious stimuli are required. The induction of NMDA receptor activation is believed to be one example of interactions with other transmitter systems in that removal of the magnesium block of the channel appears to be due to actions of peptides on their receptors. Once the NMDA receptor is activated, inhibitory controls may be compromised. Combinations of NMDA antagonists plus opioids therefore predictably synergize to produce marked antinociceptive effects. In addition, three other systems may interact with NMDA receptor mediated mechanisms in a more direct way. The influx of calcium through the receptor channel, but also via voltage-operated calcium channels, not only is a major contributor to excitability but can trigger a number of intracellular events. Of prime importance is the generation of the gas, nitric oxide (NO). Block of the production of NO produces antinociceptive effects very similar to those of NMDA receptor antagonists. Finally, NMDA mediated excitability may trigger the release of adenosine, which via A1 receptors, may act to then control further excitability.

### **Summary**

**Susan Boyce and Nadia M.J. Rupniak**

#### **Behavioural studies on the potential of NMDA receptor antagonists as analgesics**

Competitive and non-competitive NMDA receptor antagonists possess antinociceptive activity in animals, particularly in conditions of hypersensitivity and prolonged input following inflammation or nerve injury, and are analgesic in experimental and clinical pain states in man. However, these agents also induce unacceptable side effects at analgesic doses, including hallucinations, dysphoria, and disturbances of cognitive and motor function, which limit their clinical use. Antagonists acting at the NMDA/glycine modulatory site also have antinociceptive activity in animals and appear to have a reduced propensity for psychomotor stimulation and cognitive disruption than competitive and non-competitive NMDA antagonists; however, they may cause ataxia at doses close to those producing antinociception. Compounds that are selective antagonists at the NMDA NR2B subtype receptor, such as CP-101,606, appear to have the best therapeutic window with no evidence of motor stimulation, ataxia or cognitive impairment at doses far exceeding those effective in nociception assays. Clinical studies with NR2B antagonists are awaited to determine these agents offer advantage over existing NMDA antagonists as analgesic agents in man.

### **Summary**

**Christine N. Sang**

#### **Clinically available glutamate receptor antagonists in neuropathic pain states**

Results from behavioral models of neuropathic pain in animals have been generally confirmed in humans with experimental pain or patients with neuropathic pain, but the developing story in humans has been disappointing thus far. The dose-limiting psychotomimetic side effects have limited the therapeutic utility of the clinically available NMDA receptor antagonists. The current studies show that repeated dose studies with orally administered NMDA antagonists have a far less robust effect than single dose studies using intravenous

formulations. This may be the result of several factors, including the ability to achieve peak serum levels and hence peak levels in the central nervous system, the close observation in a hospital setting where transient side effects may be better tolerated, or the ability to limit the development of side effects in the proportion of poor metabolizers of the P450-2D6 isoenzyme.

The goal of drug discovery has traditionally been to maximize activity at the specific target in order to optimize therapeutic activity without toxicity. Unfortunately, studies thus far demonstrate a role for NMDA receptor antagonists in clinical pain states, but almost all studies show a narrow therapeutic ratio. This may be potentially overcome by the use of drug combinations, the development of newer low affinity NMDA channel antagonists and more selective systemic NMDA-receptor antagonists (which modulate binding sites within the NMDA complex, or have affinity at specific NMDA receptor subtypes), and the selective administration of NMDA receptor antagonists. The heterogeneity of the pain state may make this approach difficult, requiring instead for the ideal analgesic to interact at several selective sites with the potential for acting synergistically in terms of efficacy but not toxicity. Pharmacological advances have rapidly followed the recognition that the NMDA receptor is made of heteromeric composition of families of subunits (specifically, NR1 and NR2). At this time, not only have receptor subtypes have been isolated and cloned, but with it has come the development of exciting new compounds to selectively target these sites.

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