

NMDA RECEPTORS: SOME NEW IDEAS

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Over the last decades there have been no quantum leaps or paradigm shifts in thinking in the treatment of pain. In fact there has been very little new - what has been new has to a large extent simply been the re-hashing of old themes. For example, we have seen new drugs, but they have simply been new drugs in old classes with very little new thought behind them. Even the COX-2 inhibitors are a rehashing of the NSAID theme. As a result, the treatment of pain, especially chronic pain, has been largely unsatisfactory, disappointing, largely ineffective, boring and, as a result, unpopular.

What has been greatly expanded in this time is our knowledge of the anatomy of pain. We now know that there are three neurons involved in the perception of pain:

1. The Primary Neurone which originates in the nociceptors in the tissues which are responsible for the transduction (or generation of the pain impulse) of pain. Its cell body lies in the dorsal root ganglion. It enters the dorsal horn of the spinal cord and ascends one level where it terminates in the dorsal horn of that level where it synapses with the secondary neurone.
2. The Secondary Neurone is responsible for the spinal part of central transmission. These neurons cross over to the lateral columns of the spinal cord on the opposite side where they ascend in one of two tracts - the neo-spinothalamic and the paleo-spinothalamic tract responsible for the fast and slow conduction of pain. Both of these tracts terminate in the thalamus (which is part of the limbic system) which gives the emotional component to pain. The paleo-spinothalamic tract gives off branches to the Reticular Activating System, which is why pain can "wake us up" or render us more aware.
3. The Tertiary Neurone originates in the thalamus and terminates in the cortex of the brain where we actually perceive pain and localise it.

There are also the descending pathways of pain, which originate in the cortex and the thalamus and descend down through the medulla where they synapse with neurons that continue to the various levels of the dorsal horns of the spinal cord. There they synapse with the "inter-neurons" - small short neurons that synapse with the synapse between the primary and secondary neurons to modify or modulate transmission over that synapse.

The interesting thing about modulation is that it can work in two ways:

1. It can ease pain. It can in other words slow down or reduce transmission between the primary and secondary neurone. This is the mode of action of the opiate group of analgesics - they are agonists of the modulatory system to decrease pain transmission between the primary and secondary neurons. Because they arise in the cortex, thought and will power and association can modulate the pain transmission. Hence the cultural differences in the handling of pain. The association of the pain can also modulate it - as for example when injured when playing sport, the person can play on apparently not feeling pain. Also, soldiers injured in the heat of battle can sometime not feel pain due to the sympathetic drive and stress of the moment.
2. The modulation system can also cause pain or worsen existing pain. The expectation of pain can actually cause pain without any painful stimulus being applied. Hence the sometimes inappropriate level of pain experienced with minor injuries etc.

There are various receptors in the skin and tissue, each sensitive to different stimuli.

1. Meissners' Corpuscle - sensitive to touch and tactile stimulation

2. Pacinian Corpuscle - sensitive to pressure and vibration
3. Merkle's Disc and Modified epithelial Cell - Touch
4. Peri-follicular nerve ending - touch
5. Free nerve ending - sensitive to Touch, Temperature and Pain. This is where the transduction of pain takes place i.e. the generation of the pain impulse, and it is these free nerve endings that are important in the sensitisation that takes place in inflammation. The free nerve endings are important in pain. They sense touch, pressure and temperature as well as chemical and long term stimuli. They release chemical mediators, which produce neurogenic inflammation, which produces, among others, prostaglandins, which sensitise the nociceptors. **This process of sensitisation is one of the factors that make the treatment of pain sometimes so difficult and unsatisfactory and it is here in sensitisation that NMDA receptors play a huge role.**

With intense, repeated and prolonged stimuli the nociceptors become sensitised. This means that, for all stimulus intensities, the threshold for activation is lowered and the frequency of firing is increased. This produces the tenderness, hyperalgesia and allodynia (pain on stimuli that do not normally produce pain) around the area of inflammation. Two factors play important roles in sensitisation n1: Chemical substances released by the injury and the neuro-effector action of the nociceptors.

1. The chemical mediators released include prostaglandins, bradykinin as well as hydrogen and potassium ions, which then sensitise the **nociceptors**.
2. The free nerve ending nociceptors are not only receptors but also function as effectors. A stimulus will travel up one branch of the free nerve ending and then down others where the impulse has certain effects. It releases Substance P and bradykinin, which have an effect on the blood vessels causing oedema and flushing. The substance P also has an effect on the mast cells causing the release of histamine, which then sensitises the nociceptors further. Substance P also has an effect on the platelets which release 5-HT, which also sensitises the nociceptors further.

So the nociceptors become more and more sensitised causing tenderness, allodynia and hyperalgesia.

The nerve fibres in the peripheral nerves - Ad and C, which conduct pain impulses also, become sensitised in

the presence of inflammatory mediators. This is seen in the case of fibres from the viscera, which under normal circumstances do not transduce or transmit pain. In the presence of bradykinin, prostaglandins and leukotrienes, these fibres become sensitised and become sensitive to noxious stimuli and can then transmit pain impulses easily. It has been shown that this sensitisation of the pain fibres is **mediated by the NMDA receptors**

As stated earlier the NMDA receptors are important in mediating sensitisation. The identification of the NMDA receptors is something relatively new in the understanding and treatment of pain as they were only identified in the late 1980's. It was then discovered that NMDA receptor antagonists inhibited the hyper-excitability of spinal cord neurons induced by C-fibre stimulation. It was concluded that activation of NMDA receptors after tissue injury and inflammation enables facilitated processing in the spinal cord.

It is now known, however, that NMDA receptors occur not only in the spinal cord but also in the periphery and supra-spinally

The question arises that, if there are N-methyl-D-Aspartate (NMDA) receptors in the body, then where does NMDA naturally or physiologically occur in the body. The answer is: "Nowhere". It is a synthetic substance used only in research to identify different types of receptors. The truth is that the NMDA receptor is, physiologically, a glutamate receptor!

Glutamate, however, does not only bind to the NMDA receptor - it has an action at a lot of other receptors as well. Glutamate is a neurotransmitter in the nervous system and it exerts its post-synaptic effects via a diverse get of membrane receptors. The glutamate receptors can be mostly divided into two groups - the metabotropic receptors and the ionotropic receptors. As far as pain in concerned it is the ionotropic receptors that are important so this discussion will be limited to them. The ionotropic receptors act as gates to ion channels. Now the ionotropic glutamate receptors are divided into three groups according to which synthetic substance binds to them - and so we have the AMPA glutamate ionotropic receptors, the kainate and NMDA glutamate ionotropic receptors.

The NMDA receptors play a crucial role in excitatory synaptic transmission (especially in pain and sensitisation), plasticity and neuro-degeneration. The NMDA glutamate ionotropic receptors also have some unique properties.

1. They control a cation channel, which is highly permeable to monovalent ions and calcium.
2. For efficient activation of the receptor and channel, simultaneous binding of glutamate AND glycine (A co-agonist) is required.
3. At resting membrane potential, the channels are blocked by extra-cellular magnesium and can only be opened by simultaneous agonist-co-agonist binding along with depolarisation.

It can be seen then that a set of three conditions (a "triad") must be fulfilled before the NMDA receptor and channel can be activated. Agonist binding, co-agonist binding and depolarisation - all at the same time.

It must be remembered that membrane channels are simply large molecules imbedded in the cell membrane. A part of that molecule has an area on it that matches or fits an agonist, not only physically but also chemically and electrically. When the agonist binds with that site on the molecule it changes the forces in that molecule like the de Waals forces and that changes the shape of the molecule and it develops channels through which certain ions and substances can pass.

The NMDA glutamate ionotropic receptor-channel molecule is made up of various subunits. NR-1, NR-2 (A, B, C, D) and NR-3 A and B. The actual effect of the receptor and the channel depends of the combination of subunits in that particular receptor. It seems that most NMDA receptors must have a NR-1 subunit combined with any of the others. It has been identified that it is the NR-1, NR-2B combination that plays an important role in pain and sensitisation. This combination makes a channel with a high conductance and also a high sensitivity to blocking by magnesium at, as mentioned above, resting membrane potential.

So we see that the NMDA receptor with the NR-1, NR-2B combination is blocked by magnesium at resting membrane potential and, once opened is highly sensitive to blocking by extra-cellular magnesium. Based on these observations, one would think that normal or high extra-cellular magnesium should prevent sensitisation and potentiate other analgesic if it is not analgesic on its own. We will see if this is indeed so.

It is now known that NMDA receptors occur in the periphery on the nociceptors and on the peripheral nerves as well as at the spinal and supra-spinal levels.

CENTRAL NMDA RECEPTORS

NMDA receptors in the spinal cord mediate central sensitisation. This is a state where the dorsal horn excitability is increased and, therefore, its response to sensory input is facilitated.

Peripheral inflammation may alter the properties of receptors in the spinal dorsal horn (possibly via repeated C-fibre firing).

Protein phosphorylation up-regulates the NMDA receptor channels, keeping them open longer, which results in persistent pain after inflammation.

NMDA receptors are not only located POST-synaptically but also PRE-synaptically. Pre-synaptically they mediate the release of substance P, which mediates an effect on the post-synaptic receptors facilitating and prolonging transmission of impulses

There is a triad, mentioned above; depolarising of the C-fibres and binding of glutamate and glycine to the NMDA receptor. In inflammation and pain states the C-fibres fire constantly so that the NMDA receptors are constantly being opened. This leads to an increase in the numbers of NMDA receptors peripherally and centrally. This leads to the state of sensitisation and seen in hyperalgesia and allodynia in the area affected.

This sensitisation and hyperalgesia can be inhibited by NMDA receptor antagonists, or blockers, that prevent them opening in response to C-fibre depolarisation. There are a number of drugs in development but they are not clinically available yet but will be shortly. These drugs will be more specific for the NR1-NR2B type NMDA receptor involved in pain. In the meantime we do have some non-specific NMDA receptor blockers available clinically at present. Due to their generic blocking of NMDA receptors these drugs do have some undesirable side effects if not used circumspectly. The most important side effect is drowsiness and the NMDA receptors do play a role in maintaining the awake state (possibly one of the reasons that pain causes arousal and an "awake" state).

Drugs that we currently have clinically are ketamine, dextromethorphan and magnesium.

DEXTROMETHORPHAN

This is a derivative of codeine and is commonly used in cough syrups. In the South African MIMS there are

many, many cough syrups but only 6 contain dextromethorphan in any quantity. Only ONE cough syrup contains ONLY dextromethorphan nl "Benylin Dry Cough" – see blow:

	Dextromethorphan	pseudoephedrine	Ammonium Chloride	Panthenol	Doxylamine	Sodium Citrate	Acetylpipridinium	Phenylephedrine	Clorpheniramine	Phenylpropanol amine
Benylin DM Decongestant cough syrup	X	X								
Broncol	X		X	X						
Cepacol	X				X	X	X			
Degoran Cough	X		X			X		X		
Demazin Antiutussive syrup	X								X	X
Benylin Dry Cough	X									

Benylin Dry Cough contains 15 mg / 5 ml of dextromethorphan. Usually, to be effective in preventing sensitisation or treating neuropathic pain the dose should be 45 mg (15ml) 6 hourly.

Taken from the MIMS:

Contra-indication: Asthma and Hepatic dysfunction
 Side Effects: CNS effects (drowsiness), GI disturbances (constipation) and respiratory depression at high doses.
 Drug Interactions: CNS depressants are potentiated, hypertension and hyperpyrexia.

KETAMINE

This drug can be used at sub-anaesthetic levels as a very good adjuvant to other agents for acute pain. Obviously it is difficult to use long term in chronic pain. Perhaps it has a use in chronic pain where a patient is admitted and put sub-anaesthetic doses along with other agents for a few days in an effort to break the sensitisation cycle in neuropathic pain? Ketamine is possible underused in this area.

Ketamine has been shown to enhance the local anaesthetic and analgesic actions of bupivacaine (and conceivably ropivacaine as well).

Ketamine has been shown to prevent the development of hyperalgesia after burn injury!

Not available in South Africa is a ketamine topical cream, which is used well for neuropathic pain.

MAGNESIUM

As mentioned earlier the NMDA NR1-NR2B subtype receptor channel is highly sensitive to blocking by extra-cellular magnesium especially at resting membrane potential - magnesium is a "physiological" blocker of NMDA receptors. It could then be logical to think that extra-cellular magnesium can play a role in prevention or reduction of sensitisation. It would almost work "pre-emptively" - by blocking the channel before the C-fibres start firing in response to pain (remember the NMDA receptors are activated by the triad mentioned earlier - one component of which is depolarisation). Once the firing starts and the channels are opened they are highly sensitive to blocking by magnesium also. Many patients presenting for anaesthesia are found to have low serum magnesium on routine pre-op blood work-up. A normal serum level of magnesium does not mean that the total magnesium is up to standard. Perhaps normal or slightly high serum magnesium can potentiate other analgesics or reduce and prevent sensitisation on its own. Let's see.

Intra-abdominal local analgesia is notorious for being unreliable and relatively ineffective. The main reason for this that a large volume of local anaesthetic has to be used and, to prevent overdose and toxicity; the local anaesthetic must be diluted making it all but ineffective. Various agents have been added to the local anaesthetic including bicarbonate to adjust the pH, in an effort to make it more effective.

In the South African Journal of Regional Anaesthesia of May 2004 there appeared an article where magnesium (or ketamine) was added to bupivacaine for intra-abdominal local anaesthesia after laparoscopic cholecystectomy. This was found to be very effective in reducing the pain following lap-chole surgery. The time to first dose of analgesic was prolonged, PCA morphine consumption's was less and shoulder pain incidence and severity were less.

The conclusion reached was that the co-administration of either magnesium or ketamine with bupivacaine is effective in reducing post-op shoulder pain and analgesic requirement following lap-chole surgery. (Anecdotally: a number of surgeons have started using this technique in Pretoria with great success).

The theory behind this technique is that both ketamine and magnesium are NMDA receptor blockers and this effect on the peripheral NMDA receptors in the peritoneum is responsible for the reduction in pain and analgesic requirements.

European Journal of Anaesthesiology 2001

"Magnesium as part of balanced general anaesthesia with propofol, remifentanyl and mivacurium: a double blind, randomised prospective study in 50 patients" Using: Magnesium sulphate 50 mg / kg bolus (or Placebo)

Propofol 1-2 mg / kg

Maintenance: propofol, remifentanyl, and mivacurium

Significant reduction in remifentanyl use (0,09ug/kg as opposed to 0,14 ug/kg for placebo) and mivacurium use. Propofol use stayed the same. There was a trend towards lower post-operative pain and less pain medication required in 24 hours post surgery.

NO side effects were noted.

The effects of a single bolus of 50 mg/kg lasted for 2hours (usual duration of effect for magnesium). In cases longer than two hours a repeat bolus OR infusion might be required.

Anaesthesia and analgesia July 1998

"Magnesium Sulphate Reduces Intra- and Postoperative Analgesic Requirements"

Magnesium Sulphate 50 mg/kg followed by an infusion of 8 mg/kg/hr.

Found:

Intraoperative fentanyl consumption significantly reduced Magnesium reduced NOT ONLY postoperative analgesic requirements BUT ALSO intraoperative.

But what about complications?

Potential complications include:

Prolonged action of non-depolarising muscle relaxants

Vasodilatation

Cardiac conductivity disorders

Sedation - NMDA's are necessary for normal function of CNS. Magnesium is a "generic blocker" of all NMDA receptors.

None of these complications occurred in this study. In fact, intra-operatively, between the magnesium group and the control group: haemodynamic and respiratory variables were the same - no instability in either group.

Conclusion: Magnesium administration led to significant reduction of intra and postoperative analgesic requirements. BUT before using it clinically bear in mind the possible side effects - especially in impaired renal function and A-V conduction disturbances

Acta Anaesthesiologica Scand 2002

"A comparative study of the analgesic effect of tramadol, tramadol plus magnesium, and tramadol plus ketamine for postoperative pain management after major abdominal surgery."

PCA mixtures used:

T - Tramadol 5 mg/ml

TM - Tramadol 5 mg/ml + magnesium 30 mg/ml (3gm in 100ml)

TK - Tramadol 5 mg/ml + ketamine 1 mg/ml

PCA settings (According to tramadol)

Loading dose 1 mg/kg

Background infusion 0,4 mg/kg/hr

Bolus 0,2 mg/kg - lockout 20 min.

Pain scores were significantly lower (and similar) in **TM** and **TK** than **T** alone

Conclusion: Adding magnesium or ketamine to tramadol gives:

Better analgesia

Good patient comfort

Decreased bolus requirement

This effect is possibly due to the blocking of NMDA receptors.

Ketamine is associated with nausea and vomiting which are even worse with tramadol. Ketamine also is known for dreams and hallucinations Magnesium on the other hand, at these doses, has no side effects at all.

Magnesium - a last few points

As many patients have low magnesium levels preop, and as magnesium levels decrease after major surgery, the prevention of hypomagnesemia may be important for reducing postoperative analgesic requirements.

By blocking the NMDA (NR1-NR2B), magnesium potentiates ALL analgesics including NSAID's. The best analgesic effect is seen with ketorolac as ketorolac also has a central working.

Magnesium also has an application in chronic and neuropathic pain - on its own and as an adjuvant to other drugs such as dextromethorphan and gabapentin.

References in body of the text, others available on request.

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Composition: Ketorolac tromethamine 10 mg/ml, 30 mg/ml. Contains ethyl alcohol 10 % m/v. **Indications:** Short-term management of moderate post-operative pain. **Contra-indications:** • Active peptic ulcer, gastro-intestinal bleeding • Anticoagulation therapy • Haemorrhagic diatheses • Hypersensitivity to ketorolac/other NSAIDs, allergies to aspirin/other prostaglandin synthesis inhibitors • Cerebrovascular bleeding, operations with high risk of bleeding/incomplete haemostasis • Moderate/severe renal impairment (serum creatinine > 442 µmol/l) or patients at risk of renal failure due to volume depletion or dehydration • Pregnancy, labour, delivery or lactation • Children younger than 16 years • Prophylactic analgesic before surgery • Neuraxial administration • Combination with oxypentifylline. **Warnings:** • Serious gastro-intestinal toxicity, including irritation, bleeding, ulceration or perforation, especially in debilitated patients/the elderly. • Use with caution in impaired renal function/history of kidney disease as it is a potent inhibitor of prostaglandin synthesis. • Anaphylactic reactions may occur in patients with or without a history of hypersensitivity to aspirin, other NSAIDs or Tora-dol. **Dosage:** • Adults: Short-term IV or IM use not to exceed 2 days. Use of IV infusion not to exceed 24 hours. • Opiate analgesics may be used concomitantly. • Single-dose IM: 10 – 60 mg (< 65 years); 10 – 30 mg (> 65 years) • Single dose IV: 10 – 30 mg (< 65 years); 10 – 15 mg (> 65 years) • Multiple-dose: Patients < 65 years (max. 90 mg/d): 10 – 30 mg IM, 4 – 6 hourly, or IV bolus 10 – 30 mg, 6 hourly or IV-infusion initially 30 mg, then continuous infusion of 5 mg/h. Patients > 65 years or renally impaired (max. 60 mg/d): 10 – 15 mg IM, 4 – 6 hourly or 10 – 15 mg IV bolus, 6 hourly. For compatibility of Tora-dol with other pharmaceuticals, refer to package insert. **Side effects:** nausea, dyspepsia, gastro-intestinal pain, abdominal discomfort, gastritis, diarrhoea, eructation, constipation, flatulence, fullness, sweating, melaena, peptic ulcer, rectal bleeding, stomatitis, vomiting, haemorrhage, perforation, pancreatitis, oesophagitis, drowsiness, dizziness, headache, dry mouth, nervousness, paraesthesia, abnormal thinking, depression, euphoria, convulsions, inability to concentrate, insomnia, vertigo, myalgia, abnormal dreams, hallucinations, hyperkinesia, aseptic meningitis, anxiety, psychotic reactions, increased urinary frequency, oliguria, acute renal failure, hyponatraemia, hyperkalaemia, haemolytic uremic syndrome, flank pain, raised serum urea and creatinine, urinary retention, interstitial nephritis, nephrotic syndrome, signs of renal impairment, flushing, bradycardia, pallor, hypertension, palpitations, hypotension, chest pain, abnormal liver function tests, dyspnoea, asthma, pulmonary oedema, pruritis, urticaria, Lyell's/Stevens-Johnson syndrome, exfoliative dermatitis, maculopapular rash, purpura, thrombocytopaenia, postoperative wound bleeding, haematoma, epistaxis, increased bleeding time, abnormal taste, abnormal vision, tinnitus, hearing loss, asthenia, oedema, weight gain, injection site reactions and fever. **Precautions:** • Tora-dol inhibits platelet aggregation, reduces thromboxane concentrations, prolongs bleeding times. • In the elderly, terminal plasma half-life of Tora-dol is prolonged and plasma clearance reduced. • Fluid retention, hypertension, oedema can occur; use with caution in patients with cardiac decompensation, hypertension, similar conditions. • Caution is advised in carrying out activities requiring alertness. • Elevation of one or more liver test may occur. **Interactions:** other NSAIDs, oxypentifylline, probenecid, methotrexate, lithium, furosemide, ACE-inhibitors. **Overdosage:** abdominal pain, nausea, vomiting, hyperventilation, erosive gastritis, renal dysfunction, peptic ulcer. Dialysis does not appreciably clear ketorolac. **Packs:** Carton of 5 ampoules **Reg. No.:** [S4] Tora-Dol 1 %: 28/2.7/0570 • Tora-Dol 3 %: 28/2.7/0571. This product information represents an abbreviated version of the complete Tora-dol Injection Package Insert. Details are available on request from Roche Products (Pty) Ltd, 4 Brewery Street, Isando, 1600, Tel: (011) 928 8700 or REAL (Roche Ethical Assistance Line) (tollfree) 0800 212125. TDL08/05 Exp 12/07