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The NR2B subunit of glutamate receptors as a potential target for relieving chronic pain: prospects and concerns ▼

The amino acid glutamate, the major excitatory neurotransmitter in the mammalian brain, is involved in the regulation of numerous integrative brain functions including cognition, memory processing, motor control, neuronal migration and brain development. The NR2B subunit of the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor is implicated in nociception, and is therefore a probable target for novel anti-nociceptive drugs, as outlined in the review by Zhuo [1]. Another recent review proposed that NR2B antagonists could also be useful as analgesics [2].

Notably, the reviews point out that, because the NR2B subunit is implicated in the positive regulation of neuronal excitability in the mammalian forebrain, where it is relatively ubiquitous compared with other CNS and PNS (peripheral) regions, NR2B receptor-antagonists are expected to exhibit analgesic and antinociceptive activities with relatively fewer side effects compared with current pain-relief drugs (Table 1). Indeed, several studies have demonstrated that NR2B antagonists, such as CP101606 [3,4], Ro256981 [4] and ifenprodil [4–6], produced marked antinociceptive effects in animal models for inflammatory and neuropathic pain. Notably, NR2B antagonists are also being developed as potential drugs for treating traumatic brain injury [7–9] and Parkinson's disease [10].

Mouse models

However, several points will need to be addressed before the potential of NR2B antagonists for treating chronic pain over prolonged periods can be realized. We should bear in mind that existing animal models for chronic pain are imperfect and can at best approximate chronic pain in humans. This is first and foremost because pain is monitored indirectly in animals, being estimated by examining their responses to nociceptive stimuli, and such responses do not necessarily mean that there is a concomitant sensation [11]. Moreover, nociceptive pathways could be different in mice and humans, so that drugs showing activity in mouse models for nociception might not necessarily be effective for humans. A notable example is NK1 (substance P) receptor antagonists, which showed promising antinociceptive activity in mice, attenuating nociceptive responses sensitized by inflammation or nerve damage, yet failed in clinical trials [12]. The latter example illustrates that certain drugs might attenuate behavioral responses to noxious sensory stimuli in animal tests but might fail to provide the level of sensory blockade required for effective clinical analgesia in humans. The complexity of extrapolating conclusions from nociceptive studies in mice to human chronic pain is highlighted by the large spectrum heterogeneity of nociceptive sensitivity among mice strains [13], an additional facet of the complexity of applying data from genetically homogenous inbred mice strains to diverse human populations [14].

Tolerance and psychotomimetic effects

As a rule, chronic pain drugs require long-term treatment. Hence, a major concern is that tolerance could develop secondary to physiological modifications in pain-associated neuronal pathways. Indeed, drug efficacy of both non-steroidal anti-inflammatory drugs (NSAIDs) and opiate drugs diminishes following prolonged treatment periods [15–17]. Studies of NR2B antagonists have not so far addressed such concerns. Although the notion of tolerance is common for many pain-relief drugs, the potential development of NR2B antagonists for treating chronic pain carries the extra concern of possible adverse psychotomimetic effects or interference with cognitive functions. This concern arises from the key role of NMDA-type receptors in cognition [18–20]. Indeed, psychotomimetic side-effects have limited the clinical use of subtype nonselective NMDA channel blockers, such as MK801, ketamine or memantine [21]. Notably, a recent study demonstrated that transgenic mice overexpressing the NR2B subunit exhibited improved recognition memory [22], accentuating the concerns of possible cognitive deficits associated with chronic NR2B blockade.

Dysfunction of glutamatergic neurotransmission is strongly implicated

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Table 1. Some concerns with current and prospective drugs for chronic pain

Current drugs

Class	Example	Disadvantages
Opioid agonists	Morphine	Habit forming, abuse, rapid tolerance
NSAIDs	Diclofenac	Might exacerbate peptic ulcers
	Acetaminophen	Long-term use could damage liver
Corticosteroids	Cortisone	Teratogenic; suitable only for short-term use
Anticonvulsants	Carbamazepine	Narrow therapeutic range, CNS side effects
Tricyclic antidepressants	Imipramine	Anticholinergic, antihistaminergic and anti-adrenergic side-effects
α-2-adrenoceptor agonists	Clonidine	Hypotensive
Acetylcholinesterase inhibitors	Neostigmine	Nausea and vomiting
Local anesthetics	Mexiletine	Limited efficacy
Muscle relaxants	Carisoprodol	Limited efficacy
Vanilloids	Capsaicin (topical)	Xeroderma, erythema

Prospective drugs

Class	Reference	Concerns
NR2B antagonists	[1,2]	Cognitive effects?
Cannabinoid CB1 agonists	[30]	Cognitive or psychotomimetic effects? Abuse potential?
Fatty acid amide hydrolase inhibitors	[31]	Cognitive or psychotomimetic effects?
P2X purinergic blockers	[32]	Immune modulation?
Nicotine agonists	[33]	Habit forming?
PAR-2 blockers	[34]	Immunosuppressive?
Vitamin D analogs	[35]	Hypercalcemic, immunosuppressive
NGF antagonists	[36]	Cognitive effects

Abbreviations: NGF, nerve growth factor; NSAIDs, non-steroidal anti-inflammatory drugs.

in schizophrenia, and agents that enhance NMDA receptor function via its glycine modulatory site reduce negative symptoms in some schizophrenic patients [23]. Moreover, altered forebrain and hippocampus expression of NR2B subunit has been observed in schizophrenic patients [24,25]. Therefore, NR2B agonists have the potential for treating schizophrenia or other psychiatric disorders. Such notions highlight the involvement of the NR2B subunit in cognition and the extra care required for developing NR2B antagonists as drugs for chronic use. However, current data suggest that NR2B antagonists are devoid of psychotomimetic effects and, hence, are more likely to be useful pain-relief drugs compared with non-selective NMDA antagonists [1,2].

Other potential effects

Another word of caution relates to the possible involvement of NMDA receptors in immune function [26,27], although it is presently unclear whether the NR2B subunit is expressed by human lymphocytes. Finally, we should keep in mind that, because the NR2B subunit of the NMDA receptor is implicated in early CNS organization and development [28], using NR2B antagonists during pregnancy and lactation periods could be teratogenic.

In conclusion, NR2B antagonists have the potential to be developed as novel drugs for the treatment of chronic pain

Box 1. Open questions associated with the chronic use of NR2B antagonists

- How appropriate are NR2B-overexpressing mice as a model for persistent pain in humans?
- Would NR2B antagonists that block nociception in NR2B-overexpressing mice be effective for treating persistent pain in humans?
- Will super-sensitization of glutamatergic nociceptive pathways be associated with chronic use, so that drug discontinuation will be problematic?
- Will NR2B antagonists be useful for treating persistent pain over extended periods without loss of efficacy possibly arising from upregulation of alternative nociceptive pathways?
- Could cognitive deficits arise from chronic administration of NR2B antagonists?
- Would there be adverse effects on fetus CNS development?
- Will NR2B antagonists demonstrate synergy with other pain-relief drugs?
- Is NR2B a drug target for treating psychiatric conditions?

Box 2. Some Internet resources on chronic pain

(1) NINDS Chronic Pain Information Page
http://www.ninds.nih.gov/health_and_medical/disorders/chronic_pain.htm
(2) MEDLINEplus: Pain
http://www.nlm.nih.gov/medlineplus/pain.html
(3) American Chronic Pain Association
http://www.theacpa.org/
(4) Chronic Pain Association of Canada
http://ecn.ab.ca/cpac/
(5) Chronic Pain Foundation
http://www.chronicpainfoundation.com/
(6) American Academy of Pain Management
http://www.aapainmanage.org/aapm/links.html
(7) Funding - THE MANAGEMENT OF CHRONIC PAIN
http://www.niams.nih.gov/rtac/funding/grants/pa/pa01-115.htm

with fewer side effects compared with current pain-relief drugs (Table 1). NR2B antagonists also promise to have favorable safety profiles compared with subtype nonselective NMDA blockers, which failed in human trials because of psychotomimetic activities. However, considering the key role of the NR2B subunit in cognition, possible cognitive effects of their long-term use must be assessed carefully during subsequent development phases (Box 1). Indeed, the cognitive effects of all new drugs perhaps require more substantial monitoring during development [29]. (See Box 2 for some Internet resources on chronic pain.)

References

1 Zhuo M. (2002) Glutamate receptors and persistent pain: targeting forebrain NR2B subunits. *Drug Discov. Today* 7, 259–267
2 Chizh, B.A. *et al.* (2001) NMDA receptor antagonists as analgesics: focus on the NR2B subtype. *Trends Pharmacol. Sci.* 22, 636–642
3 Taniguchi, K. *et al.* (1997) Antinociceptive activity of CP-101,606, an NMDA receptor NR2B subunit antagonist. *Br. J. Pharmacol.* 122, 809–812
4 Boyce, S. *et al.* (1999) Selective NMDA NR2B antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunit in dorsal horn. *Neuropharmacol.* 38, 611–623
5 Sakurada, T. *et al.* (1998) Involvement of spinal NMDA receptors in capsaicin-induced nociception. *Pharmacol. Biochem. Behav.* 59, 339–345
6 Chizh, B.A. *et al.* (2001) Supraspinal versus spinal sites of the antinociceptive action of the subtype-selective NMDA antagonist ifenprodil. *Neuropharmacol.* 40, 212–220
7 Chazot, P.L. (2000) CP-101,606 Pfizer Inc. *Curr. Opin. Investig. Drugs* 1, 370–374
8 Merchant, R.E. *et al.* (1999) A double-blind, placebo-controlled study of the safety, tolerability and pharmacokinetics of CP-101,606 in patients with a mild or moderate traumatic brain injury. *Ann. New York Acad. Sci.* 890, 42–50
9 Bullock, M.R. *et al.* (1999) An open-label study of CP-101,606 in subjects with a severe traumatic head injury or spontaneous intracerebral hemorrhage. *Ann. New York Acad. Sci.* 890, 51–58
10 Steece-Collier, K. *et al.* (2000) Antiparkinsonian actions of CP-101,606, an antagonist of NR2B subunit-containing *N*-methyl-D-aspartate receptors. *Exp. Neurol.* 163, 239–243
11 Le Bars, D. *et al.* (2001) Animal models of nociception. *Pharmacol. Rev.* 53, 597–652
12 Hill, R. (2000) NK1 (substance P) receptor antagonists – why are they not analgesic in humans? *Trends Pharmacol. Sci.* 21, 244–246
13 Mogil, J.S. and Adhikari, S.M. (1999) Hot and cold nociception are genetically correlated. *J. Neurosci.* 19, RC25
14 Gurwitz, D. and Weizman, A. (2001) Animal models and human genome diversity: the pitfalls of inbred mice. *Drug Discov. Today* 6, 766–768
15 Pasero, G. *et al.* (1995) A multi-centre, double-blind comparative study of the efficacy and safety of aceclofenac and diclofenac in the treatment of rheumatoid arthritis. *Curr. Med. Res. Opin.* 13, 305–315
16 Rainov, N.G. *et al.* (2001) Long-term intrathecal infusion of drug combinations for chronic back and leg pain. *J. Pain Symptom Manage.* 22, 862–871
17 Borgland, S.L. (2001) Acute opioid receptor desensitization and tolerance: is there a link? *Clin. Exp. Pharmacol. Physiol.* 28, 147–154
18 Freitas da Rocha, A. *et al.* (2001) *N*-methyl-D-aspartate channel and consciousness: from signal coincidence detection to quantum computing. *Prog. Neurobiol.* 64, 555–573
19 Shapiro, M. (2001) Plasticity, hippocampal place cells and cognitive maps. *Arch. Neurol.* 58, 874–881
20 Malhotra, A.K. *et al.* (1997) NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 14, 301–307
21 Kornhuber, J. and Weller, M. (1997) Psychotogenicity and *N*-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. *Biol. Psychiatry* 41, 135–144
22 Tang, Y. *et al.* (2001) Differential effects of enrichment on learning and memory function in NR2B transgenic mice. *Neuropharmacol.* 41, 779–790
23 Goff, D.C. and Coyle, J.T. (2001) The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am. J. Psychiatry* 158, 1367–1377
24 Grimwood, S. *et al.* (1999) NR2B-containing NMDA receptors are up-regulated in temporal cortex in schizophrenia. *NeuroReport* 10, 461–465
25 Gao, X.M. *et al.* (2000) Ionotropic glutamate receptors and expression of *N*-methyl-D-aspartate receptor subunits in subregions of human hippocampus: effects of schizophrenia. *Am. J. Psychiatry* 157, 1141–1149
26 Kuo, J.S. *et al.* (2001) The involvement of glutamate in recall of the conditioned NK cell response. *J. Neuroimmunol.* 118, 245–255
27 Lombardi, G. *et al.* (2001) Characterization of ionotropic glutamate receptors in human lymphocytes. *Br. J. Pharmacol.* 133, 936–944
28 Jin, D.H. *et al.* (1997) Developmental expression, subcellular localization and tyrosine phosphorylation of NR2A and NR2B in the rat brain. *Mol. Cells* 7, 64–71
29 Harrison, J.E. (2002) Routine cognitive testing for all drugs? *Drug Discov. Today* 7, 101–102
30 Rice, A.S. (2001) Cannabinoids and pain. *Curr. Opin. Investig. Drugs* 2, 399–414
31 Fowler, C.J. *et al.* (2001) Fatty acid amide hydrolase: biochemistry, pharmacology and therapeutic possibilities for an enzyme hydrolyzing anandamide, 2-arachidonoylglycerol, palmitoylethanolamide and oleamide. *Biochem. Pharmacol.* 62, 517–526
32 Chizh, B.A. and Illes, P. (2001) P2X Receptors and Nociception. *Pharmacol. Rev.* 53, 553–568
33 Decker, M.W. *et al.* (2001) The therapeutic potential of nicotinic acetylcholine receptor agonists for pain control. *Expert Opin. Investig. Drugs* 10, 1819–1830
34 Kawabata, A. *et al.* (2001) Peripheral PAR-2 triggers thermal hyperalgesia and nociceptive responses in rats. *NeuroReport* 12, 715–719

35 Van Veldhuizen, P.J. *et al.* (2000) Treatment of vitamin D deficiency in patients with metastatic prostate cancer may improve bone pain and muscle strength. *J. Urol.* 163, 187–190

36 Ro, L.S. *et al.* (1999) Effect of NGF and anti-NGF on neuropathic pain in rats following chronic constriction injury of the sciatic nerve. *Pain* 79, 265–274

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Three-dimensional information is not essential for drug discovery ▼

In a recent review in *Drug Discovery Today* [1], Jeff Augen describes the increasing role of *in silico* techniques in the discovery process. The paper is interesting in many respects, including its historical aspect.

However, when describing the drug discovery process, the author seems to exclude the possibility of using a lead discovery strategy when there is no proper structural information on the target of choice. This is emphasized by the figure in the paper, which shows a flow chart of the multiple stages from genomics to clinical trials. The arrows in this figure – and the contents of the paper – seem to suggest that the discovery process is a linear pathway where there is no way to discover new drugs if the protein structure is unknown because this is a required step before moving to the screening stage.

Obviously, HTS is one common strategy to get hits without any knowledge of the structure of the target, which is good because many structures of receptors are yet unknown. Of course, a properly designed library would give better hits than a random one, and the use of three-dimensional (3D) structural information in the design process would increase the odds of getting hits.

Another common strategy, which is complementary to HTS, is property-based drug design, where only the properties of the ligands are used to build predictive models, without any knowledge of the target's structural features. This has been extensively demonstrated by a vast number of QSAR studies (quantitative SARs), where non-structural descriptors are combined to correlate with some observed biological feature (affinity, ADME-related data, toxicity, and so on). Non-structural descriptors (i.e. topological indices, chemical fingerprints, knowledge-based parameters, Lipinski-like 'rules') are also of key importance as rapid filters in a virtual screening process. The nature of these descriptors make them ideal for high throughput elimination of the less favoured constructs among hundred-million member virtual libraries. And, in several cases, this virtual 'screening-out' could result in a library small enough to be synthesized and sent to the HTS automation devices.

This does not change the fact that 3D structural information, when available, is unrivalled for increasing the hit rate by the use of pharmacophoric constraints and/or high-throughput docking calculations. Fortunately, however, for most discovery projects, the undetermined folding of the corresponding protein is not a bottleneck.

Reference

1 Augen, J. (2002) The evolving role of information technology in the drug discovery process. *Drug Discov. Today* 7, 315–323

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