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Chapter IV

Glutamatergic mechanisms in different disease states: overview and therapeutical implications – An introduction

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Summary. Glutamate is the most widely distributed excitatory transmitter in the central nervous system (CNS). It is acting via large – and still growing – families of receptors: NMDA-, AMPA-, kainate-, and metabotropic receptors. Glutamate has been implicated in a large number of CNS disorders, and it is hoped that novel glutamate receptor ligands offer new therapeutic possibilites in disease states such as chronic pain, stroke, epilepsy, depression, drug addiction and dependence or Parkinson's disease. While an extensive preclinical literature exists showing potential beneficial effects of NMDA-, AMPA-, kainate- and metabotropic receptor ligands, only NMDA receptor antagonists have been characterized clinically to any appreciable degree. In these trials it has been shown that while several compounds are therapeutically active, they also produce serious side effects at therapeutic doses. Current interest largely centers on the development of receptor subtype-selective compounds, namely compounds selective for receptors containing the NR2B subunit. Preclinical findings and the first clinical results are encouraging, and it may be that such subunit-selective compounds may have a sufficiently wide therapeutic window to be safe for human use.

Keywords: Glutamate – NMDA receptor – AMPA receptor – Kainate receptor – Metabotropic receptor – NR2B – Animal model – Clinical trial – Pain – Stroke – Epilepsy – Depression – Anxiety – Addiction – Dependence – Withdrawal – Parkinson

Introduction

Glutamate is the main excitatory neurotransmitter in the central nervous system. Thus, it is not surprising that glutamate is implicated in a whole range of both normal and pathological mechanisms at various levels in the CNS. The aim of this chapter is to give an overview of some of the disease states in which glutamate is know to play or thought to play an important role. Glutamatergic transmission and the relevant glutamate receptors are well characterized, and hopes are high that several disease states can be positively influenced by interfering with or modulating glutamatergic neurotransmission.

The papers that make up this chapter will address the role of glutamate in chronic pain, depression, schizophrenia, addiction, dependence, and withdrawal. Of course, this selection of topics is not comprehensive. Other pathological conditions where an involvement of glutamatergic mechanisms receives substantial interest include stroke, Parkinson's disease, anxiety, and learning and memory deficits.

Glutamate receptors – short overview

Glutamate is distributed ubiquitously in the CNS. It acts on at least 4 different classes of receptors, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolproprionic acid (AMPA), kainate, and metabotropic receptors.

NMDA receptors are composed of several subunits that make up an ion channel. The activity of the ion channel can be controlled by different binding sites within the channel and on the receptor proteins (agonist binding site and modulatory, allosteric binding sites). The NMDA receptor subunits belong to two families, NR1 (NR1A-G) and NR2 (NR2A-D). The subunit composition of the receptor can vary, and the receptor/channel physiology strongly depends on

subunit composition (see e.g. McBain and Mayer, 1994; Mori and Mishina, 1995; Ozawa et al., 1998; Dingledine et al., 1999, for reviews). While the NR1 subunit is very widely expressed in the brain at high levels, the different NR2 subunits show distinct temporal and regional patterns of distribution through development and in the adult brain (Ozawa et al., 1998).

AMPA receptors are also composed of different subunits (GluR1-GluR4). The activity of the receptor/ion channel can be influenced by an agonist binding site but also by modulatory, allosteric binding sites (see e.g. Bettler and Mulle, 1995; Ozawa et al., 1998; Dingledine et al., 1999, for reviews). AMPA receptors are very widely distributed, often in parallel with NMDA receptors, with particularly high levels in several telencephalic regions (Ozawa et al., 1998).

Kainate receptors are also associated with an ion channel and are composed of different subunits (GluR5-GluR7; KA1, KA2), and are widely distributed, with high expression levels in several forebrain areas (see e.g. Bettler and Mulle, 1995; Ozawa et al., 1998; Dingledine et al., 1999, for reviews).

The metabotropic receptors constitute a large family of receptors. Currently, these receptors are classified into 3 different groups (group I: mGluR1, mGluR5; group II: mGluR2, mGluR3; group III: mGluR4, mGluR6, mGluR7, mGluR8) that are differentially coupled to intracellular transduction mechanisms (see e.g. Pin and Duvoisin, 1995; Ozawa et al., 1998). The different receptor subtypes have a highly specific, regionally limited distribution pattern (Ozawa et al., 1998), and it is noteworthy that activation of metabotropic glutamate receptors can also mediate inhibitory effects on transmitter release (Schoepp, 2001).

From this complex receptor distribution, morphology and physiology, it follows that there is a plethora of possibilities to pharmacologically influence glutamatergic neurotransmission in various regions the CNS. Yet, it is becoming increasingly clear that, given the multitude of functions that glutamate receptors have a role in, it is most important to target specific subtypes of a specific receptor type as selectively as possible in order to avoid serious side effects that prevent the therapeutic use of drugs. The breaking down of the functional relevance of the receptors to the level of different receptor types, and further, to the level of different subtypes and the implication of this for the development of glutamatergic therapeutics will be a recurrent issue in the contributions to this chapter.

Clinical utility of glutamate receptor ligands

There are a number of glutamatergic drugs that are already in clinical use in a variety of indications. However, surprisingly, all these drugs act as channel blockers at NMDA receptors. Although there have been clinical trials with competitive NMDA receptor antagonists and glycinB site antagonists, these trials have been unsuccessful so far, either because of untolerable side effects at therapeutic doses and/or because of lack of medical efficacy (e.g. Davis et al., 1997; cf. Lees, 1997). Non-competitive NMDA receptor antagonists also produce a number of potentially serious side effects the most promiment of which are psychotomimesis, agitation, sedation, ataxia, muscle relaxation, and impairment of learning and memory, and they may also have abuse potential due to reinforcing properties (Butelman, 1989; Beardsley et al., 1990; De Sarro and De Sarro, 1993; Muir et al., 1994; Tzschentke and Schmidt, 1995; Muzet et al., 1999). Nevertheless, it has been possible to develop a number of drugs that have been introduced to the clinics. Examples include memantine (in dementia, spasticity and Parkinson's disease) (Kornhuber and Weller, 1997; Jain, 2000), dextrometorphan (in pain and as an antitussivum) (Weinbroum et al., 2000), and ketamine (in pain and as a general anaesthetic) (Schmid et al., 1999; Power and Barratt, 1999). Furthermore, the therapeutic activity of other clinically used drugs appears to be at least partially related to the NMDA channel blocking properties (amantadine [Kornhuber et al., 1994; Danielczyk, 1995], acamprosate [Spanagel and Zieglgänsberger, 1997]).

As mentioned above, no AMPA, kainate or metabotropic receptor ligands are available yet as therapeutic drugs, and although big efforts are made to exploit these pharmacological mechanisms, potential drugs are still at the stage of preclinical development or at best, in early clinical development. AMPA receptors are distributed almost ubiquitously in the CNS. Therefore, AMPA receptor ligands will have a high propensity for side effects, unless they target a specific subpopulation of receptors with a limited and specific distribution, e.g. those AMPA receptors located in the spinal cord (as opposed to supraspinal receptors) for the treatment of pain. The development of metabotropic receptor ligands as therapeutical

drugs has been hampered by the structural and functional diversity of metabotropic receptors that makes it necessary to find highly specific receptor ligands, which has proven to be difficult to date.

NR2B subtype-selective drugs

An instructive example of how the development of subtype-selective glutamate receptor ligands may lead to new therapeutical drugs is offered by the current intense interest in NR2B-subtype selective NMDA receptor antagonists.

The significant therapeutic progress that is assumed (or hoped) to be achieved with NR2B-selective compounds does not lie so much in an enhanced therapeutic efficacy but rather in an improved side effect profile. Non-selective NMDA receptor antagonists have a number of serious side effects (see above). These effects are commonly observed in experimental animals, and in particular psychotomimetic effects, agitation and sedation have also been observed in humans in clinical trials.

Unfortunately, among the few NR2B-subtype selective compounds available so far, extensive data exist only on the behavioral effects of ifenprodil and eliprodil, while data on the newer compounds are still very scarce and largely only available in abstract form, making a critical evaluation of the data difficult. Although ifenprodil and eliprodil may be selective for NR2B subunit-containing receptors when it comes to binding at NMDA receptors, these compounds also possess activity at adrenergic $\alpha 1$ and $\alpha 2$ receptors, and possibly at sigma receptors, and they act as calcium channel blockers, all of which may contribute to their side effect profile (Adeagbo and Magbagbeola, 1985; Contreras et al., 1990).

The general picture that emerges is that NR2B-selective compounds are not entirely devoid of side-effects such as muscle relaxation, sedation or cognitive disruptions, but that they do have a better therapeutic window than non-subtype selective compounds. In other words, while therapetically required doses of non-selective drugs also cause serious side-effects, therapeutically relevant doses of subtype-selective drugs are largely devoid of these side-effects, which are only seen when higher-than-therapeutically-necessary doses are administered. In clinical trials, both ifenprodil and eliprodil were largely devoid of untoward behavioral or psychological effects (Patat et al., 1994; Branchereau and Rouffy, 1995).

Unlike PCP and related compounds, eliprodil is not self-administered by experimental animals. Also, ifenprodil and eliprodil do not generalize to a PCP or dizocilpine cue, and eliprodil does also not generalize to an ethanol cue in drug-discrimination studies. Ifenprodil and eliprodil did not produce a conditioned place preference (in fact, for eliprodil a conditioned place aversion has been reported). Eliprodil does not stimulate the firing of ventral tegmental dopaminergic cells. These findings suggest that NR2B-selective coumpounds might be largely devoid of abuse potential (Sanger and Zivkovic, 1989; Diana et al., 1993; Balster et al., 1994; Sukhotina et al., 1998).

To the contrary, it has also been reported that ifenprodil did not show anticonvulsant activity in amygdala-kindled and genetically epilepsy-prone rats or antinociceptive effects up to doses which produced severe motor impairment and psychotomimetic effects, and high doses of ifenprodil and eliprodil were found to induce muscle relaxation and to reduce locomotion, rearing and grooming in rats and mice, indicative of sedative effects (De Sarro and De Sarro, 1993; Chizh et al., 2001).

Of the newer NR2B-selective compounds, CP-101606 had neuroprotective, analgesic and anti-parkinsonian effects at doses that did not produce any measurable behavioral side effects in clinical trials as well as in animal experiments (Taniguchi et al., 1997; Boyce et al., 1999; Bullock et al., 1999). Ro-25-6981 was neuroprotective under several conditions and reduced several forms of seizures at doses that did not impair rotarod performance (Boyce et al., 1999). Co-101244 showed analgesic and anti-parkinsonian effects without producing ataxia or psychotomimetic effects (Blanchet et al., 1999). Finally, CI-1041 was shown to have analgesic activity at doses that did not produce ataxia (Carter et al., 2000).

Unfortunately, for these newer drugs available data is still very limited, and only scarce data exist concerning their CNS side effect profile. The available data certainly suggest that therapeutically effective doses produce only limited side effects but more data clearly have to be generated in order to be able to build an appropriate picture of the CNS side effect profiles of these drugs.

Another issue of concern with NMDA receptor antagonists is their propensity to induce morphological alterations at the cellular level in certain cortical areas (vacuolization). Although these effects are seen only under certain conditions, and although the relevance

of the findings from the animal models for the human situation is a matter of considerable debate, these effects have already brought an end to the pharmaceutical development of several NMDA receptor antagonists. In this context it appears interesting to note that eliprodil was found not to produce vacuolization, and even a very high dose of eliprodil did not induce the expression of heat shock protein (a measure of cellular stress) in cingulate and retrosplenial cortices (Hargreaves et al., 1994; Wang et al., 1996).

Unfortunately, at present it is still not entirely clear why NR2B-selective compounds should have reduced CNS side effects. NR2B subunit-containing NMDA receptors show a relatively wide, yet distinct distribution in the brain and are also present in brain regions that are thought to mediate psychotomimesis and other behavioral (side-) effects. The apparent absence of NR2B subunits in the cerebellum of adult rats and humans may nicely explain the lack of pronounced ataxic and muscle-relaxant effects of NR2B subunit-specific compounds, and the relatively low expression of NR2B subunits in limbic regions such as the ventral tegmental area and the nucleus accumbens may be related to the lack of psychotomimetic and rewarding effects of these compounds (Wang et al., 1995; Schito et al., 1997; Jin et al., 1997). In line with this is the observation that the NR2B-selective compound CI-1041 increased DA turnover (DOPAC/DA ratio) in the striatum but not in the nucleus accumbens which may be a possible explanation for its anti-parkinsonian effects in the absence of psychotomimetic effects (Coughenour et al., 2000; Serpa et al., 2000). On the other hand, of all brain regions, NR2B subunits are expressed at highest levels in telencephalic structures such as hippocampus, striatum, cerebral cortex and olfactory bulb (Wang et al., 1995; Schito et al., 1997; Jin et al., 1997). In particular, the high levels of NR2B subunits in the hippocampus are difficult to reconcile with the relative lack of pronounced disruptive effects on learning and memory of NR2B selective compounds. Furthermore, a relationship between the age-related expression of NR2B subunits and behavioral/cognitive performance has been demonstrated (Clayton et al., 2000), showing the importance of NR2B subunit-containing NMDA receptors for cognitive functioning. Also, overexpression of NR2B subunits in the forebrain of transgenic mice leads to enhanced learning and memory capabilities of the animals (Tang et al., 1999), again demonstrating that this subunit is importantly involved in cognitive processes. As mentioned above, such findings are difficult to reconcile with the purported lack of cognitive disrupting effects of NR2B subunit-selective compounds.

Thus, the improved side effect profile cannot be accounted for entirely by the absence of NR2B subunit-containing NMDA receptors from 'critical' brain regions. Of relevance might be the fact that probably more than just one specific NMDA receptor subtype has to be blocked by an antagonist in order to produce strong CNS side effects, i.e. although NR2B subunit-containing NMDA receptors are located in 'critical' brain regions, the degree of overall NMDA receptor blockade that can be achieved by NR2B-selective compounds may not be sufficient to produce serious untoward effects.

Another interesting concept is the idea that NR2B-selective compounds may be acting as modulatory 'partial agonists' at the NMDA receptor. This concept is supported by the observation that ifenprodil and eliprodil can attenuate the effects of dizocilpine and other channel blockers in some, albeit not all, circumstances. For example, ifenprodil was found to attenuate the dizocilpine-induced locomotor stimulation and deficits in spontaneous alternation in the Y-maze (Fraser et al., 1996). Thus, the partial agonistic properties of these compounds might only reach an intermediate level of NMDA receptor inactivation (thereby reducing the occurrence of side effects, but thereby possibly also reducing the beneficial effects) (cf. Parsons et al. (1998) for further discussion of this issue).

Conclusions

In conclusion, the available data concerning the CNS side effects of NR2B-selective compounds, as compared to non-selective NMDA antagonists, give rise to cautious optimism. A problem that remains is that although some of the newer NR2B-selective drugs appear to have a favourable side-effect profile, they may also have only limited efficacy in disease states at tolerable doses, and there is still a considerable uncertainty about the degree to which therapeutical effects and side-effects can be separated in drugs acting at the NMDA receptor. NR2B-selective compounds will not turn out to be a panacea with high therapeutic potency and no side effects, but they represent an important step towards the development of effective, yet safe NMDA antagonists. The compounds that are already available may already proof to have a good tolerability, but it is likely that there will still be much room for

further improvement, both in terms of efficacy and in terms of tolerability.

A comparable detailed discussion of therapeutic issues concerning drugs acting at other glutamate receptors would be a.) beyond the limits of this paper, and b.) hardly possible because the available data are extremely scarce and do not allow for any broader discussion of animal or human experiments. It will probably take several more years until one can reasonably assess whether ligands for AMPA, kainate, or metabotropic receptors can be therapeutically active *and* safe drugs.

While this introduction had its focus somewhat on NMDA receptor antagonists, the subsequent papers will focus on different disease states and the extent to which these disease states can be influenced by various glutamate receptor ligands. As will be evident from these papers, hopes are high and preclinical data are accumulating that drugs acting at different glutamate receptors may be beneficial in a large variety of disease states.

It will be most interesting to see if (or when) these interesting and encouraging findings will lead the way to new drugs for human use.

References

Adeagbo AS, Magbagbeola AO (1985) Pharmacological actions of ifenprodil in the rat isolated anococcygeus muscle. J Pharm Pharmacol 37: 833–835

Balster RL, Nicholson KL, Sanger DJ (1994) Evaluation of the reinforcing effects of eliprodil in rhesus monkeys and its discriminative stimulus effects in rats. Drug Alcohol Depend 35: 211–216

Beardsley PM, Hayes BA, Balster RL (1990) The self-administration of MK-801 can depend upon drug-reinforcement history and its discriminative stimulus properties are phencyclidine-like in rhesus monkeys. J Pharmacol Exp Ther 252: 953–959

Bettler B, Mulle C (1995) AMPA and kainate receptors. Neuropharmacology 34: 123–139

Blanchet PJ, Konitsiotis S, Whittemore ER, Zhou ZL, Woodward RM, Chase TN (1999) Differing effects of N-methyl-D-aspartate receptor subtype selective antagonists on dyskinesias in levodopa-treated 1-methyl-4-phenyl-tetrahydropyridine monkeys. J Pharmacol Exp Ther 290: 1034–1040

Boyce S, Wyatt A, Webb JK, O'Donnell R, Mason G, Rigby M, Sirinathsinghji D, Hill RG, Rupniak NM (1999) Selective NMDA NR2B antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunit in dorsalhorn. Neuropharmacology 38: 611–623

Branchereau A, Rouffy J (1995) Double-blind randomized controlled trial of ifenprodil tartrate versus placebo in chronic arterial occlusive disease of the legs at stage II of the Leriche and Fontaine classification. J Mal Vasc 20: 21–27

Bullock MR, Merchant RE, Carmack CA, Doppenberg E, Shah AK, Wilner KD, Ko G, Williams SA (1999) An open-label study of CP-101,606 in subjects with a severe traumatic head injury or spontaneous intracerebral hemorrhage. Ann NY Acad Sci 890: 51–58

Butelman ER (1989) A novel NMDA antagonist, MK-801, impairs performance in a hippocampal-dependent spatial learning task. Pharmacol Biochem Behav 34: 13–16

Carter RB, Wilent W, Huber M, Xu Z, Vanover KE, Woodeward RM (2000) Anti-allodynic and anti-hyperalgesic effects of the NR2B subunit-selective NMDA antagonist CI-1041 in rat models of inflammation and neuropathy. Soc Neurosci Abstr 26: 1646

Chizh BA, Reissmueller E, Schlütz H, Scheede M, Haase G, Englberger W (2001) Supraspinal vs spinal sites of the antinociceptive action of the subtype-selective NMDA antagonist ifenprodil. Neuropharmacology 40: 212–220

Clayton DA, Mesches MH, Rasiner CA, Bickford P, Browning MD (2000) Age-related deficit in NR2B subunit expression correlates with behavioral impairment in Fisher 344 rats. Soc Neurosci Abstr 26: 1409

Contreras PC, Bremer ME, Gray NM (1990) Ifenprodil and SL 82.0715 potently inhibit binding of [3H] (+)-3-PPP to sigma binding sites in rat brain. Neurosci Lett 116: 190–193

Coughenour LL, Barr B, Espitia S, Pugsley TA, Whetzel SZ, Dooley D, Mieske C, Ilyin V, Rock DM, Stoehr S, Boxer PA (2000) Neurochemical pharmacology of CI-1041 (PD196860): a novel subtype selective NMDA antagonist. Soc Neurosci Abstr 26: 1406

Danielczyk W (1995) Twenty-five years of amantadine therapy in Parkinson's disease. J Neural Transm [Suppl 46]: 399–405

Davis SM, Albers GW, Diener HC, Lees KR (1997) Termination of acute stroke studies involving selfotel treatment. Lancet 349: 32

De Sarro GB, De Sarro A (1993) Anticonvulsant properties of non-competitive antagonists of the N-methyl-D-aspartate receptorin genetically epilepsy-prone rats: comparison with CPPene. Neuropharmacology 32: 51–58

Diana M, Rossetti ZL, Gessa G (1993) Rewarding and aversive effects of ethanol: interplay of GABA, glutamate and dopamine. Alcohol Alcohol [Suppl 2]: 315–319

Dingledine R, Borges K, Bowie D, Traynelis SF (1999) The glutamate receptor ion channels. Pharmacol Rev 51: 7–61

Fraser CM, Cooke MJ, Fisher A, Thompson ID, Stone TW (1996) Interactions between ifenprodil and dizocilpine on mouse behaviour in models of anxiety and working memory. Eur Neuropsychopharmacol 6: 311–316

Hargreaves RJ, Hill RG, Iversen LL (1994) Neuroprotective NMDA antagonists: the controversy over their potential for adverse effects on cortical neuronal morphology. Acta Neurochir [Suppl 60]: 15–19

Jain KK (2000) Evaluation of memantine for neuroprotection in dementia. Expert Opin Investig Drugs 9: 1397–1406

Jin DH, Jung YW, Ko BH, Moon IS (1997) Immunoblot analyses on the differential distribution of NR2A and NR2B subunits in the adult rat brain. Mol Cells 7: 749–754

Kornhuber J, Weller M (1997) Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. Biol Psychiatry 41: 135–144

Kornhuber J, Weller M, Schoppmeyer K, Riederer P (1994) Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties. J Neural Transm [Suppl 43]: 91–104

Lees KR (1997) Cerestat and other NMDA antagonists in ischemic stroke. Neurology 49 [Suppl 4]: S66–S69

McBain CJ, Mayer ML (1994) N-Methyl-D-aspartic acid receptor structure and function. Physiol Rev 74: 723–760

Mori H, Mishina M (1995) Structure and function of the NMDA receptor channel. Neuropharmacology 34: 1219–1237

Muir KW, Grosset DG, Gamzu E, Lees KR (1994) Pharmacological effects of the non-competitive NMDA antagonist CNS 1102 in normal volunteers. Br J Clin Pharmacol 38: 33–38

Muzet M, d'Arbigny P, Luthringer R, Jhanwar-Uniyal M, Boeijinga PH, Andrieux JM, Macher JP (1999) Effects of gacyclidine, a non-competitive NMDA receptor antagonist, in human healthy volunteers. Soc Neurosci Abstr 25: 1090

Ozawa S, Kamiya H, Tsuzuki K (1998) Glutamate receptors in the mammalian central nervous system. Prog Neurobiol 54: 581–618

Parsons CG, Danysz W, Quack G (1998) Glutamate in CNS disorders as a target for drug development: an update. Drug News Perspect 11: 523–569

Patat A, Molinier P, Hergueta T, Brohier S, Zieleniuk I, Danjou P, Warot D, Puech A (1994) Lack of amnestic, psychotomimetic or impairing effect on psychomotor performance of eliprodil, a new NMDA antagonist. Int Clin Psychopharmacol 9: 155–162

Pin JP, Duvoisin R (1995) The metabotropic glutamate receptors: structure and functions. Neuropharmacology 34: 1–26

Power I, Barratt S (1999) Analgesic agents for the postoperative period. Nonopioids. Surg Clin North Am 79: 275–295

Sanger DJ, Zivkovic B (1989) The discriminative stimulus effects of MK-801: generalization to other N-methyl-D-aspartate receptor antagonists. J Psychopharmacol 3: 198–204

Schito AM, Pizzuti A, Di Maria E, Schenone A, Ratti A, Defferrari R, Bellone E, Mancardi GL, Ajmar F, Mandich P (1997) mRNA distribution in adult human brain of GRIN2B, a N-methyl-D-aspartate (NMDA) receptor subunit. Neurosci Lett 239: 49–53

Schmid RL, Sandler AN, Katz J (1999) Use and efficacy of low-dose ketamine in the management of acute postoperative pain: e review of current techniques and outcomes. Pain 82: 111–125

Schoepp DD (2001) Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. J Pharmacol Exp Ther 299: 12–20

Serpa KA, Wright JL, Kesten SR, Meltzer LT (2000) Antiparkinson (AP) effects of CI-1041 (PD 0196860), a subtype selective NMDA antagonist, in the 6-OHDA rat model. Soc Neurosci Abstr 26: 1409

Spanagel R, Zieglgänsberger W (1997) Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends Pharmacol Sci 18: 54–59

Sukhotina I, Dravolina O, Bespalov A (1998) Place conditioning of mice with the NMDA receptor antagonists, eliprodil and dizocilpine. Eur J Pharmacol 362: 103–110

Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, Liu H, Tsien JZ (1999) Genetic enhancement of learning and memory in mice. Nature 401: 63–69

Taniguchi K, Shinjo K, Mizutani M, Shimada K, Ishikawa T, Menniti FS, Nagahisa A (1997) Antinociceptive activity of CP-101,606, an NMDA receptor NR2B subunit antagonist. Br J Pharmacol 122: 809–812

Tzschentke TM, Schmidt WJ (1995) N-Methyl-D-aspartatic acid-receptor antagonists block morphine-induced conditioned place preference in rats. Neurosci Lett 193: 37–40

Wang YH, Bosy TZ, Yasuda RP, Grayson DR, Vicini S, Pizzorusso T, Wolfe BB (1995) Characterization of NMDA receptor subunit-specific antibodies: distribution of NR2A and NR2B receptor subunits in rat brain and ontogenic profile in the cerebellum. J Neurochem 64: 176–183

Wang S, Yang Q, Moller CJ, Sharp FR, Haglid KG (1996) Eliprodil prevents expression of the 70 kDa heat shock protein in MK801-injured neurones. Pharmacol Toxicol 79: 166–168

Weinbroum AA, Rudnick V, Paret G, Ben-Abraham R (2000) The role of dextromethorphan in pain control. Can J Anaesth 47: 585–596

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