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INFLUENCE OF NMDA AND NON-NMDA ANTAGONISTS ON ACUTE AND INFLAMMATORY PAIN IN THE TRIGEMINAL TERRITORY

A placebo control study

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Abstract – NMDA and non-NMDA receptors are involved in spinal transmission of nociceptive information in physiological and pathological conditions. Our objective was to study the influence of NMDA and non-NMDA receptor antagonists on pain control in the trigeminal system using a formalin-induced orofacial pain model. Motor performance was also evaluated. Male *Rattus norvegicus* were pre-treated with topiramate (T) (n=8), memantine (M) (n=8), divalproex (D) (n=8) or isotonic saline solution (ISS) (n=10) intraperitoneally 30 minutes before the formalin test. Formalin 2.5% was injected into the right upper lip (V2 branch) and induced two phases: phase I (early or neurogenic) (0–3 min) and phase II (late or inflammatory) (12–30 min). For motor behavior performance we used the open-field test and measured latency to movement onset, locomotion and rearing frequencies, and immobility time. Pre-treatment of animals with M and D only attenuated nociceptive formalin behavior for phase II. T increased locomotion and rearing frequencies and reduced immobility time. Treatment with M increased immobility time and with D reduced locomotion frequency. Our results showed that the NMDA antagonist (M) is more potent than the non-NMDA antagonists (D and T) in the control of pain in the inflammatory phase. The non-NMDA topiramate improved motor performance more than did D and M, probably because T has more anxiolytic properties.

KEY WORDS: divalproex, formalin test, memantine, NMDA and non-NMDA receptors, topiramate.

Influência dos antagonistas dos receptores NMDA e não-NMDA sobre a dor aguda e inflamatória ao nível do território do trigêmeo: um estudo placebo controlado

Resumo – Receptores NMDA e não-NMDA estão envolvidos na transmissão das informações nociceptivas em condições fisiológicas e patológicas. Com o objetivo de estudar a influência dos antagonistas dos receptores NMDA e não-NMDA sobre o controle de dor no sistema trigeminal utilizamos modelo de dor orofacial induzida pela formalina. Testes de desempenho motor foram também avaliados. Ratos machos da espécie *Rattus norvegicus* foram tratados com topiramato (T) (n=8), memantina (M) (n=8), divalproato de sódio (D) (n=8) ou solução salina isotônica (SSI) (n=10), por via intraperitoneal, 30 minutos antes dos testes com a formalina. Formalina 2.5% foram injetadas na região do lábio superior dos animais (segundo ramo do trigêmeo) induzindo comportamento em duas fases distintas: fase I (precoce ou neurogênica) (0–3 min) e fase II (tardia ou inflamatória) (12–30 min). Para avaliação da atividade motora utilizou-se o teste do campo aberto mensurando-se a latência para o início dos movimentos, número de casas andadas, freqüência de levantamentos e tempo de imobilidade. Animais pré-tratados com M e D atenuaram a fase inflamatória do teste da formalina. O T aumenta o número de casas andadas, freqüência de levantamentos e reduz o tempo de imobilidade. Nossos resultados mostram que o antagonista NMDA é mais potente do que os antagonistas não-NMDA para o controle da fase inflamatória da dor. O topiramato entretanto aumenta a atividade motora provavelmente porque apresente propriedades ansiolíticas.

PALAVRAS-CHAVE: divalproato de sódio, memantina, receptores do NMDA e não-NMDA, teste da formalina, topiramato.

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Glutamate (Glu) is a major excitatory neurotransmitter in the mammalian central nervous system, acting both at ligand-gated (ionotropic) ion channels and G-protein-coupled metabotropic receptors. Ionotropic receptors are subdivided into NMDA (glutamine-N-methyl-D-aspartic acid) and non-NMDA [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid] receptors. They are involved in spinal transmission of nociceptive information in physiological and pathological conditions[1]. Presynaptic glutamate-immunoreactive terminals are present in high densities within lamina II of the trigeminal nucleus caudalis (TNC)[2]. However, only NMDA receptors are found within trigeminal ganglion cells[3]. Intense stimulation of primary afferent fibers initially activates AMPA and peptide receptors and, when the frequency of stimulation exceeds the threshold, the voltage-dependent Mg-block of NMDA receptors is removed, allowing activation of these receptors to take place[4]. NMDA receptors may also be modulated by peptides such as substance P (SP), which is released with glutamate from the primary afferent fibers to extend and maintain the nociceptive process[5]. Administration of Glu or its NMDA or non-NMDA receptor agonists results in mechanical or thermal allodynia and hyperalgesia[6]. Descending pathways from the brainstem rostral ventro-medial medulla (RVM) modulate spinal nociceptive transmission during inflammatory pain and play a role in the development of persistent pain[7]. The activity of the RVM pain modulatory circuitry increases during persistent inflammation and gives rise to enhanced descending pain inhibition. NMDA can produce a descending facilitation effect after inflammation, suggesting that this process is dependent on NMDA-receptor activation and that it occurs early after inflammation. However, NMDA and AMPA receptor antagonists in the RVM can also inhibit this facilitation.

NMDA receptor-initiated events that lead to neuronal plasticity in the spinal cord produce wind-up and maintain central sensitization[8]. The central sensitization of the dorsal horn neurons following peripheral inflammation secondary to peripheral nerve injury like that induced by formalin is dependent upon NMDA activity in the dorsal horn[9]. Examples of available therapeutic non-NMDA antagonists are topiramate and divalproex sodium, while examples of available NMDA antagonists include memantine, ketamine and MK 801. Topiramate has a negative modulatory effect on non-NMDA (AMPA/KA) glutamate receptors[10]; it induces inhibition of voltage-sensitive sodium channels, increasing GABA-induced chloride flux and reducing neuronal excitability. Memantine has moderate affinity for the NMDA (NR2B) receptor-channel binding site and has fast unblocking kinetics and a strong voltage dependency[11]. It is also known to bind to nicotinic receptors and 5-HT3 receptors with an affinity range comparable to that for NMDA receptor binding. NR_2B subunits are located primarily in laminas I and II of the dorsal horn. These subunits are involved in wind-up and central sensitization[12], suggesting a major role for NR_2B subunits in the NMDA receptor function that mediates nociception. Furthermore, a recent study has shown that selective knockdown of NR_2B in the dorsal horn using siRNA can suppress formalin-induced nocifensive behaviors[13]. Contrasting results, however, showed a strong negative correlation between the recovery period of mechanical allodynia and the level of the NR_2B protein expression. This might indicate that the suppression of NR_2B is used to compensate for the enhanced nociceptive barrage[14]. Several investigators have demonstrated that pharmacological agents such as Ifenprodil that target NR_2B subunits can be used to control pain[15]. The loss of NR_2B subunits in the spinal cord as the nociceptive stimulus progresses[14] suggests that pharmacological agents targeting NR_2B may be less effective in chronic pain than in acute pain. In the formalin model of pain, the early and late phases are affected by memantine[11], although it inhibits the late phase at dose levels substantially lower than those required for suppression of the early phase[16]. Expression of the early phase is not dependent on NMDA-receptor stimulation, and the effects of memantine on this phase may therefore reflect primarily non-specific non-NMDA-receptor-mediated activity. However, the development and expression of the late phase is believed to be NMDA-receptor dependent[17]. We investigated and confronted NMDA and non-NMDA antagonists (memantine versus divalproex sodium and topiramate) to assess the preventive analgesic, motor and anxiolytic effects on the trigeminal pain model.

METHOD

Subjects

Male rats (*Rattus norvegicus*) (240–340g) were housed in standard plastic cages (4 per cage) with sawdust bedding in a temperature-controlled room (23±1ºC) and kept in a 12h light-dark cycle. Animals were allowed free access to food pellets and water. The trial was carried out in the Health Sciences Experimental Laboratory, Jardim Botânico, Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil. Animals were randomized in a double-blind way and administered either 0.9% saline solution (control group n=10) (1 mL/kg) or active drugs (topiramate 10 mg/kg, memantine 10 mg/kg or divalproex sodium 60 mg/kg) intraperitoneally (i.p). 30 minutes before the open-field and formalin tests.

Treatment

The animals were divided into two groups: the first group was the open-field test group and the second group, the formalin test group. Both groups were divided into subgroups: the topiramate subgroup (Topamax®, Jansen-Cilag, Brazil), (topira-

mate reconstituted in 0.9% saline solution; 10 mg/mL) (n=8); the memantine subgroup (Ebix®, Lundbeck, Brazil) (memantine reconstituted in 0.9% saline solution; 10 mg/mL) (n=8); the divalproex sodium subgroup (Depakote®, Abott, Brazil) (divalproex reconstituted in 0.9% saline solution; 60 mg/mL) (n=8); and the 0.9% saline-solution subgroup (control subgroup) (n=10). All subgroups received the drug 30 minutes before the open-field and formalin tests. A 1 mL syringe with a 25–gauge needle was used to inject the drugs intraperitoneally.

Motor performance and exploratory activity

Open-field test – Motor ability and spontaneous behavior in the open field test was studied in all subgroups. The open field employed was constructed according to Broadhurst (1960). The testing area was round, with a diameter of 97 cm. The circular wall was 32.5 cm high and was constructed of aluminum sheeting. The arena was situated on a wooden floor. The floor and the wall were painted white. The arena floor was divided into three concentric circles. The small inner circle had a diameter of 23 cm; the second circle had a diameter of 61 cm; and the arena wall defined the outside circle. Each circle was divided into essentially equal size areas. The number of areas in the inner, middle and outer circles was 1, 6 and 12, respectively. A 100-W ceiling light was placed 48 cm above the arena floor. Cheesecloth was draped from the ceiling and dropped outside the arena wall. The cloth served to diffuse the light and functioned as a one-way screen. Thirty minutes after the drugs were administered, the rats were observed individually for 5 minutes and the different groups were intermixed. Hand-operated counters were used to score latency to movement onset (latency to get out of the inner circle), locomotion frequency (number of floor units entered), rearing frequency (number of times the animals stood on their hind paws) and immobility time (number of seconds without any movement during testing). The apparatus was washed with a water-alcohol (5%) solution before behavioral testing to eliminate possible bias due to odors left by previous rats.

Formalin test – Formalin was diluted in 0.9% saline at a concentration of 2.5%. Formalin test sessions took place during the light phase between 11:00 AM and 07:00 PM in a quiet room maintained at 23–24ºC. The animals were put inside the 30×30×30 cm test box with three mirrored sides. The rats did not have access to food or water during the test. Animals from each subgroup were weighed and placed inside a Plexiglas observation chamber for an acclimation period of 10–20 min. Then a 40 µL bolus of 2.5% formalin was injected into the animals' right upper lips using a 0.5 mL syringe with a 29-gauge needle. The recording time was divided into 10 blocks of three minutes and the pain score determined for each block by measuring the number of seconds (amplitude of the response) that the animal spent rubbing and flicking (R/F) over the injected area with the ipsilateral forepaw or hind paw. The data collected between 0 and 3 minutes post formalin injection represented phase I (early, neurogenic or phasic phase), and data collected between 12 and 30 minutes post formalin injection represented phase II (late, inflammatory or tonic phase). Rats were euthanized at the end of the experiment by cervical dislocation.

Ethical aspects

All experiments in this study conformed to international guidelines on the ethical use of animals, and every effort was made to minimize the suffering and number of animals used. All experiments adhered to the guidelines of the IASP Committee for Research and Ethical Issues (1983).

Statistical analysis

We used the Student t-test for the formalin test, and the ANOVA and Tukey test for motor behavioral performance. Statistical significance was determined at $p<0.05$. Data are presented as mean ±SEM.

RESULTS

The animals' response to the injection of 2.5% formalin into the right upper lip produced a biphasic pattern; two major intervals of intensive rubbing/flicking (R/F) activities were observed, the first between 0 and 3 min (early phase) and the second between 12 and 30 min (late phase), with almost no nociceptive response between 3 and 12 min.

The control group (saline solution) was used to determine standard values for early and late phases. The memantine group attenuated the nociceptive formalin behavior only in the inflammatory phase ($p<0.0001$). The results for the neurogenic phase were the same as those for the control group (p=0.911) (Table 1, Fig 1). The antinociceptive effect of topiramate was not observed in either the inflammatory or neurogenic phase (p=0.296 and p=0.200) (Table 2, Fig 2). The antinociceptive effect of divalproex sodium

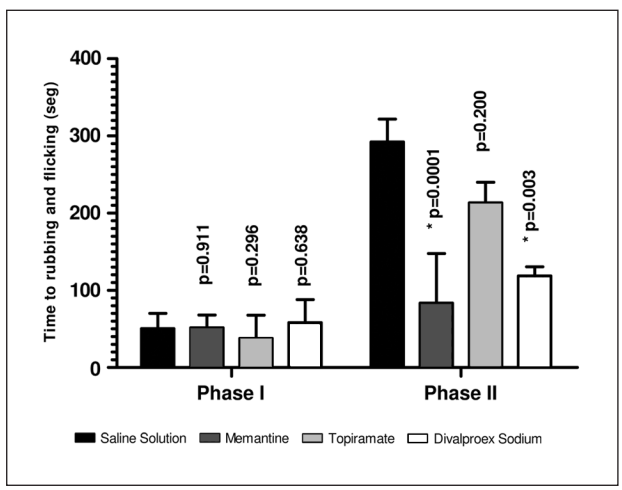

Fig 1. Behavior in the neurogenic and inflammatory phases for the different groups. Statistically significant differences for t-Student ($p<0.05$) (mean and standard deviation).

Table 1. Statistical results for the formalin test for the different drug groups and saline control group (t-test).

Groups	Mean±SD	p groups	Significance
Isotonic Saline Solution (ISS)			
Phase I	50.5±19.82	–	–
Phase II	292.1±29.78	–	–
Memantine (M)			
Phase I	51.5±16.67	–	–
Phase II	83.5±64.19	–	–
Topiramate (T)			
Phase I	37.75±30.11	–	–
Phase II	213.62±26.49	–	–
Divalproex Sodium (D)			
Phase I	58±29.98	–	–
Phase II	118.75±11.76	–	–
Memantine × Topiramate			
Phase I	–	0.278	NS
Phase II	–	0.050	S
Memantine × Divalproex			
Phase I	–	0.600	NS
Phase II	–	0.624	NS
Topiramate × Divalproex			
Phase I	–	0.199	NS
Phase II	–	0.140	NS
Memantine × ISS			
Phase I	–	0.911	NS
Phase II	–	0.0001	S
Topiramate × ISS			
Phase I	–	0.296	NS
Phase II	–	0.200	NS
Divalproex × ISS			
Phase I	–	0.638	NS
Phase II	–	0.003	S

Table 2. Open-field test results for the different groups.

Groups	Mean±SD	p groups × Memantine	p groups × Topiramate	p groups × Divalproex
Saline				
Latency to movement onset	3.71±0.75	0.674**	0.048*	0.479*
Locomotion frequency	67.14±5.7	0.109**	0.001	0.203**
Rearing frequency	14.71±3.19	0.041*	0.007*	0.202**
Immobility time	40.57±9	0.002*	<0.001*	0.418**
Memantine				
Latency to movement onset	3.57±0.78	–	0.001*	0.407**
Locomotion frequency	61.14±5.8	–	0.001*	0.418**
Rearing frequency	10±4.04	–	0.002*	0.485**
Immobility time	78.57±7.5	–	<0.001*	0.183**
Topiramate				
Latency to movement onset	4.87±1.1	0.001*	–	0.915**
Locomotion frequency	99.37±7.3	0.001*	–	0.001*
Rearing frequency	19.25±1.8	0.002*	–	0.020*
Immobility time	0	<0.001*	–	0.001*
Divalproex Sodium				
Latency to movement onset	5.75±4.8	0.407**	0.915**	–
Locomotion frequency	48.75±21	0.418**	0.001*	–
Rearing frequency	11.75±5.4	0.485**	0.020*	–
Immobility time	57.37±41.5	0.183**	0.001*	–

Mann-Whitney test (*Significance, **No Significance).

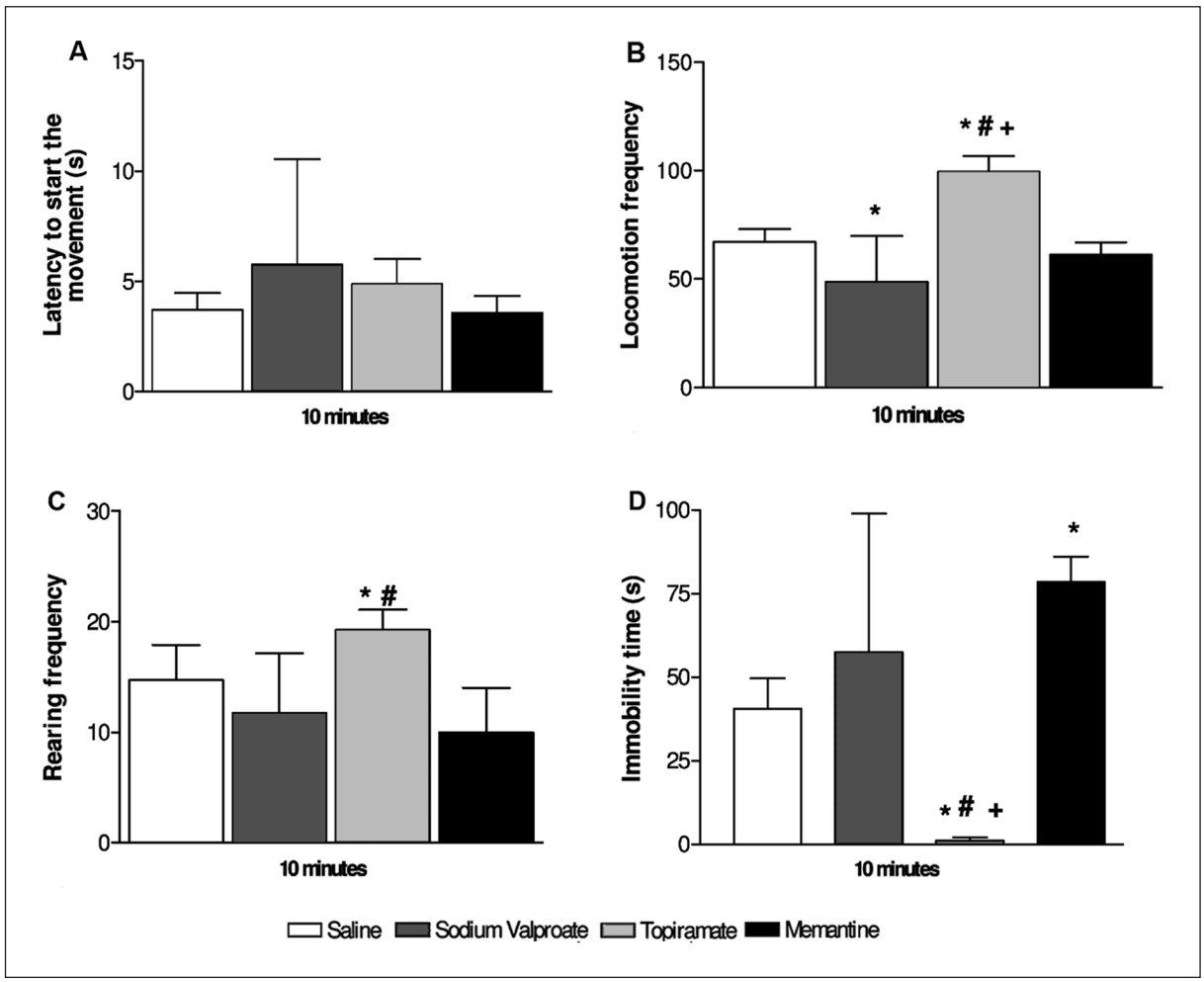

*Fig 2. (A) Time to leave the center of the open field (latency to movement onset) in seconds. (B) Locomotion frequency, number of entries into the boxes during the 5-minute observation period. (C) Rearing frequency, number of times the animal stands on its hind legs. (D) Immobility time, time spent sitting in the open field in seconds. Statistically significant differences for ANOVA and Tukey's tests (p<0.05): *comparison with the saline (control) group; # comparison with divalproex sodium group; + comparison with memantine group.*

was only observed for the inflammatory phase (p=0.003); its effect in the neurogenic phase was not statistically significant (p=0.638) (Table 1, Fig 1). Comparison of the NMDA (memantine) and non-NMDA groups only revealed a statistical significance for memantine and topiramate during the inflammatory phase, with memantine having the greater antinociceptive power (p=0.05) (Table 1, Fig 1).

The open-field test results are shown in Table 2 and Fig 2. Latency to movement onset was the same for all groups. Frequency of locomotion for the topiramate group was higher than for all other groups, and rearing frequency was higher for the topiramate group than for the saline and sodium-valproate groups. Immobility time was lower in the topiramate group than in all other groups.

DISCUSSION

The present study evaluated the effects of (NMDA and non-NMDA) glutamate receptor antagonists on trigeminal pain and motor behavior. Using a panel of commercial (NMDA and non-NMDA) glutamate receptor antagonists, we found that NMDA (memantine) is a more potent inhibitor of the inflammatory phase than are non-NMDA antagonist receptors.

During the early phase of the formalin test, chemoreceptors are activated on the peripheral terminals of primary afferents to evoke the release of proinflammatory peptides, producing neurogenic pain[16]. The late phase is either the result of sensitization of dorsal horn neurons (central sensitization), inflammation-induced hyperactivity of primary afferent nociceptors, or a combination of both[18]. During this phase glutamate is released[19] and glutamate receptor expression increases[20]. These changes produce pain behavior.

The majority of sensorial primary afferent fibers contain glutamate, which is released both centrally and peripherally following formalin injection over the plantar

area or over the trigeminal branches[21]. The expression of glutamate receptors on peripheral sensory axons is up-regulated during inflammation. Inflammation increases the release of excitatory amino acids (EAA) from inflammatory cells, which may further activate EAA autoreceptors by positive feedback, resulting in sustained enhancement of nociceptor activation. Previous studies have shown that application of an NMDA or non-NMDA receptor antagonist to the spinal cord preferentially inhibited spinal nociceptive responses triggered by input from superficial and deep tissue[22].

Using a formalin test, several researchers showed that memantine inhibited the late phase[23], while in other studies it appeared to affect both phases[11]. Memantine inhibited the late phase at dose levels substantially lower than those required for suppression of the early phase[16]. Expression of the early phase is not dependent on NMDA receptor stimulation and, therefore, the effects of memantine on this phase may reflect primarily non-specific or non-NMDA receptor-mediated activity. In our study, memantine only inhibited the later phase.

Topiramate is a non-NMDA antagonist that acts on AMPA and kainic acid (KA) and was initially indicated for use in anticonvulsant treatment, although it has recently been used for headaches such as migraine[24]. Sodium valproate is another non-NMDA receptor antagonist that has been used for migraine prophylaxis[25]. Our results show that NMDA antagonists are more effective than non-NMDA antagonists in inhibiting inflammatory behavior. As non-NMDA inhibitors are the therapy of first choice in the preventive treatment of migraine, NMDA inhibitors such as memantine could also be expected to be candidates for the prophylactic treatment of migraine attacks.

In the last 15 years, memantine has shown good tolerability, and the number of patients treated with this drug exceeds 200000. It is used for Alzheimer disease, but further possible therapeutic uses include: AIDS; glaucoma; hepatic encephalopathy; multiple sclerosis; tinnitus; Parkinson's disease; tardive dyskinesia; drug tolerance, sensitization and addiction; epilepsy; spasticity; and chronic pain[26].

Memantine selectively blocked formalin-induced tonic nociceptive responses in rats[16] and also provided a very good separation between the acute and prolonged phases in a rat formalin model following intrathecal administration[27]. It was found to have both therapeutic and prophylactic antinociceptive effects (10 and 15 mg/kg) against carrageenan-induced hyperalgesia[28]. It also blocked and reversed thermal hyperalgesia and mechanical allodynia in rat models of painful mononeuropathy without obvious effects on motor reflexes following systemic (10–20 mg/Kg)[29].

Very large doses of memantine 25–75 mg/Kg given acutely i.m. or orally to macaques (1.5–2.5 Kg) were reported to selectively reduce mechanical allodynia induced by ligation of the seventh spinal nerve[30]. Intraplantar pretreatment with memantine significantly attenuated formalin-induced lifting and licking behaviors, but flicking behavior was not affected. Control experiments indicated that the effects of memantine were not via systemic redistribution and suggest that peripheral NMDA receptors on unmyelinated sensory axons in the skin contribute to nociceptor activation and can be manipulated to reduce pain of peripheral origin[31].

In our study, we assessed the effects of NMDA and non-NMDA antagonists on motor reflex behavior using the open-field test. This test is used to study not only spontaneous locomotion but also response to novelty, anxiety/fear levels and non-associative memory. The effects of non-NMDA antagonists such as topiramate on motor performance in the open-field test were similar to those of saline solution. Behavior in the open field was not impaired by topiramate; indeed, as in other studies[32], an apparent anxiolytic effect was observed. Habituation (a decrease in locomotor activity during the 5-minute observation period), which is a form of simple non-associative learning, was also not compromised by TPM[32]. The effects of acute or chronic treatment with sodium valproate on rat behavior observed in the open-field test by other researchers were reduced grooming frequency and time spent in grooming. Locomotion, rearing or defecation after acute treatment, however, were not affected[33].

The effects of NMDA antagonists such as memantine on motor performance in the open-field test included enhanced horizontal activity (immobility time) and vertical activity (rearing frequency)[34], while other studies showed that acute or sub-chronic treatment with memantine produced no effects on locomotor activity. However, assessment of exploratory activity in the open-field showed that memantine reduced rearing, ambulation and grooming behavior according to the dose[35].

Our results showing that non-NMDA (divalproex) and NMDA antagonists inhibited the late phase of pain in the trigeminal territory suggest that both kinds of drugs could be considered candidates for treatment of trigeminal pain syndromes utilizing this model of pain induced. The literature regarding experiments with non-NMDA antagonists (topiramate and sodium divalproate) suggests that they are a suitable choice for the prophylactic treatment of migraine. Our findings in pre-clinical research suggest that NMDA (memantine) is more potent than non-NMDA (topiramate) in the prophylaxis of pain in the trigeminal territory.

The positive results observed for the NMDA group could be secondary to motor inhibition caused by this drug. However, our results for the memantine group showed that: a) latency to movement onset was the same as that for the saline and non-NMDA groups; b) locomotion frequency was the same as that for the saline and divalproex groups; c) rearing frequency was the same as that for the saline and divalproex groups; d) immobility time was the same as that for the divalproex group. Although immobility time was greater in the memantine group, other motor results suggest that the reduction of pain behavior in the inflammatory phase was not influenced by motor inability. The better results for motor behavior in the non-NMDA group (topiramate) suggest that this drug has anxiolytic proprieties.

Our results suggest that memantine is a much more potent inhibitor of peripheral and central sensitization induced by formalin than are non-NMDA antagonists. As non-NMDA receptor antagonists (topiramate and divalproex) are used commercially as prophylactic options in migraine, we hypothesize that memantine could be a further option in the prophylactic treatment of this condition. Future clinical studies using memantine in the prophylactic treatment of migraine patients will allow this hypothesis to be evaluated.

REFERENCES

1. Jeftinija S. Excitatory transmission in the dorsal horn is in part mediated through APV-sensitive NMDA receptors. Neurosci Lett 1989;96:191-196.
2. Tallaksen-Greene SJ, Young AB, Penney JB, Beitz AJ. Excitatory amino acid bindings sites in the trigeminal principal sensory and spinal trigeminal nuclei of the rat. Neurosci Lett 1992;141:79-83.
3. Watanabe M, Mishina M, Inoue Y. Distinct gene expression of the N-methyl-D-aspartate receptor channel subunit in peripheral neurons of the mouse sensory ganglia and adrenal gland. Neurosci Lett 1994;165:183-186.
4. Mayer ML, Westbrook GL. Permeation and block of N-Methyl-D-aspartic acid receptors channels by divalent cations in mouse cultured central neurones. J Physiol 1987;394:501-527.
5. Liu H, Mantyh PW, Basbaum AI. NMDA-receptor regulation of substance P release from primary afferent nociceptors. Nature 1997;386:721-724.
6. Zhou S, Bonasera L, Carlton SM. Peripheral administration of NMDA, AMPA or KA results in pain behaviors in rats. Neuroreport 1996;22:895-900.
7. Terayama R, Guan Y, Dubner R, Ren K. Activity-induced plasticity in brain stem pain modulatory circuitry after inflammation. Neuroreport 2000;11:1915-1919.
8. Woolf CJ. Windup and central sensitization are not equivalent. Pain 1996;66:105-108.
9. Coderre TJ, Melzack R. The contribution of excitatory amino acids to central sensitization and persistent nociception after formalin-induced tissue injury. J Neurosci 1992;12:3665-3670.
10. Schneiderman JH. Topiramate: pharcokinetics and pharmacodynamics. Can J Neurol Sci 1998;25:S3-S5.
11. Medvedev IO, Malyshkin AA, Belozertseva IV, et al. Effects of low-affinity NMDA receptor channel blockers in two rat models of chronic pain. Neurophamacology 2004;47:175-183.
12. Kovács G, Kocsis P, Tarnawa I, Horváth C, Szombathelyi Z, Farkas S. NR2B containing NMDA receptor dependent windup of single spinal neurons. Neuropharmacology 2004;46:23-30.
13. Tan PH, Yang LC, Shih HC, Lan KC, Cheng JT. Gene knockdown with intrathecal siRNA of NMDA receptor NR2B subunit reduces formalin-induced nociception in the rat. Gene Ther 2005;12:59-66.
14. Caudle RM, Perez FM, Del Valle-Pinero AY, Iadarola MJ. Spinal cord NR1 serine phosphorylation and NR2B subunit suppression following peripheral inflammation. Mol Pain 2005;1:25.
15. Chazot PL. The NMDA receptor NR2B subunit: a valid therapeutic target for multiple CNS pathologies. Curr Med Chem 2004;11:389-396.
16. Eisenberg E, Vos BP, Strassman AM. The NMDA antagonist Memantine blocks pain behavior in a rat model of formalin-induced facial pain. Pain 1993;54:301-307.
17. Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. Brain Res 1990;518:218-226.
18. Gordon SM, Dionne RA, Brahim J, Jabir F, Dubner R. Blockade of peripheral neuronal barrage reduces postoperative pain. Pain 1997;70:209-215.
19. Gottschalk A, Smith DS, Jobes DR et al. Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. JAMA 1998;279:1076-1082.
20. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL Jr, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 1994;78:205-209.
21. Omote K, Kawamata T, Kawamata M, Namiki A. Formalin-induced release of excitatory amino acids in the skin of the rat hindpaw. Brain Res 1998;787:161-164.
22. Shu YS, Zhao ZQ. Comparison of NMDA and non-NMDA receptor antagonist-induced inhibition in hindpaw withdrawal response to noxious thermal stimulation. Sheng Li Xue Bao 1998;50:337-340.
23. Danysz W, Parsons CG, Kornhuber J, Schmidt WJ, Quack G. Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents – preclinical studies. Neurosci Biobehav Rev 1997;21:455-468.
24. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. JAMA 2004;291:965-973.
25. Ghose K, Niven B. Prophylactic sodium valproate therapy in patient with drug-resistent migraine. Methods Find Exp Clin Pharmacol 1998;20:353-359.
26. Parsons CG, Danysz W, Quack G. Memantine is clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist – a review of preclinical data. Neuropharmacology 1999;38:735-767.
27. Chaplan SR, Malmberg AB, Yaksh TL. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. J Pharmacol Exp Ther 1997;280:829-838.
28. Einsenberg E, LaCross S, Strassman AM. The effects of the clinically tested NMDA receptor antagonist memantine on carageenan-induced thermal hyperalgesia in rats. Eur J Pharmacol 1994;255:123-129.
29. Eisenberg E, LaCross S, Strassman AM. The clinically tested N-methyl-D-aspartate receptor antagonist memantine blocks and reverses thermal hyperalgesia in a rat model of painful mononeuropathy. Neurosci Lett 1995;187:17-20.
30. Carlton SM, Rees H, Gondesen K, Tsuruoka M, Willis WD. Behavioral and electrophysiological effects of memantine in a primate model of peripheral neuropathy. Soc Neurosci Abs 1994;568:18.
31. Davidson EM, Carlton SM. Intraplantar injection of dextrorphan ,ketamine or memantine attenuates formalin-induced behaviors. Brain Res 1998;785:136-42.
32. Alaverdashvili M, Kubová H, Mares P. Motor performance and behavior of immature rats are not compromised by a high dose of topiramate. Epilepsy Behav 2005;7:222-230.
33. Barros HM, Tannhauser SL, Tannhauser MA, Tannhauser M. Effect of sodium valproate on the open-field behavior of rats. Braz J Med Biol Res 1992;25:281-287.
34. Danysz W, Essmann U, Bresink I, Wilke R. Glutamate antagonists have different effects on spontaneous locomotor activity in rats. Pharmacol Biochem Behav 1994;48:111-118.
35. Kos T, Popik P. A comparison of the predictive therapeutic and undesired side-effects of the NMDA receptor antagonist, memantine, in mice. Behav Pharmacol 2005;16:155-161.