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REVIEW

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Chronic headache and nitric oxide inhibitors

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Abstract Sensitization of myofascial pain pathways may play an important role in the pathophysiology of chronic headache. Animal studies have shown that sensitization of pain pathways may be caused by or associated with activation of neuronal nitric oxide synthase (nNOS) and the generation of nitric oxide (NO). Furthermore, it has been shown that NOS inhibitors reduce central sensitization in animal models of persistent pain. On the basis of these findings, we investigated the analgesic effect of the NOS inhibitor, L-N^G-methyl arginine hydrochloride, and demonstrated that this drug significantly reduced headache as well as myofascial factors in patients with chronic tension-type headache. In addition, we demonstrated that infusion of the NO donor, glyceryl trinitrate, induces headache in these patients, probably by enhancing the sensitizing effect of pre-existing myofascial input. These studies strongly indicate that NO plays a crucial role in the pathophysiology of tension-type headache. We suggested that the analgesic effect of NOS inhibition in patients with chronic tension-type headache is most likely due to reduction of central sensitization at the level of the spinal dorsal horn or trigeminal nucleus, or both. Furthermore, these data suggest that inhibition of NOS may become a novel means of future treatment of chronic headache.

Key words Chronic headache • Nitric oxide inhibitors

Introduction

Chronic tension-type headache is one of the most-common types of primary headaches [1]. Increased tenderness of pericranial myofascial tissues to manual palpation is the most prominent abnormal finding in patients with chronic tension-type headache [2–5]. Painful impulses from these tissues may be referred to the head and perceived as headache, and myofascial mechanisms may, therefore, play a major role in the pathophysiology of tension-type headache [6]. Progress in basic pain research [7] and an increasing numbers of studies on tension-type headache [8] have increased our knowledge of the mechanisms underlying chronic head pain. Thus, substantial experimental evidence indicates that central sensitization, i.e., increased excitability of neurons in the CNS, generated by prolonged nociceptive input from the periphery, plays an important role in the pathophysiology of chronic pain [9] and chronic tension-type headache [8].

Nitric oxide and central sensitization in animal models

The freely diffusible gas nitric oxide (NO) is a messenger molecule involved in various biological functions [10], including neurotransmission [11]. NO contributes to sensory transmission in the peripheral [12] and central nervous system [13]. Furthermore, animal studies have shown that central sensitization may be caused by or associated with activation of neuronal nitric oxide synthase (NOS) and the generation of NO [13–15]. Moreover, prolonged elevation of NO within the spinal dorsal horn is important in maintaining the central sensitization [16]. Finally, it has been shown that inhibition of NOS reduces central sensitization in animal models of persistent pain [14, 17, 18] and that nociceptive responses in these models are enhanced by NO donors [19, 20].

Inhibition of NOS in chronic tension-type headache

In order to test the hypothesis that inhibition of NO and thereby central sensitization would reduce chronic headache, we investigated the analgesic effect of the NOS inhibitor L-N^G-methyl arginine hydrochloride (L-NMMA) in patients with chronic tension-type headache [21]. In a double-blind, placebo-controlled crossover study, 16 patients received L-NMMA or placebo on 2 days. L-NMMA reduced headache intensity significantly more than placebo (Fig. 1). To explore the mechanisms of this analgesic effect we also studied myofascial factors in relation to NOS inhibition [22]. We found that both muscle hardness and tenderness were significantly reduced following treatment with L-NMMA, while there was no significant reduction at any time after treatment with placebo (Figs. 2, 3).

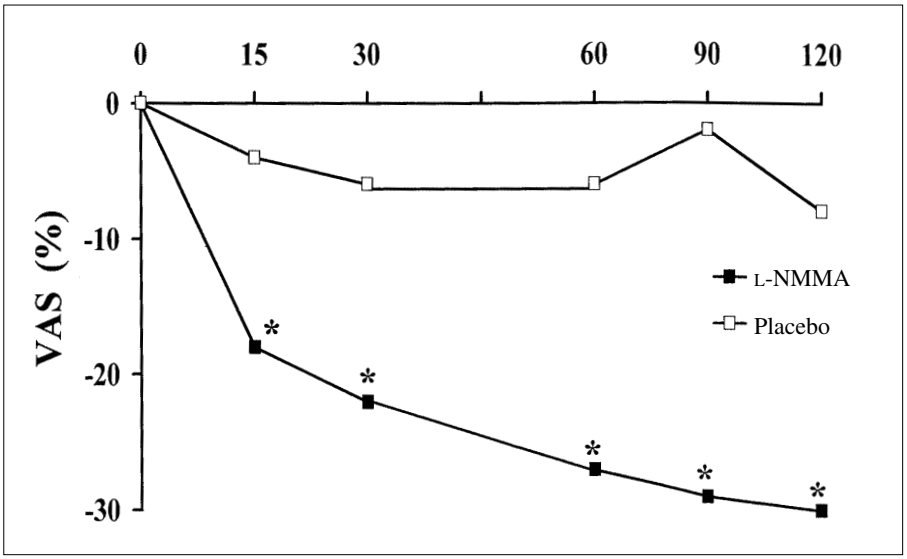

Fig. 1 Percentage changes from baseline pain intensity on a 100-mm Visual Analogue Scale (*VAS*) in patients with chronic tension-type headache. Patients were allocated randomly to receive 6 mg/kg L-NMMA or placebo over 15 min on 2 days separated by at least 1 week. The pain intensity was significantly more reduced following treatment with L-NMMA compared with placebo (p=0.01). *p<0.05 compared with baseline (time=0). The plots represent mean scores. (Modified from [21] with permission)

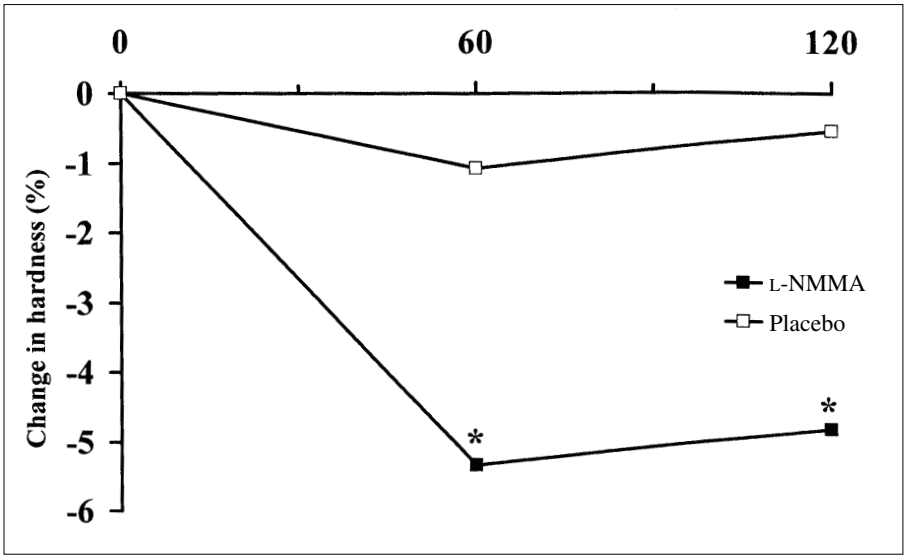

Fig. 2 Percentage changes in muscle hardness in patients with chronic tension-type headache. Muscle hardness was significantly more reduced following treatment with L-NMMA than with placebo in patients (p=0.04). *p<0.05 compared with baseline (time=0). The plots represent mean scores. (Modified from [22] with permission)

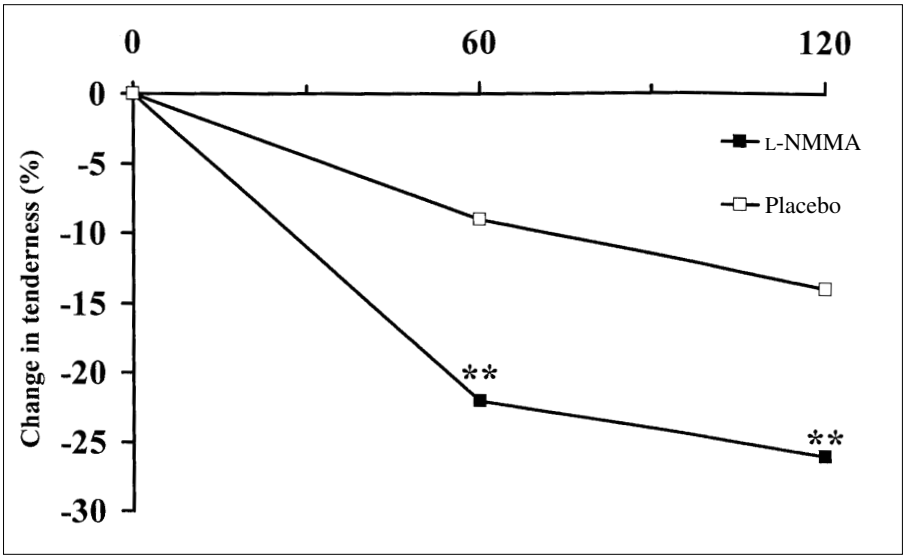

Fig. 3 Percentage changes in total tenderness score (TTS) in patients with chronic tension-type headache. The TTS tended to be reduced following treatment with L-NMMA compared with placebo (p=0.11). Within each treatment, the TTS was significantly reduced at 60 and 120 min after the start of the infusion of L-NMMA, while there was no significant changes at any time after treatment with placebo. **p<0.01 compared with baseline (time=0). The plots represent mean scores. (Modified from [22] with permission)

We suggest that the antinociceptive effect of NOS inhibition in patients with chronic tension-type headache is most likely due to reduction of central sensitization at the level of the spinal dorsal horn/trigeminal nucleus [21–23].

NO induction in chronic tension-type headache

It is an important question whether NO may induce or enhance central sensitization in patients with chronic tension-type headache. We aimed to investigate this using the NO donor, glyceryl trinitrate (GTN), model of experimental headache [24]. Sixteen patients and 16 healthy controls were randomized to receive intravenous infusion of GTN over 20 min. Patients developed significantly stronger headache on a GTN day than on a placebo day (Fig. 4). Furthermore, patients developed significantly stronger headache after GTN than controls. However, the most interesting finding of this study was that GTN infusion in patients resulted in a biphasic response with an immediate and a delayed headache (8 h after start of infusion) (Fig. 4). Moreover, in 87% of patients the delayed headache fulfilled tension-type headache criteria [24]. It is most likely that immediate headache after infusion of GTN originates from direct action of NO on perivascular sensory nerves or from NO-induced arterial dilatation, or both [24], while the delayed headache may be due to augmentation of pre-existing central sensitization [24].

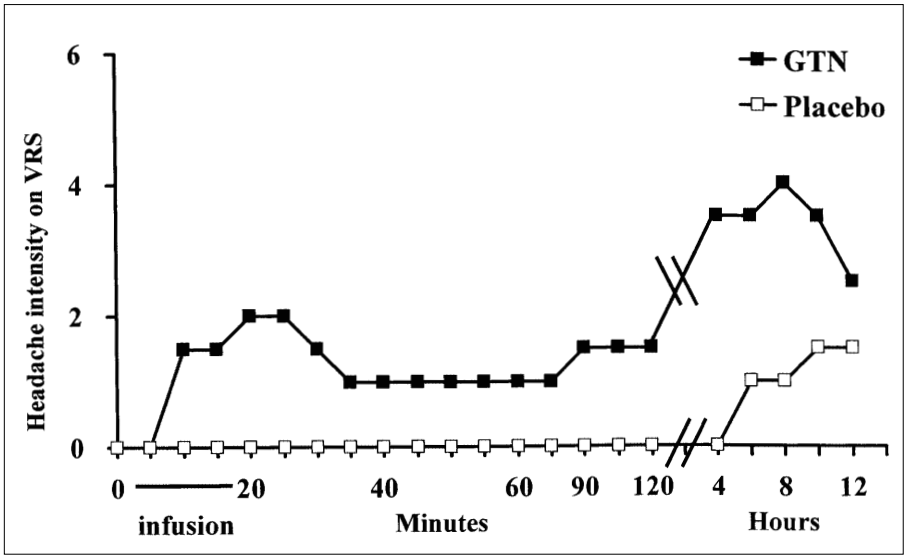

Fig. 4 Median headache intensity over time during (20 min) and after infusion of glyceryl trinitrate (*GTN*) and placebo in patients with chronic tension-type headache. Patients were allocated randomly to receive 0.5 μg/kg GTN per min or placebo on 2 headache-free days separated by at least 1 week. Headache was scored on a 10-point Verbal Rating Scale (*VRS*). The area under the headache curve (intensity x duration) on a GTN day was significantly higher than on a placebo day (p=0.008). The headache intensity reached its peak value at 8 h after the start of the GTN infusion. (Reproduced from [24] with permission)

Concluding remarks and future perspectives

In summary, these data demonstrate that the administration of a NOS inhibitor results in the reduction of headache, pericranial myofascial tenderness, and muscle hardness in patients with chronic tension-type headache. Since a reduction of central sensitization is the most likely mechanism of action of L-NMMA, this supports the importance of central sensitization in chronic tension-type headache. It is probable that reduction of central sensitization may become a new means of future treatment of chronic headache as well as other chronic pain disorders. However, there are still unanswered questions which should be addressed in future studies. Thus, L-NMMA inhibits all three types of NOS (endothelial NOS, neuronal NOS, inducible NOS) and study of selective inhibitors of NOS is needed to find out which type of NOS is involved in chronic head pain and its exact site of action. We are only beginning to understand the complex mechanisms leading to chronic tension-type headache, but the most-recent data obtained in clinical studies are promising and hopefully will lead to new treatment modalities in chronic head pain.

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References

1. Rasmussen BK, Jensen R, Schroll M, Olesen J (1991) Epidemiology of headache in a general population: a prevalence study. J Clin Epidemiol 44:1147–1157
2. Bendtsen L, Jensen R, Jensen NK, Olesen J (1995) Pressure-controlled palpation: a new technique which increases the reliability of manual palpation. Cephalalgia 15:205–210
3. Jensen R, Rasmussen BK, Pedersen B, Olesen J (1993) Muscle tenderness and pressure pain thresholds in headache. A population study. Pain 52:193–199
4. Langemark M, Olesen J (1987) Pericranial tenderness in tension headache. A blind, controlled study. Cephalalgia 7:249–255
5. Lipchick GL, Holroyd KA, Talbot F, Greer M (1997) Pericranial muscle tenderness and exteroceptive suppression of temporalis muscle activity: a blind study of chronic tension-type headache. Headache 37:368–376
6. Jensen R, Bendtsen L, Olesen J (1998) Muscular factors are of importance in tension-type headache. Headache 38:10–17
7. Mense S (1993) Nociception from skeletal muscle in relation to clinical muscle pain. Pain 54:241–289
8. Bendtsen L (2000) Central sensitization in tension-type headache – possible pathophysiological mechanisms. Cephalalgia 20:486–508
9. Woolf CJ, Salter MW (2000) Neuronal plasticity: increasing the gain in pain. Science 288:1765–1769
10. Moncada S, Palmer RM, Higgs EA (1991) Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev 43:109–142
11. Garthwaite J, Charles SL, Chess WR (1988) Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. Nature 24:385–388
12. Aley KO, McCarter G, Levine JD (1998) Nitric oxide signaling in pain and nociceptor sensitization in the rat. J Neurosci 1:7008–7014
13. Meller ST, Gebhart GF (1993) Nitric oxide (NO) and nociceptive processing in the spinal cord. Pain 52:127–136
14. Haley JE, Dickenson AH, Schachter M (1992) Electrophysiological evidence for a role of nitric oxide in prolonged chemical nociception in the rat. Neuropharmacology 31:251–258
15. Wu J, Lin Q, McAdoo DJ, Willis WD (1998) Nitric oxide contributes to central sensitization following intradermal injection of capsaicin. Neuroreport 9:589–592
16. Lin Q, Palecek J, Paleckova V, Peng YB, Wu J, Cui M, Willis WD (1999) Nitric oxide mediates the central sensitization of primate spinothalamic tract neurons. J Neurophysiol 81:1075–1085
17. Hao J, Xu X (1996) Treatment of chronic allodynia-like response in spinally injured rats: effects of systemically administered nitric oxide synthase inhibitors. Pain 66:313–319
18. Mao J, Price DD, Zhu J, Lu J, Mayer DJ (1997) The inhibition of nitric oxide-activated poly(ADP-ribose) synthase attenuates transsynaptic alteration of spinal cord dorsal horn neurons and neuropathic pain in the rat. Pain 72:355–366
19. Kitto KF, Haley JE, Wilcox GL (1992) Involvement of nitric oxide in spinally mediated hyperalgesia in the mouse. Neurosci Lett 14:1–5
20. Coderre TJ, Yashpal K (1994) Intracellular messengers contributing to persistent nociception and hyperalgesia induced by L-glutamate and substance P in the rat formalin pain model. Eur J Neurosci 1:1328–1334
21. Ashina M, Lassen LH, Bendtsen L, Jensen R, Olesen J (1999) Effect of inhibition of nitric oxide synthase on chronic tension-type headache: a randomised crossover trial. Lancet 353:287–289
22. Ashina M, Bendtsen L, Jensen R, Lassen LH, Sakai F, Olesen J (1999) Possible mechanisms of action of nitric oxide synthase inhibitors in chronic tension-type headache. Brain 122:1629–1635
23. Bendtsen L, Ashina M (2000) Sensitization of myofascial pain pathways in tension-type headache. In: Olesen J, Tfelt-Jensen P, Welch KMA (eds) The headaches, 2nd edn. Lippincott Williams and Wilkins, Philadelphia, pp 573–577
24. Ashina M, Bendtsen L, Jensen R, Olesen J (2000) Nitric oxide-induced headache in patients with chronic tension-type headache. Brain 123:1830–1837