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Research Report

Involvement of brain opioid receptors in the anti-allodynic effect of hyperbaric oxygen in rats with sciatic nerve crush-induced neuropathic pain

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ABSTRACT

Earlier research has demonstrated that hyperbaric oxygen (HBO_2) can produce an antinociceptive effect in models of acute pain. Recent studies have revealed that HBO_2 can produce pain relief in animal models of chronic pain as well. The purpose of the present investigation was to ascertain whether HBO_2 treatment might suppress allodynia in rats with neuropathic pain and whether this effect might be blocked by the opioid antagonist naltrexone (NTX). Male Sprague Dawley rats were subjected to a sciatic nerve crush under anesthesia and mechanical thresholds were assessed using an electronic von Frey anesthesiometer. The time course of the HBO_2-induced anti-allodynic effect in different treatment groups was plotted, and the area-under-the-curve (AUC) was determined for each group. Seven days after the nerve crush procedure, rats were treated with HBO_2 at 3.5 atm absolute (ATA) for 60 min and exhibited an anti-allodynic effect, compared to nerve crush-only control rats. Twenty-four hours before HBO_2 treatment, another group of rats was implanted with Alzet® osmotic minipumps that continuously released NTX into the lateral cerebral ventricle for 7 days. These NTX-infused, HBO_2-treated rats exhibited an allodynic response comparable to that exhibited by rats receiving nerve crush only. Analysis of the AUC data showed that HBO_2 significantly reduced the nerve crush-induced allodynia; this anti-allodynic effect of HBO_2 was reversed by NTX. These results implicate opioid receptors in the pain relief induced by HBO_2.

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1. Introduction

Inadequate management of pain may result in poor clinical outcomes and reduced quality of life for the patient. Effective treatment of chronic pain, in particular, presents a challenge to modern medicine. Pain relief is not an approved clinical indication of HBO_2 treatment (Gesell, 2008). Nonetheless, there is evidence that hyperbaric oxygen (HBO_2) treatment can mitigate both acute and chronic pain. There are observations in the literature that HBO_2 treatment can reduce pain in clinical patients who are afflicted with various chronic pains, including complex regional pain syndrome (CRPS) (Peach, 1995; Tuter et al., 1997; Kiralp et al., 2004), idiopathic trigeminal neuralgia (Gu et al., 2012), fibromyalgia (Yildiz et al., 2004), migraine (Wilson et al., 1998), cluster headache (Di Sabato et al., 1993) and other painful conditions (Dall'Era et al., 2006; Jones et al., 2006; Handschel et al., 2007).

Experimentally, HBO_2 treatment can reduce allodynia in rats with peripheral nerve injuries (Thompson et al., 2010; Li et al., 2011; Gu et al., 2012; Zhang et al., 2012) and experimental arthritis (Warren et al., 1979; Wilson et al., 2006, 2007). Research from our laboratory demonstrated that HBO_2 treatment effectively reduced pain in animal models of acute pain (Ohgami et al., 2009; Zelinski et al., 2009a; Chung et al., 2010; Quock et al., 2011). Our results from these experiments show that HBO_2-induced antinociception is significantly attenuated by the opioid antagonist naltrexone (NTX). Hence, we concluded that HBO_2 treatment might lead to activation of central opioid receptors that can modulate pain.

The purpose of the present investigation was to determine whether the pain-relieving effect of HBO_2 treatment in chronic pain might also involve a central opioid pain-relieving mechanism.

2. Results

2.1. Time course of the mechanical threshold

Fig. 1 compares the time course of the normalized mechanical thresholds in different treatment groups: control; nerve crush (NC) alone; nerve crush followed seven days later by a 60-min HBO_2 treatment at 3.5 atm absolute (ATA) (NC+HBO_2); nerve crush followed six days later by implantation of a continuously-releasing NTX osmotic minipump and, on the seventh day, by a 60-min HBO_2 treatment at 3.5 ATA (NC+NTX+HBO_2).

Mechanical thresholds temporarily increased in all three NC groups following the nerve crush procedure but started to decrease by day 4 after NC. Compared to the control group, the thresholds of the NC group continued to fall until stabilizing at approximately 40% lower than the control threshold. Treatment with HBO_2 on day 7 was followed by an increase in the mechanical threshold back to levels comparable to the control group. In rats implanted with NTX-releasing minipumps on day 6 followed by HBO_2 treatment on day 7, the mechanical threshold approximated that of the NC only group.

Monitoring of the mechanical thresholds continued up to 29 days following NC. At that time, the thresholds of the control and NC+HBO_2 groups were in one cluster within 10% of the starting threshold, and the thresholds of the NC only and NC+NTX+HBO_2 groups were in another cluster 40–50% lower than the original threshold on day 0.

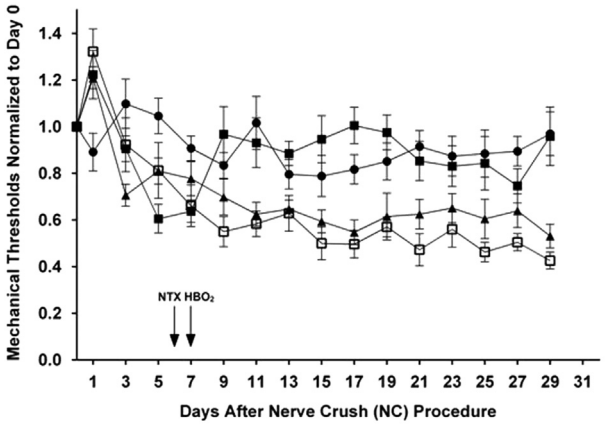

Fig. 1 – Time course of normalized mechanical thresholds of rats following: •, control; ▲, nerve crush (NC) alone; ▪, nerve crush followed seven days later by a 60-min HBO_2 treatment at 3.5 ATA (NC+HBO_2); and □, nerve crush followed six days later by implantation of a continuously-releasing naltrexone osmotic minipump and, on the seventh day, by a 60-min HBO_2 treatment at 3.5 ATA (NC+NTX+HBO_2). All mechanical thresholds were normalized to averaged baseline thresholds on day 0. Each symbol represents the mean +/- SEM of the response of 8–9 rats per group.

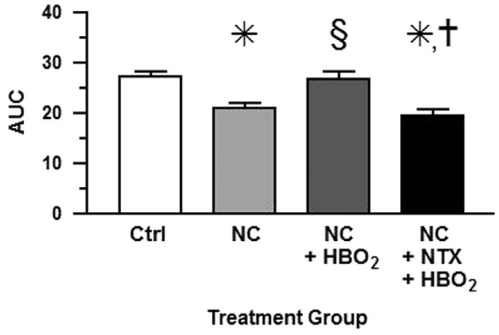

Fig. 2 – AUCs of changes in mechanical threshold. Each bar represents the mean AUC and each vertical line represents the SEM of 8–9 rats per group. Significance of difference: ✳, $P<0.05$, compared to the control group; §, $P<0.05$, compared to NC group; and †, $P<0.05$, compared to NC+HBO_2 (one-way ANOVA and post-hoc Bonferroni's multiple comparison test).

2.2. AUCs of changes in mechanical thresholds

Fig. 2 compares the area under the curve (AUC) of the four different treatment groups. The AUC of the mechanical threshold to allodynia of the NC group was significantly lower as compared to that of the untreated control group ($P<0.05$). Treatment with HBO_2 significantly increased the AUC as compared to that of the NC control ($P<0.05$) and