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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.

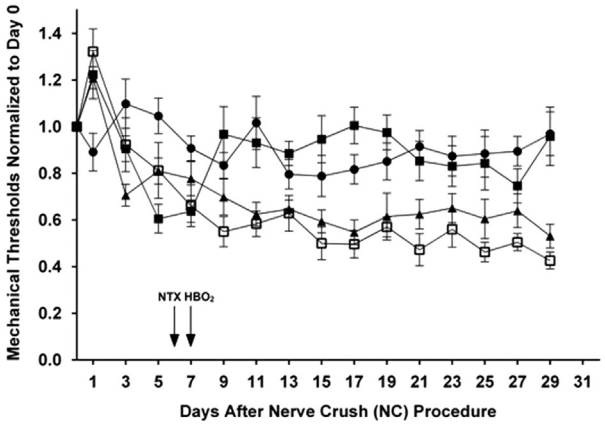

Fig. 1 – Time course of normalized mechanical thresholds of rats following: •, control; ▲, nerve crush (NC) alone; ▪, nerve crush followed seven days later by a 60-min HBO_2 treatment at 3.5 ATA (NC+HBO_2); and □, nerve crush followed six days later by implantation of a continuously-releasing naltrexone 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.

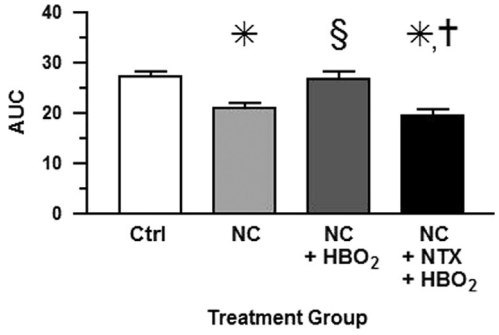

Fig. 2 – AUCs of changes in mechanical threshold. Each bar represents the mean AUC and each vertical line represents the SEM of 8–9 rats per group. Significance of difference: ✳, $P<0.05$, compared to the control group; §, $P<0.05$, compared to NC group; and †, $P<0.05$, compared to NC+HBO_2 (one-way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

returned the AUC of the mechanical threshold back to that of the untreated control level, i.e., an anti-allodynic effect.

However, when NTX, a nonspecific opiate antagonist, was administered by continuous i.c.v. minipump infusion, the treatment completely blocked the anti-allodynic effect of HBO_2 ($F=8.93$, $P=0.0002$).

3. Discussion

There are reports that HBO_2 treatment effectively relieved neuropathic pain in rats with peripheral nerve injury. Thompson et al. (2010) demonstrated that HBO_2 treatment could cause antinociception in two rat models of neuropathic pain, ligation of the L5 spinal nerve and chronic constriction injury (CCI) of the sciatic nerve. Rats were treated for 90 min with HBO_2 at 2.4 ATA daily for 14 consecutive days. HBO_2 treatment clearly improved mechanical thresholds (i.e., less hypersensitivity during the two weeks of treatment and for up to five days following the last HBO_2 treatment). Based on evidence that HBO_2 reduced carrageenan-induced inflammation (Sümen et al., 2001; Wilson et al., 2006), it was posited that HBO_2 reduced inflammation-associated neuropathic pain through this anti-inflammatory action. Wilson et al. (2007) also demonstrated that HBO_2 treatment was equieffective with aspirin in reducing both joint inflammation and hyperalgesia in rats following intraarticular injection of carrageenan.

Li et al. (2011) subjected rats to daily HBO_2 treatment at 2.4 ATA for 60 min for seven days following CCI of the sciatic nerve. Mechanical and cold allodynia responses on days 4 and 7 after CCI were significantly reduced in rats that received HBO_2 treatment. CCI-induced hyperalgesia and allodynia is generally associated with increased levels of tumor necrosis factor (TNF)-α (George et al., 2000) and interleukin (IL)-1β (George et al., 2004). Sciatic nerve homogenates from HBO_2-treated rats contained significantly reduced levels of TNF-α but not IL-1β on days 4 and 7 after CCI, suggesting that reduced production of TNF-α might contribute to HBO_2-induced relief of neuropathic pain (Li et al., 2011).

More recently, Gu et al. (2012) conducted similar experiments in rats with CCI of the sciatic nerve. Rats were treated with NBO_2 (normobaric 100% oxygen), HBA (hyperbaric air) and HBO_2 at 1.5, 2.0 or 3.0 ATA for daily 70-min treatments on seven consecutive days. HBO_2 but not NBO_2 or HBA treatment significantly lowered the severity and shortened the duration of thermal hyperalgesia as well as mechanical allodynia. In both situations, 3.0 ATA but not 1.5 or 2.0 ATA HBO_2 produced significant pain relief. CCI caused induction of c-Fos and activation of astrocytes in the dorsal horn neurons of the spinal cord ipsilateral to the nerve injury. Both the early HBO_2 treatment and the late HBO_2 treatment attenuated the c-Fos induction as well as the astrocyte activation (Gu et al., 2012). CCI caused significant elevation in amounts of phosphorylated protein levels of NMDA receptor subtypes NR1 (pNR1) and NR2B (pNR2), extracellular signal-regulated kinases (pERK), calmodulin-dependent kinase II (pCaMKII) and cAMP response element-binding (pCREB) protein. HBO_2 treatment starting early after the CCI procedure reversed all these changes except for pNR1.

In previous research from our laboratory, we reported that HBO_2 treatment could produce relief of acute pain in a time-dependent manner in the glacial acetic acid-induced abdominal constriction test. Mice treated with an i.p. injection of glacial acetic acid then placed into a hyperbaric chamber exhibited a reduced number of abdominal constrictions during a 6-min observation period under HBO_2 at 3.5 ATA (Ohgami et al., 2009; Quock et al., 2011).

When mice were subjected to HBO_2 treatment for 60 min, the antinociceptive state persisted for at least 90 min after treatment before gradually subsiding (Zelinski et al., 2009a). Mice that received four daily 60-min HBO_2 treatments exhibited an unusually long-lasting biphasic antinociceptive effect (Chung et al., 2010). There was an early-phase antinociceptive response that lasted approximately 6 h before dissipating by 12 h. However, a late-phase antinociceptive response re-emerged at 24 h and peaked five days after the last HBO_2 treatment which lasted for up to three weeks.

The present results show that a single 60-min HBO_2 treatment caused a rapid increase in mechanical threshold that was maintained at the same level as the control group through day 29 after NC. This improvement in the mechanical threshold occurred despite the fact that the implanted minipump was depleted of NTX by day 13. This suggests a long term consequence of opioid receptor blockade during and immediately after the HBO_2 treatment. This is reminiscent of a previous observation that naltrexone blockade of opioid receptors during the 4-day window of HBO_2 treatment antagonized the late-phase of HBO_2-induced antinociception two weeks after the last HBO_2 treatment (Chung et al., 2010).

The findings of this study are also consistent with these earlier results that implicate an involvement of a central opioid mechanism in the antinociceptive effects of HBO_2. The antinociceptive effect observed 90-min after a 60-min HBO_2 treatment at 3.5 ATA was abolished by i.p. pretreatment with NTX (Zelinski et al., 2009a). The early-phase antinociception that occurs 3 h after the last of four daily 60-min HBO_2 treatments was also significantly antagonized by i.c.v. pretreatment with NTX. Other results show that HBO_2-induced antinociception is sensitive to antagonism by norbinaltorphimine, a κ opioid antagonist (Portoghese et al., 1987), and rabbit antiserum against dynorphin$_{1\text{-}17}$, an endogenous κ opioid ligand (Chavkin et al., 1982). This suggested that HBO_2-induced antinociception in the mouse abdominal constriction test involves stimulated neuronal release of dynorphin$_{1\text{-}17}$, which then activates brain κ opioid receptors.

The results of the present study strongly implicate brain opioid receptors are involved but the specific subtype is unclear because of the nonselective nature of NTX blockade of opioid receptors. But it is clear that opioid receptors are probably implicated in the anti-allodynic effect of HBO_2 on allodynia induced in rats by peripheral nerve injury. The continuous infusion of NTX into the lateral cerebral ventricle indicates that the site of these opioid receptors is central but does not identify a specific brain site. Within the brain, high densities of opioid receptors are located in the limbic system (septum and hippocampus), corpus striatum, hypothalamus, periaqueductal gray (PAG), nucleus raphe magnus (NRM), and dorsal raphe of the rostral ventral medulla (Mansour et al., 1987).

Earlier investigations have shown involvement of opioid receptors in the arcuate nucleus of the anterior hypothalamus and PAG in analgesia elicited by defeat in a social conflict

model (Miczek et al., 1985). The arcuate nucleus of the anterior hypothalamus contains proopiomelanocortin (POMC) neurons that project to the PAG (Pilcher et al., 1988), which, in turn, plays a vital role in descending antinociceptive pathways (Heinricher et al., 2009). In a previous study, our laboratory has demonstrated that the anesthetic gas nitrous oxide may stimulate a neuronal release of β-endorphin from central sites (Zelinski et al., 2009b), including the arcuate nucleus and PAG (Ohgami et al., 2010) to produce an acute antinociceptive effect in the rat hot plate test (Hara et al., 1994). HBO_2-induced antinociception may also involve this arcuate–PAG pathway.

In summary, the central infusion of an opioid receptor blocker disrupts the antiallodynic effect of HBO_2 in rats with peripheral nerve injury. While not precluding the possible contribution of a peripheral anti-inflammatory action of HBO_2 to the relief of neuropathic pain, these findings further support our contention that HBO_2 also activates a centrally-mediated, pain-modulating pathway.

4. Conclusion

HBO_2 treatment causes an anti-allodynic effect in rats with sciatic nerve crush-induced neuropathic pain. The reversal of the anti-allodynic effect by centrally-administered NTX suggests that brain opioid mechanisms may be involved in the relief of neuropathic pain induced by HBO_2.

5. Experimental procedures

5.1. *Animals*

Male S/A albino rats, 160–180 g, were purchased from Simonsen Laboratories (Gilroy, CA) and used in this research. Experiments were approved by the Washington State University Institutional Animal Care and Use Committee (IACUC) with post-approval review and carried out in accordance with The Guide for the Care and Use of Laboratory Animals, 8th Edition (National Academies Press, Washington, DC, 2010). All measures to minimize pain or discomfort were taken by the investigators, including prophylaxis of post-operative pain (meloxicam) and infection (ampicillin).

Rats were individually housed in plastic cages in the Wegner Hall Vivarium at Washington State University with access to food and water ad libitum. The facility, which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), was maintained on a 12-h light:dark cycle (lights on 07:00–19:00 h) under standard conditions (22±1 °C room temperature, 33% humidity). Rats were kept in the holding room for at least four days after arrival in the facility for acclimation prior to use.

5.2. *Sciatic nerve crush procedure*

The sciatic nerve crush procedure was carried out under anesthesia with ketamine (100 mg/kg, i.m.) and xylazine (7.5 mg/kg, i.m.). Prior to surgery, the skin of the right hind limb was shaved and sterilized with 10% povidone iodine solution. An incision was made through the skin on the posterior thigh, and the muscle was blunt-dissected to expose the right sciatic nerve. The nerve was crushed with a pair of forceps for 10 s then crushed again at a 180° angle for another 10 s. In control animals, the sciatic nerve was exposed in identical manner but was not subjected to crush. At the end of surgery, the incised skin was closed with two wound clips. Rats received i.m. injections of ampicillin and meloxicam for prophylaxis of post-surgical infection and pain. After seven days, rats were subjected to HBO_2 treatment (3.5 ATA for 60 min) and allodynia was assessed for at least 25 days.

5.3. *Assessment of allodynia*

Allodynia was assessed in Plexiglas® test chambers (dimensions 21 cm L × 21 cm W × 25 cm H) mounted atop a sheet of galvanized steel mesh (hardware cloth) mounted at a height of 24 cm to allow access to the rats' paws from underneath. Rats were acclimated to the test chambers for 45 min before testing. An electronic von Frey anesthesiometer (Stoelting, Wood Dale, IL) was used to provoke a flexion reflex followed by a flinch response, and the mechanical threshold pressure was recorded. Assessments were carried out in triplicate at 5-min intervals. The mechanical threshold was measured every other day starting five days before nerve crush surgery; the three data were averaged to arrive at the baseline.

5.4. *Exposure to hyperbaric oxygen (HBO_2)*

Rats were placed in individual standard mouse cages (dimensions 27 cm L × 17 cm W × 12 cm H), two of which were inserted inside a B-11 research hyperbaric chamber (Reimers Systems, Inc., Lorton, VA) as previously described (Ohgami et al., 2008). The chamber was ventilated with 100% O_2, U.S.P. (A-L Compressed Gases Inc., Spokane, WA) at a flow rate of 20 L/min to minimize CO_2 accumulation. The pressure within the cylindrical clear acrylic chamber (28 cm diameter × 56 cm L) was increased from 1.0–3.5 ATA over 2 min. The pressure was held at 3.5 ATA for 60 min. The animals breathed spontaneously during HBO_2 treatment. After completion of the HBO_2 exposure, the chamber was decompressed over 2–3 min.

Under the conditions of a small, sealed hyperbaric chamber, it was not possible to quantify the CO_2 in the chamber. However, a Model 602-3 POET II anesthesia monitor (Criticare Systems, Waukesha, WI) failed to detect any CO_2 when the sample probe was inserted into the outlet of the hyperbaric chamber.

Control groups of rats were exposed to room air at 1.0 ATA (absence of 100% O_2 and 3.5 ATA). Preliminary experiments demonstrated that neither 100% O_2 nor 3.5 ATA alone produced any antinociceptive effect; only the combination of 100% O_2 and 3.5 ATA evoked an antinociceptive response (Liu et al., 2013; Liu et al., unpublished manuscript under review).

5.5. *Surgery for continuous intracerebroventricular delivery of drug*

On the day prior to HBO_2 treatment, rats were anesthetized with ketamine (100 mg/kg, i.m.) and xylazine (7.5 mg/kg, i.m.).

Rats were mounted in a stereotaxic headholder (Cartesian Research, Inc., Sandy, OR), and brain infusion cannulae (Alza, Cupertino, CA) were implanted into the right lateral cerebral ventricle at stereotaxic coordinates −1.00 mm AP, 1.5 mm ML and −2.00 mm DV, relative to bregma (Paxinos and Watson, 2007). Each brain infusion cannula consisted of a 12.8-mm length of 28-G stainless steel tubing embedded in a polycarbonate pedestal that was secured to the skull with screws and dental cement. A side connector protruded from the pedestal and was connected to a dorsally subcutaneously implanted Alzet® osmotic minipump model 1007D (100-µl reservoir, 0.5±0.1 µl/hr pumping rate, delivers for up to one week) with polyvinylchloride tubing. The concentration of NTX stored in each minipump was 2.0 mg/ml. The osmotic minipumps were connected to the brain infusion cannula 24 h prior to the first HBO_2 treatment and allowed to deliver their content over the next seven days. The incision was closed with a wound clip.

5.6. *Drugs*

Naltrexone hydrochloride (NTX) was purchased from Tocris Bioscience (Ellisville, MO). NTX was freshly prepared in 0.9% physiological saline solution. Meloxicam (MetaCam®, Boehringer Ingelheim, Ridgefield, CT) and ampicillin (Apothecon®, Princeton, NJ) were used for post-operative prophylaxis of post-operative pain and infection. The doses were 2.0 mg/kg meloxicam and 100 mg/kg ampicillin administered i.m.

5.7. *Statistical analysis of data*

To assess differences in mechanical thresholds between treatment groups, all mechanical thresholds were normalized to average baseline thresholds on day 0. Areas under the curves (AUC) were calculated according to the linear trapezoidal rule and analyzed by analysis of variance (ANOVA) and post-hoc Bonferroni's multiple comparison test.

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