Brain Research 1648 (2016) 434–437

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Hyperbaric oxygen treatment suppresses withdrawal signs in morphine-dependent mice

Daniel Nicoara [a,1], Yangmiao Zhang [b,2], Jordan T. Nelson [a,3], Abigail L. Brewer [a], Prianka Maharaj [b], Shea N. DeWald [a], Donald Y. Shirachi [d], Raymond M. Quock [a,b,c,*]

[a] Department of Psychology, Washington State University, Pullman, WA, USA
[b] Department of Integrative Physiology and Neuroscience, Washington State University, Pullman, WA, USA
[c] Translational Addiction Research Center, Washington State University, Pullman, WA, USA
[d] Department of Physiology and Pharmacology, University of the Pacific Thomas J. Long School of Pharmacy and Health Sciences, Stockton, CA, USA

ARTICLE INFO

Article history:
Received 8 March 2016
Received in revised form
22 July 2016
Accepted 13 August 2016
Available online 14 August 2016

Keywords:
Hyperbaric oxygen
Morphine
Opiate withdrawal
Physical dependence
Mouse

ABSTRACT

Hyperbaric oxygen (HBO_2) therapy reportedly reduces opiate withdrawal in human subjects. The purpose of this research was to determine whether HBO_2 treatment could suppress physical signs of withdrawal in opiate-dependent mice. Male NIH Swiss mice were injected s.c. with morphine sulfate twice a day for 4 days, the daily dose gradually increasing from 50 mg/kg on day 1 to 125 mg/kg on day 4. On day 5, withdrawal was precipitated by i.p. injection of 5.0 mg/kg naloxone. Mice were observed for physical withdrawal signs, including jumping, forepaw tremor, wet-dog shakes, rearing and defecation for 30 min. Sixty min prior to the naloxone injection, different groups of mice received either a 30-min or 60-min HBO_2 treatment at 3.5 atm absolute. HBO_2 treatment significantly reduced naloxone-precipitated jumping, forepaw tremor, wet-dog shakes, rearing and defecation. Based on these experimental findings, we concluded that treatment with HBO_2 can suppress physical signs of withdrawal syndrome in morphine-dependent mice.

1. Introduction

Hyperbaric oxygen (HBO_2) is the clinical application of 100% oxygen under higher-than-normal atmospheric pressure to achieve therapeutic outcomes. On the recommendation of the Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society, HBO_2 therapy is approved by the U.S. Food and Drug Administration (FDA) for 14 clinical conditions (Weaver, 2014) but currently not for treatment of opiate addiction. According to a published report, HBO_2 was beneficial in patients with narcomania (narcotic addiction) in the post-intoxication and abstinence periods (Epifanova, 1995). However, this study remains unconfirmed.

Previously, we reported that HBO_2 produced an antinociceptive effect in mice that was dependent on both nitric oxide (NO) and opioid receptors (Zelinski et al., 2009). Further studies suggested that HBO_2 might be capable of stimulating neuronal release of endogenous opioid peptides (Heeman et al., 2013). The purpose of the present investigation was to determine in an animal model whether HBO_2 might be capable of reducing the morphine withdrawal syndrome.

2. Results

The intraclass correlation coefficients (ICCs) for two independent raters assessing the impact of HBO_2 treatment on physical withdrawal signs were as follow: jumps ($\alpha=0.995$, $P=0.000$); rears ($\alpha=0.878$, $P=0.000$); and fecal boli ($\alpha=0.826$, $P=0.000$). ICCs were not determined for tremors or wet-dog shakes because they were scored in real time by a single rater.

Morphine-dependent mice exhibited averages of 24.6 ± 8.5 jumps, 15.6 ± 2.4 tremors, 2.9 ± 0.7 wet-dog shakes, 92.2 ± 6.8 rears, and 6.3 ± 0.8 fecal boli during a 30-min observation period following administration of naloxone. After both 30- and 60-min HBO_2 treatments, there were statistically significant decreases in all five endpoints: jumps [Welch's $F(2, 15.737)=4.510$, $P=0.028$]; tremors [Welch's $F(2, 26.911)=6.815$, $P=0.004$]; wet-dog shakes

* Correspondence to: Department of Psychology, Washington State University, P. O. Box 644820, Pullman, WA 99164, USA.
E-mail address: quockr@wsu.edu (R.M. Quock).
[1] Present address: College of Osteopathic Medicine, Pacific Northwest University of Health Sciences, 200 University Parkway, Yakima, WA, USA.
[2] Present address: Department of Neurological Surgery, Oregon Health & Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR, USA.
[3] Present address: College of Pharmacy, Washington State University, P.O. Box 1495, Spokane, WA, USA.

http://dx.doi.org/10.1016/j.brainres.2016.08.017
0006-8993/

[Welch's F(2, 26.586)=5.790, P=0.008]; rears [F(2, 27)=5.384, P=0.011]; and fecal boli [Welch's F(2, 17.719)=8.963, P=0.002] (Figs. 1-5).

3. Discussion

We found that naloxone precipitated five cardinal signs of opiate withdrawal—jumping, forepaw tremor, wet-dog shakes, rearing, and defecation (Gabra et al., 2008; Seyedi et al., 2014; Wu et al., 2014)—in morphine-dependent mice. The frequency of all five withdrawal signs was significantly reduced by HBO_2 treatment.

The implications of this research are of profound importance. Current therapies used to treat heroin addiction largely employ opiate medications, including agonists, partial agonists and antagonists. While these drugs can provide relief from the opiate withdrawal syndrome, they are still prone to development of physical dependence and risk of relapse (Kleber, 2007).

Although one isolated study reported that HBO_2 alleviated

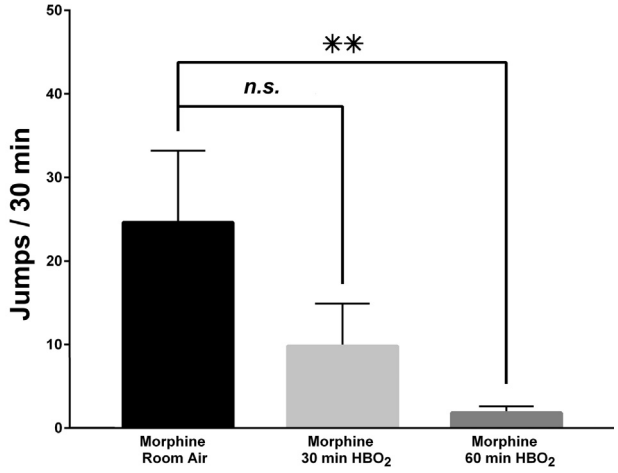

Fig. 1. Effect of HBO_2 on naloxone-induced jumping in chronic morphine-treated mice. Data are presented as the mean ± SEM (Morphine+Room Air, N=14; Morphine+30-min HBO_2, N=14; and Morphine+60-min HBO_2, N=21). Significance of difference: **, $P<0.01$, compared to Morphine+Room Air control group.

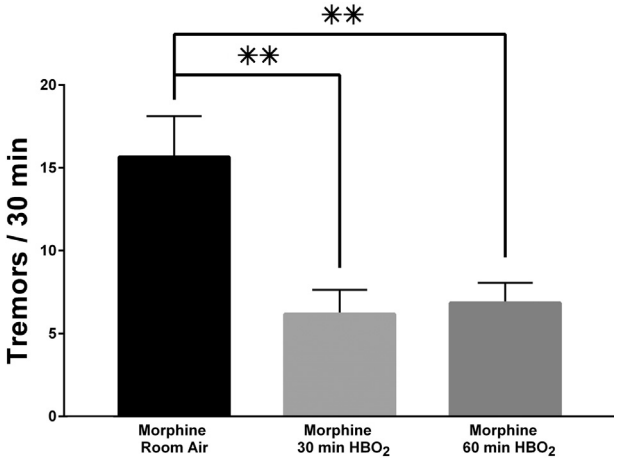

Fig. 2. Effect of HBO_2 on naloxone-induced tremor in chronic morphine-treated mice. Data are presented as the mean ± SEM (Morphine+Room Air, N=18; Morphine+30-min HBO_2, N=14; and Morphine+60-min HBO_2, N=21). Significance of difference: **, $P<0.01$, compared to Morphine+Room Air control group.

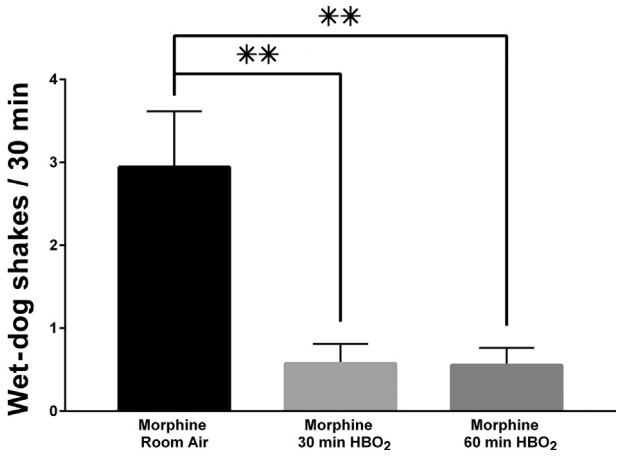

Fig. 3. Effect of HBO_2 on naloxone-induced wet-dog shakes in chronic morphine-treated mice. Data are presented as the mean ± SEM (Morphine+Room Air, N=18; Morphine+30-min HBO_2, N=14; and Morphine+60-min HBO_2, N=21). Significance of difference: **, $P<0.01$, compared to Morphine+Room Air control group.

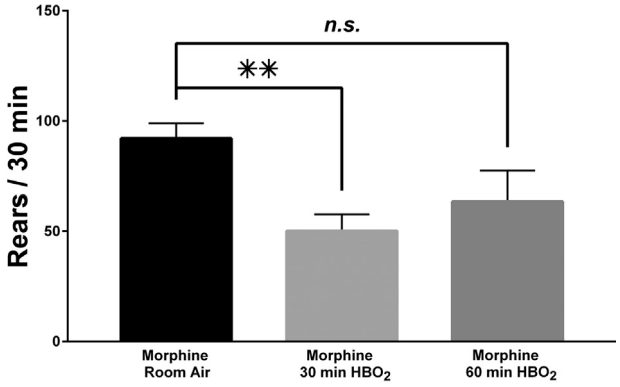

Fig. 4. Effect of HBO_2 on naloxone-induced rearing in chronic morphine-treated mice. Data are presented as the mean ± SEM (Morphine+Room Air, N=14; Morphine+30-min HBO_2, N=10; and Morphine+60-min HBO_2, N=12). Significance of difference: **, $P<0.01$, compared to Morphine+Room Air control group.

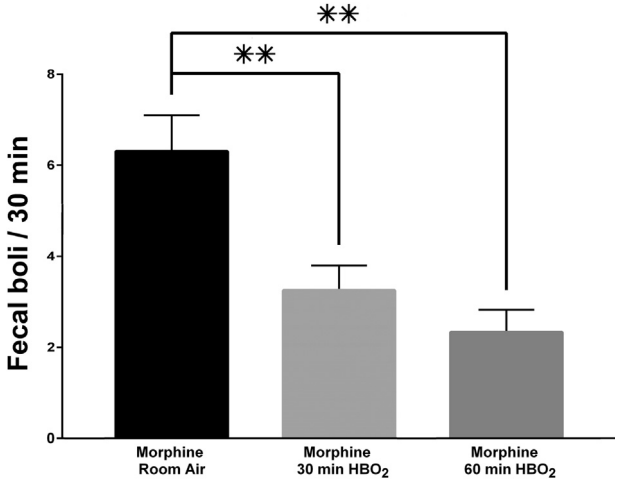

Fig. 5. Effect of HBO_2 on naloxone-induced defecation in chronic morphine-treated mice. Data are presented as the mean ± SEM (Morphine+Room Air, N=14; Morphine+30-min HBO_2, N=10; and Morphine+60-min HBO_2, N=12). Significance of difference: **, $P<0.01$, compared to Morphine+Room Air control group.