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HIGH DOSES OF PSEUDOEPHEDRINE HYDROCHLORIDE ACCELERATE ONSET OF CNS OXYGEN TOXICITY SEIZURES IN UNANESTHETIZED RATS

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Abstract—Pseudoephedrine (PSE) salts (hydrochloride and sulfate) are commonly used as nasal and paranasal decongestants by scuba divers. Anecdotal reports from the Divers Alert Network suggest that taking PSE prior to diving while breathing pure O_2 increases the risk for CNS oxygen toxicity (CNS-OT), which manifests as seizures. We hypothesized that high doses of PSE reduce the latency time to seizure (LS) in unanesthetized rats breathing 5 atmospheres absolute (ATA) of hyperbaric oxygen. Sixty-three male rats were implanted with radio-transmitters that recorded electroencephalogram activity and body temperature. After ⩾7-day recovery, and 2 h before ''diving'', each rat was administered either saline solution (control) or PSE hydrochloride intragastrically at the following doses (mg PSE/kg): 0, 40, 80, 100, 120, 160, and 320. Rats breathed pure O_2 and were dived to 5 ATA until the onset of behavioral seizures coincident with neurological seizures. LS was the time elapsed between reaching 5 ATA and exhibiting seizures. We observed a significant dose-dependent decrease in the LS at doses of 100–320 mg/kg, whereas no significant differences in LS from control value were observed at doses ⩽80 mg/kg. Our findings showed that high doses of PSE accelerate the onset of CNS-OT seizures in unanesthetized rats breathing 5 ATA of poikilocapnic hyperoxia. Extrapolating our findings to humans, we conclude that the recommended daily dose of PSE should not be abused prior to diving with oxygen-enriched gas mixes or pure O_2.

Key words: hyperbaric, diving, pseudoephedrine, seizures, CNS oxygen toxicity, Divers Alert Network.

INTRODUCTION

Pseudoephedrine (PSE) salts, notably hydrochloride and sulfate, are commonly used as a decongestant for the nasal and paranasal sinuses among divers and other consumers (Roth et al., 1977). PSE is a sympathomimetic drug and psychostimulant (Hoffman and Lefkowitz, 1996), and belongs to the family of phenylethylamines and amphetamines (Hoffman and Lefkowitz, 1996; Kobayashi et al., 2003). Its primary action, vasoconstriction, results from direct and indirect activation of α- and β-adrenergic receptors causing reduction of nasal membrane inflammation and mucus production (Cohn, 1965; Drew et al., 1978).

During the last decade, reports have highlighted multiple side effects of PSE (Clark and Curry, 1990), especially if taken in high doses, including dizziness (CDC, 1996), headache (Munari et al., 1989), nausea (CDC, 1996), insomnia (Chervinsky et al., 2005), tachycardia (Taylor et al., 2000), hallucinations (Sills et al., 1984), seizures (Porta et al., 1986) and stroke (Singhal et al., 2002). In addition, overdosing with PSE facilitates the onset of non-convulsive seizures in humans (Ismailogullari et al., 2011) and rats (Zhi and Levy, 1990). The fact that seizure is one possible side effect of PSE in excess is interesting when its use is considered in the context of diving. Anecdotal evidence collated and highlighted by Divers Alert Network (DAN),[1] and published elsewhere (Vann et al., 2009) suggests that ingesting PSE before making a dive using a self-contained underwater breathing apparatus (SCUBA) with enriched-air nitrox (EAN), or a rebreather with pure oxygen may predispose the diver to seizures: i.e., CNS oxygen toxicity (CNS-OT).

To date, several studies have been conducted in humans on the neurophysiological side-effects of PSE and other non-prescription sympathomimetic drugs (Dickerson et al., 1978; Bucke et al., 1983; Kaminszczik and Barbon, 1983; Keene et al., 1984; Pentel, 1984; Clark and Curry, 1990; Sherkat et al., 2011). While anecdotal evidence suggests a causal relationship between taking PSE prior to making a high oxygen dive and the onset of CNS-OT seizure, it is unknown whether or not PSE accelerates the onset of seizure when breathing hyperbaric oxygen (HBO_2). Accordingly, we investigated the effects of different doses of PSE hydrochloride on the latency time to seizure (LS) of CNS-OT in male Sprague–Dawley rats breathing HBO_2 during a simulated dive in a hyperbaric chamber. The

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Abbreviations: ATA, atmospheres absolute; CNS-OT, CNS oxygen toxicity; DAN, Divers Alert Network; EEG, electroencephalogram; HBO_2, hyperbaric oxygen; LD_{50}, lethal dose, 50%; LS, latency time to seizure; PSE, pseudoephedrine; T_B, body temperature.

[1] http://www.diversalertnetwork.org/medical/articles/Pseudoephedrine_Enriched-Air_Diving; DAN is Divers Alert Network, the ''largest association of recreational scuba divers in the world. . .DAN's mission is to help divers in need of medical emergency assistance and to promote dive safety through research, education, products and diving services.''

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rodent animal model is used frequently, rather than humans, for studies of the pathogenesis of CNS-OT when seizure is the end point of the experiment (Rodrigues et al., 2012; Demchenko et al., 2012a; Pilla et al., 2013). Typically, humans seize much more quickly (Donald, 1947a,b) than rats (Arieli and Hershko, 1994) at 2.5–3.0 atmospheres absolute pressure (ATA) oxygen. Consequently, unanesthetized rats are typically tested with 4–6 ATA oxygen to induce CNS-OT quickly enough to avert the risk and confounding effects of pulmonary oxygen toxicity (Demchenko et al., 2012b).

The purpose of this study was to test the hypothesis that oral administration of PSE 2 h prior to diving accelerates the onset of CNS-OT in unanesthetized, unrestrained rats breathing HBO_2.

EXPERIMENTAL PROCEDURES

Animals and surgical procedures

The animal use protocol prepared for this study was reviewed and approved by the University of South Florida's Institutional Animal Care and Use committee (AAALAC accredited, #000434). Sixty-three adult male Sprague–Dawley rats (250–350 g, Harlan Laboratories, Indianapolis, IN, USA) were surgically implanted with radio-telemetry devices as described previously (Pilla et al., 2013). The transmitter module was placed in the abdominal cavity to detect core body temperature (T_B) and the two electrical leads were tunneled subcutaneously and implanted between Lambda and Bregma, one on either side of midline to measure electroencephalogram (EEG) activity (Pilla et al., 2013). After surgery, animals recovered for at least 7 days before being tested. Rats were weighed twice: immediately before surgery and 1 week later, just prior to exposure to HBO_2. Body weight increased by 14.8 (± SEM – standard error of measurement) g on average during the week prior to making the dive in HBO_2. The study was completed over a 16-month period.

Telemetry receiver unit and video recording setup

As previously described (Pilla et al., 2013), signals from the radio-transmitter were collected from a receiver (DSI PhysioTel, model RPC-1, St. Paul, MN, USA) hard-wired through the wall of the hyperbaric chamber and linked to an acquisition interface unit (ACQ 7700 Ponemah, St. Paul, MN, USA) outside the chamber. The acquisition unit connected to a computer for data collection and storage in real time. Chamber pressure and temperature were measured by the same acquisition interface unit. Each animal was continuously monitored via a video camera (AXIS 221 Network Camera, St. Paul, MN, USA) connected to the computer.

Hyperbaric chamber setup

As reported earlier (Pilla et al., 2013), the hyperbaric research station consisted of two chambers: a plexiglass chamber used to house the unrestrained rat during the experiment and a main hyperbaric chamber (7.8 ATA maximum working pressure), that contained the plexiglass animal chamber. Both chambers were connected to an air compressor in series with a dryer. The inner plexiglass animal chamber had a supplementary input for 100% O_2. All electrical wires and connections were confined to the outer chamber, which was pressurized with air in order to reduce the fire hazard of using pure oxygen under pressure.

Diving profile and seizure determination

At the start of each experiment, the rat was gavaged with the selected dose of PSE or water (control), as described below. The rat was sealed inside the animal chamber and ventilated continuously with fresh air to eliminate expired CO_2 buildup and to prevent body heat accumulation. The experimental diving protocol was initiated 80 min later. The animal chamber was kept in normobaric air for 10 min, then ventilated in 100% O_2 at room pressure for 15 min. Next, the two chambers were pressurized in parallel to 5 ATA at a rate of ~0.7 ATA/min. Thus, 2 h had elapsed when the diving protocol was initiated and the animal was compressed to 5 ATA, which was sufficient time to establish peak levels of PSE in the blood (Kuntzman et al., 1971; Kanfer et al., 1993). The LS value was calculated from the time the rat first reached 5 ATA of O_2 pressure until the onset of behavioral seizures—regular tonic–clonic twitches of head and forelimbs—that coincided with increased EEG activity. Increased EEG activity always preceded behavioral seizures by several seconds (Pilla et al., 2013). Following seizure onset, the plexiglass chamber was flushed with air for ~3 min, then both chambers were decompressed in parallel at a rate of 1 ATA/min. Rats were allowed 15-min recovery in normobaric air before being euthanized. Typically, seizures ended within seconds of lowering inspired O_2. However, in a minority of the animals tested, seizures recurred intermittently during decompression.

PSE hydrochloride preparation and administration

Animals were divided into six groups, each group receiving a different dose of drug (in mg PSE/kg body weight): 0 (control), 40, 80, 100, 120, 160 or 320 dissolved in sterile 0.9% NaCl solution (Hospira, Lake Forest, IL, USA). The test solutions were prepared the morning of the experiment to prevent differences in hydration status of PSE. Naïve animals were used for each exposure because we previously found that animals exhibit decreased LS times as a function of increasing numbers of HBO_2-induced seizure (Pilla et al., 2012a). This is similar to the kindling effect that is commonly described in epilepsy literature (Gaito, 1976; Racine, 1978; McNamara et al., 1980). The highest dose selected was 320 mg/kg of body weight, which is equivalent to half of the LD_{50} (lethal dose, 50%) for PSE reported for rat (Pfizer, 2007). Lower doses, used in previous studies with rats (Till and Benet, 1979a,b; Tongjaroenbuangam et al., 1998), were chosen in order to generate a dose–response curve.