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Hypobaric hypoxia exposure in rats differentially alters antidepressant efficacy of the selective serotonin reuptake inhibitors fluoxetine, paroxetine, escitalopram and sertraline

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ABSTRACT

Treatment-resistant depression, a chronic condition that affects 30% of depressed patients on antidepressants, is highly linked to suicidal behavior. Chronic hypoxia exposure via living at altitude (hypobaric hypoxia) or with chronic hypoxic diseases is demographically linked to increased risk for depression and suicide. We previously demonstrated that housing rats at altitude for a week incrementally increases depression-like behavior in the forced swim test (FST) in females, but not males. In animal models, high altitude exposure reduces brain serotonin, and selective serotonin reuptake inhibitors (SSRIs) can lose efficacy when brain serotonin levels are low. To address whether residence at moderate altitude is detrimental to SSRI function, we examined SSRI efficacy in the FST after a week of housing rats at altitudes of 4500 ft. or 10,000 ft. as compared to at sea level. In females, the tricyclic antidepressant desipramine (positive control) functioned well in all groups, increasing latency to immobility and decreasing immobility, by increasing climbing. However, the SSRIs fluoxetine, paroxetine and escitalopram were ineffective in females in all groups: only paroxetine improved swimming in the FST as expected of a SSRI, while all three unexpectedly reduced climbing. Fluoxetine was also ineffective in male rats. Sertraline was the only SSRI with antidepressant efficacy at altitude in both females and males, increasing swimming, climbing and latency to immobility, and reducing immobility. Hypobaric hypoxia thus appears to be detrimental to efficacy of the SSRIs fluoxetine, paroxetine and escitalopram, but not of sertraline. Unlike the other SSRIs, sertraline can improve both serotonergic and dopaminergic transmission, and may be less impacted by a hypoxia-induced serotonin deficit. A targeted approach may thus be necessary for successful antidepressant treatment in patients with depression who live at altitude or with chronic hypoxic diseases, and that sertraline may be the SSRI of choice for prescription for this population.

1. Introduction

Major depressive disorder (MDD) affects over 20% of the world population (Chopra et al., 2011), with lifetime prevalence as high as 12% in men and 25% in women (Trivedi and Daly, 2008). Based on increased use of healthcare resources and severe personal and societal costs, MDD is ranked amongst diseases most debilitating to society (Mrazek et al., 2014). Up to a third of MDD patients in treatment exhibit treatment-resistant depression (TRD), a persistent non-responsiveness to multiple interventions with antidepressants (Trivedi and Daly, 2008). TRD is associated with functional impairment, poor quality of life, lifetime prevalence, self-injury and suicidal behavior (Al-Harbi, 2012; Joiner Jr et al., 2005). People with depressive disorders face a suicide risk 60–70% higher than the general public (Moller, 2003). The World Health Organization report on global mental health (WHO, 2001) estimates that 15–20% of MDD patients worldwide ended their lives by suicide between 1990 and 2000, and that depression is expected to become the second highest ranking cause of burden of

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disease by 2020.

Demographic studies show that living at altitude is a risk factor for depression and suicide, since rates of both MDD (Asiri, 2014; DelMastro et al., 2011; Gamboa and Arregui, 2011) and suicide (Betz et al., 2011; Brenner et al., 2011; Haws et al., 2009; Kim et al., 2011) increase with altitude of residence. The altitude-suicide link is seen world-wide, independent of sociocultural and other risk factors, and is currently documented in the US (Betz et al., 2011; Brenner et al., 2011; Haws et al., 2009; Kim et al., 2011), South Korea (Kim et al., 2011), Brazil (Bezerra Filho et al., 2012), Austria (Helbich et al., 2013), Saudi Arabia (Asiri, 2014), Spain (Alameda-Palacios et al., 2015) and Peru (Zaeh et al., 2016). Suicide rates are found to increase incrementally with altitude from approximately 2000 ft. above sea level (Brenner et al., 2011). Living at altitude involves chronic exposure to hypobaric hypoxia (the low partial pressure of oxygen at altitude), and a similar pattern of increased depression and suicide is seen in people exposed to normobaric hypoxia via chronic hypoxic disease conditions. People suffering from chronic hypoxic disorders, such as chronic obstructive pulmonary disease (COPD), asthma, chronic bronchitis, cardiovascular disease and cigarette smoking exhibit higher odds ratios for MDD and suicide, as opposed to those with chronic diseases not linked to hypoxia (osteoporosis, diabetes), and those with no chronic disease (Goodwin et al., 2003; van den Bemt et al., 2009; Webb et al., 2012). MDD and suicide rates increase incrementally with severity of hypoxic disease and past vs. current status of disease (Chung et al., 2014; Kuo et al., 2010). Chronic hypoxia exposure has therefore been proposed to worsen MDD status and suicidal behavior (Katz, 1982; Young, 2013).

We had previously established a rodent model to examine the impact of hypobaric hypoxia on depression-like behavior (DLB). After a week of housing at altitudes of sea level, 4500 ft., 10,000 ft., or 20,000 ft., female rats exhibit an altitude-related increase in DLB in the forced swim test (FST) (Kanekar et al., 2015), but males do not. Chronic hypoxia has been found to cause deficits in brain serotonin levels, which may play a role in this observed increase in DLB. After high altitude exposure (> 18,000 ft), serotonin levels can drop in the whole rat brain, forebrain and striatum (Prioux-Guyonneau et al., 1982; Ray et al., 2011). Brain serotonin levels also appear to be disrupted with moderate altitude exposure in our model (C.S. Sheth, unpublished observations). Hypobaric hypoxia could thus lower brain serotonin levels, to contribute to increased depression.

Selective serotonin reuptake inhibitors (SSRI) account for over 80% of the US antidepressant market (Lin et al., 2011). SSRIs are often the first-line option for antidepressant treatment, due to lower side effects, good tolerability and low overdose toxicity (Nemeroff and Owens, 2004). SSRIs block the serotonin transporter to prevent cellular reuptake of serotonin released into the synapse, thereby increasing synaptic serotonin levels and improving depression status. However, when brain serotonin levels are low, SSRIs can lose antidepressant efficacy. In mice with low functioning isoforms of tryptophan hydroxylase 2 (TPH2, the rate-limiting enzyme in serotonin synthesis), brain serotonin levels are decreased and the SSRIs citalopram and paroxetine exhibit lower antidepressant efficacy in the FST, as compared to mice with fully functioning TPH2 (Guzzetti et al., 2008; Kulikov et al., 2011). In rats, acute depletion of brain serotonin with para-chlorophenylalanine (PCPA) (Page et al., 1999) or 3, 4-methylenedioxymethamphetamine (MDMA or “Ecstasy”) (Durkin et al., 2008) led to a loss of function of the SSRI fluoxetine in the FST. A hypoxia-induced deficit in brain serotonin may thus reduce SSRI efficacy, potentially leading to more TRD in SSRI-treated MDD patients at altitude and/or with chronic hypoxic disorders.

In the current study, we used this translational animal model (Kanekar et al., 2015) to examine the impact of housing at altitude on antidepressant efficacy of four widely-prescribed SSRIs, fluoxetine (Prozac®), paroxetine (Paxil®), escitalopram (Lexapro®) and sertraline (Zoloft®), as compared to the tricyclic antidepressant (TCA) desipramine. Due to noted sex-based differences in depression and antidepressant effects (Dalla et al., 2010), and data from our previous study (Kanekar et al., 2015), we investigated the impact of hypobaric hypoxia on both females and males in this model.

2. Materials and methods

2.1. Animals

For all experiments, male and female Sprague-Dawley rats, of 125–150 g body weight, were received from Charles River Laboratories (Raleigh, NC). Animals were housed individually and given food and water ad libitum. After a week of acclimatization, rats were randomly assigned to the different altitude and treatment groups. All animal studies are in compliance with the ARRIVE guidelines and were performed in accordance with the NIH Guide for Care and Use of Laboratory Animals. All animal procedures were approved by the Institutional Animal Care and Use Committees (IACUCs) of both the University of Utah and the Veterans Affairs Salt Lake City Health Care System. To ensure that females did not face any additional stresses to that experienced by males (Kanekar et al., 2015), vaginal testing for estrous cycle stage was not conducted in these studies.

2.2. Study groups

The altitude groups used for this study include the sea level (SL), 4500 ft. (4.5 K) and 10,000 ft. (10*K*) groups also used in our prior depression study (Kanekar et al., 2015). These animals undergo a week-long period of acclimatization at local conditions (4500 ft) prior to being set up for a week in the three different altitude conditions (Table 1).

Since the SL group did not serve as an adequate control for this study, we added two more control groups to study efficacy of a candidate SSRI, fluoxetine hydrochloride. A baseline group (Day 0 or D0 group) was tested after acclimatization at local conditions (4500 ft., Table 1). In a second group, rats were acclimatized at sea level, followed by another week at sea level (Normoxic Control or NC group) (Table 1). These animals were put into the sea level chamber immediately upon arrival to our facility, and housed in the sea level chamber for the two weeks prior to behavioral testing.

2.3. Altitude simulations

Altitude simulations were achieved using hypobaric or hyperbaric chambers to reduce or increase pressure from ambient barometric pressure at the University of Utah Research Park (4500 ft). Animals were placed in the hyperbaric chamber set to simulate sea level conditions (21% ppO_2, 760 mm Hg barometric pressure) or in the hypobaric chamber to simulate 10,000 ft. (15% ppO_2, 523 mm Hg). Rats in the 4500 ft. group were housed at local conditions (Salt Lake City, UT: 18% ppO_2, 644 mm Hg), in the same room as the altitude chambers.

Table 1
Altitude housing of the experimental study groups.

Study group	Week 1	Week 2	Fluoxetine efficacy	
	Acclimatization	Altitude setting	Females	Males
Sea level	4500 ft.	Sea Level (0 ft.)	no	no
4500 ft.	4500 ft.	4500 ft.	no	no
10,000 ft.	4500 ft.	10,000 ft.	no	no
Baseline (D0)	4500 ft.	–	no	no
Normoxia control (NC)	Sea level	Sea level	yes	yes