

Thin air, high altitudes cause depression in female rats

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In a novel study, University of Utah (U of U) researchers have shown that hypobaric hypoxia (the reduced oxygen experienced at high altitude) can lead to depression.

In the March 2015 edition of *High Altitude Medicine and Biology* online, the U of U researchers and a colleague from Tufts University show that <u>female rats</u> exposed to high-altitude conditions, both simulated and real, exhibit increased depression-like behavior. Male rats, interestingly, showed no signs of depression in the same conditions.



"The significance of this animal study is that it can isolate hypoxia as a distinct risk factor for depression in those living at altitude (hypobaric hypoxia) or with other chronic hypoxic conditions such as COPD, asthma or smoking, independent of other risk factors," says Shami Kanekar, Ph.D., research assistant professor of psychiatry and lead author on the study.

The researchers housed rats for a week at simulated altitudes of sea level, 10,000 feet and 20,000 feet using altitude chambers, and at local conditions of 4,500 feet, the elevation of Salt Lake City where the research took place. They then used a widely accepted behavioral test in which depression is gauged by how much persistence rodents demonstrate in a swim test. "In female rats, increasing altitude of housing from sea level to 20,000 feet caused a parallel increase in depression-like behavior," Kanekar says.

The correlation between altitude and high rates of depression and suicide is strikingly obvious in the Intermountain West region of the United States where elevations are considerably higher than in the rest of the country. In 2012, the eight states that comprise the Intermountain West-Utah, Colorado, Wyoming, Montana, Idaho, Nevada, Arizona and New Mexico-had suicide rates exceeding 18 per 100,000 people compared with the national average of 12.5 per 100,000, according to the American Foundation for Suicide Prevention. The high rates of self-inflicted death in the West have earned the region a gloomy moniker: the Suicide Belt.

Several studies, including work by Perry F. Renshaw, M.D., Ph.D., M.B.A., USTAR professor of psychiatry at the U of U and senior author on this latest study, suggest altitude is an independent risk factor for suicide, and further that depression rates also increase with altitude and may contribute to the increased suicide risk.



Because rats are not subject to the same psychological and societal pressures as people, the current study bolsters the argument that physiological changes triggered by hypobaric hypoxia (the low oxygen at high altitude) can contribute to depression. What these changes are, and whether they also occur in people, will be the subject of future studies.

"There are many potential risk factors that contribute to depression and suicide at altitude, and we are not discounting any of these other factors at all," says Renshaw. Several such factors that are prevalent in the Intermountain West include poverty, rural residence, low population density, gun ownership and psychiatric disorders such as bipolar disease. "But this new study shows that one factor inherent to living at altitude-hypobaric hypoxia-can cause depression. Hypobaric hypoxia thus clearly is linked to the high depression rates in regions of altitude, and this factor may need to be addressed."

According to Renshaw, a potential cause for depression at altitude might be found in low levels of serotonin, a neurotransmitter that is thought to contribute to feelings of well-being and happiness. Hypoxia impairs an enzyme involved in synthesis of serotonin, likely resulting in lower levels of serotonin that could lead to depression. In addition, Renshaw's group has shown that brain cellular metabolism can be damaged by hypoxia in rats as well as in humans.

This deficit in brain function may contribute to what Renshaw calls "The Utah Paradox". Despite having the highest use of antidepressants in the country, Utah also has the highest Depression Index, as defined by a National Mental Health Survey in 2007. Animal studies imply that SSRIs such as Prozac® may not work when brain serotonin levels are low. In current studies, Kanekar and Renshaw are therefore evaluating the effectiveness of currently available antidepressants in hypobaric hypoxia, with a major focus on SSRIs, the most commonly prescribed antidepressants in the United States. Future studies involve exploring



novel therapeutic options for hypoxia-related depression.

"The fact that both depression and suicide rates increase with altitude implies that current antidepressant treatments are not adequate for those suffering from depression at <u>altitude</u>, leading to high levels of unresolved <u>depression</u> that can contribute to higher levels of suicidal ideation and suicide attempts," says Kanekar.

Provided by University of Utah Health Sciences

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