Living High and Feeling Low: Altitude, Suicide, and Depression

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Learning objectives: After participating in this activity, learners should be better able to:
- Assess epidemiologic evidence that increased altitude of residence is linked to increased risk of depression and suicide
- Evaluate strategies to address hypoxia-related depression and suicidal ideation

Abstract: Suicide and major depressive disorder (MDD) are complex conditions that almost certainly arise from the influences of many interrelated factors. There are significant regional variations in the rates of MDD and suicide in the United States, suggesting that sociodemographic and environmental conditions contribute. Here, we review epidemiological evidence that increases in the altitude of residence are linked to the increased risk of depression and suicide. We consider the possibility that chronic hypobaric hypoxia (low blood oxygen related to low atmospheric pressure) contributes to suicide and depression, which is suggested by animal models, short-term studies in humans, and the effects of hypoxic medical conditions on suicide and depression. We argue that hypobaric hypoxia could promote suicide and depression by altering serotonin metabolism and brain bioenergetics; both of these pathways are implicated in depression, and both are affected by hypoxia. Finally, we briefly examine treatment strategies to address hypoxia-related depression and suicidal ideation that are suggested by these findings, including creatine monohydrate and the serotonin precursors tryptophan and 5-hydroxytryptophan.

Keywords: 5-HTP, altitude, creatine, depression, hypoxia, serotonin, suicide, tryptophan

Major depressive disorder (MDD) has a lifetime prevalence of over 16%[1] and is associated with significant personal and social costs, including lost work productivity,[2] disability,[3] diminished quality of life, increased mortality,[4] and increased rates of suicide attempts[5] and completed suicides.[6] Although MDD is often regarded as a single disorder, it may encompass a variety of different etiologies with overlapping symptoms and signs.[7] Regional rates of MDD and suicide vary substantially,[8] suggesting that large-scale environmental factors may contribute to the pathogenesis of MDD and suicide in some cases.[9,10] Here, we provide an integrative review of evidence that the altitude of a person's residence is one such factor. On the basis of these and other data, we explore the hypothesis that chronic hypobaric hypoxia (low body-oxygen levels related to low atmospheric pressure) mediates this connection. The association between altitude of residence and suicide risk has previously been reviewed by Young,[11] who built on Katz's proposal[12] that hypoxia could contribute to affective symptoms via alterations in serotonin metabolism. Here, we expand upon Young's review of the epidemiological evidence and examine in greater detail the biological pathways through which hypoxia could lead to psychiatric symptoms—in particular, by including a discussion of hypoxia's effects on brain bioenergetics. For this review, we identified empirical studies published in peer-reviewed journals in English using several search engines (PubMed, PsycINFO, and Google Scholar) encompassing publication dates up to 1 April 2016. The following initial search parameters were used: depression altitude OR major depressive disorder altitude OR suicide altitude OR depression elevation OR major depressive disorder elevation OR suicide elevation OR depression hypoxia OR suicide hypoxia. The initial search revealed 326 records, which were manually screened for relevance and duplication by the first author. Of the 326 initial records, 34 (10%) were selected for initial inclusion, with the remaining 292 (90%) excluded because of lack of relevance. Of the 34 records selected, 12 (3.6%) were determined to describe epidemiologic data pertaining to the associations between suicide or depression and altitude of residence and were included in Table 1. The

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Table 1

Large Epidemiological Studies of the Associations Between Altitude and Suicide or Depression

Study	Source	Years included	n	Factors controlled for	Association
Cheng et al. (2002)[13]	U.S. Census Data	Not reported	Not reported	Population per square mile, psychiatrists per 100,000 population, percentage population below poverty level	Suicide deaths per 100,000 persons in mountain states were significantly higher than low-altitude states (18.1 vs. 11.3; p = .01), general population (18.1 vs. 13.0; p = .01), high-poverty states (18.1 vs. 12.2; p = .01), low-psychiatrist states (18.1 vs. 12.3; p = .01), and geographically isolated states (18.1 vs. 13.2; p = .01)
Cheng et al. (2005)[14]	CDC Wonder Database	1979–98	Not reported	N/A	Capital county mean altitude correlated with overall suicide rate (r = 0.75; p < .0001)
Brenner et al. (2006)[15]	CDC Wonder Database	1979–98	Not reported	N/A	County mean altitude strongly correlated with suicide rate (r = 0.50; p < .001) but negatively correlated with overall death rate (r = −0.31; p < .001).
Haws et al. (2009)[16]	CDC Wonder Database	1990–94	Not reported	Age-adjusted rates	Age-adjusted suicide rates correlated with state peak altitude (r = 0.62; p < 3.9e-06) and state capital city elevations (r = .74; p < 3.4e-09)
DelMastro et al. (2011)[17]	NSDUH	2004–06	203,870 respondents in 345 regions	N/A	Substate region mean altitude correlated with annual incidence of severe psychological distress (r = 0.18; p = .0005) and percentage of people having at least one major depressive episode per year (r = 0.27; p < .0001)
Brenner et al. (2011)[18]	CDC Wonder Database	1979–98	596,704 suicide deaths; 42,868,100 total deaths	Age, gender, Caucasian race, median household income, population density of each county	Age-adjusted suicide rates strongly correlated with altitude (r = 0.50; p < .001) Both firearm-related (r = 0.40; p < .001) and non-firearm-related suicides (r = 0.31; p < .001) correlated with altitude
Betz et al. (2011)[19]	NVDRS	2006	8871 suicide deaths in 15 states	State total population	Suicide rate was 17.7/100,000 in high-altitude states, 11.9/100,000 in middle-altitude states, and only 5.7/100,000 in low-altitude states
Kim et al. (2011)[20]	CDC Wonder Database	1979–98	~597,027 suicide deaths in 2618 counties	Gun ownership, population density	Altitude more strongly correlated with age-adjusted suicide rate (r = 0.79; p < .001) than gun ownership (r = 0.49; p < .001) or population density (r = −0.33; df = 47; p = .010) on a state level Total age-adjusted suicide rate positively correlated with county average elevation (r = 0.51; p < .001), as did firearm-related (r = 0.41; p < .001) and non-firearm-related (r = 0.32; p < .001) suicide rates
Selek (2013)[21]	Turkish Statistical Institute	2007–08	Not reported	N/A	No correlation between province mean elevation and suicide rate in either 2007 (r = −0.09; p = .425) or 2008 (r = −0.10; p = .372)

Table 1
Continued

Study	Source	Years included	n	Factors controlled for	Association
Huber et al. (2014)[22]	NVDRS	2005–08	35,725 suicide deaths in 922 counties	N/A	Differences in county suicide rates in bipolar disorder were best modeled by gender ratio ($F = 18.57$; $p < .0001$), then by altitude ($F = 8.28$; $p = .004$), then by gun ownership ($F = 7.08$), population density ($F = 5.56$), ethnicity ($F = 2.31$), and race ($F = 1.10$).
Kim et al. (2014)[23]	National Statistical Office of South Korea	1997–2007	Not reported	Mean income of 231 administrative districts	Suicide rates were positively correlated with district mean altitude ($r = 0.46$; $p < .0001$) Suicide rates increased by 1.8% per meter increase in altitude before controlling for mean income and, with that controlled, by 1.5% per meter
Alameda-Palacios et al. (2015)[24]	Institute of Statistics and Cartography of Andalusia	2007–12	4412	N/A	Altitude more strongly correlated with age-adjusted suicide rate ($r = 0.47$; $p < .001$) than rate of antidepressant prescriptions ($r = 0.18$; $p = .008$), deprivation index ($r = 0.33$; $p < .001$), or population density ($r = -0.33$; $p < .001$)

CDC, Centers for Disease Control and Prevention; N/A, not applicable; NSDUH, National Survey on Drug Use and Health; NVDRS, National Violent Death Reporting System.

remaining 22 records (6.7%), which included animal studies, epidemiologic data of secondary relevance, and clinical studies, were integrated elsewhere into the review. Additional studies of relevance were identified through review of the works cited by studies identified in the initial search.

SUICIDE AND DEPRESSION AT ALTITUDE

Epidemiological data suggest that both suicide and depression are associated with altitude of residence (see Table 1), though the evidence linking suicide and altitude is more extensive. The majority of studies that point to this relationship have been conducted in the United States, though a few have examined other countries. Suicide rates in the United States vary widely. A Mental Health America Survey conducted in all 50 states from 2002 to 2006 found that the District of Columbia had the lowest age-adjusted annual rate, at 5.3/100,000, while Alaska had the highest, at 23.1/100,000.[25] Utah, which had the highest prevalence of depression, recorded an annual suicide rate of 17.1/100,000. Apart from Alaska and West Virginia, the states with the highest suicide rates were clustered in the intermountain states, namely Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming. More recently, the Substance Abuse and Mental Health Services Administration reported substantial regional variations in the annual (2014) prevalence of adults having serious thoughts of suicide, from a low of 3.3% (Connecticut) to a high of 4.9% (Utah).[26]

The intermountain states have higher mean altitudes than the rest of the country. The mean altitude of Utah, for instance, is 1860 meters, whereas the mean altitude of Connecticut is 150 meters.[27] Thus, altitude of residence could contribute to the excess risks of depression, suicide, and suicidal ideation in the intermountain region. Cheng and colleagues[13] first observed (2002) that mountain states have higher suicide rates, even after controlling for factors like poverty, access to psychiatric care, and population density. They later (2005) suggested that suicide rates in the 50 U.S. capital counties were strongly correlated with altitude ($r = 0.75$; $p < .0001$),[14] and a subsequent study (2006) found that suicide rates in 3060 U.S. counties correlated with altitude even after controlling for county median income and population density.[15] The quality of these early studies is difficult to evaluate, however, as they were reported only as poster presentations, and the number of suicide deaths analyzed was not noted in the published abstracts. Moreover, although the second study controlled for some demographic factors that could affect suicide rates, it failed to control for other important confounds, such as rates of firearm ownership and rates of substance abuse.

More recently, Haws and colleagues[16] evaluated the correlation between states' peak altitudes, capital city altitudes, and 1990–94 suicide rates reported by the Centers for Disease Control and Prevention (CDC). After adjusting for age, race, and sex, suicide rates remained highly correlated with both peak altitude ($r = 0.62$; $p < 3.9e\text{-}06$) and capital city altitude ($r = 0.74$; $p < 3.4e\text{-}09$). Again, however, this study did not

control for many possible confounds and used markers of altitude that may not reflect the variability in altitude across each state. Similarly, in a study of suicide rates and all-cause mortality in 2584 U.S. counties, using 1979–98 CDC mortality data and the altitude of the geographic center of each county, although all-cause mortality decreased with increasing altitude ($r = -0.31$; $p < .001$), suicide rates increased with altitude ($r = 0.50$; $p < .001$), even after controlling for age, gender, race, median household income, and population density.[18] The correlation with altitude held for both firearm-related ($r = 0.40$; $p < .001$) and non-firearm-related ($r = 0.31$; $p < .001$) suicides, suggesting regional variations in rates of firearm ownership do not explain differences in suicide risk. The authors also noted a threshold effect, with a dramatic increase in suicide rates occurring between 610 and 914 meters, suggesting that the relationship between altitude and suicide risk may be nonlinear. This study marked an advance over previous work, as it examined county-level altitude data rather than state-level data, reducing the altitude variability in each area. Still, county-level data do not completely eliminate altitude variability and therefore may overrepresent exposure to high altitudes in areas with dramatic changes in altitude and where populations are clustered in relatively low-lying areas.

Further effort to control for confounding factors and better account for local variations in altitude was exhibited in a study published by Kim and colleagues.[20] The authors analyzed the same CDC data above for a larger collection of counties (3108) and examined the association between mean county altitude and suicide rates. They found that age-adjusted suicide rates correlated more strongly with county mean altitude ($r = 0.79$; $p < .001$) than with state-level rates of firearm ownership ($r = 0.49$; $p < .001$). As in the previous study, both firearm-related ($r = 0.40$; $p < .001$) and non-firearm-related ($r = 0.32$; $p < .001$) suicide rates correlated with altitude. They also compared the strength of correlation with suicide rates for altitude and other county-level demographic factors, including the following: numbers of child psychiatrists, psychiatrists, and health care workers; percentages of persons in poverty and of persons aged 25 or older with varying educational levels; ratio of male population, white male population, white female population, and divorced female population; unemployment rate for persons age 16 and older; per capita income; and population density. In their regression model, they found that only altitude, percentage of persons in poverty, per capita income, white female population ratio, and divorced female population ratio were significantly and positively correlated with suicide rates. The authors noted that they were nevertheless unable to control for other factors that could affect suicide rates, such as rates of substance abuse and cultural differences, and that they were also unable to take into account county-level variations in rates of firearm ownership.

Similarly, a study of 8871 suicide deaths recorded by the National Violent Death Reporting System in 2006 in 15 states divided them into low-altitude (83.4%), middle-altitude (11.8%), and high-altitude (4.8%) groups.[19] The suicide rates adjusted for population distribution (as most of the population lives near sea level), however, were 17.7/100,000 at high altitude, 11.9/100,000 at middle altitude, and only 5.7/100,000 at low altitude. High-altitude suicide victims differed from low- and middle-altitude victims with respect to race, depressed mood, suicide attempts, substance use disorders, violence, firearm-related suicide, employment, and several other variables, suggesting to the authors that these sociodemographic factors may have contributed to excess suicide risk in these states. Still, the study did not adjust for these variables in comparing suicide rates between regions, leaving open the possibility of a contribution from altitude. Finally, an analysis of 35,725 completed suicides from the National Violent Death Reporting System from 2005 to 2008, representing 922 U.S. counties, demonstrated that altitude of residence was a significant, independent predictor of suicide in bipolar disorder, and that individuals with bipolar disorder committed suicide at the highest mean altitude compared to persons with unipolar depression, schizophrenia, or anxiety disorders.[22]

Other countries have exhibited similar associations. Suicide rates in Andalusia, a mountainous region of Spain, are higher than the nation's average, and age-adjusted suicide rates in Andalusia from 2007 to 2011 were positively correlated ($r = 0.47$; $p < .001$) with the altitude of each health administration area, which was calculated as the average altitude of the population centers constituting it.[24] This correlation was stronger than that with the Deprivation Index, a measure of regional socioeconomic distress, though the study's authors still thought that poverty may be the primary cause of increased suicide rates in Andalusia (which is one of the poorest areas in Spain), and the study did not control for socioeconomic confounds like per capita income and unemployment rates.

In a small study in Saudi Arabia, the point prevalence of suicidal ideation among depressed patients admitted to a high altitude (~2400 m) psychiatric hospital was 11.6%, compared to only 2.1% among patients admitted to a nearby low-altitude (~sea level) hospital,[28] though this difference may have resulted from variations in admission criteria or related factors rather than altitude, and the study's approach precludes conclusions about variations in rates of suicidal ideation in the country's population as a whole. Most robustly, a large study of suicide rates in the 231 administrative districts in South Korea from 1997 to 2007 showed that suicide was strongly correlated with altitude ($r = 0.46$; $p < .0001$) even after adjusting for the mean income of each district, with suicide rates increasing 1.5% per meter increase in mean altitude.[23] These data expanded upon findings reported in the previously mentioned study by Kim and colleagues,[20] which also found that suicide rates in South Korea were correlated with average county altitude ($r = 0.39$; $p < .001$).

The increased risk of suicide associated with altitude of residence may be partially explained by increased rates of

depression, though in general the correlation between altitude and suicide is stronger than that between altitude and depression. In the United States, the prevalence of depression varies widely across regions. The Mental Health America survey mentioned above found that the annual prevalence of major depressive episodes varied from 7.3% (South Dakota) to 10.1% (Utah).[25] A more recent Substance Abuse and Mental Health Services Administration survey found that South Dakota again had the lowest annual prevalence of major depressive episodes, at 5.3%, while Maine had the highest at 8.2%, and Utah had 8.0%.[26] Although socioeconomic factors clearly contribute to such figures, altitude of residence is correlated with depression risk. The National Survey on Drug Use and Health for 2004–06 encompassed 203,870 responders in 345 regions and reported the incidence of serious psychological distress and the percentage of responders who had at least one major depressive episode in the previous year. Comparison with each region's mean altitude demonstrated a correlation with both the incidence of serious psychological distress ($r = 0.18$; $p = .0005$) and the percentage of people having at least one major depressive episode in any of the study years ($r = 0.27$; $p < .0001$).[17]

Altitude may also affect other psychiatric conditions, such as attention-deficit/hyperactivity disorder (ADHD) and substance use disorders. Analysis of the regional percentages of children diagnosed with ADHD from the 2007 National Survey of Children's Health and 2010 National Survey of Children with Special Health Care Needs showed that the prevalence of ADHD decreased with altitude.[29] Conversely, the percentage of people reporting cocaine use in the 1999–2001 National Survey on Drug Use and Health correlated with regional mean altitude ($r = 0.34$; $p < .0001$).[30] Likewise, methamphetamine use is strongly correlated with mean state altitude ($r = 0.66$; $p < .0001$) after adjusting for age, ethnicity, education, socioeconomic level, employment, rates of methamphetamine laboratory incidents (a proxy for regional methamphetamine production), and other demographic variables.[31] These data suggest that increased altitude of residence can have a broad spectrum of neuropsychiatric effects, which may independently contribute to higher rates of suicide at higher altitudes and may help to explain why altitude is more strongly associated with suicide than with depression.

Not all studies have supported the association between altitude and depression or suicide. In one study, suicide rates in Turkey in 2007–08 were not correlated with altitude across 81 provinces with altitudes from sea level to 1890 meters.[21] The study's authors noted, however, that since suicide rates in Turkey are low overall, at 3.97/100,000, the lack of correlation may have resulted from inadequate power. Likewise, in a cross-sectional study of 287 persons older than 60 recruited from the Ladakh region of India (altitude 3000–3800 meters) and from Qinghai Province of China (altitude 3700 meters), subjects were screened for depression using the Geriatric Depression Scale and clinical interviews.[32] Only 2% met *Diagnostic and Statistical Manual of Mental Disorders–IV* criteria for MDD, which the authors regarded as lower than anticipated if altitude affects mood. The study had several limitations, however: it involved a nonrandom sample that may have missed relevant cases, and encompassed only two months; the yearly prevalence of MDD may therefore have been underestimated. Moreover, the lack of association between altitude and depression in this population might be explained by genetic adaptation, as natives of Ladakh and other Himalayan areas have shown relative genetic and geographic stability over many generations,[33] and people from this region are enriched in single-nucleotide polymorphisms related to adaptation to altitude.[34]

It should also be noted that other factors associated with increasing altitude—apart from sociodemographic factors like poverty and firearm ownership—could affect suicide rates and account for the apparent link between altitude and suicide. Lithium is protective against suicide when used in clinical doses,[35] and higher lithium levels in groundwater correlate with lower regional suicide rates.[36–39] In Austria, altitude is positively correlated with suicide rates but also negatively correlated with lithium levels; thus lower lithium levels at altitude could account for higher suicide rates.[40] In 15 U.S. regions, however, since lithium levels increased with altitude, they could not explain observed associations between altitude and suicide.[38]

DEPRESSION, SUICIDE, AND HYPOXIA

One speculated link between altitude, suicide, and depression is relative hypobaric hypoxia (lower blood oxygen concentration due to lower inhaled oxygen).[11] The effective concentration of inspired oxygen is represented by its partial pressure (PIO2), which is calculated as $PIO2 = FIO2 \times (Pb - 6.3\ kPa)$, where FIO2 is the fraction of inspired oxygen, Pb is the barometric pressure, and 6.3 kPa is the partial pressure of water vapor at 37°C.[41] FIO2 is effectively constant at 20.9%, irrespective of altitude,[42] but barometric pressure decreases with altitude in a curvilinear fashion.[43] Accordingly, PIO2 decreases with altitude.[44] At sea level, PIO2 is approximately 19.6 kPa.[42] By contrast, Salt Lake City, Utah, has an average altitude of around 1370 meters[45] and an average PIO2 of approximately 16.6 kPa. The PIO2 level at a given altitude can also be affected slightly by changes in humidity and transient changes in barometric pressure, but these effects are generally negligible compared to the effect of altitude.

Reductions in PIO2 due to altitude cause almost immediate reductions in the arterial partial pressure of oxygen (PaO2), which, in turn, produce lower oxygen pressures throughout the body. These changes contribute to a variety of altitude-related symptoms such as fatigue, insomnia, and headaches, and even to life-threatening conditions such as high-altitude pulmonary edema and high-altitude cerebral edema.[46] The evidence also indicates that acute exposure to high altitude causes psychiatric symptoms. In Peru, electrical workers stationed at ~3000 meters exhibited significantly more symptoms of depression and anxiety than those

stationed at sea level,[47] with the odds ratio of significant depressive symptoms for those at high altitude compared to sea level being almost 4.[48] Similarly, clinicians stationed at the Pheriche Clinic in Nepal (~4240 meters) reported a series of six foreign trekkers with new-onset anxiety disorders. In each case, there was no previous psychiatric history, and the predominant symptoms were panic-like.[49] In the Everest COMEX-97 experiment, eight experienced mountaineers were confined to a hypobaric chamber for 55 days and exposed to gradual reductions in atmospheric pressure until reaching the equivalent of 9000 meters.[50] They exhibited reductions in cognitive performance both at simulated high altitude and for three days after recompression,[51] and experienced increases in anxiety (as measured by the State-Trait Anxiety Inventory), which correlated with both effective altitude (r = 0.86) and cerebral symptoms of altitude sickness.[52] Adverse effects on mood were also evident, as measured by the Profile of Mood States (POMS).[53] In another study, 60 active-duty U.S. marines were assessed before, during, and after participation in a 30-day altitude training exercise (2053 to 3600 meters).[54] Participants completed the POMS at 23 days prior to the exercise, on the first and last days of the exercise, and at 30 and 90 days post-exercise. At baseline, POMS total scores averaged 22.7, slightly less than the comparator group of male college students, and depression and anger subscales were 7.2 and 9.1, compared to 8.6 and 8.9 in the comparator group. Post-exercise, POMS total scores in the marines were 35.7, with depression scores at 10.4 and anger scores at 13.3, all substantially higher than baseline and also higher than for the comparator group.

Animal studies also imply that relatively short-term hypoxia is associated with depression. In rats, one week of simulated high altitude (equivalent to 3048 meters) produces increased immobility and decreased time to prolonged immobility in the forced swim test (FST), both of which are regarded as depression-like behavior.[55] This effect may be sex dependent: when male and female rats were housed at four different simulated altitudes (6096, 3048, and 1370 meters, plus sea level) only females exhibited increases in depression-like behavior.[56] One drawback of this research, however, is that the FST may not accurately represent depression-like behavior in the setting of simulated high altitude; the increased time spent immobile could simply reflect increased weakness and fatigue.

Another factor limiting the relevance of high-altitude exposures lasting days to months, to increased rates of depression and suicide in mountainous regions is that the latter trends presumably represent processes acting over years to decades, whereas many of the acute effects of high altitude are resolved by compensatory responses. Physiologic adaptations to altitude occur over multiple timescales, with changes in heart and respiratory rates happening within minutes, alterations in carbon dioxide–mediated ventilatory response occurring in days, increases in hemoglobin concentration and capillary density occurring in weeks to months, and increases in the hypoxic ventilatory response occurring over the course of years.[42] Still, long-term adaptations to altitude may be neither universal nor complete.[57] Indeed, even though compensatory responses tend to restore normal arterial oxygen concentrations in high-altitude subjects, they fail to restore normal partial PaO2. A comparison of arterial blood oxygen concentrations in healthy nonsmokers chronically residing at sea level and at 1400 meters demonstrated that the average PaO2, weighted for the age distribution of the samples, was 12.7 kPa at sea level and 9.9 kPa at 1400 meters.[58] Thus, increased altitude can contribute to reduced PaO2 and, because brain partial pressure of oxygen is limited by PaO2,[59] to reduced brain oxygen.

There is also a parallel association between depression, suicide, and chronic medical conditions that cause hypoxia.[12] Although chronic physical illnesses in general increase suicide risk,[60,61] conditions associated with hypoxia do so disproportionately. Patients with current asthma are at higher risk for suicidal ideation and suicide attempts than those with past asthma or no asthma, even after adjusting for confounds such as poverty,[62] and the rate of completed suicide for adolescents with asthma is over twice those for adolescents without asthma.[63] Chronic obstructive pulmonary disease (COPD) is also linked to increased odds of suicidal ideation and suicide attempts compared to nonhypoxic chronic medical conditions,[64,65] and the risk of depression in COPD is almost twice that in nonhypoxic illnesses.[66] Cigarette smoking, which causes hypoxia in the absence of pulmonary disease,[67] is also associated with increased risk for suicide and depression.[68] Current smokers have more than twice the risk of depression compared to former smokers or nonsmokers.[69] In adolescents, smokers' odds of developing depression were 1.7 times those for nonsmokers.[70] Current smoking in adults is linked to a dose-dependent increase in suicide rates,[71] and while long-term abstinence reduces this risk, relapse leads to a return to high risk.[72] To be sure, however, hypoxia due to COPD, smoking, or asthma may differ from hypobaric hypoxia in severity, duration, and the use of supplemental oxygen. Moreover, other factors, such as increased inflammation—rather than hypoxia itself—could mediate the increased psychiatric symptoms associated with these conditions.

POSSIBLE MECHANISMS

Two biological pathways are promising as links between hypobaric hypoxia and increased risks of depression and suicide (see Figure 1), though other, yet to be identified pathways could also be implicated. One promising possibility concerns changes in serotonergic signaling.[12] Reductions in serotonin levels and serotonin metabolite levels, as well as changes in specific serotonin receptors, have been found in the circulating platelets, cerebrospinal fluid (CSF), and postmortem brain tissues of suicide victims.[73] Alterations in serotonin signaling are clearly implicated in the pathogenesis of MDD.[7,74–76] It has also been shown in some studies that

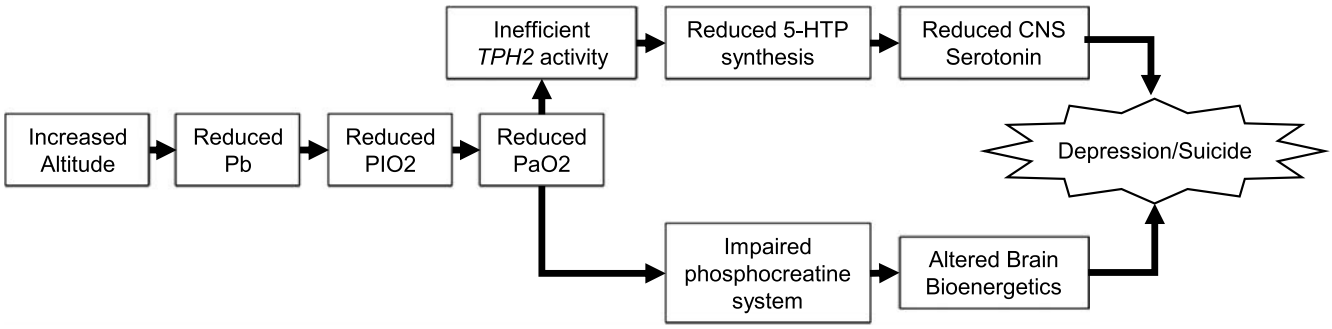

Figure 1. Postulated mechanisms through which altitude of residence could contribute to depression and suicide. CNS, central nervous system; PaO2, partial pressure of arterial oxygen; Pb, barometric pressure; PIO2, partial pressure of inspired oxygen; TPH2, tryptophan hydroxylase 2; 5-HTP, 5-hydroxytryptophan.

hypoxia can alter the synthesis and metabolism of neurotransmitters such as serotonin, dopamine, and norepinephrine in a brain region–dependent manner. In one study, simulated altitudes up to 7000 meters for 24 hours did not appear to affect norepinephrine turnover, and exhibited a biphasic relationship to dopamine turnover, with increased dopamine levels (45%–89%) at altitudes around 1800 meters and reduced dopamine levels (18%–58%) at 7000 meters.[77] In another study, simulated high altitudes of 5200 and 7000 meters were associated with up to a 30% reduction in serotonin turnover, though the lower altitude of 1800 meters was not.[78] In a third experiment, simulated high altitude for one week increased brain levels of dopamine (~100%) and norepinephrine (~60%) but decreased levels of serotonin (~27%), particularly in the frontal cortex.[79] In a study using very short (2 hour) exposures to hypoxia, there was no evidence of reduction in whole-brain neurotransmitter levels, including serotonin, but this finding may have been due to simultaneous impairment of both serotonin synthesis and catabolism, as monoamine oxidase is oxygen dependent. With inhibition of monoamine oxidase, reduced norepinephrine (11%), dopamine (17%), and serotonin levels (26%) were observed over the course of one hour of hypoxia.[80] Again, however, the relevance of these short-term experiments for population trends is tenuous, and to our knowledge no studies assay serotonin or other neurotransmitter levels for epidemiologically relevant periods in animal models, and none which compare blood, brain, or CSF serotonin levels in persons residing at high and low altitudes. Human data regarding the effects of hypoxia on serotonin and other monoamines are extremely limited. Cigarette smoking is known to produce chronic hypoxia, and postmortem brain levels of serotonin and 5-hydroxyindoleacetic acid (5-HIAA), which is the major metabolite of serotonin, are generally lower in smokers than in nonsmokers.[81] Similarly, in some clinical populations, smoking is associated with lower levels of serotonin as measured by fenfluramine challenge or CSF 5-HIAA.[83] Admittedly, however, smoking could alter serotonin levels via other mechanisms.[82] A study that compared the effect of prolonged (2–7 month) exposure to high altitude in soldiers who suffered pulmonary edema and those who did not found no difference in circulating serotonin levels, but the study did not have a sea-level control group.[84] We have been unable to identify studies that directly examined the effects of hypobaric hypoxia on serotonin levels in humans.

Hypobaric hypoxia could reduce serotonin synthesis by affecting the activity of tryptophan hydroxylase.[85] Serotonin synthesis begins with dietary tryptophan, a common amino acid. Tryptophan is converted to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase, and 5-HTP is converted to serotonin by aromatic L-amino acid decarboxylase.[86] Tryptophan hydroxylase 2 (TPH2), the primary isoform present in the central nervous system, mediates the rate-limiting step in central serotonin synthesis.[87,88] The activity of tryptophan hydroxylase is oxygen dependent, and in vivo the enzyme is partially unsaturated with respect to oxygen at physiologic concentrations of tryptophan.[89,90] In animal models, exposure to low atmospheric oxygen reduces tryptophan hydroxylase activity, whereas exposure to supplemental oxygen increases it.[91] In humans, serotonin synthesis is increased by brief (15 minute) exposure to supplemental oxygen, as measured by positron emission tomography.[92]

Relative serotonin depletion due to hypoxia could be associated with resistance to standard antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants, accounting for over 80% of the market in the United States[93] and 63% of market in Europe.[94] SSRIs prevent reuptake of serotonin and thereby increase its synaptic availability.[95] When serotonin production is inhibited, however, the efficacy of SSRIs can be impaired. Mice with low serotonin synthesis secondary to the C1473G *Tph2* polymorphism exhibit increased depression-like behavior,[96] and their responsiveness to citalopram and paroxetine in the forced swim test is reduced.[97] Similarly, humanized R439H *Tph2* knock-in mice, which exhibit significant reductions in serotonin synthesis, exhibit further reductions in tissue serotonin levels when exposed to fluoxetine, which is not observed in wild-type mice; this effect can be prevented by administration of 5-HTP.[98] Furthermore, these mice exhibit increased social-defeat stress and less improvement in social interaction in response to fluoxetine.[99]

Antidepressants with broader activities may treat depression related to serotonergic deficits more effectively than SSRIs, however, as rats exposed to simulated high altitude respond to desipramine, but not to fluoxetine, in the FST.[100] The clinical relevance of these findings should be interpreted with caution, however, because of variability in the relationships between mutations in serotonergic pathways, antidepressant response, and depression-like behaviors across inbred mouse strains.[101]

Still, in aggregate, these data suggest that factors contributing to serotonin depletion, including hypobaric hypoxia, could reduce antidepressant efficacy in MDD. Although the effects of hypobaric hypoxia on antidepressant response have not been studied in humans, other human populations with reduced serotonin levels exhibit reduced SSRI response. *TPH2* polymorphisms that could alter serotonin production have been associated with unipolar depression[102,103] and bipolar disorder,[104–106] and are thought to affect suicide risk in MDD.[107,108] They may also predict nonresponse to conventional antidepressants.[109,110] Conceivably, *TPH2* polymorphisms could augment the contribution of high altitude to MDD.

These observations suggest potential treatments for depression associated with hypoxia. It has been proposed that because the affinity of tryptophan hydroxylase for oxygen is dependent on tryptophan concentration, tryptophan supplementation could correct hypoxia-related deficits in serotonin synthesis.[11] Tryptophan has demonstrated antidepressant efficacy both as an adjunctive agent[111] and as monotherapy,[112] though its short half-life of roughly two hours[113] and its historical association with eosinophilia myalgia syndrome[114] both present some barriers to clinical use. Similarly, supplementation with 5-HTP, which bypasses the oxygen-dependent step in serotonin production, could correct alterations in serotonin metabolism associated with altitude. In the 1970s and 1980s, 5-HTP was explored as an antidepressant. Like tryptophan, it crosses the blood-brain barrier, elevates brain serotonin levels, and has antidepressant efficacy,[115,116] though it, too, has a short half-life and is also extensively converted to serotonin in the gut. For these reasons, its clinical use would require high doses, use of a sustained-release form,[117] or combination with a decarboxylase inhibitor such as carbidopa.[118]

Another potential link between altitude and depression is the effect of hypobaric hypoxia on brain bioenergetics. The creatine kinase reaction mediates the reversible transfer of a high-energy phosphate group from phosphocreatine (PCr) to adenosine diphosphate (ADP), resulting in the production of adenosine triphosphate (ATP) and creatine (Cr). This reaction is especially important for the rapid regeneration of ATP in metabolically active cells such as neurons and working muscle. Alterations in the efficiency of the creatine kinase reaction could, accordingly, correlate with neuronal dysfunction.[119] Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) demonstrates reduced total nucleotide triphosphate (β-NTP) concentrations and higher PCr concentrations in adults with depression compared to healthy volunteers,[120–122] suggesting that depression involves alterations in the creatine kinase pathway. Intriguingly, this pattern is more common in women than men,[123] which could help explain higher rates of depression observed in women. These alterations are also associated with an increased likelihood of treatment response to SSRIs and triiodothyronine, and administration of triiodothyronine is associated with reductions in brain PCr and increases in β-NTP.[120] Brain PCr levels are also disrupted in the frontal lobes of adolescents with bipolar depression.[124]

Proton MRS (^{1}H-MRS) studies provide similar results.[125,126] Patients with first-episode depression exhibit reduced n-acetylaspartate (NAA) to total creatine (PCr + Cr) ratios in several brain areas, including prefrontal white matter[127,128] and prefrontal cortex,[129] and exhibit progressive decreases in NAA/PCr+Cr ratios in pregenual anterior cingulate cortex with continued illness.[130] Similar abnormalities are also found in geriatric depression[131] and bipolar depression.[132] One published report of ^{1}H-MRS in adolescents with depression also shows alterations in brain metabolism.[133]

A limited body of evidence suggests that hypoxia promotes changes in energy metabolism in the brain and other metabolically active tissues in ways that mirror changes in depression. For instance, prolonged hypoxia (for days to weeks) leads to reductions in energy reserve in cardiac and skeletal muscle.[134] It has been demonstrated via ^{31}P-MRS that hypobaric hypoxia is associated with reductions in PCr/ATP ratios in cardiac muscle in an animal model.[135,136] Similarly, exposure for approximately two weeks to high altitude is associated with reductions in cardiac ATP/PCr ratios that are correlated with reductions in cardiac muscle volume.[137] Several weeks of hypoxia in a postnatal rat model lead to reductions in several metabolites in the brain, including PCr and NAA, and to an increased PCr/Cr ratio, suggesting inefficient brain energy consumption.[138] Similarly, hypobaric hypoxia alters mitochondrial dynamics in the hippocampi of rats[139] and is associated with neurodegeneration and apoptosis of hippocampal pyramidal cells.[140] To our knowledge, however, no animal studies address the bioenergetic effects of months to years of exposure to moderately high altitude, which is the timescale and environment most relevant to the epidemiological data reported. Still, because reductions in PaO2 at altitude are not corrected after physiologic adaptations, and because PaO2 governs the partial pressure of oxygen in tissue,[59] it has been hypothesized that subchronic (~30 days) exposure to high altitude leads to long-term and potentially permanent changes in mitochondrial density, morphology, and performance,[141] including reductions in creatine kinase levels.[142]

Human studies suggest that brief (~20 hours) exposure to normobaric hypoxia results in reductions in the cardiac PCr/ATP ratio, which is associated with impairments in diastolic function.[136] Chronic hypoxia related to COPD was associated with a reduced brain ratio of PCr to inorganic phosphate (Pi), and to an increased Pi/ATP ratio, in a small

study involving ten patients.[143] These results suggest a shift from oxidative phosphorylation to glycolysis. Subchronic hypobaric hypoxia also has effects on multiple aspects of cognition, which may indicate widespread bioenergetic deficits.[144] Evaluation of 40 age- and gender-matched healthy individuals residing at 1370 meters (Salt Lake City, UT) or at sea level (Belmont, MA, or Charleston, SC) showed that residents at 1370 meters have less reduced PCr+Cr in the anterior cingulate cortex compared to those at sea level.[145] Generally, then, hypoxia appears to affect energy metabolism in the brain and other metabolically demanding tissues in animals and humans, though the nature and extent of this change are difficult to extrapolate from studies published so far. Moreover, in many of the above studies, PCr levels appear to be reduced, whereas they are frequently noted to be increased in depression.

In many studies, antidepressants increase, and thereby normalize, brain NAA/PCr+Cr ratios, including in drug-naive patients with first-episode depression[146,147] and post-stroke depression.[148] Accordingly, Cr supplementation could ameliorate depression.[149,150] In rats, creatine monohydrate administration reduces immobility in the FST, though only in females.[151] Recently, however, it was shown that Cr supplementation combined with exercise reduced depressive symptoms in male mice exposed to four weeks of stress, as measured by the FST and tail suspension test. The authors also found that serotonin levels in the dorsal and median raphe nuclei, which had been reduced by stress, improved significantly with exposure to the combination of Cr and exercise.[152] Similarly, exposing mice to 20 mg/kg of corticosterone for 21 days produces a depression-like phenotype on the FST and tail suspension test, which is associated with reductions in hippocampal neurogenesis. These alterations are improved by exposure either to fluoxetine or to Cr at 10 mg/kg, suggesting that Cr exhibits a neuroprotective effect in this paradigm.[153]

In humans, the administration of oral Cr alters brain Cr, PCr, and β-NTP.[154] The antidepressant effects of Cr may also be more pronounced in women. In a pilot study, five adolescent females with SSRI-resistant MDD were treated with 4 g of Cr daily for eight weeks; at baseline, depression ratings were inversely related to brain β-NTP levels. Cr supplementation increased brain PCr levels.[155] In another study, adolescent females with SSRI-resistant depression treated with 2, 4, or 10 g of Cr daily for 8 weeks exhibited increases in brain PCr concentrations correlated with improvements in mood.[156] Notably, however, the direction of change of PCr concentrations in this study was discordant with that observed in depressed patients responding to triiodothyronine.[120] Still, clinical evidence for the efficacy of Cr is growing. In a large, placebo-controlled trial, Cr augmentation of escitalopram was related to significant improvements in depression scores compared to placebo in treatment-naive adult women with MDD.[157] In this study, Cr response was associated with normalization of the brain's rich club hub network connections and increases in prefrontal NAA concentrations.[158] Reductions in brain PCr levels are also more pronounced in female methamphetamine users, who are more likely to exhibit depression than male counterparts.[159] Supplementation with Cr, even in the absence of an antidepressant, improves brain PCr levels and depression scores in women with depression and methamphetamine dependence.[160] To our knowledge, only one study of Cr augmentation in depression has found no effect, but it was small (n = 14) and recruited subjects who may have been less ill, as they were required to have failed to respond to only three weeks of antidepressant treatment.[161]

CONCLUSION

Growing evidence, based on large data sets, suggests that altitude of residence is specifically associated with increased risks of suicide and depression, which may help explain the disproportionately high rates of suicide observed in mountainous regions. Relative hypobaric hypoxia due to altitude of residence may mediate this connection, as hypoxia affects both serotonin metabolism and the efficiency of brain bioenergetics, each of which may contribute to depression.

These observations suggest several avenues for future research. There is clearly a need to evaluate the effects of prolonged exposure to altitude on serotonin metabolism and brain bioenergetics in both humans and in animal models. With respect to clinical studies, evidence for the antidepressant efficacy of Cr, coupled with the effects of altitude on bioenergetic pathways incorporating Cr, imply that Cr may be effective for treating depression in persons residing at higher altitudes. This may be particularly true in women with depression, given the evidence of preferential response to Cr in women. Similarly, given the effects of altitude on serotonin metabolism, the evidence that depression due to hypoxia is resistant to SSRIs, and the possibility of ameliorating deficits in serotonin production with tryptophan or 5-HTP, these supplements should also be investigated for altitude-associated depression. Because Cr and serotonin precursors affect different pathways, it may also be possible to use them in combination to produce synergistic effects. Future research could use these compounds as augmenting agents for SSRIs or as stand-alone agents. They also have promise for treating depression in populations suffering chronic hypoxic medical conditions such as asthma, COPD, and obstructive sleep apnea. Clinical trials in these areas could be coupled with neuroimaging techniques to assess brain connectivity and metabolism, and could also incorporate genetic markers (such as polymorphisms in *TPH2*, serotonin receptors, or mitochondrial enzymes) to determine whether genetic differences contribute to altitude-related depression and treatment response.

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