Elevated incidence of suicide in people living at altitude, smokers and patients with chronic obstructive pulmonary disease and asthma: possible role of hypoxia causing decreased serotonin synthesis

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Recent research indicates that suicide rates are elevated in those living at higher altitudes in both the United States and South Korea. A possible mechanism that was proposed is metabolic stress associated with hypoxia. This commentary discusses these results, and also the association between elevated suicide rates and other conditions associated with hypoxia (smoking, chronic obstructive pulmonary disease and asthma). Tryptophan hydroxylase may not normally be saturated with oxygen, so mild hypoxia would decrease serotonin synthesis. Low brain serotonin is known to be associated with suicide. Thus, the commentary proposes and discusses the hypothesis that decreased brain serotonin synthesis associated with hypoxia is a mechanism that may contribute to suicide in conditions causing hypoxia. Finally the commentary proposes various studies that could test aspects of this hypothesis.

Introduction

Thirty years ago Katz[1] discussed the possible clinical implications of the fact that tryptophan hydroxylase and tyrosine hydroxylase are not normally fully saturated with one of their substrates, oxygen. He suggested that the decrease in biogenic amine synthesis resulting from mild hypoxia might lead to decreased appetite, libido and motivation; attention deficits; lassitude; and dysregulation of sleep and wakefulness. This idea never became popular. However, the purpose of this commentary is to update the idea that decreased biogenic amine synthesis due to mild hypoxia might have significance in psychiatry. I propose that low brain serotonin synthesis due to hypoxia may be a factor in the high suicide rates seen in people living at altitude, smokers and patients with chronic obstructive pulmonary disease (COPD) and asthma. After presenting the background information, I discuss the hypothesis and propose research studies that could provide information about its validity.

Background

The role of oxygen in the regulation of biogenic amine synthesis

During mild hypoxia, glucose metabolism remains unaffected.[2] Although most of the oxygen in the brain is used for the production of energy, numerous enzymes in the brain require oxygen, many of which are affected by mild hypoxia.[3] Among these is tryptophan hydroxylase, which is the rate-limiting enzymes in the synthesis of serotonin. In addition to tryptophan it uses oxygen molecules as a substrate to provide the oxygen atom in the hydroxyl group in serotonin. Katz[4] determined the Km for oxygen for the enzyme in rat brain synaptosomes to ensure that the medium surrounding the enzymes was as close to physiologic as possible. The Km varied with the concentration of tryptophan. At the concentration of tryptophan in cerebrospinal fluid (CSF; 10 µM) the Km for oxygen was 3–4 mm Hg, but with a lower concentration of tryptophan (2 µM) it increased to 8–10 mm Hg. Katz[4] estimated that at the oxygen concentration found in the rat brain,[5] tryptophan hydroxylase was

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about 75% saturated with oxygen at the physiologic tryptophan concentration, but would be less at lower tryptophan levels.

Only 1 study has looked at the effect of altered oxygen on tryptophan hydroxylase activity in humans.[6] Serotonin synthesis in the brain was measured using positron emission tomography and α-[^{11}C]methyl-L-tryptophan as a tracer.[7] Serotonin synthesis was, on average, 50% higher when the participants were breathing 60% oxygen than when they were breathing 15% oxygen, indicating that tryptophan hydroxylase is not normally fully saturated with oxygen in the human brain.

Serotonin and suicide

More than 35 years ago Åsberg and colleagues[8] reported that low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the CSF is a predictor of suicide. As discussed in reviews,[9,10] this finding has been replicated many times, and although CSF results are not always consistent, other serotonin-related measures suggest that serotonin synthesis or function is low in those with serious suicidal ideation, suicide attempts or later suicide. The association of low serotonin with lowered mood, impulsivity and aggression may contribute to its association with suicide.

Altitude and suicide

Haws and colleagues[11] investigated the possible role of altitude in the greater suicide rate seen in the western United States. They found highly significant correlations between suicide rates and both the highest elevation in each state and the elevation of the state capital. Kim and colleagues[12] followed up this observation with a more detailed study that used a greater spatial resolution (3108 counties) and looked at a number of other variables. They performed a multiple regression analysis using elevation and 2 other factors known to be associated with suicide (population density and gun ownership) as independent factors. Elevation was significantly related to suicide, whereas population density was not significant and gun ownership just reached significance. County altitude had one of the highest β values among the variables included in the analysis. They also found a strong association between suicide rates and county altitude in South Korea, but no other possible variables were studied. Taken together, all these results provide good preliminary evidence that an association might exist between altitude and suicide. Kim and colleagues[12] suggested that the mediating mechanism might be metabolic stress associated with mild hypoxia.

While there are short-term adaptations to mild hypoxia, such as an increase in red blood cells, and developmental changes, such as greater lung volume, as discussed later in this commentary, there is selection for various polymorphisms in populations living at altitude for many generations. This suggests that the short-term and developmental adaptations to altitude may diminish hypoxia, but do not prevent it.

Smoking and suicide

Aubin and colleagues[13] pointed out that mild hypoxia might also contribute to the association between smoking and suicide. This section presents data relevant to smoking and suicide, and subsequent sections present results relating suicide with 2 other conditions that can result in hypoxia, COPD and asthma.

A recent meta-analysis concluded that there was a significant association between smoking and completed suicide.[14] Compared with those who never smoked, the relative risk for suicide in current smokers was 1.81 and for former smokers was 1.28. In a review, Hughes[15] discussed the possibility that smoking is a causal factor in suicide or a non-causal marker as well as the hypothesis of self-medication for suicide risk and reported that there was no conclusive evidence for any of these hypotheses. However, there is some, although not conclusive, evidence for the causal hypothesis. In a longitudinal study,[16] current and past smoking predicted increased suicidal ideation and attempts independent of demographic or psychiatric factors and of previous suicidal ideation and attempts. Long-term smoking abstinence decreased risk, but resuming smoking reincreased the risk. Previous suicidal ideation and attempts did not increase the risk of future smoking. In another study, taking into account familial risk factors (e.g., parental suicidal behaviour, nicotine dependence and conduct disorder, offspring conduct disorder, depression, alcohol or illicit drug abuse or dependence) did not alter the association between smoking and suicidal behaviour in the offspring.[17] Finally, in an ecological study the reduction of the suicide rate in Hungary from 1985 to 2008 was associated independently with increased antidepressant use and decreased tobacco consumption.[18]

Li and colleagues[14] suggested that a causal link between smoking and suicide might be related to medical conditions caused by smoking (e.g., cancer, cardiovascular disease, COPD), activation of the hypothalamic–pituitary–adrenal axis by nicotine and lowered brain serotonin. These 3 mechanisms are not mutually exclusive, and the focus of this commentary is that low brain serotonin due to hypoxia may be a contributing factor to suicidality.

In a postmortem study, Benwell and colleagues[19] found lower levels of serotonin and 5-HIAA in the brains of people who had smoked between 7 and 20 cigarettes a day relative to nonsmokers. The causes of death for both groups were ischemic heart disease, bronchopneumonia or cancer. If smokers have lower brain serotonin levels, then a pertinent question is whether behaviours, other than suicide, linked to low serotonin are altered in smokers. Dakwar and colleagues[20] reported that a lifetime history of smoking was associated with increased aggression and impulsivity in both healthy volunteers and those with personality disorders. Both aggression and impulsivity are linked to low serotonin.[21]

Smoking could lower serotonin by 2 mechanisms. First, while short-term nicotine administration in rats increases brain serotonin, longer-term nicotine lowers serotonin.[22] Second, hypoxia due to smoking may lower serotonin synthesis in the brain. Smoking can cause hypoxia in the brain in 2 ways. First, carbon monoxide in cigarette smoke forms carboxyhemoglobin, which reduces the oxygen-carrying capacity of the blood. Second, smoking can cause cardiovascular and various chronic lung diseases that can lead to hypoxia.[23]

COPD and suicide

Recently, Goodwin[24] studied the association between COPD and both suicidal ideation and suicide attempts. She found that COPD was associated with increased odds of suicidal ideation, but that this association was no longer significant after adjusting for nicotine dependence. However, suicide attempts were increased in individuals with COPD and remained so after adjustment for demographic factors, depression, panic disorder, drug and alcohol dependence and nicotine dependence. Smoking is only 1 cause of COPD, so the high rate of suicide attempts may not be due only to smoking.

Asthma and suicide

In a recent review Goodwin[25] summarized a number of studies suggesting an association between asthma and suicidal ideation, suicide attempts and death by suicide. She pointed out that studies looking at common chronic medical conditions found that the association between suicide attempts and asthma and other respiratory diseases was stronger than the association between suicide and most other medical conditions. She suggested that there is not currently enough evidence to indicate causality, especially in view of the lack of a plausible mechanism. She also stated that potential confounds, including asthma medications, have not been ruled out. A recent study that was not included in the review looked at a number of possible confounds.[26] After adjustments for demographics, poverty, smoking, allergies and mood disorders, current asthma was associated significantly with both suicidal ideation and suicide attempts. However, neither suicidal ideation nor suicide attempts were associated with former asthma.

Discussion

The essential components for the argument supporting the hypothesis are, first, that different conditions that lead to hypoxia all seem to have elevated suicidality and, second, that hypoxia should lead to low serotonin, which is associated with suicidality. The purpose of this commentary is not to suggest that lowered brain serotonin due to hypoxia is a major factor in suicide, but that it may be a contributing factor in some circumstances. Given other factors, some of which may be predisposing factors to suicide in general and some of which may be related to each of the conditions discussed here, the effect of hypoxia on serotonin, even if a small contributor to overall risk, may be enough to push some individuals over a threshold that leads to suicide.

Betz and colleagues[27] examined 8871 suicides that occurred at different altitudes. Suicide completers at high and low altitudes differed in multiple demographic and psychiatric variables. For example, those at high altitude were more likely than those at low altitude to have had a crisis in the 2 weeks before the suicide, physical problems and health problems. While it is certainly plausible that such factors should have contributed to suicide, this is not incompatible with the hypothesis proposed here. Low serotonin due to hypoxia could act in conjunction with other factors, including psychosocial stressors, to precipitate lower mood and suicide.

A number of studies have looked at suicide in relation to physical diseases and have found elevated rates. An obvious explanation is the burden of those diseases. If hypoxia is a contributing factor, one might expect that suicide rates would be higher among people with COPD and asthma than among patients with some other burdensome physical disorders without hypoxia. While results tend to vary from study to study, there is some support for this idea. For example, Druss and Pincus[28] found a significant increase in suicidal ideation in patients with asthma and chronic bronchitis, but not in those with hypertension, arthritis, thyroid disease, diabetes or cancer, when adjusting for major depression, depressive symptoms, heavy alcohol use and demographic factors. With similar adjustments, suicide attempts were increased significantly only in those with asthma (odds ratio [OR] 4.3), chronic bronchitis (OR 2.6) and cancer (OR 4.5). Goodwin and colleagues[29] adjusted for demographic factors and a number of Axis I disorders and found an association between suicide attempts and lung disease (OR 1.8, 95% confidence interval [CI] 1.1–2.7), ulcer (OR 2.1, 95% CI 1.3–2.4) and AIDS (OR 44.1, 95% CI 10.5–185.6), but not arthritis, hypertension, diabetes, heart attack, kidney problems, stroke, autoimmune disease or stomach problems. Recently Webb and colleagues[30] found that coronary heart disease, stroke, COPD and osteoporosis were linked to suicide, whereas cancer, hypertension, diabetes, asthma, osteoarthritis, back pain and epilepsy were not. The association with suicide was explained by clinical depression with all conditions except osteoporosis. This study differs from a number of others, including those discussed previously, in finding no association between asthma and suicide and in finding that the association between COPD and suicide was explained by depression. However, given that low serotonin might contribute to depression as well as suicide, the fact that the association between COPD and suicide might or might not be mediated by depression is not relevant to the hypothesis. Overall, these studies provide modest support for the idea that impairment of lung function may predispose patients to suicide more than some other physical diseases.

Suggestions for future research

A hypothesis is useful only if it can be tested. Proving a causal association for factors, other than genetics, associated with suicide can be difficult, and future research is not likely to provide any direct proof of the link between hypoxia, low serotonin and suicide. Nonetheless, the theory leads to various testable ideas that could strengthen support for the hypothesis.

Humans can adapt to different environmental situations through a number of mechanisms. The Sherpas of Tibet have lived at altitude for 500 years and during this time have become enriched in single nucleotide polymorphisms (SNPs) that contribute to their adaptation to altitude.[31,32] These SNPs exist at a lower frequency in populations living at low altitude. Therefore, a certain frequency of SNPs that are adaptive to high altitude would be expected in those who have moved recently and are living at altitude. If living at altitude does

promote suicide through hypoxia rather than because of confounds, then the frequency of adaptive SNPs in those who commit suicide while living at altitude should be lower than the frequency of adaptive SNPs in those who do not commit suicide while living at altitude. Similarly, the frequency of the SNPs that are adaptive at high altitude may be lower in smokers and in patients with COPD and asthma who commit suicide than in those who do not commit suicide.

Adaptation to environmental factors can also occur during development. For example, people born at high altitudes have a greater lung volume that those born at lower elevations.[33] Therefore, if hypoxia does contribute to the higher suicide rate at altitude, the ratio of those who were born at a lower altitude and moved to a higher elevation to those who were born at a high altitude and remained there should be higher among suicide completers than among those in the same community who do not commit suicide.

If hypoxia does lower brain serotonin, then those living at altitude should, on average, have lower brain serotonin synthesis than those living at lower elevations. This could be studied by measuring 5-HIAA in CSF, taken from patients for diagnostic purposes, if the patient did not have a disorder thought to influence serotonin. Mean levels of 5-HIAA taken from patients at altitude should be lower than mean levels taken from patients close to sea level.

Possible clinical implications

In rat synaptosomes, the Km of tryptophan hydroxylase for oxygen is higher at lower concentrations of tryptophan.[4] As a result, at lower tryptophan levels the affinity of tryptophan hydroxylase for oxygen will be less than at higher tryptophan levels. If the regulation of tryptophan hydroxylase in humans is similar, this has implications for depressed patients with mild hypoxia. Depressed patients tend to have lower tryptophan levels than controls due to increased metabolism of tryptophan.[34] Therefore, in depressed patients with mild hypoxia, low tryptophan would exacerbate the effects of low oxygen on serotonin synthesis, thereby increasing any possible effect of low serotonin as a risk factor for suicide. Giving supplemental tryptophan would increase the saturation of tryptophan hydroxylase with tryptophan and therefore also with oxygen, thereby helping to normalize low serotonin levels. However, testing the use of tryptophan in this way would be premature unless or until there is more evidence to support the idea that hypoxia lowers serotonin synthesis, thereby increasing suicide.

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