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Research Article

How Chronic Fear Results In Hypoxia in Tissues and Cancer in Humans through Bohr Effect

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Abstract

Fear is a number of chain reactions in the brain that occurs when one encounters a potentially harmful stimulus. The amygdala is the part of the brain that receives information from many parts of the brain and interprets this information to generate the emotion of fear. When the amygdala generates a fear emotion, it transmits impulses to the hypothalamus. The hypothalamus then sends impulses to many numbers of different parts of the body to trigger a fight-or-flight response. Fear hormones are secreted by the adrenal gland. The effect of adrenaline (epinephrine) is increasing heart rate, hypocapnia and declines blood flow to the brain. The effect of cortisol is increasing blood glucose levels by converting stored glycogen and fats into blood sugar. It also suppresses the immune system and causes inflammation. The prime cause of cancer is increasing the amounts of ROS in healthy cells. The aim of this review is to show the effect of chronic fear on the cause of cancer in humans by reviewing related clinical studies and biochemistry of fear and cancer. The role of fear, adrenaline and cortisol in causing the hypoxia in tissues is mentioned in this article.

Keywords: Fear, Epinephrine, Cortisol, Cancer, Inflammation, Hypocapnia, Hypoxia

Introduction

Fear

Fear is a feeling triggered by perceived danger or threat that happens in certain types of organisms, which causes a change in metabolic and organ functions and finally a change in behaviors, such as fleeing, hiding, or freezing from perceived traumatic events. Fear in human beings may happen in response to a specific stimulus occurring in the present, or in anticipation or expectation of a future threat perceived as a risk to body or life. [1] The fear response arises from the perception of danger, leading to confrontation with, escape from or avoiding the threat which also known as the fight-or-flight response, that in extreme cases of horror and terror, can be a freeze response or paralysis. In humans and animals, fear is modulated by the process of cognition and learning. Thus fear is judged as rational or appropriate and irrational or inappropriate. An irrational fear is called phobia. [2] Psychologists such as John B. Watson, Robert Plutchik, and Paul Ekman have suggested that there is only a small set of basic or innate emotions and that fear is one of them. This hypothesized that set includes such emotions as acute stress reaction, anger, angst, anxiety, fright, horror, joy, panic and sadness. Fear is closely related to, but should be distinguished from anxiety, which occurs as the result of threats that are perceived to be uncontrollable or unavoidable. The fear response serves survival by generating appropriate behavioral responses, so it has been preserved throughout evolution. [3]

Cancer

The most important difference between normal and cancer cells is how they respire. Normal cells use the sophisticated process of respiration to efficiently turn any kind of nutrient which is fat, carbohydrate or protein into the high amounts of energy in the form of ATP. This process needs oxygen and breaks food down completely into harmless carbon dioxide and water. Cancer cells use a primitive process of fermentation to inefficiently turn either glucose from carbohydrates or the amino acid glutamine from protein into small amounts of energy in the form of ATP. This process does not require oxygen, and only partially breaks down food molecules into lactic acid and ammonia, which are toxic waste products. Nearly all studies from 1934 to 2016, mention that in all cancer cells there is some mitochondrial damages and abnormal deformations mostly in mitochondrial cristae. The prime cause of cancer is mitochondrial damage, which is caused by increasing the amount of ROS and inflammation inside or around eukaryotic cells. [4]

Bohr Effect

The Bohr Effect is a physiological phenomenon which had been first described in 1904 by the Danish physiologist Christian Bohr, stating that hemoglobin's oxygen binding affinity is inversely related both to acidity and to the concentration of carbon dioxide (CO_2). Because carbon dioxide reacts with water to form carbonic acid, an increase in CO_2 results in a decline in the blood pH, resulting in hemoglobin proteins releasing their load of oxygen. Conversely, a decrease in carbon dioxide (CO_2) provokes an increase in pH, which results in hemoglobin picking up more oxygen. The Bohr effect increases the efficiency of oxygen transportation throughout the blood. After hemoglobin binds to oxygen in the lungs due to the high oxygen concentrations, the Bohr effect facilitates its release in the tissues, particularly those tissues in the most need of oxygen.

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Materials and methods

The brain structures that are the center of most neurobiological events associated with fear are the two amygdalae, located behind the pituitary gland. Each amygdala is part of a circuitry of fear learning [5]. They are essential for proper adaptation to stress and specific modulation of emotional learning memory. In the presence of a threatening stimulus, the amygdalae generate the secretion of hormones that influence fear and aggression [6]. Once a response to the stimulus in the form of fear or aggression commences, the amygdalae may elicit the release of hormones into the body to put the person into a state of alertness, in which they are ready to move, run, fight, etc. This defensive response is generally referred to in physiology as the fight-or-flight response regulated by the hypothalamus, part of the limbic system [7]. Once the person is in safe mode, meaning that there are no longer any potential threats surrounding them, the amygdalae will send this information to the medial prefrontal cortex (mPFC) where it is stored for similar future situations, which is known as memory consolidation [8].

Some of the hormones involved during the state of fight-or-flight include epinephrine, which regulates heart rate and metabolism as well as dilating blood vessels and air passages, norepinephrine increasing heart rate, blood flow to skeletal muscles and the release of glucose from energy stores, and cortisol which increases blood sugar, increases circulating neutrophilic leukocytes, calcium amongst other things [9,10].

After a situation which incites fear occurs, the amygdalae and hippocampus record the event through synaptic plasticity [11]. The stimulation to the hippocampus will cause the individual to remember many details surrounding the situation [12]. Plasticity and memory formation in the amygdala are generated by activation of the neurons in the region. Experimental data supports the notion that synaptic plasticity of the neurons leading to the lateral amygdalae occurs with fear conditioning [13]. In some cases, this forms permanent fear responses such as posttraumatic stress disorder (PTSD) or a phobia [14]. MRI and fMRI scans have shown that the amygdalae in individuals diagnosed with such disorders including bipolar or panic disorder are larger and wired for a higher level of fear [15].

Pathogens can suppress amygdala activity. Rats infected with the toxoplasmosis parasite become less fearful of cats, sometimes even seeking out their urine-marked areas. This behavior often leads to them being eaten by cats. The parasite then reproduces within the body of the cat. There is evidence that the parasite concentrates itself in the amygdala of infected rats [16]. In a separate experiment, rats with lesions in the amygdala did not express fear or anxiety towards unwanted stimuli. These rats pulled on levers supplying food that sometimes sent out electrical shocks. While they learned to avoid pressing on them, they did not distance themselves from these shock-inducing levers [17].

Several brain structures other than the amygdalae have also been seen to be activated when individuals are presented with fearful vs. neutral faces, namely the occipitocerebellar regions including the fusiform gyrus and the inferior parietal / superior temporal gyri. Interestingly, fearful eyes, brows and mouth seem to separately reproduce these brain responses. Scientists from Zurich studies show that the hormone oxytocin related to stress and sex reduces activity in one's brain fear center [18-21].

As shown in (Figure 1), fear increases the secretion of the hormone adrenaline and this hormone causes the incline in cortisol levels in body.

Fear and Inflammation

Michopoulos V, *et al.* stated that the study of inflammation in fear- and anxiety-based disorders has gained interest as growing literature indicates that pro-inflammatory markers can directly modulate affective behavior. Heightened concentrations of inflammatory signals, including cytokines and C-reactive protein, have been discussed in post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder (PD) and phobias which are agoraphobia, social phobia, etc. However, not all reports show a positive association between inflammation and fear- and anxiety-based symptoms, suggesting that other factors are important in future assessments of inflammation's role in the maintenance of these disorders that are sex, co-morbid conditions, types of trauma exposure, and behavioral sources of inflammation. The most parsimonious explanation of increased inflammation in PTSD, GAD, PD, and phobias is via the activation of the stress response and central and peripheral immune cells to release cytokines. Dysregulation of the stress axis in the face of increased sympathetic tone and decreased parasympathetic activity characteristic of anxiety disorders could further augment inflammation and contribute to increased symptoms by having direct effects on brain regions critical for the regulation of fear and anxiety such as the prefrontal cortex, insula, amygdala, and hippocampus. Taken together, the available data suggest that targeting inflammation may serve as a potential therapeutic target for treating these fear- and anxiety-based disorders in the future. However, the field must continue to characterize the specific role pro-inflammatory signaling in the maintenance of these unique psychiatric conditions.

Melamed S, *et al.* concluded that the stress caused by chronic fear of terror may be associated with low-grade inflammation. This hypothesis was examined in employed men and women with the presence of low-grade inflammation measured by high sensitivity C-reactive protein (CRP). Apparently healthy employed adults (N = 1153) undergoing periodic health check-ups in a tertiary hospital in Israel completed a questionnaire. Fear of terror (scored 1-5) was assessed by three items measuring the extent to which respondents have deep concern for personal safety, elevated tension in crowded places, and fear of terror strikes causing harm to one's self or one's family members.

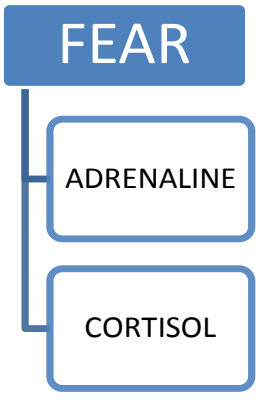

Figure 1. Fear results in the secretion of adrenaline.

The main outcome measure was the presence or absence of an elevated CRP level (> 3.0 mg/L). Women scored significantly higher on fear of terror compared with men (M = 2.16 vs. M = 1.68, respectively; p < 0.0001). Most of the study participants who scored high (4 or 5) on fear of terror, reported having experienced this feeling for 1 year or more. In women only, there was a positive association between fear of terror and risk of elevated CRP level (adjusted OR = 1.7, 95% CI 1.2-2.4) in a multivariate model adjusting for generalized anxiety, depressive symptoms, and potentially confounding demographic and biomedical variables. Chronic fear of terror in women, but not in men, is associated with elevated CRP levels, which suggests the presence of low-grade inflammation and a potential risk of cardiovascular disease.

In conclusion, fear and anxiety increase the inflammation and suppress the immune system in human body. Secretion of cortisol causes the decline in immune system response throughout the body.

Fear, Hypocapnia, Blood Glucose and Hypoxia

Chronic fear causes the secretion of cortisol in the body which increases the blood glucose levels. The research studies below show that high blood glucose is linked with the hypoxia in tissues through the Bohr Effect. Adrenaline hormone causes hypocapnia and decreases the blood flow to the brain. Therefore; hypoxia in tissues specifically in the brain is the result of the chronic fear.

Study done in 2010 by Heinis and Simon: When cultured in collagen, embryonic pancreatic cells were hypoxic and expressed HIF1alpha and rare beta-cells differentiated. In pancreata cultured on filter (normoxia), HIF1alpha expression decreased and numerous beta-cells developed. During pancreas development, HIF1alpha levels were elevated at early stages and decreased with time. To determine the effect of pO2 on beta-cell differentiation, pancreata were cultured in collagen at increasing concentrations of O2. Such conditions repressed HIF1alpha expression, fostered development of Ngn3-positive endocrine progenitors, and induced beta-cell differentiation by O2 in a dose-dependent manner. By contrast, forced expression of HIF1alpha in normoxia using DMOG repressed Ngn3 expression and blocked beta-cell development. Finally, hypoxia requires hairy and enhancer of split (HES)1 expression to repress beta-cell differentiation. These data demonstrate that beta-cell differentiation is controlled by pO2 through HIF1alpha. Modifying pO2 should now be tested in protocols aiming to differentiate beta-cells from embryonic stem cells [22].

One study by Cheng, *et al.* [23] demonstrated that Hypoxia-inducible factor-1alpha (HIF-1alpha) is a transcription factor that regulates cellular stress responses. While the levels of HIF-1alpha protein are tightly regulated, recent studies suggest that it can be active under normoxic conditions. We hypothesized that HIF-1alpha is required for normal beta cell function and reserve and that dysregulation may contribute to the pathogenesis of type 2 diabetes (T2D). Increasing HIF-1alpha levels markedly increased expression of ARNT and other genes in human T2D islets and improved their function [23].

Regazzetti, *et al.* [24] showed that in both human and murine adipocytes, hypoxia inhibits insulin signaling as revealed by a decrease in the phosphorylation of insulin receptor. In 3T3-L1 adipocytes, this inhibition of insulin receptor phosphorylation is followed by a decrease in the phosphorylation state of protein kinase B and AS160, as well as an inhibition of glucose transport in response to insulin. These processes were reversible under normoxic conditions. The mechanism of inhibition seems independent of protein tyrosine phosphatase activities. Overexpression of HIF-1alpha or -2alpha or activation of HIF transcription factor with CoCl(2) mimicked the effect of hypoxia on insulin signaling, whereas downregulation of HIF-1alpha and -2alpha by small interfering RNA inhibited it. We have demonstrated that hypoxia creates a state of insulin resistance in adipocytes that is dependent upon HIF transcription factor expression. Hypoxia could be envisioned as a new mechanism that participates in insulin resistance in adipose tissue of obese patients. [24]

Halberg, *et al.* [25] demostrated that Adipose tissue can undergo rapid expansion during times of excess caloric intake. Like a rapidly expanding tumor mass, obese adipose tissue becomes hypoxic due to the inability of the vasculature to keep pace with tissue growth. Consequently, during the early stages of obesity, hypoxic conditions cause an increase in the level of hypoxia-inducible factor 1alpha (HIF1alpha) expression. Using a transgenic model of overexpression of a constitutively active form of HIF1alpha, we determined that HIF1alpha fails to induce the expected proangiogenic response. In contrast, we observed that HIF1alpha initiates adipose tissue fibrosis, with an associated increase in local inflammation. "Trichrome- and picrosirius red-positive streaks," enriched in fibrillar collagens, are a hallmark of adipose tissue suffering from the early stages of hypoxia-induced fibrosis. Lysyl oxidase (LOX) is a transcriptional target of HIF1alpha and acts by cross-linking collagen I and III to form the fibrillar collagen fibers. Inhibition of LOX activity by beta-aminoproprionitrile treatment results in a significant improvement in several metabolic parameters and further reduces local adipose tissue inflammation. Collectively, our observations are consistent with a model in which adipose tissue hypoxia serves as an early upstream initiator for adipose tissue dysfunction by inducing a local state of fibrosis [25].

Glaasford, *et al.* [26] showed that Apelin, a novel peptide with significant cardioactive properties, is upregulated by insulin in adipocytes. However, the mechanism by which insulin promotes apelin production is unknown. Hypoxia-inducible factor-1 (HIF-1), a heterodimeric transcription factor involved in the angiogenic and metabolic responses to tissue hypoxia, has been shown to be activated by insulin in various settings. We therefore hypothesized that HIF-1 regulates insulin-mediated apelin expression in adipocytes. 3T3-L1 cells were differentiated into adipocytes in culture. For experiments, serum-starved 3T3-L1 cells were exposed to insulin and/or a 1% O_2 environment. Apelin expression was assessed using quantitative real-time PCR and ELISA. To directly assess the role of HIF-1 in apelin production, we differentiated mouse embryonic fibroblasts (MEFs) containing a targeted deletion of the HIF-1alpha gene into adipocytes and measured their response to insulin and hypoxia. Apelin expression in mature 3T3-L1 adipocytes was increased significantly by insulin and was attenuated by pharmacological inhibition of insulin signaling. Exposure of cells to either hypoxia or the chemical HIF activators cobalt chloride (CoCl(2)) and dimethyloxaloylglycine (DMOG) resulted

in significant upregulation of apelin, consistent with a role for HIF in apelin induction. Moreover, hypoxia-, CoCl(2)-, DMOG-, and insulin-induced apelin expression were all attenuated in differentiated HIF-1alpha-deficient MEFs. In summary, in cultured 3T3-L1 adipocytes and differentiated MEFs, HIF-1 appears to be involved in hypoxia- and insulin-induced apelin expression [26].

Chen, *et al.* [27] demostrated that Low plasma levels of adiponectin (hypoadiponectinemia) and elevated circulating concentrations of plasminogen activator inhibitor (PAI)-1 are causally associated with obesity-related insulin resistance and cardiovascular disease. However, the mechanism that mediates the aberrant production of these two adipokines in obesity remains poorly understood. In this study, we investigated the effects of hypoxia and reactive oxygen species (ROS) on production of adiponectin and PAI-1 in 3T3-L1 adipocytes. Quantitative PCR and immunoassays showed that ambient hypoxia markedly suppressed adiponectin mRNA expression and its protein secretion, and increased PAI-1 production in mature adipocytes. Dimethyloxallyl glycine, a stabilizer of hypoxia-inducible factor 1alpha (HIF-1alpha), mimicked the hypoxia-mediated modulations of these two adipokines. Hypoxia caused a modest elevation of ROS in adipocytes. However, ablation of intracellular ROS by antioxidants failed to alleviate hypoxia-induced aberrant production of adiponectin and PAI-1. On the other hand, the antioxidants could reverse hydrogen peroxide (H2O2)-induced dysregulation of adiponectin and PAI-1 production. H2O2 treatment decreased the expression levels of peroxisome proliferator-activated receptor gamma (PPARgamma) and CCAAT/enhancer binding protein (C/EBPalpha), but had no effect on HIF-1alpha, whereas hypoxia stabilized HIF-1alpha and decreased expression of C/EBPalpha, but not PPARgamma. Taken together, these data suggest that hypoxia and ROS decrease adiponectin production and augment PAI-1 expression in adipocytes via distinct signaling pathways. These effects may contribute to hypoadiponectinemia and elevated PAI-1 levels in obesity, type 2 diabetes, and cardiovascular diseases [27]

Moritz and Meier, *et al.* in 2002 showed that to become insulin independent, patients with type 1 diabetes mellitus require transplantation of at least two donor pancreata because of massive beta-cell loss in the early post-transplantation period. Many studies describing the introduction of new immunosuppressive protocols have shown that this loss is due to not only immunological events but also non-immunological factors. To test to what extent hypoxia may contribute to early graft loss, we analyzed the occurrence of apoptotic events and the expression of hypoxia-inducible factor 1 (HIF-1), a heterodimeric transcription factor consisting of an oxygen-dependent alpha subunit and a constitutive beta subunit. Histological analysis of human and rat islets revealed nuclear pyknosis as early as 6 h after hypoxic exposure (1% O_2). Moreover, immune-reactivity to activated caspase-3 was observed in the core region of isolated human islets. Of note, both of these markers of apoptosis topographically overlap with HIF-1alpha immune-reactivity. HIF-1alpha mRNA was detected in islets from human and rat as well as in several murine beta-cell lines. When exposed to hypoxia, mouse insulinoma cells (MIN6) had an increased HIF-1alpha protein level, whereas its mRNA level did not alter. In conclusion, our data provide convincing evidence that reduced oxygenation is an important cause of beta-cell loss and suggest that HIF-1alpha protein level is an indicator for hypoxic regions undergoing apoptotic cell death. These observations suggest that gene expression under the control of HIF-1 represents a potential therapeutic tool for improving engraftment of transplanted islets [28].

As a result, adrenaline hormone causes hypocapnia and decreases the blood flow to the brain as well. Therefore; hypoxia in tissues specifically in the brain is the result of the chronic fear.

Hypoxia, Inflammation and Cancer

The most important fundamental/basic difference between normal and cancer cells is how they make energy. Normal cells use the sophisticated process of respiration to efficiently turn fat, carbohydrate, or protein into high amounts of energy. This process requires oxygen and breaks food down completely into carbon dioxide and water. Cancer cells use a primitive process called fermentation to inefficiently turn either glucose which is primarily from carbohydrates or the amino acid glutamine which is from protein into small amounts of energy. The most important findings from these researches are that fats cannot be fermented. This process does not require oxygen, and only partially breaks down food molecules into lactic acid and ammonia, which are toxic waste products. Normal cells sometimes have to change to fermentation process if they are temporarily experiencing an oxygen shortage. However, no cell in its right condition would ever choose to use fermentation when there is enough oxygen. It doesn't produce nearly as much energy and creates toxic byproducts. Briefly, fermentation is primitive and wasteful. Cancer cells use fermentation even when there's plenty of oxygen around, which is the explanation of the Warburg Effect, considered the metabolic signature of cancer cells. If a cell turning glucose into lactic acid when there is oxygen available, this would be a cancer cell [29]. Hypoxia as well as inflammation in tissues and normal cells increase the amounts of ROS in cells which is the prime cause of cancer [30-36].

Discussion

From all aspects which is written in the materials and methods, chronic fear makes the adrenal glands to secrete adrenaline hormone which increases the amounts of cortisol latterly. Cortisol hormone causes inflammation increasing blood glucose levels and suppressing the immune system response. Adrenaline on the other hand, causes hypocapnia and hyperventilation which through Bohr Effect causes hypoxia which leads to the incline in the amounts of ROS in tissues. Adrenaline also decreases the blood flow to the brain which decreases the amounts of oxygen in the brain. [22-28] (Figure 2).

Fear and Evolution

From an evolutionary-psychology perspective, different fears may be different adaptations that have been useful in our evolutionary past. They may have developed during different time periods. Some fears, such as fear of heights, may be common to all mammals and developed during the mesozoic period. Other fears, such as fear of snakes, may be common to all simians and developed during the cenozoic time period. Still others, such as fear of mice and insects, may be unique to humans and developed during the paleolithic and neolithic time periods (when mice and insects become important carriers of infectious diseases and harmful for crops and stored foods). Fear

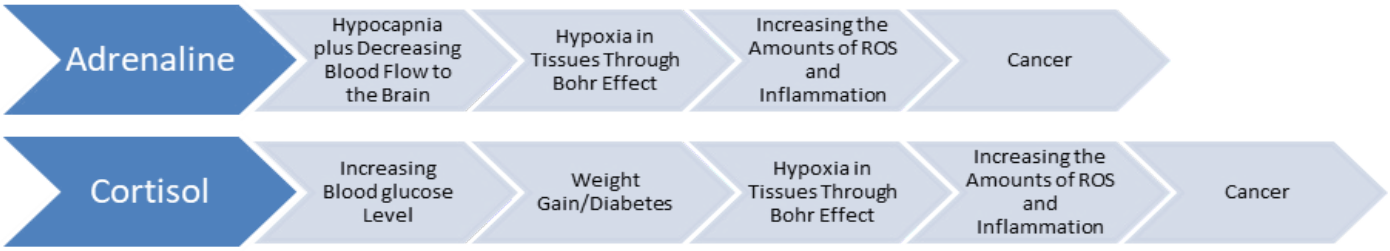

Figure 2. The impact of cortisol and adrenaline hormones on causing cancer.

Figure 3. Side effects of the chronic fear.

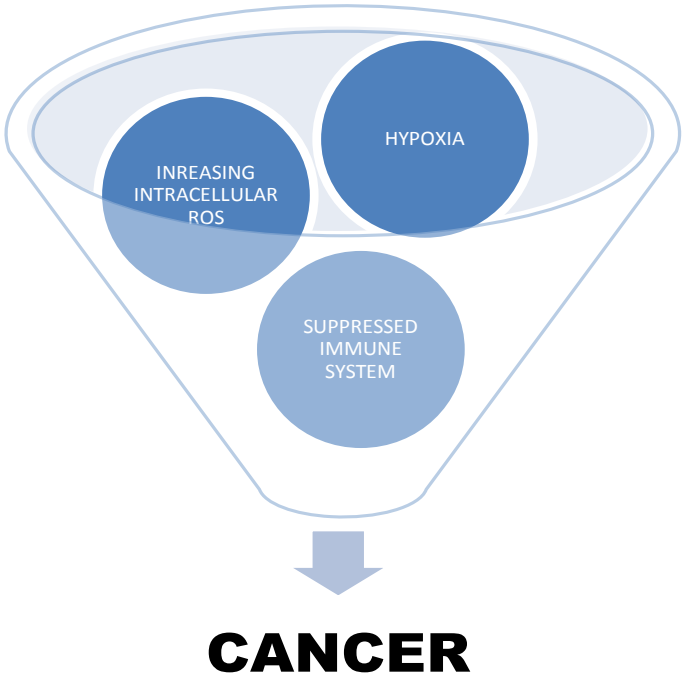

Figure 4. The reason of cancer incidence from chronic fear.

is high only if the observed risk and seriousness both are high and it is low if risk or seriousness is low [20,21] (Figures 3 and 4).

Conclusion

The prime cause of cancer is increasing the amounts of Reactive Oxygen Species (ROS) and inflammation inside healthy human eukaryotic cells which through the Butterfly Effect results in the damage and wrong messages from DNA to the mitochondria and causes the shutdown of them. Fear causes the increase in the amounts of adrenaline and cortisol hormones from adrenal glands. Cortisol hormone suppresses the immune system, causes inflammation and increases the blood glucose level. Adrenaline causes hypocapnia, decreases the blood flow to the brain and suppresses the function of the digestive system. Hypocapnia and high blood glucose in blood results in the hypoxia in tissues through the Bohr Effect. based on Otto Warburg Hypothesis, chronic hypoxia is related to the cause of cancer in healthy cells. Low blood flow to the brain causes hypoxia in the brain tissues as well. In conclusion, chronic fear results cancer incidence in humans through increasing the amounts of ROS, inflammation and hypoxia in tissues especially in the brain and digestive systems.

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