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Research Article

The Impact of Stress, Anxiety, Fear and Depression in The Cause of Cancer in Humans

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Abstract

Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination. Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being. Fear in human beings may occur 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. In psychology, stress is a feeling of strain and pressure. Also, this is one type of psychological pain. Cancer as mentioned by Drs. Zaminpira and Niknamian, is an Evolutionary Metabolic Disease (EMHC) which is caused by increasing the amounts of Reactive Oxygen Species (ROS) through the Butterfly Effect (BE) inside human eukaryotic cells. Therefore; increasing inflammation is a promising factor in the cause of cancer. The aim of this review and meta-analysis is to find the link between the depression, stress, fear and anxiety and the possibility of causing cancer. These emotional states have been observed in cancer patients as well. Anxiety and Fear are the two main emotional states which are the side effects of cancer disease, and also, high amounts of emotional stress and depression have been discussed in this review to raise the possibility in causing cancer.

Keywords: Anxiety; Fear; Depression; Stress; Cancer; Inflammation; ROS

Introduction

Depression, Anxiety, Stress and Fear

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being. A depressed mood is a normal temporary reaction to life events such as loss of a loved one. It is also a symptom of some physical diseases and a side effect of some drugs and medical treatments. Depressed mood is also a symptom of some mood disorders such as major depressive disorder or dysthymia [1].

Anxiety is an emotion characterized by an unpleasant state of inner turmoil, often accompanied by nervous behavior, such as pacing back and forth, somatic complaints, and rumination [2]. It is the subjectively unpleasant feelings of dread over anticipated events, such as the feeling of imminent death [3]. Anxiety is not the same as fear, which is a response to a real or perceived immediate threat, whereas anxiety is the expectation of future threat [4]. Anxiety is a feeling of uneasiness and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. It is often accompanied by muscular tension, restlessness, fatigue and problems in concentration. Anxiety can be appropriate, but when experienced regularly the individual may suffer from an anxiety disorder [5].

In psychology, stress is a feeling of strain and pressure. Also, this is one type of psychological pain [6]. Small amounts of stress may be desired, beneficial, and even healthy. Positive stress helps improve athletic performance. It also plays a factor in motivation, adaptation, and reaction to the environment. Excessive amounts of stress, however, may lead to bodily harm. Stress can increase the risk of strokes, heart attacks, ulcers, dwarfism, and mental illnesses such as depression [7].

Fear is a feeling induced by perceived danger or threat that occurs in certain types of organisms, which causes a change in metabolic and organ functions and ultimately a change in behavior, such as fleeing, hiding, or freezing from perceived traumatic events. Fear in human beings may occur 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. The fear response arises from the perception of danger leading to confrontation with or escape from/avoiding the threat (also known as the fight-or-flight

response), which in extreme cases of fear (horror and terror) can be a freeze response or paralysis [8].

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 a phobia. 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 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, the emotion 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 [9].

Cortisol and Epinephrine

Cortisol is a steroid hormone, in the glucocorticoid class of hormones. It is produced in humans by the zona fasciculata of the adrenal cortex within the adrenal gland [10]. It is released in response to stress and low blood-glucose concentration. It functions to increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid in the metabolism of fat, protein, and carbohydrates [11].

Epinephrine, also known as adrenalin or adrenaline, is a hormone, neurotransmitter, and medication [12,13]. Epinephrine is normally produced by both the adrenal glands and certain neurons. It plays an important role in the fight-or-flight response by increasing blood flow to muscles, output of the heart, pupil dilation, and blood sugar [14,15]. It does this by binding to alpha and beta receptors. It is found in many animals and some single cell organisms [16,17].

The Immune System, Cytokines, and Inflammation

mounting a rapid innate immune system and inflammatory response to a specific trigger and then down regulating the response once a pathogen has been cleared are critical for resolving infection, repairing tissue damage, and returning the body to a state of homeostasis. Recently, however, evidence has accumulated showing that when activation of the inflammatory response is altered or prolonged, it can actually cause more damage to a host than the pathogen itself. Indeed, it is now widely recognized that chronic inflammation plays a role in several major diseases including asthma, arthritis, diabetes, obesity, atherosclerosis, certain cancers, and Alzheimer's disease. One factor that can alter adaptive innate immune system responding and prolong inflammation is stress. In this review, therefore, we consider how stress influences the regulation of inflammation in a way that may be relevant for depression.

The immune system plays a critical role in keeping the body biologically healthy, especially during times of physical injury, wounding, and infection. A key component of this system is the inflammatory response, which is mediated by pro-and anti-inflammatory cytokines that identify, neutralize, and eliminate foreign pathogens such as bacteria and viruses. Inflammation is regulated most proximally by the expression of immune response genes including IL1B, IL6, and TNF. When activated, these genes promote the secretion of pro-inflammatory cytokines that mediate systemic inflammation. Inflammation is also regulated more distally by processes occurring in the brain, which detects social-environmental cues indicating possible danger. This neuro-inflammatory link is highly adaptive insofar as it can activate the CTRA before a physical injury or bacterial infection takes place. A downside of central regulation of systemic inflammation, however, is that it gives social, symbolic, and anticipated threats—including those that have not yet happened or that may never actually occur—the ability to activate the CTRA in the absence of actual physical threat. Under normal conditions, the SNS up-regulates CTRA-related inflammatory activity via stimulation of β-adrenergic receptors, and the HPA axis downregulates CTRA-related inflammatory activity via the production of cortisol. However, under conditions of prolonged actual or perceived threat, or possibly during acute stressors indicating social threat or physical danger, glucocorticoid resistance can develop, leading to excessive inflammation that increases a person's risk for several disorders including depression, especially if activation of these pathways is prolonged.

Materials and Methods

Cortisol can weaken the activity of the immune system. It prevents proliferation of T-cells by rendering the interleukin-2 producer T-cells unresponsive to interleukin-1 (IL-1), and unable to produce the T-cell growth factor (IL-2). Cortisol also has a negative-feedback effect on interleukin-1 [18].

Though IL-1 is useful in combating some diseases, endotoxic bacteria have gained an advantage by forcing the hypothalamus to increase cortisol levels (forcing the secretion of corticotropin-releasing hormone, thus antagonizing IL-1). The suppressor cells are not affected by glucosteroid response-modifying factor [19], so the effective setpoint for the immune cells may be even higher than the setpoint for physiological processes (reflecting leukocyte redistribution to lymph nodes, bone marrow, and skin). Rapid administration of corticosterone (the endogenous type I and type II receptor agonist) or RU28362 (a specific type II receptor agonist) to adrenalectomized animals induced changes in leukocyte distribution. Natural killer cells are affected by cortisol [20].

Cortisol stimulates many copper enzymes (often to 50% of their total potential), probably to increase copper availability for immune purposes. This includes lysyl oxidase, an enzyme that cross-links collagen, and elastin. Especially valuable for immune response is cortisol's stimulation of the superoxide dismutase, [21] since this copper enzyme is almost certainly used by the body to permit superoxides to poison bacteria.

Cortisol counteracts insulin, contributes to hyperglycemia-causing hepatic gluconeogenesis [22] and inhibits the peripheral use of glucose (insulin resistance) by decreasing the translocation of glucose transporters (especially GLUT4) to the cell membrane [23]. However, cortisol increases glycogen synthesis (glycogenesis) in the liver [24]. The permissive effect of cortisol on insulin action in liver glycogenesis is observed in hepatocyte culture in the laboratory, although the mechanism for this is unknown [25,26].

As a hormone, epinephrine acts on nearly all body tissues. Its actions vary by tissue type and tissue expression of adrenergic receptors. For example, high levels of epinephrine causes smooth muscle relaxation in the airways but causes contraction of the smooth muscle that lines most arterioles.

Epinephrine acts by binding to a variety of adrenergic receptors. Epinephrine is a nonselective agonist of all adrenergic receptors, including the major subtypes α1, α2, β1, β2, and β3 [27]. Epinephrine's binding to these receptors triggers a number of metabolic changes. Binding to α-adrenergic receptors inhibits insulin secretion by the pancreas, stimulates glycogenolysis in the liver and muscle [28], and stimulates glycolysis and inhibits insulin-mediated glycogenesis in muscle [29,30]. β adrenergic receptor binding triggers glucagon secretion in the pancreas, increased adrenocorticotropic hormone (ACTH) secretion by the pituitary gland, and increased lipolysis by adipose tissue. Together, these effects lead to increased blood glucose and fatty acids, providing substrates for energy production within cells throughout the body [31].

Its actions are to increase peripheral resistance via α1 receptor-dependent vasoconstriction and to increase cardiac output via its binding to β1 receptors. The goal of reducing peripheral circulation is to increase coronary and cerebral perfusion pressures and therefore increase oxygen exchange at the cellular level. While epinephrine does increase aortic, cerebral, and carotid circulation pressure, it lowers carotid blood flow and end-tidal CO_2 or $ETCO_2$ levels. It appears that epinephrine may be improving macrocirculation at the expense of the capillary beds where actual perfusion is taking place [32].

George M. Slavich and Michael R. Irwin in 2014 concluded that we know a lot about the adverse social-environmental conditions that typically precipitate depression and about cognitive and emotional processes that mediate these effects. With the advent of new neuroimaging, immunological, and genome-wide profiling techniques, we are now poised to go one step deeper and elucidate the full set of biological mechanisms that link stress with depression. Inflammation is undoubtedly a key player in this link. As we have discussed, two general phenomena are consistent with the hypothesis that stress-related increases in inflammation are involved in depression. First, a large number of naturalistic and laboratory-based experimental studies have shown that stress is a potent activator of inflammation, and second, it is now well known that vaccinations and immunological challenges that up-regulate inflammatory activity evoke depressive-like behaviors in rodents and clinically significant episodes of depression in at least some people. In addition, these challenges have been shown to up-regulate peripheral and central cytokine production and to alter metabolic and neural activity in brain regions that have been implicated in depression. Many questions remain unanswered regarding these effects, including whether inflammation is necessary or sufficient for all cases of MDD.

Nonetheless, based on existing data, we conclude that stress likely increases risk for depression in a substantial number of people by up-regulating inflammatory activity and by altering social, cognitive, and affective processes that are known to promote this disorder. These insights are important because they can help update contemporary theories of depression with information about biological mechanisms that are involved in the pathogenesis of MDD. For the potential of these insights to be fully realized, they will need to be translated into new strategies for modifying processes that promote depression (Sanislow et al., 2010). At a very general level, such processes include neurocognitive mechanisms like negative cognitive appraisals and neural sensitivity to social threat, which have been associated with inflammation and depression; immunological processes such as preclinical levels of inflammation, which could presage the development of chronic inflammation and disease; and psychosocial factors such as parental behaviors, which have been found to influence the effects of social-environmental adversity on proinflammatory signaling. The hope is that by targeting these and other dynamics, we may one day be able to reduce the prevalence of depression and the substantial financial burden and personal suffering associated with this common and costly disorder [33].

Sheldon Cohen et al. [34] did a research about stress and disease promotion. In Cohen's first study, after completing an intensive stress interview, 276 healthy adults were exposed to a virus that causes the common cold and monitored in quarantine for five days for signs of infection and illness. Here, Cohen found that experiencing a prolonged stressful event was associated with the inability of immune cells to respond to hormonal signals that normally regulate inflammation. In turn, those with the inability to regulate the inflammatory response were more likely to develop colds when exposed to the virus. In the second study, 79 healthy participants were assessed for their ability to regulate the inflammatory response and then exposed to a cold virus and monitored for the production of pro-inflammatory cytokines, the chemical messengers that trigger inflammation. He found that those who were less able to regulate the inflammatory response as assessed before being exposed to the virus produced more of these inflammation-inducing chemical messengers when they were infected. The immune system's ability to regulate inflammation predicts who will develop a cold, but more importantly it provides an explanation of how stress can promote disease, when under stress, cells of the immune system are unable to respond to hormonal control, and consequently, produce levels of inflammation that promote disease. Because inflammation plays a role in many diseases such as cardiovascular, asthma and autoimmune disorders, this model suggests why stress impacts them as well [34].

Michopoulos V. et al. [35] concluded 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. Indeed, heightened concentrations of inflammatory signals, including cytokines and C-reactive protein, have been described in posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic disorder (PD), and phobias (agoraphobia, social phobia, etc.). However, not all reports indicate 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 (i.e., 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 [35].

Based on evidence that psychological stress may induce a chronic inflammatory process, we hypothesized 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. 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 <.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 [36].

Vignes M. et al. & Bouayed J, et al. [37,38] summarized the data to support a link between oxidative stress and anxiety. While all of the data demonstrate that there is a link between oxidative stress and high-anxiety-related behavior, a cause-effect relationship has yet to be completely established. Some of these studies suggest that oxidative stress causes anxiety-related behaviors but do not explain the underlying mechanisms. While there are some limits in the approach to establish the anxiogenic effect of oxidative stress, the available data are consistent this causal relationship. The potential causal role of oxidative stress on anxiety may generate interest in antioxidants. Masood et al. were able to show that oxidative stress-related anxiety can be reversed in mice upon inhibition of NADPH oxidase or phosphodiesterase-2, enzyme that is indirectly implicated in oxidative stress mechanisms. Surprisingly, they found that diazepam, which is a well-known anxiolytic, does not fully reverse the oxidative stress-related anxiety. These results point to a possible use for antioxidants in the prevention or reduction of high anxiety. Recent work has shown that some dietary polyphenols have both anxiolytic and antioxidant effects, which may be beneficial to anxious subjects [37,38].

It is well known that low/moderate concentrations of reactive oxygen species (ROS) affect a great number of physiological functions [39]. However, when ROS concentration exceeds the anti-oxidative capacity of an organism, animal cells enter a state termed oxidative stress, in which the excess ROS induces oxidative damage on cellular components [40]. As a result, oxidative stress has been implicated in a large range of diseases, including cancer [41,42].

The brain is highly vulnerable to oxidative stress due to its high O_2 consumption, its modest antioxidant defenses and its lipid-rich constitution [43,44]. Human brain utilizes 20% of oxygen consumed by the body even though this organ constitutes only about 2% of the body weight [45]. When the production of oxygen-derived metabolites prevails over the brain defence systems, however, oxidative damage to nucleic acids, proteins and neuronal membrane lipids, which are rich in highly polyunsaturated fatty acids, can occur [46]. In presence of oxidative stress, the lipid-rich constitution of brain favors lipid peroxidation that results in decrease in membrane fluidity and damage in membrane proteins inactivating receptors, enzymes and ion channels. As a result, oxidative stress can alter neurotransmission, neuronal function and overall brain activity [47]. Oxidative stress has been associated with several diseases which are specific for nervous system impairment including neurodegenerative diseases and neuropsychiatric diseases, such as schizophrenia and major depressive disorder [42-44]. The intrinsic oxidative vulnerability of the brain has led some authors to suggest that oxidative damage may be a plausible pathogenic factor for certain neurological diseases including neuropsychiatric disorders [40-46].

Stress and Illness including Cancer

There is likely a connection between stress and illness. Theories of the stress–illness link suggest that both acute and chronic stress can cause illness, and several studies found such a link [48]. According to these theories, both kinds of stress can lead to changes in behaviour and in physiology. Behavioural changes can be smoking and eating habits and physical activity. Physiological changes can be changes in sympathetic activation or hypothalamic pituitary adrenocorticoid activation, and immunological function [49]. However, there is much variability in the link between stress and illness [50].

Stress can make the individual more susceptible to physical illnesses like the common cold [51]. Stressful events, such as job changes, may result in insomnia, impaired sleeping, and health complaints [52]. Research indicates the type of stressor (whether it's acute or chronic) and individual characteristics such as age and physical well-being before the onset of the stressor can combine to

determine the effect of stress on an individual. An individual's personality characteristics (such as level of neuroticism) [53], genetics, and childhood experiences with major stressors and traumas [54] may also dictate their response to stressors.

Chronic stress and a lack of coping resources available or used by an individual can often lead to the development of psychological issues such as depression and anxiety [55]. This is particularly true regarding chronic stressors. These are stressors that may not be as intense as an acute stressor like a natural disaster or a major accident, but they persist over longer periods of time. These types of stressors tend to have a more negative impact on health because they are sustained and thus require the body's physiological response to occur daily. This depletes the body's energy more quickly and usually occurs over long periods of time, especially when these microstressors cannot be avoided (i.e. stress of living in a dangerous neighborhood). See allostatic load for further discussion of the biological process by which chronic stress may affect the body. For example, studies have found that caregivers, particularly those of dementia patients, have higher levels of depression and slightly worse physical health than noncaregivers [56].

Studies have also shown that perceived chronic stress and the hostility associated with Type A personalities are often associated with much higher risks of cardiovascular disease. This occurs because of the compromised immune system as well as the high levels of arousal in the sympathetic nervous system that occur as part of the body's physiological response to stressful events [57]. However, it is possible for individuals to exhibit hardiness – a term referring to the ability to be both chronically stressed and healthy. [58]. Many psychologists are currently interested in studying the factors that allow hardy individuals to cope with stress and evade most health and illness problems associated with high levels of stress. Stress can be associated with psychological disorders such as delusions [59], general anxiety disorder, depression, and post-traumatic stress disorder. However, everyone experiences some level of stress, and diagnosis of stress disorders can only be performed by a licensed practitioner. According to a 2016 review article, pathological anxiety and chronic stress lead to structural degeneration and impaired functioning of the hippocampus [60].

It has long been believed that negative affective states, such as feelings of anxiety and depression, could influence the pathogenesis of physical disease, which in turn, have direct effects on biological process that could result in increased risk of disease in the end. However, studies done by the University of Wisconsin-Madison and other places have shown this to be partly untrue; although stress seems to increase the risk of reported poor health, the perception that stress is harmful increases the risk even further [61,62]. For example, when humans are under chronic stress, permanent changes in their physiological, emotional, and behavioral responses are most likely to occur [63]. Such changes could lead to disease. Chronic stress results from stressful events that persist over a relatively long period of time, such as caring for a spouse with dementia, or results from brief focal events that continue to be experienced as overwhelming even long after they are over, such as experiencing a sexual assault.

Experiments show that when healthy human individuals are exposed to acute laboratory stressors, they show an adaptive enhancement of some markers of natural immunity but a general suppression of functions of specific immunity. By comparison, when healthy human individuals are exposed to real-life chronic stress, this stress is associated with a biphasic immune response where partial suppression of cellular and humoral function coincides with low-grade, nonspecific inflammation.

Even though psychological stress is often connected with illness or disease, most healthy individuals can still remain disease-free after confronting chronic stressful events. Also, people who do not believe that stress will affect their health do not have an increased risk of illness, disease, or death. This suggests that there are individual differences in vulnerability to the potential pathogenic effects of stress; individual differences in vulnerability arise due to both genetic and psychological factors. In addition, the age at which the stress is experienced can dictate its effect on health. Research suggests chronic stress at a young age can have lifelong impacts on the biological, psychological, and behavioural responses to stress later in life [64].

As stress has a physical effect on the body, some individuals may not distinguish this from other more serious illnesses. Individuals experiencing stress are less likely to see medical care for a symptom if the symptom is ambiguous (e.g. headache) and they are currently experiencing stress. If the symptom is unambiguous however (e.g. a breast lump), and the onset of the stressor is recent, individuals are motivated to seek care as usual [65].

In animals, stress contributes to the initiation, growth, and metastasis of select tumors, but studies that try to link stress and cancer incidence in humans have had mixed results. This can be due to practical difficulties in designing and implementing adequate studies [66].

Discussion

Fear hormones are secreted by the adrenal gland, an endocrine gland located on top of the kidneys [67]. The fear hormones circulate through the bloodstream to all cells of the body [68]. The effect of adrenaline is similar to the effect of the sympathetic nerve action [69]. Adrenaline increases heart rate, increases breathing rate, dilates blood vessels to the lungs and muscles [70]. Adrenaline also decreases blood flow to the brain and decreases digestion. Cortisol increases blood sugar level by converting stored glycogen and fats into blood sugar. Cortisol also suppresses the immune response and inflammation. Fear hormones result in a longer lasting and more widespread fight-or-flight response than the effects of the nervous system [71-73]. Fear hormone action explains why one may feel the fight-or-flight response even after he/she realize there really is no danger. Daily life can involve many stimuli that are perceived as threatening [74-76]. Problems at work or at school, money or social problems, and medical problems can trigger a chronic (long term) fight-or-flight response. Even anticipating or worrying about things that might happen in the future can trigger the same response as actually experiencing it. Chronic stress occurs when the fight-or-flight response does not shut down to allow for the proper balance

between fear and relaxation. Stress can increase a person's risk of health problems [77-80].

The fight-or-flight response uses calories so the urge to eat makes sense after running. But, eating in response to daily stresses can lead to weight gain and obesity. In addition, stress increases cortisol levels causing elevated blood sugar levels that can lead to both weight gain and diabetes. When the fight-or-flight response causes blood pressure and heart rate to remain high, it puts extra strain on blood vessel walls. As a result, the linings of blood vessels can become damaged and the amounts of oxygen in blood can become lesser than normal [81,82]. An interruption of blood flow to the heart can lead to a heart attack. Blood vessels in the brain can also be blocked, resulting in brain-damaging strokes. People suffering from stress secrete cortisol at much higher rates than normal people. There is evidence that abnormally high cortisol levels may actually be the initial trigger for depression in some individuals. High cortisol levels also result in sleep deprivation. Stress also affects the function of the immune system, the body's natural means of fighting off infection. Stressed individuals produce lower levels of antibodies when exposed to pathogens. They also produce higher levels of cytokines, inflammation triggering chemicals secreted when fighting infections. Excessive inflammation is thought to increase the risks for heart disease, diabetes, and cancer. Feeling stressed mentally and physically may have serious health consequences [83,84].

A large literature exists demonstrating that major life events, especially those involving interpersonal loss and social rejection, are a key proximal risk factor for MDD. As it turns out, these stressors have been implicated not just in the development of depression but in the onset, exacerbation, or progression of a variety of health problems. These conditions include several that, like depression, are thought (or known) to be mediated at least in part by inflammation, such as asthma, rheumatoid arthritis, cardiovascular disease, chronic pain, and certain cancers. As a result, we turn now to the question of whether stress is associated with inflammation.

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Conclusion

Inflammation is partly regulated by the hormone cortisol and when cortisol is not allowed to serve this function, inflammation can get out of control. chronic stress may hamper a naturally occurring anti-inflammatory response in the body. Ordinarily, white blood cells will concentrate in the area of injury or infection where they release chemicals called cytokines to fend off the invaders, a process generally known as inflammation. While inflammation can help fight infection, too much inflammation occurring over time can actually be damaging. Under normal circumstances, the inflammation process is naturally stopped in the body when levels of a stress hormone, cortisol, begin to rise. It is harmful to the body when the inflammation process does not stop as it should. The researchers found that the white blood cells of stressed parents were less responsive to the cortisol hormone, and less likely to shut down an inflammatory response, than the less stressed parents. Their cells kept producing more cytokines. The findings highlight the fact that stress may interfere with the body's ability to shut down its own immune response after it gets started.

Therefore, the bodies of those people suffering from stress may be less likely to regulate their normal defense mechanisms. In conclusion, chronic anxiety, fear and stress results in increasing the hormone cortisol which leads to diabetes, decreasing immune response and increasing inflammation in the tissues which leads to increasing the possibility of cancer incidence. Chronic fear and anxiety increase the hormone adrenaline which decreases the blood flow to the brain and in the long time leads to hypoxia. Therefore; chronic stress, chronic fear and anxiety increase the possibility of cancer incidence basically in the brain. These three chronic disorder cause hypocapnia as well which leads to the hypoxia in body tissues through the Bohr Effect and increases the possibility of cancer incidence in the whole body tissues. In cancer patients, stress, fear, anxiety and depression worsen the disease. Depression alone has not been linked as a factor in causing any types of cancer.

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