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Chronic Stress is Allied to Low Blood Pressure: An Unconvincing Truth

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Abstract: ***As yet, chronic stress and its sequels i.e., anxiety and depression have been allied to high blood pressure. There are also various theories and studies to explain this collusion of high blood pressure and continual stressors. However, recent exploration in this field have documented incessant stress to be associated with low blood pressure. Though it seems to be an unconvincing truth, there are various conjectures to explain such association and had been dealt here. However, the reason behind the differential impact of stressors on an individual presenting either with high blood pressure or low blood pressure needs evaluation on large scale.***

Keywords: chronic stress, anxiety, depression, high blood pressure, low blood pressure

1. Introduction

A Latin word "stringere" is the mother of word stress meaning thereby as starveling, sting, pain, and physical hardship/sufferings. Hans Selye in 1936 first minted the word stress and defined it as a nonspecific response of the body to any demand. He further elaborated the definition and redefined it as "any censorious happening/event or internal drive which threatens to endanger the equilibrium of the living being" [1]. The National Institute of mental health addresses stress as simply "the brain response to any demand" [2]. It's a normal physical response to a challenging or new situation. Stress occurring as a result of sole short-term events are innocuous, but other incessant stress due to recurring conditions which are both intense and sustained over a long period of time is referred as chronic or toxic stress [3, 4]. Chronic stress, a feeling of pressured and overwhelmed for a long period of time i.e., for weeks /months /years have several detrimental effects on health thereby affecting body's immune system, cardiovascular system, neuroendocrine and central nervous system resulting in various disabilities like insomnia, weakened immune system, high blood pressure, anxiety, depression, heart disease and obesity [5]. Chronic stress leads to shrinkage of prefrontal cortex thereby affecting its functions fiercely [6]. Execution function is the paramount function of prefrontal cortex. Decision-making, judgement, planning, reasoning, and anticipation are examples of execution function and are affected by neuronal atrophy of prefrontal cortex as a result of chronic stress [7]. Chronic stress increases the size of amygdala, the part of brain responsible for physiologic and behavioral responses to stress and sustains a gamma- amino butyric acid (GABA) mediated high inhibitory tone under resting state which is a ground for organism resistance to various physiological and environmental stressors. Studies on humans and animals have shown that stress leads to hyperactivity and hyperresponsiveness of amygdala which is ascribed to be due to loss of its inhibitory control [8]. Reiterate stress is a major impetus for persistent inflammation in the body, also affecting blood brain barrier which becomes leaky thus allowing circulating inflammatory protein to get access to the brain [9]. Chronic stress leads to anxious depression, which is a newly developed subset of major depressive disorder that is characterized by symptoms of anxiety [10]. Repeated exposure to psychological stress has a profound impact on peripheral immune response and perturbs the function of brain microglia, which may contribute to neurobiological changes underlying major depressive disorder [11]. Microglia switch from supplying neurotrophic factor to proinflammatory cytokines and become more phagocytic inducing neuronal atrophy, remodeling and synaptic plasticity in vulnerable areas such as hippocampus. Thus, chronic inflammation and chronic stress forms a vicious cycle, i.e., stress leads to inflammation which further leads to more tissue stress and further inflammation leading to structural damage that may result in depression [10]

Till date, high blood pressure has been allied to chronic stress. The two interconnected system that best explains the physiology of stress are Sympathetic adreno-medullary (SAM) system and Hypothalamic-pituitary adrenocortical (HPA) axis. In SAM pathway, when an individual faces stress, the cerebral cortex reads it and sends information to hypothalamus which in turns initiates adrenal medulla to secrete catecholamines. In HPA activation, hypothalamus secrete corticotrophin releasing hormone (CRH) which causes release of adrenocorticotropic hormone (ACTH) by pituitary gland which stimulate adrenal cortex to secrete glucocorticoid. The consequences of all these are hike in blood pressure [5].

Anxiety and depression as a consequence of chronic stress are allied to hypotension

Recent studies and documentation have allied low blood pressure with consequences of chronic stress i.e., depression and anxiety. In a study done by Hildrum B et.al. on 60799 subjects, it has been proven that there is an association of low blood pressure with anxiety and depression which is not caused by cardiovascular disease [12]. In another study done by Joung K I et.al. on 10,708 subjects, it has been shown that low blood pressure is associated with suicidal ideation [13].

Though the exact mechanism is still obscure there are various theories to explain this unconvincing truth.

Role of Neuropeptide Y (NPY):

Stressors educe a flow of various responses: neuronal, endocrine, & behavioral, that foster homeostatic adaptation to changing or terrifying environment. These pathological, neurochemical, and behavioral mechanism later express in the form of stress associated grave conditions like anxiety disorder, post-traumatic stress disorder (PTSD) and depression. NPY have been shown to be an influential neuromodulators of stress related emotionality [14]. It is a

protective neurochemical that mediates stress resilience and has anxiolytic property. It is a 36 amino acid peptide first isolated from brain extracts and was found to be one of the most abundant neuropeptides within the brain [15]. Within the stress responsive areas of brain such as cortex, amygdala, hypothalamus and locus coeruleus, NPY receptors are localized on or impact the function of neurons expressing GABA, corticotrophin releasing factor (CRF), & norepinephrine.

It has been known that there are various genetic variants of preproNPY gene that is held responsible for differential expression of individuals to stress response and emotionality. Those individuals who harbor genotype associated with low NPY expression are known to face more pessimistic emotional experience and low ability to cope with stress when exposed to painful stressors as compared to those having genotype with high NPY expression [14]. Since NPY has a role in stress resilience, there is a negative correlation between stress induced behavioral disruption and cerebral NPY expression in animal models of PTSD. Exogenous NPY prevents negative consequences of stress. Stress is also a factor contributing to and resulting from neurodegenerative disease such as Alzheimer's, Parkinson's and Huntington's disease in which NPY appears to play an important neuroprotective role [15].

Clinical investigation has revealed that the plasma and cerebro-spinal fluid (CSF) of depressed patients and PTSD individuals contain decreased concentration of NPY and even lower NPY in clinically depressed patients with history of suicide attempts [16]. Low NPY immunoreactivity has been found in post-mortem brain tissue of suicide victims [17]. CSF level of NPY increases after electroconvulsive therapy in depressed patients while corticotropin-releasing hormone decrease concurrently [18].

The neurons that regulate blood pressure express high quantities of NPY. The generation of NPY transgenic rat overexpressing this peptide under its natural promoter has shown to reduce blood pressure and catecholamine release [19]. In a study done by Hildrum B et.al., it has been proven that anxiety and depression are associated with low blood pressure especially when grave symptoms are present over decades. This study also denies the axiom that emotional stress is associated with hypertension [20].
Exact mechanism of action of NPY on blood pressure is not well known. Although it is considered as anxiolytic and hypotensive, a dual nature of its action (as hypotensive and hypertensive) is seen depending upon the site of its administration. Administered centrally, peptide has potent sympatholytic, hypotensive and anxiolytic effect. In contrast, acute administration of NPY into systemic circulation raises blood pressure [19, 21].

NPY is expressed by the same neurons of the brain that handles stress i.e., hypothalamus and limbic system which itself explains why NPY has an impact on stress related changes in emotional state as well as on stress coping. Limbic system comprises of hippocampus, amygdala, and hypothalamus which caters function related to the processing of emotion and memory [15]. Because NPY is maximally placed in the same area of brain which is related to stress, chronically stressed neurons may be releasing more & more NPY centrally to combat stress as it has anxiolytic and has stress resilient property, and because exogenous NPY when administered centrally has a hypotensive effect, it can be hypothesized that sustained release of NPY centrally by these stress related organs may be one of the reasons of low blood pressure in chronically stressed persons.

Role of cortisol:
Previous findings have reported hypersecretion of cortisol in patients of major depression. However, dysregulation of HPA axis has been documented in individual with other form of psychological stress including anxiety, PTSD. Dysregulation doesn't always present as high cortisol level. Some form of chronic stress is associated with blunted amplitude of cortisol secretion and impaired responsiveness to acute stressors. This may be another reason for the association of chronically elevated symptoms of anxiety and depression with decreased blood pressure [22, 20].

Role of Hyperventilation:
Hyperventilation is characterized by an increase in breathing frequency and/or increase in amplitude of breathing movement which is witnessed in patients of anxiety and stress. Hyperventilation leads to drop in blood pressure by two ways: Firstly, when one hyperventilates, signals are sent to the brain that it is deficient of air supply though it is getting too much. Consequent upon which people starts to yawn or take deeper breath making hyperventilation worse thus causing a further drop in blood pressure. Secondly, hyperventilation and low blood pressure now together leads to symptoms that can worsen hyperventilation. Heart beats faster at low blood pressure which is harder to compensate leading to chest pain and a feeling of light headedness, dizziness and fainting attacks. All these physical symptoms increase anxiety, increase hyperventilation and continue to sustain a lower blood pressure [new23, 24].

Role of Hypoventilation:
Both hyperventilation and hypoventilation are seen in anxiety and stress [24]. Many people breath poorly when they have anxiety, thus leading to CO_2 retention. CO_2 causes dilatation of blood vessels thus lowering blood pressure [25].

Role of Hypocalcemia:
Hyperventilation is an autonomic response to extreme stress and anxiety. Hyperventilation causes sloughing out of CO_2, leading to respiratory alkalosis [23]. The blood pH is thereby increased which causes bound hydrogen ion to dissociate from albumin, which increases the fraction of albumin available for ionized Ca^{2+} binding leading to hypocalcemia [26]. In a study done by Du C et.al. it has been proven that higher dairy and calcium intake predicted lower perceived stress and positive mood [27].

Adrenal Fatigue:
The theory of adrenal fatigue was first introduced by Chinopractor in 1998. Till date it is considered a fabricated condition promoted by popular websites lacking the scientific evidences. However, some medical societies claim this condition to be caused by chronic exposure to stressful conditions (mental / emotional / physical stress) leading to overuse of adrenal gland where these glands are unable to

keep pace with the increasing demands to stressful and horrendous situation [28]. Extended subjection of a person to stress drains the adrenals leading to low cortisol production. Patient then presents with tiredness and low blood pressure [29]. It is proposed that this condition can be diagnosed by symptom scoring systems alone or day time salivary profile for the cortisol level [30].

The various causes of low blood pressure in a chronically stressed individual has been summarized in Figure 1.

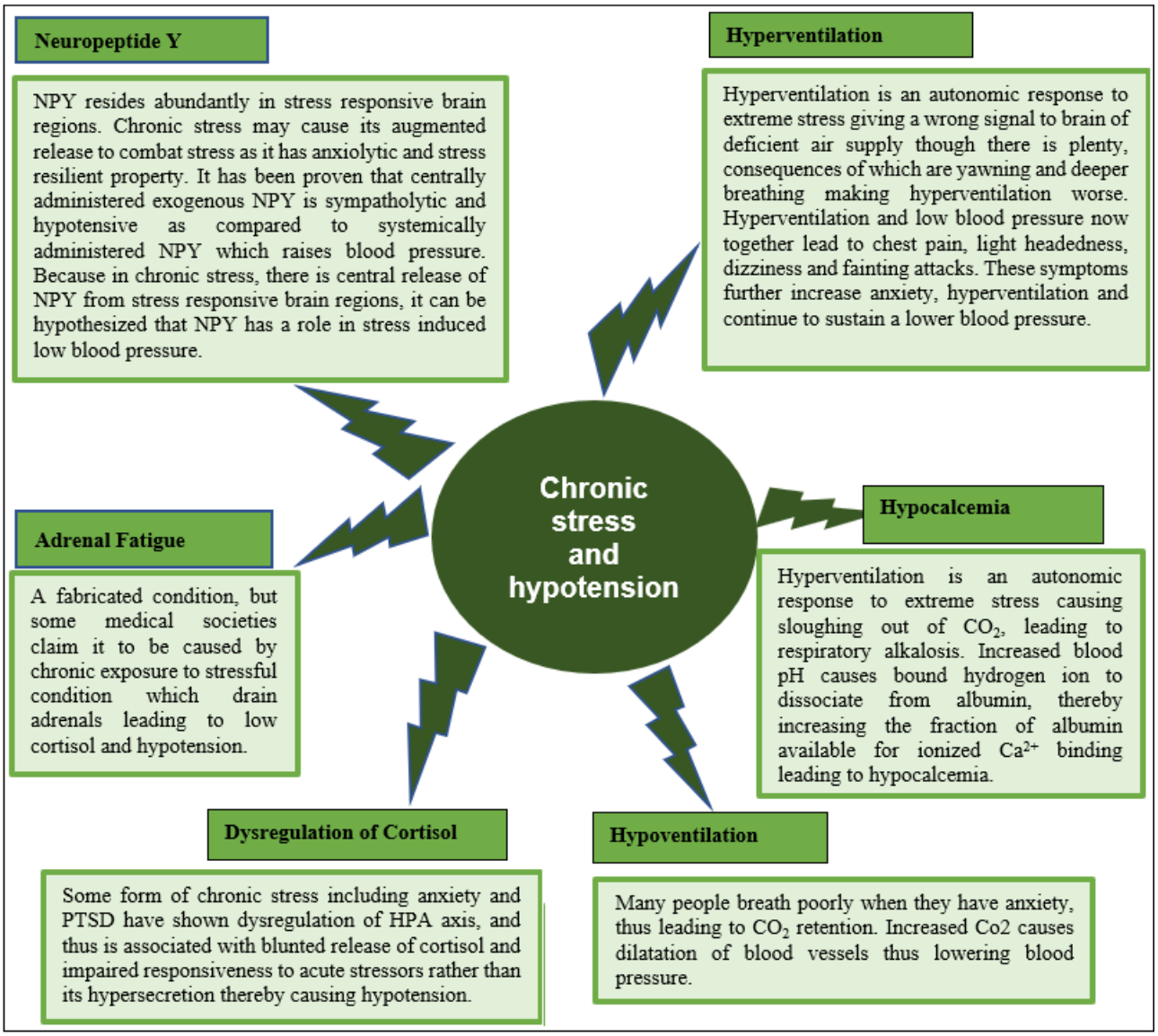

Figure 1: Causes of hypotension in chronic stress summarized

2. Conclusion

Everyone is aware of the fact that high blood pressure is associated with prolonged stress and it has been proven and explained in various literatures. However, there are few theories to explain the prevalence of low blood pressure in chronically stressed individuals which has been dealt here. Low blood pressure in stressed individual has been validated through various studies too but the cause remains dubious.

So, what are the factors which leads to the differential impact of stressors on an individual? What environmental and or genetic factors are responsible for such differential expression needs to be evaluated in further studies on large scale.

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