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Psychological stressors as interventions: Good out of the evil

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1. ABSTRACT

Stress in general can be defined as a state of threatened balance, equilibrium or harmony that tends to disturb the homeostasis of the body. Stress can be of many kinds viz. psychological, physiological, social, emotional, and nutritional. Albeit the distinct kinds of stress stated in the aforementioned stress list, it is hard to bring out a clear distinction between them since each stress may precede or succeed the manifestation of any other. The studies discussed in the review elucidate effects of psychological stressors (PS) on diseases such as cancer, AIDS, epidermal abnormalities, obesity, and various inflammatory diseases like colonic inflammations, Coronary Artery Disease (CAD), Coronary Heart Disease (CHD), asthma. From these studies, further attempt was made to establish the basic mechanisms which come into play during a stressor stimulus and consequently modulate the physiology of the body. In this review we have highlighted effects of PS on diseases while simultaneously building on the modes of operation of PS to alter physiology and its further implications in developing potential psychotherapeutic methods for disease treatment.

2. INTRODUCTION

2.1. Introduction to stress

A comprehensive definition of stress is a difficult task to achieve. Philosophers such as Hippocrates and biologists like Hans Selye (2) attempted to define stress, however it is yet to be precisely embodied. Although stress is something which we may not define with clarity and pervasiveness but we could perceive it. Perhaps this is the best way to present stress to initiate the current review. However for scientific purpose of this review we need to take a more objective outlook towards stress. Traditionally stress comes in various forms which include exercise, fasting, fright, temperature, high altitudes, bleeding infection, surgery, trauma, disease, weaning, nutrition, social reorganization, and environmental effects. We can thus derive from preceding discussion that stress is a state of threatened balance, equilibrium or harmony that eventually disturbs the homeostasis of the body. Stress can be of different kinds such as psychological, physiological, emotional, and social stress as well as due to infections. Further studies are required however to quantitate, characterize and distinguish these various stresses. To

address this issue intuitively, we have considered a situation involving psychological stress. The state of psychological stress can initiate from or lead to emotional stress or a social stress or in certain cases a state of physiological stress as well. Therefore, any present stressed state, here psychological stress state in broader perspective may be preceded or succeeded by another stress state. However, the question is where to draw line between all these stresses. This becomes especially important in scientific studies where one may not be able to exclude not so obvious correlation between different stresses. Thus at one point of time it becomes really difficult to explain which kind of stress is actually under scientific study. This further limits the exact interpretation of multiple stress related states which again may not be independently corresponded to an individual stress. The main reason for this anomaly is lack of defined set of criteria based on which we can address the kinds of stress. This is probably because not many attempts have been made in the field of understanding stress with respect to predefined biological conditions based on a set of biomarkers which are expressed in different stressed states. Although the studies have been done which particularly emphasize on cortisol as a biomarker for stress but there are certain limitations to it such as (a) cortisol concentrations fluctuate, (b) cortisol may not distinguish between different kinds of stress. This molecular status of stress research warrants further experimentation to establish more reliable markers for stress. To the best of our knowledge, only a few groups have tried to relate some more reliable biomarkers to a stressed state including some proteins, metabolites, and metallic components in murine and bovine models (3-6). But it certainly remains to be further established that what are the biological conditions associated to different stress based on which we can classify them precisely.

This impreciseness in defining and distinguishing between different kinds of stress can be dealt with by addressing stressors related to a particular condition. The advantage of defining stressors is that the level of confusion regarding the stress under study boils down to minimum because now the cause for a stressed state is precisely defined and hence the state. Stressors are of many kinds such as psychological, social, peer pressure, physiological, infectious, traumatic and nutritional. Hence, unlike psychological stress, PS precisely defines the consequent state under study while simultaneously being specific on its cause. Thus at any instant of time, it is known which stressor and stressor associated state is being referred to irrespective of the broad category of stress they belong to. Hence, to summarize in brief while stress is a state, stressor is the cause and can be addressed independently.

Based on above discussion, it is now clear that it is perhaps easier to understand stress in context of different stressors. Hence, in the review, the term “stressors” will be mostly used to address the different stimuli related to state of psychological stress.

2.2. Distinction between chronic and acute stressors

There is a necessity to bring out a clear distinction between acute and chronic stressors that arises from the fact that both kinds of stressors may have different consequences on the stressed state. As a result the experimental aftermath and interpretations are dependent both on the type of stressors as well as the effects these stressors produce. For instance, it is possible in some cases that the effects of a stressor response may not last long enough (i.e. are acute) or express immediately to significantly affect a diseased state. In such a situation, it becomes important to concentrate on the effects of stressors which are relatively long lasting (i.e. chronic) and express over a period of time. Hence, it becomes mandatory to distinguish the two on all possible grounds (7-10). In fact, Elliot and Eisdorfer’s (1982) taxonomy characterizes stressors on the basis of duration and course and strongly discriminate between acute and chronic stressors (11). Considering the literal meaning of the words, chronic and acute stressors are distinguished based on temporal differences. Chronic stressors are the ones which are persistent unlike acute stressors which only stay for a shorter duration. Similarly, it can be stated for the effects of stressors while adding further to it that chronic effects of a stress could be recurrent. It simply means that in case of chronic effects the symptoms of a stressed state may reoccur during the lifetime of the individual. It is to be made clear here that it is not always true that an acute stress leads to acute effects i.e. the effects that last for a relatively shorter duration. (12-15) Based on this explanation it now becomes clear that acute and chronic effects of stressors are not only defined temporally but also distinction has to be made more precisely on the basis of set of biomarkers that again are qualitatively and quantitatively distinct in both conditions. This identification of markers for acute and chronic effects of stressors will not only mark a distinction between the two but will also help in quick diagnosis of the type of stressor effects and hence its consequences which can be markedly different for the two cases. (7, 16) For example the expression of acute phase proteins or expression of certain proteins for a longer time or some other class of proteins can result in two completely different physiological consequences. Besides its significance, only a very few studies clearly mention the kind of stressors and stressor effects under study. (17-19). It is perhaps due to reasons as mentioned above that the boundary between acute and chronic stressors is not yet well defined and it is difficult to identify them. Following the argument, the sharp distinction related to effects of chronic and acute stressors is not well taken in the review, though they have been put into focus when required.

A further briefing on the difference in the physiological response especially immune response in case of chronic and acute stressors can be done taking into account the evolutionary aspect of stress response. (20) In the past, any kind of threat or stress, whether in the form of bacterial infection or the sight of a snake or a predator was met as “Fight or Flight response” by body’s physiology. Since the same physiological response involved a danger of injury during flight or fight which makes the body more susceptible to infection as pathogens have got a free way to the inside of body, the redistribution of immune cells especially innate immune cells in the body to the most prone areas of pathogen entry was evolutionary favored. This not only reduces the chances of infection but also

preserve the energy of the body by activating the innate immune system rather than specific immune system. In modern times where there is no such kind of predator hunt for human beings the predator prey stress is now replaced by kind of acute stressors like examination stress or a presentation stress which produce the same kind of effect. This preserved energy can then be directed for the flight or fight response. On the contrary the chronic stressors are generally marked by malfunctioning of the immune system. (21) Thus with an evolutionary point of view, it is clear that acute and chronic stressor differ in their physiological responses.

Thus, keeping all these things in mind, the complicacies and inconsistencies in defining, classifying stress are still a big issue and a basic scaffold can only be built on the basis of experimental studies. The bits and pieces of stress related studies still remain to be compiled.

For the current review it is necessary to predefine all the points of uncertainties related to stress and its defined fields as stated above to avoid any further confusion in the review regarding the use of these terms. In the whole review, we will more or less stick to the concept of stressors.

3. PSYCHOLOGICAL STRESSORS AND DISEASES

It has always been a common observation that people who tend to be psychologically strong and sound seem to fight with their diseases better or the other way round. That is people who are under a stressed state appear to be more susceptible to diseases. This was the basic idea behind reviewing the research so far been done in this regard. The main aim was to look for the studies which show any kind of correlation positive, negative or nil between disease and stress. And if there is then, are there any further studies where the possible mechanism of how stress affects a diseased state has been highlighted or worked out. The results of search were really interesting but scattered. So, here we have tried to put them in a basic scaffold from where they can be further worked out to complete the infrastructure. Following are some of the studies related to stress and diseases which highlight the role of stress in some very important and most prevalent of the diseases like AIDS, cancer, diabetes. On the other hand some studies not exactly with the diseases rather than on different aspect of wound recovery, inflammation and healing.

3.1. Cancer and stressors

An estimate of cancer prevalence in US by American cancer society goes to 11,028,000. There are different PSs related to cancer at different time points starting from the prognosis of the cancer, continuing through the course of cancer treatment, after the therapy and beyond. So far, most of the studies that have been done are related to breast cancer among female population belonging to different age groups, different regional and social backgrounds as well as different social status (22). The reported stressors associated with women breast cancer include social stressors due to the difficulty in dealing with the society as well as adjusting in the social group after disease prognosis, peer pressure where especially women undergoing cancer treatment show increased level of anxiety and stress due to either lack of support or increased sense of dependence on their partners during the course of disease (23). Emotional stressors are another kind of stressors that accompany breast cancer and include various emotional experiences after cancer prognosis or related to treatment techniques or therapies they undergo. These stressors intensify during the course of disease. A detailed study by Silvia Schmid-Buchi *et al* discusses about the various emotional and social distresses associated with breast cancer patients as well as their relatives post-treatment. (24) Thus, as far as breast cancer is concerned women are susceptible to different kind of stressors which have been independently studied. Henceforth, two main reasons for breast cancer being the major theme of study by different research groups can be a) breast cancer is the second most prevalent forms of cancer worldwide and there are a good number of studies which establish different stressed states associated with cancer; b) diversity of stressors related to a breast cancer patient provides a greater scope to study the affect of different kind of stressors for a single disease condition. Thus, breast cancer has more or less become a model for stress related studies in human population.

An account of breast cancer related studies asserts that while variability in certain factors like age group doesn't significantly affect the stress-disease correlation, other factors like different regional and social backgrounds as well as different social status showed significant affects on disease progression. This can be justified as the latter factors may influence the psychological state of a person more significantly unlike former. A set of studies done by Alice *et al.* support that those cancer patients which belong to lower socioeconomic backgrounds have poorer adjustment to cancer which further relates to social stressor This is also true for patients with prostate and colorectal cancer. (22) Thus, this very basic study gives a first idea of psychological factors associated with cancer.

All the recent studies further reviewed here show a dependence of cancer progression on stress established on the basis of positive effects of various psychological interventions in cancer recovery and survivability. The studies where stress among the breast cancer patients is relieved by various psychological interventions provided in the form of different programs like mindfulness based stress reduction program (MBSR) or cognitive behavioral stress management intervention (CBSM) especially after the primary cancer treatment not only show better coping to the stress, improved quality of life (QOL), reduced anxiety symptoms, reduced negative affects and a positive attitude for life but also show better recovery rates and lowered probability of cancer recurrence. (25-27) Biological marker that was used to monitor stressed and non-stressed states was cortisol and showed reduction in serum levels immediately after these psychological interventions. In these studies it has been shown that these psychological interventions mediate the immune system in a positive way which give better resistance to cancer and reduce its chances of recurrence.

According to set of experiments performed on breast cancer patients after they underwent primary cancer treatment viz. surgery, Antoni *et al* showed that CBSM buffers the adjuvant therapy by increasing the production of Th1 cytokines, IL2 and IFN-γ in PBMC of patients that were a part of intervention unlike patients which were not. The "buffering" action of CBSM was deduced from the fact that during a 12 month follow up, the levels of all the cytokines mentioned above stayed elevated only for a 6 month period, the duration for which adjuvant therapy was given. Moreover, women assigned to CBSM also showed greater cellular immune function deduced from *in vitro* studies on lymphocyte proliferation responses to anti-CD3 stimulation at 3 month follow up which can be linked to changes in Th1 and Th2 cytokine regulation as stated by some groups. (26, 28) In fact, it has been suggested that cell mediated immune indices may be the most sensitive to the stress-reducing effects of these interventions based on the studies of three groups. (26, 29-31) But again it becomes important to consider that the observed increased lymphocyte proliferative response after CBSM intervention can just be modulating system as stated by Mc Gregor *et al* interpreted from experimental conditions. Hence, it still needs to be established that whether the observed changes in immune system are simply buffering effects or *de novo* activation of some immune pathways irrespective of external therapeutics administered.

The non-randomized controlled design study to evaluate the effects of MBSR (27) also showed similar kind of modulator results on immune system. The most important consequences of MBSR has been observation of the temporal sequence of activation of various cytokines starting from cortisol release and followed by IL-4, IL-10 production preceding IFN-γ and NKCC activity suppression which may indicate the plausible pathway of stress mediation. As the study used non-randomized group of people, a piece of argument can be easily framed against the reliability of the study. But since the above mentioned CBSM studies done on randomized group also account for stress relief, the results related to MBSR in cancer patients can be relied upon.

The effect of social stressors was elucidated by studies (24) where effected women were assigned to weekly support groups, which emphasized on building strong supportive bonds, encouraging emotional expressions, dealing directly with fears of dying and death, reordering life priorities, improving relationships with family and friends, enhancing communication and shared problem solving with physicians and learning self hypnosis to control pain. It was found that at a 10 year follow-up, there was a statistically significant survival advantage for women in the group therapy. On average it increased the life expectancy with improved quality of life (QOL) for 18 months. Similar studies on group of patients suffering from melanoma as well as leukemia and lymphoma showed similar responses to psychosocial support. (32).

Another kind of studies relate hypnosis and cancer where patients undergoing cancer chemotherapy duly attended psychological interventions consisting of training in progressive muscular relaxation and cue controlled relaxation, direct hypnotic suggestion and a new procedure called nausea management training. The new thing about this study was that the improved conditions in the diseased state was attributed to more regularity and willingness to receive chemotherapy due to reduced side effects like vomiting, nausea and better control over them through nausea management training rather than neuroendocrine regulation. The psychological interventions seemed to have prophylactic effects. Another important outcome of the study was establishment of enhanced lymphocyte responsiveness and IL-1 with increased Creative Imagination Scale Scores in experimental group in reference to control group.

A very important immunologic factor that has been linked with cancer progression and metastasis is Natural killer cell cytotoxicity (NKCC). Anderson *et al* have come up with an important finding that high distress in newly diagnosed breast cancer patients not only shows lower T cell proliferation in response to anti-CD3 stimulation *in vitro* but also have a lower NKCC with or without IFN-γ activation. (29, 30)

Though it is difficult to state at this point of time that what factor in psychological interventions viz. reduced anxiety, better stress management skills , better coping skills or being in a supportive group is the most influencing of all on immune systems, it is clear that interventions can manipulate physiological systems. Similarly, the mechanisms by which these psychological interventions affect the immune system have not been pin pointed yet. Rather there are a number of proposed mechanisms based on the studies above (Figure 1).

One of the mechanisms as proposed by Antoni *et al* (25) states that increased glucocortcoid levels in synergism with catecholamines, which also show increased levels of expression in a stressed state, facilitates the cancer growth through various glucocorticoid receptor mediated activation or repression of target genes. Increased level of glucocorticoid is known to down-regulate cellular immune responses. It also affects the transcription of many cytokines like IL-2 and INF-γ which has a stimulatory effect on NK cytotoxicity as well as lymphokine activated killer cells. These inhibitory effects can be further related with the down-regulation of IL-12 receptor on these cells as well as through down-regulation of the surface expression and function of triggering receptors involved in NK cell cytotoxicity. As both of the biomolecules are a part of neuroendocrine and Sympathetic nervous system respectively, this implies the involvement of both these systems in response to stress condition in coordination with the limbic system. The same is suggested by Anderson *et al.* (29, 30)

In second mechanism proposed by Gregor *et al,*(26) they relate the improved benefit finding attitude among breast cancer patients after CBSM as a major factor behind the variations in immune response. The group states that benefit finding leads to perception of potential stressors as a challenge rather than threat which fits the model

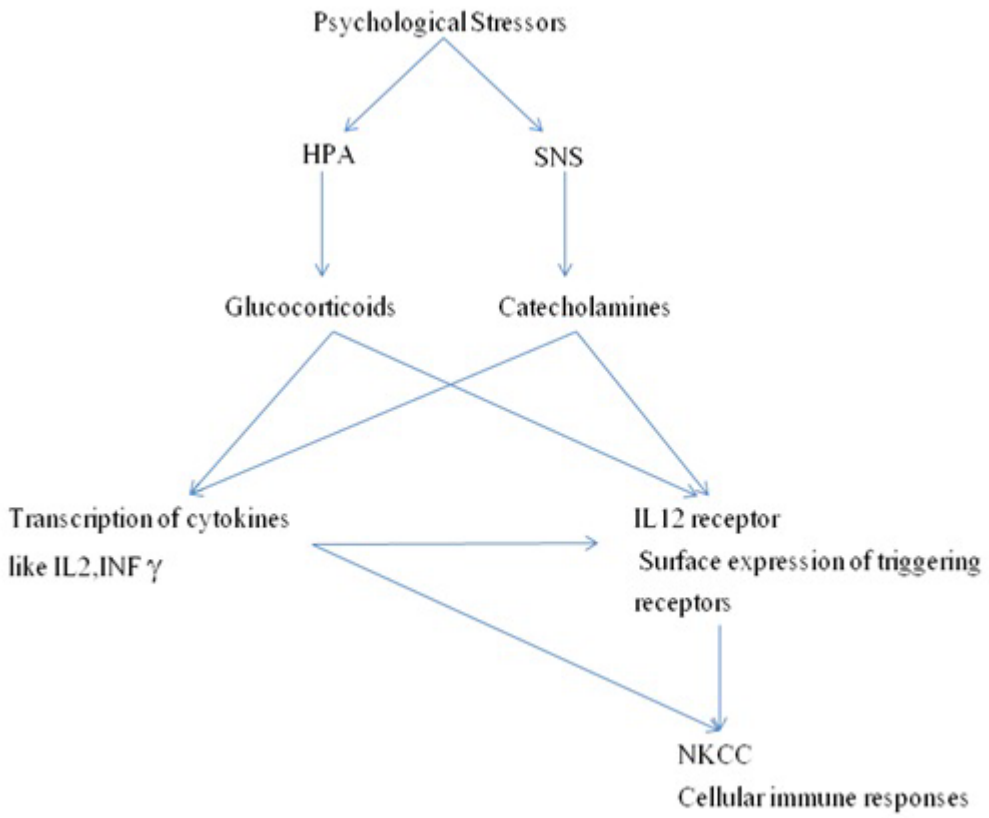

Figure 1. PSs and Cancer. Increased level of glucocorticoids and catecholamines through HPA and SNS axis during stress affects the transcription of cytokines like IL-2 and INFγ which either directly regulate the natural killer cell cytotoxicity and cellular immune response or indirectly by downregulation of IL-12 receptor as well as other NK cell activating receptors. Glucocorticoids and catecholamines can also directly affect the IL-12 receptor expression and hence downstream mechanism.

suggested by Epel *et al* (33). This perception consequently results in positive psychological processes such as efficient allostasis, anabolic changes, and improved immune function. The same group also hypothesizes the involvement of neuroendocrine system as is done by Antoni *et al* to mediate these downstream pathways.

The third is an indirect mechanism in which an increased inclination of patients towards receiving chemotherapy after hypnosis influenced the disease progression. Thus, the exact mechanisms of psychological interventions still remain to be established and need further investigation (34, 35).

3.2. AIDS and stressors

According to most recent surveys done in 2006 an estimated of 39.5 million individuals were diagnosed with HIV infection worldwide. AIDS diagnosis as well as progression is equally stressful as cancer. In fact, there is now a growing population of people of HIV-infected people who face both disease-specific and general life stressors because of increasing dependence on stringent treatments for maintaining an optimal health which are really demanding both physically and psychologically. Besides this, AIDS add up to higher degree of social stressors as well as peer pressure. Due to lack of adequate knowledge of the disease in people of the society they are more reluctant to accept AIDS patients that add another level of difficulties for them. Moreover, due to the reduced support and increased dissatisfaction in the relation with one AIDS suffering partner the psychological state of patient is further worsened. From above, it is thus easily comprehensible that the kinds of stressors in cancer and AIDS are almost similar. Hence, the studies to see the effect of stress on disease progression and increased survivability are also similar to certain extent.

The very first studies that actually demonstrated the effects of stress and social support on AIDS progression was done by Jane Lesserman *et al*, 1999 where they demonstrated a positive correlation of stressful life events, reduced social support and cumulative depressive symptoms with disease progression. (36, 37) In continuation with these primary studies, as is the case with cancer, the relation of stressors with AIDS has been highlighted with respect to consequences of psychological interventions on progression of AIDS. Adam W. Carrico and Michael H. Antoni (38) have evaluated the effect of

various psychosocial interventions on stress hormone levels of HIV-infected population. The group took into consideration number of interventions, viz. cognitive stress behavioral management, written emotional expression interventions, and relaxation training and meditation based interventions. The studies were part of long term follow-up and hence to be more confidant with the changes observed during psychological interventions, besides monitoring CD4+ cell count and viral load, the ability of lymphocytes to proliferate when challenged by antigens (like plant mitogens viz. Phytohemagglutinin (PHA)) as it may partially compensate for CD4+ cells decline during HIV progression was tracked. Similarly, NK cell count as well as NKCC was monitored as they are also known to have a compensatory role for reduced CD4+ counts. Besides considering IgG antibody levels in response, secondary infections were also taken into consideration. In this trial of CBSM done on randomized group of gay men, HIV positive men who received CBSM displayed significant increases in CD4+ cell counts, NK cells, PHA lymphocyte responses and NKCC pre to post notification of disease.

Another collection of behavioral studies have suggested that a composite of three positive psychological resources viz. positive effect, finding meaning, and positive or optimistic expectancy was negatively related to mortality and immune system decline (CD4+ cell counts) during a five year follow up with a percentage of 6% non-survivors who had all three resources versus 17% of population of people who did not have it. In fact optimism has been examined as the predictor of disease progression in five studies with one study providing a proof that patients with moderate optimism had the highest CD4+ cell counts.(39) In a study by Ironson *et al* (40), they found a linear relationship of optimism with CD4+ cell counts and viral load suppression. At this point, it is necessary to mention that according to recent findings, with a high state of optimism, there is an increased probability of acquiring a stressed state. This has been attributed to the violation of optimists' positive expectancies and subsequent disappointment, but empirical evidence suggests that it is more likely to be a consequence of optimists' greater engagement during difficult stressors. (41) Hence, the validation of linear relationship of stress and optimism has to be reconsidered. In fact in the study by Milan *et al* with 412 HIV Infected men and women a curvilinear relationship between optimism and CD4 cell decline was found. (36) Similar studies on HIV positive men with hemophilia found that having an optimist outlook predicted lower mortality. (42)

A set of contradictory results of studies done with a group of 74 gay men and 47 men found no relationship between dispositional optimism and disease progression although the latter study found that optimistic explanatory style was related to a faster decline in CD4+ cell counts during a 2-year follow-up. (43, 44) Hence, it becomes important to consider the moderate level of optimism as well as mode of its expression especially while explaining such contradictory studies. Although these findings are mixed, the larger and more recent studies showed a positive relationship between moderate optimism and better health outcomes.

Spirituality viewed as another type of coping when adopted by a group of men and women with and without HAART showed slower decline in CD4+ cell counts and better control over viral load similar to optimism studies. (40) Another aspect that was looked for in the same studies was effects of emotional expression on the health of people with HIV. It was reported that while emotional expression (during writing about a trauma) was beneficial for CD4+ counts and viral load, depth processing (emotional/cognitive processing) was even better. (40)Similar positive effects on CD4+ cell counts and viral load were associated with personality traits like openness, conscientiousness, extraversion, agreeableness, and neuroticism which may again be correlated with better stress relief (45) and hence the consequences.

An important emphasis has to be given here on the mixed results observed related to different intervention studies affecting CD4+ cell counts. According to five major studies on interventions affecting CD4 counts (one of the marker of HIV infection) (46-50) and one study on natural killer cells as an immune status marker did not show any difference among treated and control groups. A limitation of the studies concerns the fact that analysis did not control for patients' medical status and HAART medication adherence. Besides this the studies on cytotoxic T cells activity as well as population showed mixed results. (51) The above uncertainties may be a result of certain experimental limitations which have been overcome by time. As an example many of the negative studies did not observe improvements in some indicators of psychosocial adaptation, neither there was an evidence of reduced depression. Moreover, the affects of modulated immune system may not be direct and hence other immune components may be taken into consideration as mentioned above.

Taking a look at the more intricate mechanisms involved in altering CD4+ cell count and viral load and hence the disease progression, the involvement of HPA (Hypothalamus-pituitary-adrenal axis) and Autonomic Nervous System (ANS) becomes evident in this case as well. The mechanisms that modulate immunity through neuroendocrine hormone regulation are very similar to cancer. The main player seems to be again cortisol and glucocorticoid which impairs cellular immunity and hence is a predictor of faster progression of AIDS and mortality. Various coping strategies, psychological interventions, positive attitude have been known to modulate the immunity through cortisol levels. Other studies relate higher concentrations of Norepinephrine or catecholamines with elevated viral loads and higher autonomic nervous system activity at rest prior to beginning of HAART with poorer suppression of viral load and decreased CD4+ cell reconstitution. (38) Both of the factors appear to control several aspects of leukocyte functions like cellular activation, cytokine production, cell trafficking and immune effecter responses.

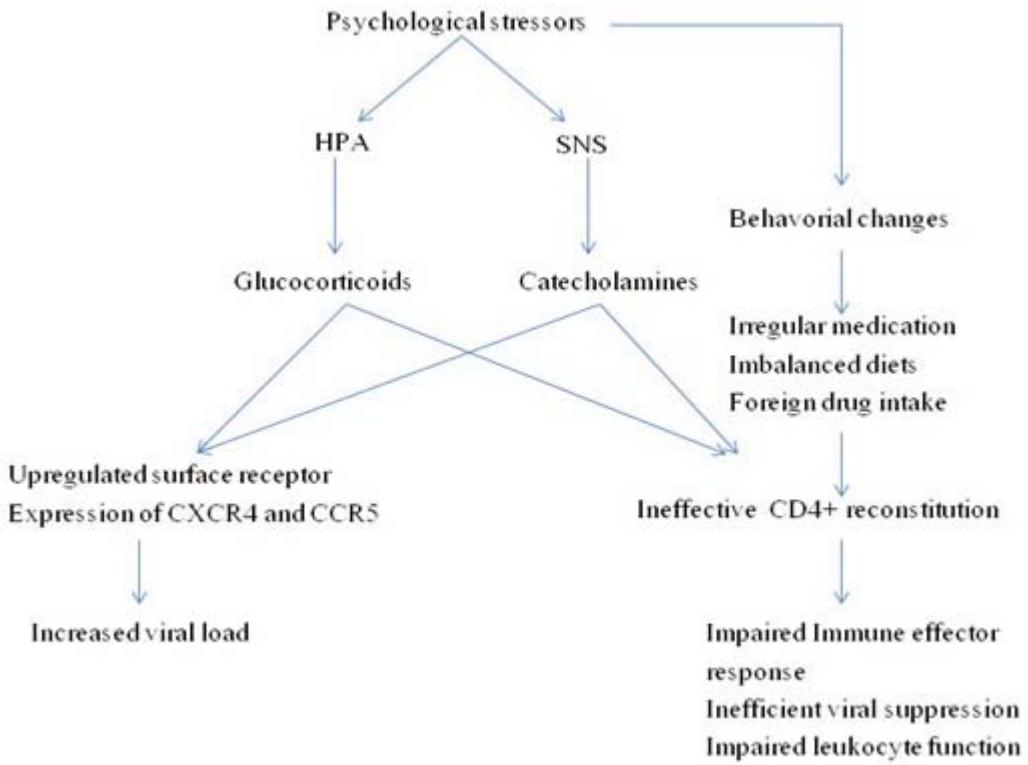

Figure 2. PSs and AIDS. Elevated glucocorticoids and catecholamines upregulate surface receptor expression while increasing the viral load and hence making the patient more susceptible to HIV infection. On the other hand the ineffective CD4+ reconstitution results in impaired immune response and hence impaired leukocyte function. The same changes are also observable as a consequence of behavioral changes like irregular medication, foreign drug intake and imbalanced diets that follow stress.

So far, according to the experimental evidences accumulated two possible mechanisms can be suggested to be active in concert or independently of each other in altering HIV progression (Figure 2). According to certain investigations, the first possible mechanism that makes a stressed person more susceptible to HIV is proposed to be a suppression of cellular immunity by increased cortisol level. The second proposed mechanism is that elevated glucocorticoid and catecholamines levels upregulate the expression of certain receptors like CXCR4 or CCR5 on T-helper cells that essentially are the target for HIV to infect and enter the cells while simultaneously aiding in virus replication and suppressing Type-I interferon response system as extrapolated from *in vitro* studies. (52, 53) The main signal transduction pathway involved in regulation of viral replication by catecholamines is cAMP/ PKA pathway. (53) Thus, while restoring the stress free normalized state in a person, all these negative effects may also be overcome. In fact as mentioned above some groups have reported that interventions lead to reduced cortisol levels and subsequently elevated immune levels. Therefore it can be a potential mechanism when the effects of stress relief in modulating immune system are looked for.

Again a line of caution has to be stated here that there are some studies done on rhesus macaque model of SIV infection where during an experimentally induced stress, there was a reduced glucocorticoid level irrespective of the increased SIV replication as well as followed immunodeficiency suggesting the possibility of involvement of some other modulating factors. In due course of continued experimentation these other factors were worked out to be induced SNS innervations of lymphoid organs marking the involvement of catecholamines. (54) Thus, it can be suggested that the two hormones can either act in conjunction or in succession to each other to give the observed consequences on immune modulation and viral replication and that all the observed changes in immune system as proposed may not be only cortisol mediated.

On the other hand, there is some support that optimists adopt healthier behaviors such as better adherence, more exercise, less illicit drug use, less smoking, more adaptive coping/proactive behavior, less use of avoidant coping, and enhanced mood. Positive states of mind have also been related to better adherence. As is evident, the indirect effects of optimism as well as hypnosis which involve an inclination towards a healthier lifestyle along with better adherence to chemotherapy may again affect the disease progression partly.

3.3. Inflammation and stressors

Chronic stress has been considered as one of the major contributors for the development of gastrointestinal disorders, such as irritable bowel syndrome or

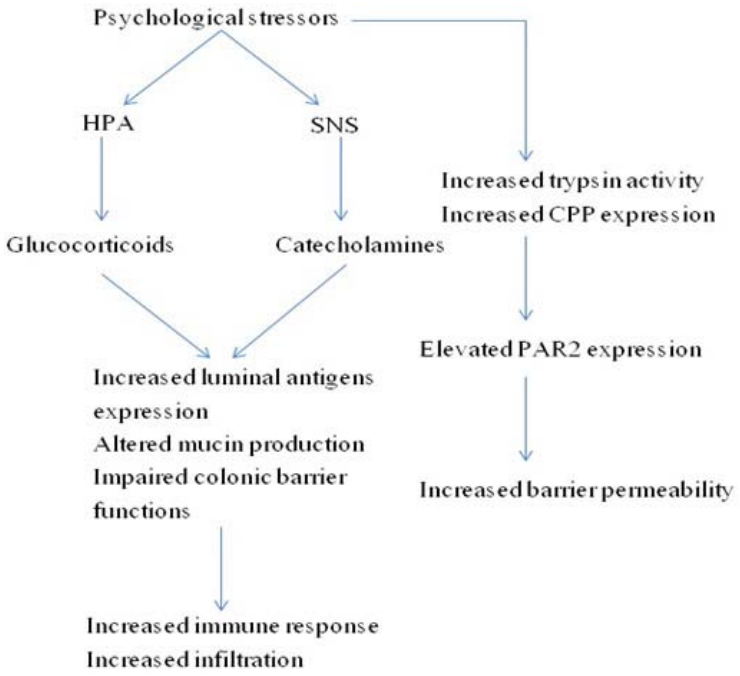

Figure 3. PSs and Inflammatory diseases. PSs through glucorticoid and catecholamines alter the colonic barrier by increased luminal antigen presentation and altered mucin production. These factors result in elevated immune response as well as increased infiltration of immune cells and hence colonic inflammation. On the other hand trypsin released by cholinergic pathways activated during stress results in colonic barrier alterations by PAR2 activation.

inflammatory bowel diseases, including ulcerative colitis. The exposure to various stressors affects the functional integrity of the gastrointestinal tract leading to altered production of mucin and impaired colonic mucosal barrier functions, which may result in increased infiltration.

In a set of investigations by Reber *et al* (17), it was found that a psychosocial chronic stressor viz. Chronic subordinate colony housing (CSC) which was given to mice during regular intervals for a period of 19 days resulted in impaired intestinal barrier functions thus increasing colonic permeability, enhanced presentation of luminal antigens to mucosal and non-mucosal immune systems as well as elevated secretion of pro- and anti-inflammatory cytokines by mesenteric lymph nodes. All these factors together contribute to colonic inflammation. Besides this the study also established dysfunction in other organs like thymus atrophy, and adrenal hypertrophy etc. in relation to chronic stressors. The mechanism involved in these observations again takes into account the altered sympathetic-adrenomedullary and HPA activity which results in altered epinephrine and glucocorticoid secretions. The thymus atrophy was related to increased expression of GC type-II receptors in response to elevated levels of GC which induces apoptosis in immature CD4+CD8+ cells during their selection process in thymus and inhibits immune cell proliferation. In fact this mechanism can also be a possible explanation for stressor mediated reduction in CD4+ cell counts as observed in the case of AIDS patients under PSs in response to elevated GC levels. Besides the GC levels the role of catecholamines in stressor induced thymus atrophy through β-adrenergic receptors is also suggested. In the same studies it was found that although initial exposure to CSC stressor resulted in elevated corticosterone levels in PBMC, during the follow up time of chronic stressor, there was a decrease in corticosterone levels. This reduction in corticosterone levels was attributed to non-responsiveness of the adrenal cells to secrete ACTH-induced corticosterone. As is evident, corticosterone levels may not be an absolute indicator of stress. Although these results can't be directly extrapolated to human system, it may be important to at least take into consideration these contradictory results with respect to studies especially related to AIDS and cancer where the elevated levels of cortisol have been monitored as a marker of stressed states during a year's follow up. Thus, the concept of cortisol as stress bio-marker needs a revision.

On a track to explain the plausible mechanism of gastrointestinal inflammatory diseases during acute stress Julien Demaude *et al* (18)suggested acute stress activation of cholinergic pathways to trigger exocrine pancreatic secretion. The group reported a significant increase in CPP, proteolytic and trypsin activities in response to acute stress. It was further suggested that the released trypsin in these conditions may activate PAR2 which can be a key mediator in colonic barrier alterations. While Reber *et al* highlight the effects of ACTH in colonic inflammation; Demaude *et al* have come up with a new mechanism of activation of cholinergic pathways that effect colonic permeability (Figure 3). Although, the results are diverse and need further investigation, it can be stated that stressors can modulate multiple physiological pathways to produce multiple inflammatory gastrointestinal disorders.

3.4. Epidermal abnormalities and stressors

It has been observed that many skin disorders including psoriasis, and atopic dermatitis are initiated, exacerbated and propagated by PSs. The role of PSs in epidermal structure and function abnormalities characterized by decreased epidermal proliferation and differentiation, impaired permeability barrier homeostasis and decreased corneum stratum integrity highlights yet another dimension of effects of stress on normal system functioning. In fact it has been observed in the studies exploring mechanisms related to wound healing after severe burns both in humans and mouse models that PSs affect the kinetics of barrier recovery while simultaneously affecting the basal permeability. (55) A similar set of investigations (56) on IPS mice demonstrated that IPS epidermis displays a decreased density of LB in the Stratum granulosum cytosol with simultaneous reductions in LB secretion. The reduced LB secretions were supposed to be a result of reduced epidermal control, fatty acid and ceramide synthesis. Also the decreased SC integrity is associated with a reduction in both the density and size of corneodesmosomes in the lower SC which is again a consequence of reduced epidermal lipid synthesis and hence contributes to epidermal layer thinning.

The reduced production and secretion of LB which causes a resultant decrease in the formation of the extracellular lamellar membranes that mediate epidermal permeability barrier function of LB can be attributed to change in glucocorticoid levels during stressed state. This has been established based on experiments where GC treatment impairs both permeability barrier homeostasis and SC integrity and cohesion. Since GC upregulation is associated with a psychological stress condition, the two seem to be interdependent. This has been experimentally validated by Euong-Ho Choi *et al.* (56) Mechanism of increase in GC production is stimulation of hypothalamic-pituitary axis which through CRH production leads to an increase in ACTH secretion by pituitary and hence increased GC secretion from adrenal glands.

Another important impact of PSs on cutaneous disorders especially skin infections was highlighted by Roka *et al* (57)which experimentally showed an increase in severity of cutaneous infections of mice. This was attributed to downregulation of epidermal antimicrobial peptide expression which was again related to increased GC levels.

Again concentrating on the other potential mechanisms of stress induced delay in healing or the epidermal abnormalities, the role of the sympathetic system based neuroendocrine hormones comes into picture. Raja k. Sivmani *et al* through a set of experimental studies on human and mouse models are suggestive of epinephrine mediated activation of the epidermal (55)keratinocyte β2AR, blunting of promigratory signaling pathways, stabilization of a stationary cell morphologic phenotype and subsequently diminished migratory speed of keratinocytes required for efficient wound re-epithelialization. The two suggested signaling pathways mediated by β2AR that result in decreased keratinocyte migration involve ERK and PI3K/AKT signaling pathways which may further mediate actin rearrangement in keratinocytes. Here it is mandatory to optimize the minimal levels of catecholamines required for wound healing since total norepinephrine depletion leads to impairment in surgical wound healing in murine models.

Thus to summarize in brief, the diversity of skin disorders involve again the mediation from neuroendocrine system involving both SNS and HPA similar to other diseased states (Figure 4). The diversification occurs in effector mechanisms where the increased GC and epinephrine levels down regulate or upregulate the expression of some proteins like antimicrobial peptides, β2AR receptors and other effector molecules through different signaling pathways that consequently affects the keratinocytes properties, and LB regulation (synthesis and secretion). These factors thus further regulate the SC integrity, barrier permeability, infection susceptibility and re-epithelialization. This gives an idea of the physiological network involved in stressor mediated skin disorders.

3.5. Obesity and stressors

The increased risk of obesity has been related to exposure to chronic stressors, such as job strain and negative psychological states such as depression besides the social factors like personal income, educational attainment and occupational status. Although the poorer health behaviors such as physical inactivity and dietary fat intake (58) associated with various PSs can be attributed to increased obesity risks. However, some findings suggest that adjusting to beneficial behaviors only minimally lead to a reduced obesity risk factor. Hence, it becomes essential to explore the stress mediated mechanisms related to high risk factor of obesity. The studies done in this regard by Mark Hamer and Emmanual Stamataki (59) suggest a contribution of inflammatory markers produced during a stressed state to obesity. Indeed adipose tissue is one of the major sites of release of inflammatory markers such as Interleukins and acute phase proteins. Hence, the secretion of certain pro-inflammatory cytokines like TNF-α and interleukins in the respective adipose tissue after a stressor stimulus may play a causal role in obesity. TNF-α may be involved in this through the regulation of free fatty acid levels, leptin production, glucose transporter numbers and insulin receptor activity and may influence the major nuclear factors involved in adipocyte growth, differentiation and function. In other words cytokines are thought to be involved in the regulation of metabolism and food intake thus possibly impacting on health behaviors (Figure 5).

3.6. Other diseases and stressors

There has been a set of experimental studies which explore the multidimensionality of stressor stimulated mechanisms to affect multiple organs. Although the studies are not detailed but they give a perspective of studying stressors in relation to diseases and potential benefits in these studies while simultaneously building evidences of stressor mediated immune responses as well as physiological functions. Some of the experimental studies are mentioned here.

PS as interventions

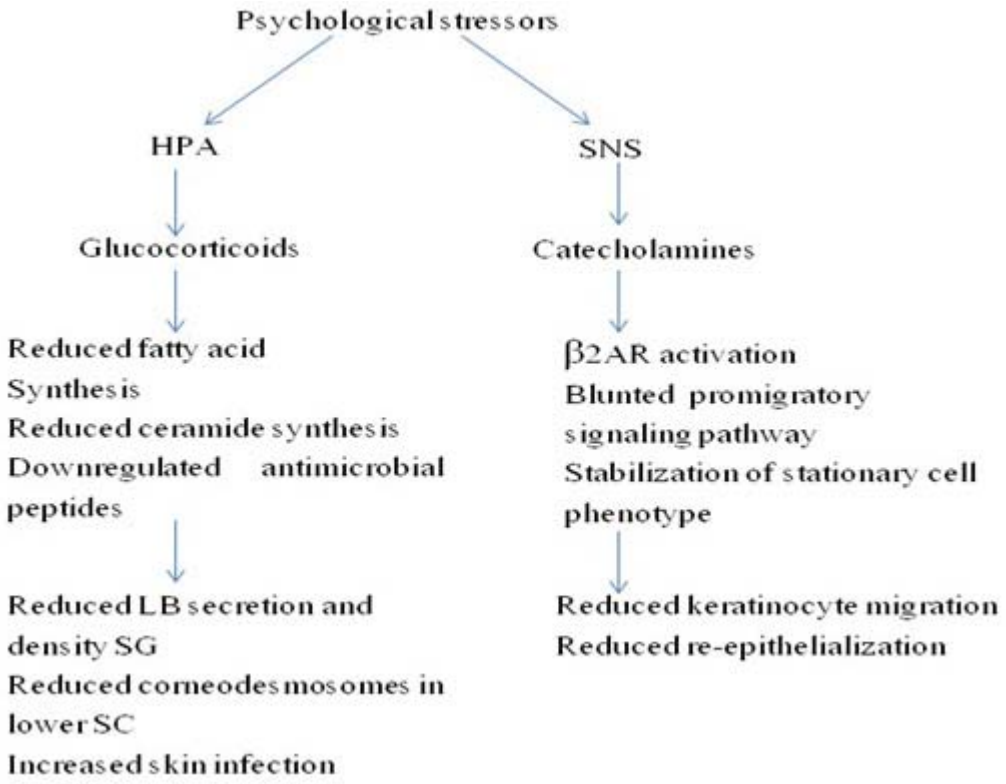

Figure 4. PSs and epidermal abnormalities. This figure shows that glucocorticoids and catecholamines activate independent pathways in response to stress. Glucocorticoids enhance the chances of skin infection and also elevate the normal skin healing time by downregulating antimicrobial peptides expression as well as reducing the fatty acid and ceramide synthesis which are important component for SG and SC respectively. Catecholamines effect the wound healing and epithelial reconstitution by preventing the further differentiation of epithelial cells and their migration to SC

Various heart related diseases especially CAD and artherosclerosis have been associated with the production of various pro-inflammatory cytokines like IL-6 and CRPs in response to acute stressors and exercise. The production of these cytokines has been related to gradual CAD progression. Some recent epidemiological investigations related to role of two main PSs viz. negative effect and psychological distress in inflammation and incidence of CHD by Hermann Nabi *et al* (60) on 6396 civil servants showed contradictory outcomes. It was observed that although a stressor stimulus was associated with increased probability of CHD, the inflammatory cytokines did not show any significant change in levels in response to PSs. Hence, there is supposed to be some other mechanism involved mediated by PSs that effects CHD. It has to be stated again that both the studies have their own limitations and the results have to be interpreted with care. But the important point to be noted here is that there is an evident association of stressors with disease progression even though what are the exact mechanisms involved in it have to be resolved still.

Similar studies on the effects of psychological states of parents in the state of asthmatic children revealed that parental perceived stress and parental depressive moods result in increased levels of ECP as well as stimulated IL-4 production in children during a period of six month follow-up. Both IL-4 and ECP are closely connected to the inflammatory processes leading to asthma symptoms such as airway constriction/obstruction and edema. Thus, it may be potential mechanism that results in morbidity among children with stressed parents. (61)

While exploring all the possible mechanisms by which PSs can affect the physiology and play a role in enhancing the diseased state leads to studies where role of PSs in the activation of antioxidant defense system and also in a significant increase in the oxidative stress markers is highlighted. It has been speculated that an elevation in the levels of these systems will result in reactive oxygen species production and may be a potential risk to the integrity of the tissues. (62)

From all the above mentioned studies it is clear that stressors can affect multiple systems causing an enhanced progression as well as severity in a range of diseases that involve multiple signaling pathways and multiple effector molecules. Nonetheless the latter studies don't establish the participation of neuroendocrine system or other stressor response systems but only focuses on the intermediate pathways which mediate the resultant effects, elevated cortisol levels in response to stressors reported in all the

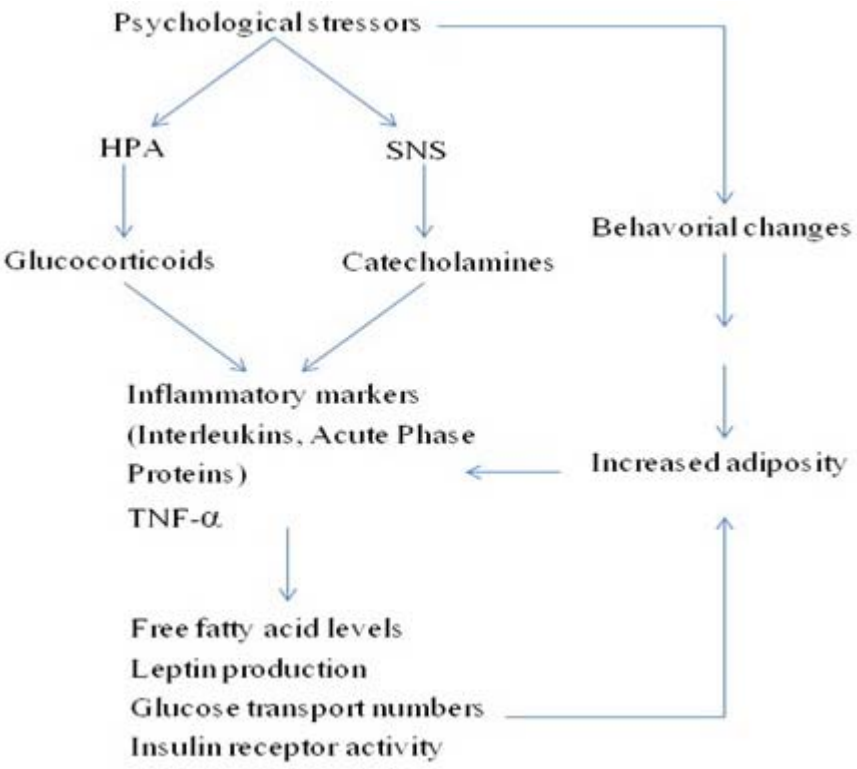

Figure 5. PSs operate through both direct and indirect mechanisms in diabetes. Glucocorticoids and catecholamines activate various inflammatory marker that by downstream activation of multiple factors result in increased adiposity which in turn activates inflammatory markers. thus forming a continuous feedback loop. On the other hand behavioral changes also result in increased adiposity and hence the inflammatory markers.

studies indicate towards the master response system to stress, HPA. But still this generalization has to be made with a caution. Hence, it also becomes important to investigate further the basic mechanisms of initial activation to a stressor.

Another very interesting study on healthy individuals has brought out a very different response of neuroendocrine which were subjected to PS. It was found that acute stressor results in mobilization of CD45RA+ Effector Memory (EMRA) within the δ1 and δ2 γδ T cell populations. The γδ T cells unlike possess the ability for immediate effector responses, such as rapid secretion of the pro-inflammatory cytokine IL-17, which helps orchestrate early immune responses. (63) The stress lymphocytosis although not fully established to have an implications for the way infection and inflammation are dealt with, they can give an insight into a new aspect of stressor mediated immune response in healthy individuals which is completely different for the diseased individuals. Again the master controller is sympathetic nervous system similar to many other stressor responses which releases epinephrine after stressor stimuli. Epinephrine through adrenergic receptors induces detachment of γδ T cells. This can be suggested as a potential mechanism of stress mediated lymphocytosis. The above results are suggestive of the fact that body or more physiologically speaking, the neuroendocrine system behaves differently in modulating the immune system in response to stressors in diseased and healthy states. Although a lot more validation and investigation has to be done in this regard, this aspect of stressor mediated lymphocytosis may give an initial insight into a possible therapeutic role of acute stressors that can be exploited to counter diseases.

It is clear now that although all these studies may present a very wide, diversified perspective of putting stressor responses, the idea is clear that PSs are involved in altering the normal physiologic state of body. The physiologic state may involve alterations in immune system generally downregulation, an effect on the permeability barriers, receptor and essential protein expression which disturb the normal responses of the body to different healing mechanisms and hence the disease recovery, susceptibility and progression.

The implications of this study can be very far reaching and broad as will be mentioned in further sections.

3.7. PSS and genetic diseases

So far, the reported studies only show the genetic aspects of increased PSs susceptibility to people with specific genetic makeup. This has been elucidated in case of hypertension development at a younger age of children who have non-functional SIPN that results in impaired blood pressure release physiology by altering the urine flow

through sodium osmolarity control and hence results in hypertension. (64)Another study on a group of mice with altered catecholamine catabolizing enzymes showed more response to stress conditions than normal. The enzyme COMT was altered by methionine substitutions. Furthermore, it has been shown that influence of genetic variation on brain activity and risk for depression is modulated by the accumulation of stressful life events. (65), (66) Thus, the present scenario of stress research has very few to say about the genetic aspects of stress manifestation as well as modulation.

4. CONCLUSION AND PERSPECTIVE

The idea is to find a correlation between psychological stressors and physiology during disease. In fact, the studies mentioned above can be scrutinized for the following basic questions. Whether there is any correlation between PSs and physiological mechanisms when considered in context of diseases. If there is a correlation, what role does these physiologic mechanisms play in a disease. Whether there is a common mechanism mediated by PSs in all the diseases studied. If yes, what are the possible implications of all these generalizations?

While answering all these questions to an appreciable degree of accuracy, it becomes important to take a deep and critical look at all the experimental studies that have been done so far. As mentioned already, the studies on a correlation between PSs and physiology have shown mixed results with certain degree of uncertainty. The reason behind this uncertainty especially when considering studies done on human population is firstly the absence of an isolated system where all the consequences observed cannot be attributed to PSs alone. Since, individuals are free after the studies and are not being checked it is very much plausible that the positive effects of psychological interventions or negative effect of stressors so monitored are partly due to intake of some special kind of drugs or food habits or some dietary imbalance not in the notice of working group during the studies. In this case the effects may not be directly linked with the PSs. Hence, considering indirect mechanisms becomes important. Secondly, in the studies where patients volunteered for the psychological intervention studies themselves it is very likely that they belonged to either an educated group of people and families with good social status. Thus, the level of psychological stress can be significantly lower in comparison to opposite groups where awareness about the disease and its consequences are lacking resulting in higher degree of psychological and social stressors. In this case the recipients of psychological interventions will actually not be benefitted too much with it and hence may not show any positive correlation.

Thirdly, there has to be more reliable biological methodologies to predict the stressed state so that a clear distinction can be made not only between a stressed and non-stressed state but also among intermediate stressed states especially during the psychological interventions studies in case of cancer and AIDS. It is necessary because the effects of psychosocial interventions may be different for different people. This may not be brought out very well in the questionnaire designed to see the stress relief. It is very much possible that a patient after set of interventions feels better but physiologically that effectiveness may be very minor to affect a disease recovery or progression. Thus, it is mandatory to standardize the qualitative and quantitative markers for different stages of stressed states. Fourthly, long term follow up studies for which it is really difficult to exclude the effect of external factors and solely considering the effects of psychological stress relief in diseases. Thus, it is necessary that all the aspects and limitations are kept in mind while performing and interpreting experiments related to PSs. But since the most recent studies especially in a period of decade or two are considerate enough to keep some of the points in mind, yield a positive correlation between PSs and physiology. Hence, the question to first answer with a certain degree of uncertainty and statistically with more number of positive results will be affirmative that there exists a correlation between PSs and physiology.

As the answer to first question is yes, it takes us to the next level of inquisitiveness that if there is a correlation which is taken to be true, what role it plays in diseases. The answer to this question leads to the next step of establishing the basic mechanisms that are involved in stressor responses. As can be deduced from above mentioned studies the stressor responses can be mediated through two important mechanisms, direct mechanisms and indirect mechanisms.

Direct mechanisms involve all the pathways that are activated directly in response to PSs. As obvious from the name this must include the neuroendocrine system especially HPA and SAM both of which are known to respond to stress by secreting ACTH and epinephrine/norepinephrine hormone respectively. ACTH further activates the adrenal cortex to release a group of hormones including cortisol. These set of hormones have various effects such as conservation of glucose for neural tissues, elevation or stabilization of blood glucose levels, mobilization of protein reserves, conservation of salt and water, suppression of wound healing and immune system. On the other hand, SAM system triggers catecholamine release from adrenal medulla that produces flight-fight response. Both these systems respond to stress in both coordinated and independent manner depending on different stressor stimuli. It is good to mention here that long lasting effects of these hormones which affect the disease related physiology are associated with the third stage of stress response from three stages viz. alarm reaction, resistance and exhaustion as proposed by Selye (67). The neuroendocrine hormones thus further produce multiple effects like immune suppression which increases disease susceptibility, a suppression in re-epithelialization, LB formation and keratinocyte proliferation which is a reason for multiple skin disorders and a delay in wound healing, release of a number of proinflammatory and inflammatory cytokines that are associated with various heart related diseases especially artherosclerosis and asthma. Along with this these hormones activate a number of downstream signaling pathways which may result in

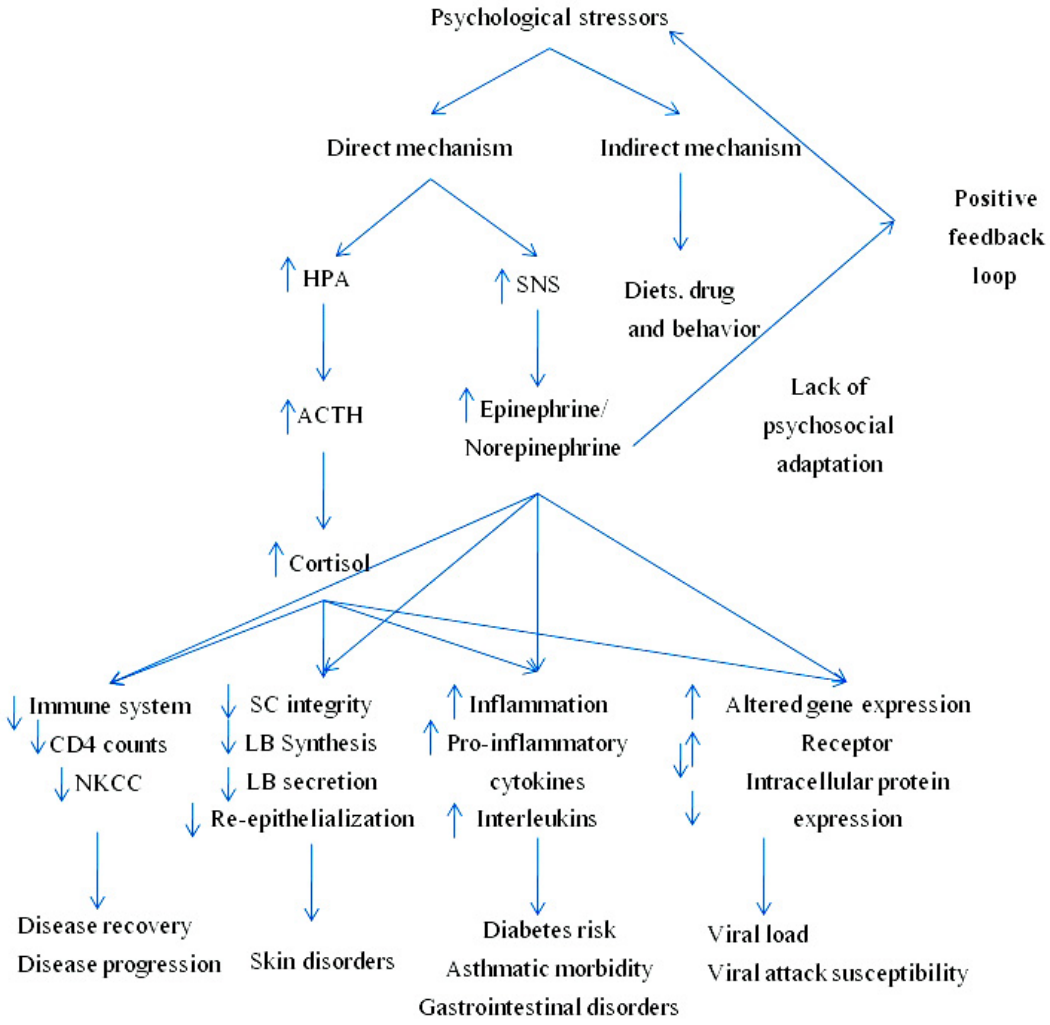

Figure 6. A schematic representing the direct and indirect mechanisms of psychological stressor response as well as positive feedback loop that operates during psychological stressor response.

over-expression of some receptors that increase the viral susceptibility or may suppress the protein expression within the cell that favors viral replication and hence may increase the severity of infection. Besides all these effects, there is a very important consequence of the elevated levels of hormones and cytokines i.e. the set of hormones and cytokines released may affect the neuronal integrity in a reverse direction that may alter the tendency of brain to adapt psychosocially. It will lead to more stressed state because a stressed individual may not be able to cope very well with the PSs. Thus, it can be easily seen now that there is a positive feedback loop controlling the whole process and worsening it in each turn which is a concerning issue.

The other mechanism through which PSs may play role in disease physiology involves indirect pathways. Here, unlike the direct mechanism the body responds to PSs in an indirect way. It has been shown that a stressor induces many behavioral changes in a stressed individual. As an example depressed individuals or individuals with high level of anxiety prefer intake of drugs, alcohol, sedatives. They also prefer low nutrient diets. Other case of social stressors especially involves low nutrient diets because of poor economy etc. All these factors definitely affect the physiology as in individuals are weak, with low nutritive diets their immune system are also not well developed. The drugs and alcohol are special players that may result in different kinds of cancerous growths or worsen the present disease situation. On the other hand, stressed states have also been associated with increased BMI due to increased consumption of sweet food during stress and hence central adiposity which is associated with cancer. (22) Similarly, a good psychological state results in better response to chemotherapy and vice versa which may again be related to the same consequence. Thus, all these factors can be very well related to disease progression and recovery and may partly contribute to the present scenario of relationship between PSs and physiology. A schematic presented in Figure 6 summarizes the mechanism and their downstream effects.

Before proceeding further with the next question, it becomes important to bring into light another drawback

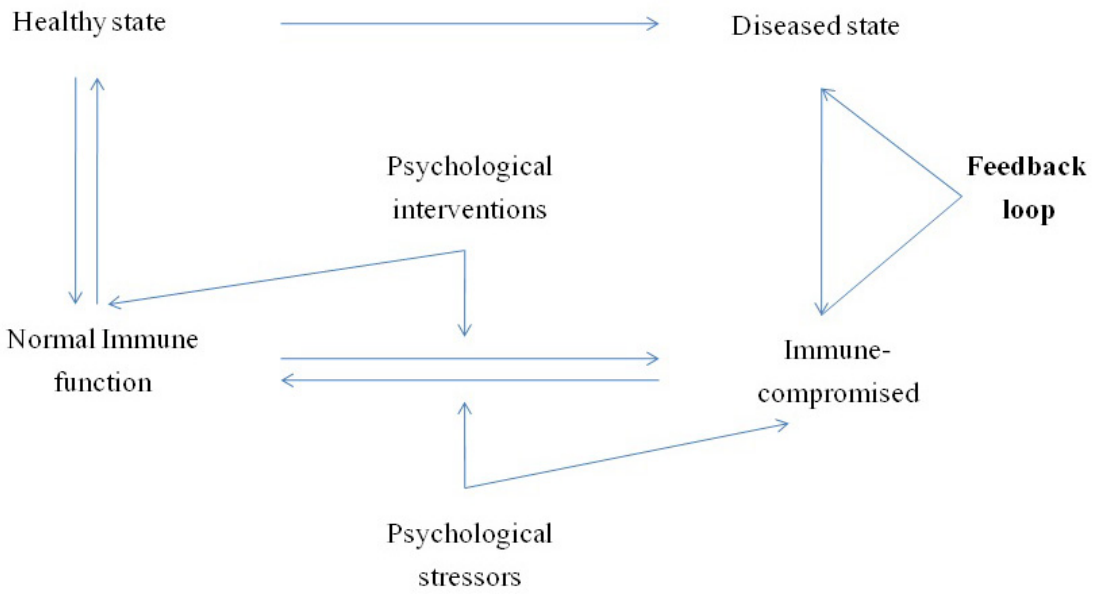

Figure 7. A schematic showing relation between PSs and several health states

of the PSs related studies. It is the lack of an established pre-condition of a stressed state i.e. the knowledge of various signaling pathways associated solely with stress is still not known. As a result when studying the effects of stressors in relation with diseases , it may not be distinguished that which effects are independently or de novo activated irrespective of a diseased state and which effects are actually being buffered in the presence of a PS during a diseased state. The similar type of argument is applicable for effects of psychological interventions in case of disease recovery. The essentiality of such distinction arises when we look at Psychological interventions as a prospective therapy for better disease recovery and treatment as discussed below. A schematic presented in Figure 6 summarizes the mechanism and their downstream effects.

Now, it is established that there can be multiple pathways by which PSs can actually mediate a number of disease related conditions. The diversification in the range of diseases it can affect for a moment makes us to think of it as a master mediator that can potentially alter all the system functions. But giving a closer look at the mechanisms mentioned it can be said that neuroendocrine system is master mediator through which more or less all the PSs operate. Although it may not be generalized for all the cases as a part of effects are indirect and many mechanisms are not explored till that regulation level but to a good approximation it will not be wrong to say that there is a common operating system for PSs stimuli and hence can be pin pointed.

qWith answers to all the questions, we are more or less ready to address the last question of the quadrate questionnaire and perhaps it is the most intriguing with far reaching implications and high expectations, i.e. "What are the implications of all these generalizations?" So far, we have established that PSs play a potential and significant role in disease progression, recovery, increased disease risk, and disease susceptibility. The different psychological interventions that help reducing the effect of different stressors during a disease will reverse the negative impact of PS on physiology. This can aid in tackling the disease better. Moreover, it has been seen that different individuals respond differently to chemotherapy. One of the reasons for this disparity could be different levels of associated stress with a diseased state in multiple individuals. Hence, knowing a stressed state of person can actually help in administering a co-therapy based on psychological interventions that enhance the responsiveness of an individual to the drug administered as well as aid in its better recovery. This is evident from the studies that showed better response to adjuvant treatment after primary cancer therapy when given interventions. Besides individual level, at a general level also this can be related to slow disease progression and better survivability rates in Cancer and AIDS patients. It may thus help not only in improving QOL but also improving the disease related states. Thus, at this moment it can be clearly stated that psychological interventions that primarily target PSs during a diseased state can be used as a co-therapy to minimize the disease progression and maximize the recovery by the mechanisms discussed above. Not only acute stressors are known to elevate innate immune responses during initial stages of stress manifestation (20) but they may also act as another key modulator or a prophylactic to enhance immune system and fight with the disease.

As a consequence, a bigger picture of understanding of PSs and the effects of psychological interventions as well as other stress relieving factors can be framed in context of diseases to develop on a potential therapy for treatment rather than recovery (Figure 7). It is well established now that there is a neuroendocrine switch that can be regulated externally, as in here by psychological interventions and stress relieving therapies. And this neuroendocrine switch regulates some of the key players in body's defense and homeostasis maintenance. It is also a fact that in general most of the

diseases are associated with a state of immune-compromise, that is to say a diseased state is a consequence of immune system not able to counter act the factors resulting in disease whether they are external or internal. In this sate a PS will further lower the immune activity by the mechanisms mentioned. PS will lead to a more immune-compromised state and hence more worsening of the disease while operating in a positive feedback loop. Here, when psychological interventions are given they counteract the effect of PSs and try to reboot the immune system to its normal homeostatic level. This reversal can be modulated by certain external factors such that it reverses the negative impact on immune system not only because of PSs but also in a way that is sufficient to fight the disease. In order to look further for potential of this therapy, it now becomes important to establish whether the interventions work through *de novo* activated pathways or buffering pathways. This is because this revelation with respect to psychosocial interventions can be used to not only influence specific diseases but in general to control a class of diseases or a sufficient range of diseases. Furthermore some studies establish positive effects of acute stress especially in lymphocytosis and innate immune responses in a healthy state. These kinds of studies are only indicative and not a strong evidence of potentials of psychotherapy. In fact, the acute stressor mediated redistribution of innate immune cells may come up as a potential method of immunity enhancement when administered at regular intervals.

Thus, the use of psychological interventions and PS in relation to disease treatment may be a potential candidate and hence has to be explored a much greater extent.

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Abbreviations: HAART: Human Anti retroviral therapy; SNS: Sympathetic Nervous system; CBSM: Cognitive Behavioral Stress Management; MBSR: Mindfulness based Stress Reduction; NKCC: Natural Killer Cell Cytotoxicity; QOL: Quality of Life; PHA: Phytohemmaglutinin; ANS: Autonomic Nervous System; CSC: Chronic Subordinate Colony Housing; PBMC: Peripheral Blood Mononuclear Cells; CHD: Coronary Heart Disease; CAD: Coronary Artery Disease; SC: Stratum Corneum; SG: Stratum Granulosum; LB: Lamellar Body; IPS: Insomniac Psychological stress; ACTH: Adrenocorticotrophic hormone; CRH: Crticotrophin Releasing Hormone; GC: Glucocorticoid; ECP: Eosiniphil Cationic Protein; EMRA: CD 45RA+ Effector Memory T cells; SAM: Sympathetic; SIPN: Stress Induced Pressure Natriuresis Adrenal Medullary axis; SIV:; Psychological Stressor: PS; CPP: Colonic Paracellular Permeability: PAR2: Protease Activated Receptor; Catechol- O- Methyl Transferase(1).

Key Words: Stress, Psychological Stressors, Disease, Biomarker, Review

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