REVIEW ARTICLE

The Brain Frame – From Molecules To Behaviour

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ABSTRACT

Since the beginning of time, behaviour of acquaintances, friends and family has been a matter of intense interest. Behavioural issues have, since then, imposed threats to human race as either evil spirits or insidious offences. To address these concerns, social, theological and scientific communities have played a vivid role, bringing to light the underlying secrets of their respective domains. Present literature shall highlight the revelations made by the scientific community regarding behaviour. According to science, behaviour is the outcome of multiple processes taking place within the body as influenced by the external environment. The external environment includes the behaviour of fellow beings, the weather and the environment (political, economic, social and technological). The food we eat shapes the internal chemical environment by providing materials to the available genetic and molecular base of the body. The molecules of the body include hormones, enzymes as well as energy providing substances like carbohydrates and fats, and structure making molecules, proteins. Any change in the external or internal body environment that imposes a demand to adapt is known as stress. Acute stress is controlled and the body adapts under the influence of physiological changes including the cortisol related cascade on top of the list. Chronic stress is beyond the physiological control leading to exhaustion of the adaptation process. This may lead to depression finally. The cortisol cascade is a multi dimensional pathway beginning from the brain (hypothalamus) that perceives the stress signal and regulates the release of the effector, cortisol from the adrenal gland. Cortisol before it reaches a level that stimulates the negative feedback loop plays a vital role in the regulation of metabolisms as well as in the control of the release of other hormones like epinephrine and insulin. This regulation by cortisol ultimately has its role in the synthesis of brain neurotransmitter serotonin that has a known affect on behaviour.

Key words: Stress , depression, cortisol, hormones, metabolism

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Behaviour is the response of organisms to internal or external stimuli. The behaviour is often the identity of humans as they are recognized and treated according to what their behaviour demands. Humans behave in response to their physical, mental and genetic status as governed by the external environment. All events that impose a demand to adapt are stress. Stress can be acute or chronic depending upon the duration of its persistence. Research has found that continuing adverse conditions are associated with risk for depression.[1-3] Chronic stress can be defined as the one which is repeated at intervals. The hypothesis is that chronic stress exacerbates the effect of acute stress on depression. The effects of acute stress are reversed by the body's physiological mechanism, but the changes brought about by chronic stress, leading to depression requires exogenous treatment. Stress can be welcome 'Eustress' e.g getting married or unwelcome 'Distress' e.g increasing work load. Eustress is constructive stress and may have a reinforcement affect on individuals, while distress is disabling with signs of a nearing collapse or exhaustion state. Acute stress is stress when the adaptive mechanisms within the body are triggered and are successful in facilitating the recovery process from the prints of stress, while Chronic stress is the repetition of the same stress repeatedly and the biological systems of the body are susceptible to exhaustion, trying to adapt. Recurrent episodes of mood disorders may become progressively independent of stressors. This exhaustion leads to depression. Thus, episodic stressors are discrete negative events that have a beginning and an ending serving as the basis for the relationship between stress and depression. Stress-depression association becomes more compact with the increasing number and severity of the negative events[4]. The stress precipitation into depression varies from individual to individual with respect to the perception of loss caused by the stress and it can be mediated by factors that an individual may be exposed to.

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STRESS- DEPRESSION MEDIATORS

Developmental mediators

Kessler and Maggee, 1993[5] investigated the power of eight retrospectively reported childhood adversities, occurring through age 16 to predict depression in an epidemiological sample and found that many were associated with depression by age 20. Early adversities may be responsible for higher levels of adult stress[6].

Socio-demographic mediators

The socio-demographic moderators may include sexual victimization, temporary separation with a loved one, harassment at work place, racial discrimination etc. Psychological mediators.

The psychological basis of depression may be the goals and values of individuals and traits such as perfectionism, neurotism, dissatisfaction with situations and incompletion of ambitions. Such mediators have outcomes like fear, anxiety, novel environment and immobilization affecting the neuroendocrine system. Biological mediators

Biological stress processes have been reported to have a major role in depression precipitation. The Hypothalamic Pituitary Adrenal (HPA) axis dysregulations have been speculated to play a critical role in the occurrence of depression, its persistence, progression and relapse[7-10]. The final molecule, cortisol holds a pivotal role in the mediation of stress development leading to depression.

HYPERCORTISOLEMIA AND DEPRESSION

Depression is termed as a life threating disorder, characterized by hypercortisolemia[11]. Depressives were noted to exhibit hypersecretion of cortisol and its metabolites. According to a study on post natal depression, the degree of depression was raised with decreasing circulating tryptophan and increased circulating cortisol[12]. The latest research concludes that hypercortisolemia in depression may result from alternative pathophysiological mechanisms involving irregular basal hypersecretion of cortisol, associated with adrenal enlargement, possibly through splanchnic sympathetic activation of the adrenal cortex[13]. This proposes a major role of the Hypothalmic-Pituitary-Adrenocortical (HPA) axis in the regulation of stress and depression related functions of the body. The released glucocorticoid (Cortisol/corticosterone) has profound implications on peripheral as well as central management of stress and depression. Release of cortisol is regulated by hormones namely Corticotropin releasing factor (CRF) and Adrenocorticotopin Hormone (ACTH). CRF is a 41 amino acid neuropeptide secreted by CRF neurons, the cell bodies of which are the densest in the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN) within the majority of cells projecting to the median eminence. The hypothalamic endocrine stress axis is a part of the CRF pathway. The presence of CRF neurons in the raphe nuclei and locus coeruleus (LC) suggests the role of CRF in modulating the serotonergic and nor-adrenergic pathways in brain, having implications in the pathophysiology of depression and anxiety disorders. During stress the CRF release is increased and it binds to the CRF receptors in the anterior pituitary and through a cascade of intracellular steps ultimately increases pro-opiomelanocortin (POMC) derived peptide Adrenocorticotopin Hormone ACTH) and â- endorphin. ACTH in turn stimulates the adrenal cortex to release glucocorticoids. It has been observed by Dunn and Berridge, 1990; Owens and Nemeroff, 1991 ; Koob and co-workers,1993 that CRF system mediates the neuroendocrine and autonomic behavioural responses to stress[14-16].

It was noted that CNS administration of CRH to laboratory animals, produced responses similar to responses to stress, like increased arterial pressure and heart rate, suppression of exploratory behaviour, induction of grooming behaviour, increased conflict behaviour, decreased food intake and sexual behaviour. Contradictory studies regarding the concentration of CRF in the CSF of depressed patients have suggested that the concentration of CRF is a measure of mild to moderate depression. Post mortem studies have revealed hypersecretion of CRF and mRNA of CRF in the Paraventricular Nucleus (PVN) of patients with depression[17,18]. This finding is consistent with the early studies[19-22]. Cortisol, thus is an important factor inducing tryptophan oxygenase, the first rate limiting enzyme of tryptophan oxidative metabolisms reducing available tryptophan for serotonin synthesis[23]. Repeated stress ultimately results in depression[24]. Depression is the result of glucocorticoid resistance caused by stress–induced activation of corticotrophin-Releasing Hormone (CRH) neurons, being unrestrained. Glucocorticoid resistance may be congenital or acquired resistance to glucocorticoid feedback in CRH neurons caused increased HPA axis activity and produces hypercortisolism. The rest of the body, including the brain is affected by hypercortisolemia, synergized with stress induced serotonergic, dopaminergic, nor-adrenergic neurons in the brain stem making the limbic forebrain system more sensitive to the neuronal inputs[25-29]. It is seen that in depression, Adrenocorticotropic Hormone (ACTH) along with cortisol secretion is

increased[30]. A study conducted by Young et al., (1993)[31] has provided evidence about the feedback loop by administering cortisol intravenously to depressives. It was found that the fast feedback control of pituitary response was insensitive. The study was unable to reveal whether it was actually cortisol insensitivity or receptor down-regulation in the limbic brain due to increased CRH and ACTH.

Though it has long been known that 5HT acts on the HPA system[32], studies have shown the cortico-steroids also act on 5HT receptors[33]. Serotonin regulates the HPA axis, CRH and ACTH release affecting the corticosteroid levels ultimately. This inter-relationship is responsible for the stress coping responses of the body[34,35].

Studies in animal models have proved this relationship. The serotonergic activation of HPA axis is also suggested for humans[36]. In animals, acute stress enhances 5HT turnover, by increasing tryptophan availability and stimulating tryptophan hydroxylase[37-39]. The released 5HT completes the HPA axis ,corticosteroid negative feedback loop, that leads to adaptation to stress[40,41]. A proper functioning 5HT synthesis and release system is thus necessary for stress response and adaptation in animals[42] and humans[43]. Chronic stress increases 5HT sensitivity, deteriorating stress adaptation by disturbing the HPA axis balance. The condition thus reached is depression characterized by hypercortisolemia, low tryptophan level and hence compromised serotonin synthesis and release. These neurochemical modulations and their role in stress adaptation and other psychiatric disorders can be observed in preclinical rodent models. These preclinical models have close relevance with clinical conditions. Major breakthroughs for clinical benefits have been derived by the observations in these models. There are numerous animal models for psychiatric disturbances that match etiology, biochemistry and neurochemistry of the corresponding clinical disorders.

It has been observed in a retrospective study carried out by Huang, 2002[44] that there were low levels of albumin in psychiatric in-patients with mood disorders as compared to controls. Studies with primary cultures of rat adipocytes have clearly elucidated the influence of glucocorticoids on Albumin gene expression enhancing it though regulated by other hormones too. Glucagon markedly increased the glucocorticoid induced gene expression of albumin, while epinephrine decreased it. Insulin and tri-iodothyronine had no affect on hepatic albumin gene expression[45].

CORTISOL: From the periphery to the centre Cortisol is the hormone secreted as a result of HPA axis activity. It is the effector of the HPA axis limb of the stress response system. The central effectors of the stress response system are the corticotrophin releasing hormone and the locus coeruleus – nor epinephrine / sympathetic systems. The CRH and the nor-epinephrine neurons innervate and stimulate each other in a positive feedback manner. The activated HPA axis is not only responsible for adaptation to stress but also for the control of the stress response[46]. Apart from stress and its visible responses, the activated HPA axis has the function to guide all energy sources to the brain. Antidepressants that modulate the HPA axis have an impact on serum cortisol levels. The activated HPA axis regulates all major metabolic events of the body, influencing other hormones secretion and modulation. The glucocorticoids released as a result, cause energy conservation for the brain and critical life processes. The general effect of glucocorticoid action is thus seen to increase glucose in the blood, decreasing its cellular utilization and directing it to the brain. An increase in blood glucose may stimulate insulin secretion and after brain glucose uptake cellular uptake and then storage may be done. The released insulin; in concert with glucocorticoids has a variety of post effects on the metabolic status and ultimately on the homeostasis of the body. Adipose tissues are the biggest energy reservoir of the body, exceeding available glycogen and protein stores[47]. Triglycerides (TGs) and free fatty acids released from the adipose tissues are a major energy source for the heart and skeletal tissues[48]. Released glucocorticoids as a result of activated HPA axis stimulate the Hormone sensitive Lipase (HSL)[49]. It is agreed in much of the previous literature that Glucocorticoids mediate many of their effects by altering gene expression with their interaction with Glucocorticoid receptors (GR)[50]. Non-genomic affects of glucocorticoids have been recently proposed. Glucocorticoids are adipogenic as well as lipolytic, depending upon the duration and concentration of cortisol exposure[51]. Campbell and co-workers observed that glucocorticoids mediated lipolysis is due to increased expression of Adipose triglyceride lipase (ATGL) protein. ATGL promotes breakdown of TGs at a higher rate than HSL and is responsible for removal of the first free fatty acid from the triglyceride and it may be the rate limiting enzyme[52].

Tryptophan is an essential amino acid with an indole nucleus. Tryptophan goes through many metabolic pathways to form different products. A protein rich diet contains tryptophan along with other amino acids for example large neutral amino acids (LNAA) like Tyrosine, valine, phenyl alanine. Ingestion of a number of amino acids that compete for the same transporter

to the brain, decreases the amount of tryptophan accessing the brain, ultimately lesser serotonin synthesis. On the contrary, a carbohydrate rich diet stimulates insulin secretion, that gives tryptophan a competitive edge by reducing LNAA from circulation enhancing protein synthesis[53]. During depression, raised cortisol concentration stimulates tryptophan pyrrolase (TDO2), the hepatic enzyme that degrades tryptophan. Further more, raised tryptophan concentration also activates the enzyme, stimulating tryptophan degradation. Excessive tryptophan breakdown decreases the tryptophan entering the brain aggravating depression[54]. Antidepressants that inhibit the enzyme activity raise the tryptophan available to access the brain e.g Flouxetine[55].

Depression has been related to the metabolic syndrome and diabetes since a very long time[56]. Metabolic syndrome[57,58] specify the following quantitative criteria: large waist circumference, high blood pressure, dyslipidemia i.e. high triglycerides and low HDL cholesterol, and fasting hyperglycemia with underlying insulin resistance. The criterion items of the metabolic syndrome collectively represent a multi-dimensional risk factor for cardiovascular disease and type 2 diabetes mellitus[59]. Lipid metabolism is influenced by changes in nutrition, body weight, insulin sensitivity and sympathetic tone. It is found that most antidepressants including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and mirtazapine, increase levels of monoaminergic serotonin and norepinephrine, and modify the balance of the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis is known to be associated with depression as well as insulin resistance[60-62]. Depression raises synthesis and secretion of cortisol, the stress steroid. The steroids are synthesized with cholesterol as their essential precursor. It is seen that raised cortisterone in rats decreases cholesterol and phospholipid synthesis in the hepatocytes[63], probably due to the feedback control. Several hormones are known to regulate the expression of hepatic Hydroxy methyl glutaryl CoA (HMG CoA), such as, insulin. glucocorticoids, glucagon and thyroid hormone[64]. Pituitary ACTH has been known for long to stimulate the adrenal receptors for low- density lipoprotein (LDL) and high density lipoprotein (HDL) scavenger receptor class B type 1 (SR-B1) to provide precursor cholesterol for glucocorticoid synthesis. This acquisition of LDL and HDL cholesterol and an increase in cholesterol synthesis is pivotal for adaptation to stress[65,66]. It has been found that there is a suppression in the hepatic HDL and LDL receptors during ACTH administration[67]. The ultimate effect of the stress system may be, increasing ACTH increases available blood cholesterol for glucocorticoid synthesis, while increasing glucocorticoids inhibit the synthesis through feedback mechanism. The role of insulin is to induce the enzyme, elevating cholesterol levels. Since hepatic LDL-C and HDL- C receptors are decreased by glucocorticoid exposure, the lipoprotein is increased in circulation. There is an increase in synthesis of Apo-A protein, raising HDL in circulation. Further on, hypertriglyceridemia is caused as a result of excessive very low density lipoprotein (VLDL) synthesis. Glucocorticoid as a whole increases the lipid milieu. Antidepressants thus have an effect on the lipid milieu too facilitating the process of normalization and maintenance of homeostasis[68].

Depression is caused by low serotonergic activity, lesser duration of 5-HT in the neuronal synapse. Depression is known to enhance uptake of serotonin back into the neuron and metabolizing it into 5- hydroxy indole acetic acid (5HIAA). Owing to the decreased access of tryptophan to the brain caused by hyper activity of hepatic tryptophan 2, 3 dioxygenase, the enzyme responsible of tryptophan degradation, lesser serotonin is synthesized. Antidepressants may have a role in inhibiting the tryptophan degrading enzyme, enhancing tryptophan access to the brain or modulating neuronal enzyme activities favouring enhanced serotonin synthesis. Further on the synthesis and trafficking of various proteins, including transporters and receptors are modulated by antidepressants. The synthesis of proteins that support vesicular transport of neurotransmitters can also be affected by antidepressants.

It can finally be concluded that the behaviour of individuals is regulated by the concerted action different molecules in the body including those of the peripheral organs, as well as the brain. The intangible term “Behaviour” has a molecular, measurable, central and peripheral basis that can be managed and modulated through diet, medication and of course meditation!!!!!!!

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