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REVIEW

Neurobiological Pathways Between Chronic Stress and Depression: Dysregulated Adaptive Mechanisms?

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Abstract: Stress-related diseases have been predicted to become major contributors to the Global Disease Burden within the next 20 years. Of these, depression is one of the principal identifiable sources of concern for public mental health, and has been hypothesized to be an outcome of prolonged stress. Examination of the hyper-responsiveness of the Hypothalamic-Pituitary-Adrenal axis, consequent elevated serum cortisol, plus the effects of this upon brain structure and function, provides a model for understanding how chronic stress may be a causal vector in the development of depression. Evidence from studies of the effectiveness of antidepressants aimed at reducing cortisol within depressed patients supports this model and suggests avenues for future research and treatment of stress-induced depression.

Keywords: stress, depression, cortisol

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Introduction

The World Health Organisation has estimated that stress-related disorders, including anxiety and depression, will be second only to ischemic heart disease in their contribution to the Global Burden of Disease by 2020.[1] Stress may originate in the home, at work, or within the wider community[2] and has been classically defined as the "nonspecific response of the body to any demand made upon it",[3] p. 14). That is, "stress" is a physiological mechanism or process by which the organism prepares itself for, and reacts to, demands (called "stressors") that it meets. These demands may be external or internal and may engender the "fight or flight" stress response.[4] Internal demands usually present in the form of pain or associated systemic malfunction, and may be subsumed within the same nomenclature as external demands that threaten survival, although they may act via different neurological and endocrine pathways.[5] This paper describes the ways in which the human organism responds to stressors, how those responses help it cope with those stressors, and the physiological and psychological sequelae of excessive stress responsivity.

Why we React to Environmental Stressors: An Evolutionary Advantage

For the overwhelming portion of animal history, life has been tenuous. Multiple threats from predators, competition for resources, infection from microbial agents, scarcity of shelter, food and water, and an environment which has been almost completely non-controllable, placed powerful selective pressures upon our non-human and human ancestors.[6] Being able to react quickly, strongly and purposefully (in terms of immediate survival) to threat from any of these sources has provided a clear reproductive advantage.[7–10] The ability to balance threat with response is characterized in "homeostasis", and determines survival.[11] This balance is depicted in the inverted-U relationship between stress arousal and performance,[12] and is mediated by hormones and other neurotransmitters, cytokines and growth factors so that, after the appropriate stress response has occurred, these mediators return to a non-aroused state of "dynamic equilibrium"[11] p. 374). However, most of the primeval threats which drove that selection process are now gone, leaving the human stress response somewhat superfluous but non-the-less active. Thus, many stress responses which modern humans emit are unnecessary or out of proportion to the challenge of 21st century stressors and may, in fact, damage the organism itself, especially if the return-to-normal-homeostasis mechanisms are impaired.[11]

Neurological and Endocrine Stress Responses

When external stressors occur, the individual becomes aware of them via sensory data which may proceed to the brain or instigate simple spinal reflexes. Sensory inputs from pain receptors or temperature receptors in the skin, retinal images, stretch receptors in muscle, auditory signals, and others, come from various parts of the body and project to different levels of the central nervous system (CNS).[5] These sensory signals may cause immediate reflexes (e.g. spinal cord responses to limb pain), reach into lower brain regions for more complex responses (e.g. brainstem reactions to blood loss) or travel to specific projection areas within the brain (e.g. visual cortex) via the thalamus for interpretation by specialised neurons.[13] Once a sensory input has been received, the stress response may take either or both of two forms, each of which is activated by the brain in reaction to specific stressor demands.[14] These two forms act via different systems and have traditionally been classified according to their temporal nature, with one acting quickly (within seconds) via sympathetic nervous impulses and the monoamines adrenaline and noradrenaline, and the second acting more slowly (within minutes or hours) via corticosteroids. However, this separation of the two systems and their respective sets of responses has recently been challenged. Joels and Baram[15] have proposed a model in which both of these response systems interact within specific brain sites and over time to form three domains of functioning that combine to enable the organism to respond to stressors most effectively immediately (i.e. within seconds) as well as over minutes, hours, days and months. However, for the purpose of this paper, the traditional two-stage/system stress response model will be followed, with some reference to the interactions between the two systems.

The distinction between acute and chronic stressors is important in understanding the form and function of the stress response. Acute stressors occur quickly and elicit fast stress responses. For example,

the sight of an oncoming car will cause a surge of neurotransmitters, sympathetic neuronal activation and hormones, followed by a rapid return to resting levels.[15] Chronic stressors are usually defined as those which last for a week or more[15] and instigate sustained gene expression and altered neuronal restructure and firing patterns.[16,17] In addition, over-responsivity to acute and chronic stressors leads to different stress-related diseases.[11] For example, acute stressors lead to allergic responses such as asthma and eczema, migraines, pain and panic attacks, whereas chronic stressors are more likely to cause psychological dysfunction (anxiety, depression, cognitive problems), cardiovascular phenomena and metabolic disorders.[11] While the stressors themselves do not cause these illnesses, they instigate stress responsivity pathways which, when prolonged or intense enough, can do so. These stress pathways to disease will be described below.

Fast Responses to Stressors: The SAM Axis

The first stress response pathway is called the *sympatho-adrenomedulary* (SAM*) axis* because it acts via the sympathetic nervous system (SNS) and the adrenal medulla to respond very quickly to stressors. For example, the SNS can double heart rate within three seconds and blood pressure (BP) within 10 seconds of a stressor being sensed.[5] Physical stressors produce afferent signals from organs to the CNS and cause an immediate response via autonomic nervous system (ANS) reflexive processes.[18] These signals are processed quickly within the autonomic ganglia, spinal cord, brain stem or hypothalamus and generate efferent "subconscious reflex responses",[5] (p. 748) to the organ to assist it to adapt to the stressor. There may also be some input from the cerebral cortex and limbic cortex.[14] By contrast, psychogenic stressors require less direct transmission of their threat, with the stress response to them being based upon prior experience of the stressor, memory of that experience and consequent emotional arousal, none of which are necessary for purely physical stressors, which cause largely reflexive stress responses.[14]

As indicated above, the SAM acts via direct and very fast sympathetic nerve stimulation of many target organs (e.g. to dilate pupils, increase heart rate, constrict blood vessels, elevate arterial BP, and inhibit salivary gland activity and digestion),[5] and also sends signals into the chromaffin cells of the adrenal medulla, causing it to secrete adrenaline into the circulation, which has major and widespread effects upon the body to enhance responsivity to stressors,[5] albeit a little slower than direct sympathetic nerve stimulation. Some of the effects of elevated serum adrenaline include increased blood flow to muscles (by vasodilation of blood vessels, increased heart rate and contractile force), increased blood fatty acid levels (via stimulation of lipolysis) to provide glucose, increased basal metabolic rate[19] and increased oxygen uptake (via dilation of the bronchioles), again to support muscle activity.[5] Circulating noradrenaline is also elevated by its release from the adrenal medulla as well as from sympathetic paraganglia, brain and spinal cord nerve cells, but mostly from the postganglionic synaptic vesicles in various organs.[19] Noradrenaline is principally concerned with physiological maintenance but also helps the body focus its resources for fight or flight by inhibiting the activity of the gastro-intestinal tract so as to marshal blood flow for muscles,[5] inducing sweating on palms, forehead and armpits for cooling during activity,[19] increasing cardiac contraction and heart rate to bring oxygen and glucose to muscles, and lipolysis to provide glucose.[19] Parasympathetic nervous system (PNS) responses work through postganglionic nuclei and the vagus nerve to cause organ relaxation and re-establish homeostasis as part of this fast stress response.

The Hypothalamic-pituitary-adrenal Axis

The second stress response pathway takes longer but also lasts longer. It acts via the *hypothalamic-pituitary-adrenal* (HPA) axis to produce elevations in circulating glucocorticoids about 10 minutes after the stressor onset.[20]

Initiation of the HPA stress response: the role of neural communication

Taking an overview, the HPA axis stress response follows the transmission of afferent sensory signals from the various organs to the diencephalon (the epithalamus, the thalamus, the hypothalamus and the subthalamus).[13] The diencephalon has been described as "a station that is interposed between cortex and lower levels of the brain stem and as such is intimately

related to motor and sensory functions in both the somatic and visceral spheres",[21] p. 222). Thus, the thalamic structures also receive signals from the cerebral cortex, basal ganglia and cerebellum.[13] These signals may be evaluations of threat, direct sensory input or lower level homeostatic inputs.[5] Many limbic structures that are intimately involved with emotional states project to the hypothalamus,[22] raising the profile of the hypothalamus as a focus for the organism's fear-based responses to threat. Reflecting this role, the hypothalamus has also been described as "a transducer between neural impulses and hormonal secretion",[4] (p. 41), the former being the input from the sensory and cortical centres of the organism, and the latter being its major method of response to those inputs.

The first step in the activation of this pathway is the innervation of the parvocellular sections of the paraventricular nucleus (PVN) of the hypothalamus, which is achieved by several processes.[14] The primary regulators of the hypothalamus are the amygdala and the hippocampus,[18] the first of which stimulates the PVN and the second acts to inhibit it,[18] while also interacting with each other.[5] Sensory information from the prefrontal cortex (PFC) is received by the basolateral amygdala, processed and sent on to the amygdala central nucleus, which innervates and stimulates the PVN via the bed nucleus of the *stria terminalis*.[22] Glucocorticoid receptors in the hippocampus provide negative feedback to the PVN,[18] inhibiting or activating corticotrophin-releasing hormone (CRH) secretion depending upon the serum concentration levels detected in the hippocampus.[18] The hippocampus also receives information from the PFC, and so both the stimulatory and inhibitory activities of the amygdala and hippocampus respectively are influenced by (and, in turn, influence) the information they receive from the PFC, where decisions are made regarding the significance of external stimuli.[14] This reciprocal relationship between hypothalamic functioning (as influenced by the amygdala and hippocampus) and the PFC has recently been demonstrated by Minton, et al,[23] who showed that flattening of the diurnal cortisol rhythm (initiated from the hypothalamus) in rats was associated with changes in dopamine release in the PFC, leading in turn to abnormalities of PFC neurocognitive functions. In this way, prior learning may influence HPA axis responsivity and the endocrine stress response itself, an hypothesis that is supported by the finding that experimental subjects who believed that they could not control the stressor which they encountered had higher and longer-lasting cortisol responses than subjects who believed that the stressor was within their control.[24] Of relevance to this cognitive evaluation of control over stressors (i.e. via the PFC), up to 35% of the variance in the magnitude of an individual's cortisol response to a stressor is a function of their pre-stressor appraisal of it.[25] When linked to the amygdala, which "makes the person's behavioral response appropriate for each occasion",[5] (p. 738) and inputs emotional responses such as fear (formed on the basis of previous experiences, thus helping the individual to form memories of aversive events), the hippocampus and the PFC act together to interpret the threat significance of stressors and then adjust the hypothalamic response accordingly.[26]

Relevant to this influence of higher-order cortical processes upon the responsivity of the HPA axis, the PVN also receives serotonergic input from the median raphe nuclei in the midbrain (but only when the stressor is perceived as uncontrollable,[15] and this activates the HPA axis via serotonin receptors on PVN neurons.[14] The midbrain receives input from the cerebral cortex (where threat is also evaluated) and sends axons to the brain stem and spinal cord, acting as a conduit for the exchange of information to and from the spinal cord to the forebrain.[18] The midbrain also contributes to movement, sensory functions and (most relevant for fight or flight responses) aggression via axons from the hypothalamus to the *ventral tegmental* area of the midbrain.[18] It has been suggested that this pathway acts in response to non-physical or "psychogenic" stressors that are recognized by genetic programming or the individual's history (i.e. classical and instrumental conditioning experiences which may have formed connections between certain stimuli and their damaging consequences).[14] These connections need to be processed in the forebrain[27] and emphasise the role of learning in stress responsivity,[28–30] as well as highlighting the importance of aggression in coping with major stressors (e.g. predators and other life-threatening sources). At least one study has shown that cognitive appraisal of "what might happen" is more powerful in predicting cortisol responsiveness than reflections upon "what did happen",[25] although this

interpretation may be challenged by operant models of behaviour which would argue that the former is dependent upon previous experiences and learning which arises from the latter, and thus both are causally intertwined.[31] This latter position has been emphasized by Roozendaal, McEwen and Chattarji,[26] who examined the links between experiences of severe stress which induced amygdaloid plasticity and then dictated future behavioural and endocrine responses to those stressors by way of the amygdala's effects upon memory consolidation.

HPA hormonal responses

The hypothalamus and pituitary gland act together to control the thyroid, adrenal glands and the gonads in addition to regulation of metabolic activities, autonomic functions and emotional-behavioural responses as well as temperature, drinking, eating, sleeping and alertness.[5] Eight major neurohormones are secreted by the hypothalamus and may be classified into two groups according to their destinations. The first group (the hypophysiotropic hormones, so named because they are secreted into the pituitary to stimulate further neurohormones) include growth hormone-releasing hormone, somatostatin, dopamine, thyrotropin-releasing hormone, CRH and gonadotropin-releasing hormone.[32] The second group is released by the hypothalamus-pituitary system and sent directly into the blood circulatory system to target organs, and includes arginine vasopressin (AVP) and oxytocin.[5] Only CRH and AVP are part of the HPA axis stress response[33] and, of these, AVP is relatively less important, although regulation of water balance within the body may become relevant if the stress response continues for some time and dehydration occurs.[34] AVP is also important as a trophic hormone in the next hormonal step in stress responsivity (see below). Prolactin-releasing hormone and growth-releasing hormone are also secreted during stress but do not appear to have important stress response-related effects upon prolactin, thyrotropin or follicle-stimulating hormone.[35]

The endocrine cascade for stress responsivity: CRH, adrenocorticotropic hormone (ACTH), cortisol

CRH (and AVP)

After relevant inputs have been received by the PVN of the hypothalamus, CRH is released from CRH-containing neurons situated within the medial parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus,[5] as well as oxytocin, AVP and vasoactive intestinal peptide, but (as mentioned above) only AVP is important here. CRH and AVP reach the pituitary gland via the portal hypophysial vessel that originates in the hypothalamic median eminence and joins with the anterior pituitary,[36] allowing for two-way exchange of blood and neurohormones between the hypothalamus and the pituitary gland.[36] On direct electrical stimulation, the PVN has been shown to increase portal levels of CRH and peripheral levels of ACTH,[37] affirming its role in CRH secretion. Additionally, chemical stimulation of the dorsomedial hypothalamus (DMH) increases ACTH secretion to the blood and elevates heart rate and mean arterial pressure.[38] It has been suggested that CRH-producing neurons in the DMH stimulate those within the PVN.[14] As well as coming from the PVN and DMH, CRH is also expressed by the central nucleus of the amygdala, with a degree of specificity of response that differs between physical and psychogenic stressors and that is not present in the PVN.[39] Those authors noted that the CRH pathways in the central nucleus of the amygdala were particularly associated with fear-related behaviours and "are more responsive to stressors with a large cognitive component" whereas "hypothalamic CRH pathways are sensitive to stressors with either large cognitive or physical components" (p. 128). In addition, CRH activates the *locus coeruleus* noradrenergic circuit which promotes general arousal and attention to selected stimuli and also inhibits appetite, libido and other vegetative functions,[40] clearly establishing optimum conditions for the organism to focus its resources upon the stressor.

Pro-opiomelanocortin (POMC) and ACTH

Once released from the PVN (and perhaps the DMH and amygdala), CRH and AVP travel to the pituitary gland and stimulate the release of pro-opiomelanocortin (POMC), although AVP has only a minor role in this process.[41] POMC is a precursor to ACTH[5] and is synthesised by a single mRNA into several smaller biologically active fragments, including the n-terminal fragment of POMC (N-POMC), ACTH and β-Lipotropin (β-LPH).[35] ACTH is composed of 39 amino acids and contains α-melanocyte stimulating hormone (α-MSH) and corticotropin-like intermediate lobe peptide (CLIP);[35] β-LPH contains

the β-melanocyte stimulating hormone (β-MSH), γ-LPH and β-endorphin.[36] If ACTH is hypersecreted, it binds with the MSH receptor and causes excess skin pigmentation (as in Addison's disease),[35] which may be linked to UV protection during intense and/or prolonged solar radiation periods. ACTH secretion follows a pulsatile flow pattern[36] that varies diurnally, a fluctuation also reflected in cortisol secretion.[5]

Cortisol (and adrenal androgens)

ACTH travels via the bloodstream from the pituitary gland to the adrenal glands located on the anterosuperior aspect of the kidneys and stimulates the adrenal cortex to secrete glucocorticoids including cortisol, which acts upon target cells via intracellular glucocorticoid receptors.[35] Also released from the adrenal glands are the androgens and aldosterone, but these have relatively little effect in the stress response.[35] The adrenal cortex has three zones: the outer *zona glomerulosa* (which produces aldosterone but not cortisol), and the two areas that produce cortisol but not aldosterone, the middle *zona fasciculata* and the inner *zona reticularis*.[32] These latter two areas also produce the androgens and both are regulated by ACTH, with excess or deficiency altering their structure[35] so that they enlarge with chronic ACTH stimulation and atrophy with under-stimulation of ACTH.[35] This may be an adaptive mechanism to assist the organism to deal with prolonged periods of stress by increasing cortisol production.

Synthesis of cortisol (and all steroids) starts with cholesterol from plasma lipoproteins, principally (80%) low density lipoproteins.[35] Cholesterol is converted to pregnenolone in the mitochondria via two hydroxylations and one side cleavage by the enzyme CYP11A.[35] The pregnenolone is transported to the smooth endoplasmic reticulum and acted upon by the enzyme CYP17 to form 17α-hydroxypregnenolone.[35] Endoplasmic reticula enzymes then act on the 17α-hydroxypregnenolone to produce 17α-hydroxyprogesterone.[35] Enzyme CYP21A2 hydroxylises the 17α-hydroxyprogesterone to 11-deoxycortisol and the 11-deoxycortisol is then transported back to the mitochondria and further hydroxylated to produce cortisol.[35]

How Cortisol Enhances Survival: the "Saving" Role of Stress

Cortisol binds to cystolic glucocorticoid receptor proteins present in most tissues, enters the cell nucleus and alters the expression of specific genes and mRNAs.[35] From these mRNAs, resulting proteins elicit the glucocorticoid response but these proteins vary according to the specific cell type and genes expressed and thus, depending on the specific tissue and gene, the glucocorticoid response may be inhibitory or stimulatory.[35] Cortisol affects intermediary metabolism, calcium homeostasis, the immune system, other endocrines, skin and connective tissue, breast, lung and cardiovascular systems, and mood, appetite, sleep, memory and vision.[5]

However, although cortisol is clearly a major regulatory hormone for everyday homeostasis, the focus of this paper is its role in rapid and dramatic response by the organism to threat—the so-called stress response—and how that may contribute to the development of depression. Cortisol has been termed "the stress hormone"[36] and works in two major ways to assist the organism to cope effectively with threat. The first of these is the enhancement of the organism's ability to respond immediately to attack by increases in heart rate, vasoconstriction and BP (to supply more oxygen to muscles) and release of stored lipids and amino acids from fatty tissue (for synthesis of glucose and protein which enhance the organism's ability to mobilise musculature for immediate and prolonged intense activity).[5] Secondly, cortisol helps the body defend itself against infectious agents (which may occur as a result of attack) by stabilising the membranes of lysosomes.[42–44] This improves their ability to engulf foreign species that have been brought into the cell by phagocytosis. The lysosome then undergoes enzymatic responses that reduce its pH so that it can necrose the engulfed infectious agent, contributing directly to the immune response to infection.[43,44]

When infected by a pathogen, the body responds with inflammation to isolate and then attack the pathogen. However, although short-term inflammation is therefore a survival-enhancing process, prolonged inflammation can be counterproductive for the organism, contributing to atherosclerosis,[32] bowel disease,[5] mood disorders, neurodegenerative diseases, diabetes and cancer.[45] Highlighting the beneficial effects of cortisol, Jantz and Sahn[46] listed several anti-inflammatory effects of corticosteroids, including: inhibition of several cytokines that are involved in inflammation; interference with transcription factors activator protein

(which is involved in the expression of genes that enhance inflammation); degradation of mRNA encoding for inflammation; inhibition of nitric oxide synthase; inhibition of bronchoconstrictors; desensitisation of β_2-adrenergic receptors; inhibition of intercellular adhesion molecules; and reduction of airway inflammation. Previous research has also suggested that cortisol reduces microvascular leakage.[47] Klaitman and Almog[48] reviewed the anti-inflammatory effects of cortisol with particular reference to sepsis and listed 17 separate anti-inflammatory effects of cortisol via lipocortins, interleukins, neutrophils and other agents. Thus, the two-stage role of cortisol in killing infectious agents and also reducing the organism's prolonged inflammatory response is of significance in promoting the overall survival of the organism.

Therefore, viewed from an evolutionary advantage perspective, rapid muscular activity in the face of threat, destruction of infectious agents and anti-inflammatory activities are responses that are likely to enhance survival and consequent gene pool transmission. During ancestral periods, major threats would have most likely been from predators and competitors, with part of the likely outcome of such attacks being damage to the skin and consequent infection from animals' claws, competitors' weapons and the contaminated detritus that was contained on them. Thus, while the fast deployment of a suitable response to isolate and destroy infectious agents within the dermis (i.e. via lysosomal engulfment and necrosis) would have assisted the organism to resist infection, prolonged sepsis would not have carried such an evolutionary advantage and hence the control of inflammation becomes a parallel mechanism for survival.

The Consequences of Dysregulation of Cortisol: The "Damaging" Role of Stress

Hypercortisolaemia

Although circulating cortisol flows back to the hypothalamus and inhibits CRH secretion there, and thus POMC and ACTH in the pituitary, this moderating mechanism may be insufficient when the organism is under chronic stressful stimulation,[49] leading to the diseases of hypercortisolism, including fibromyalgia, early over-activation of the immune system that is followed by depressed activation, susceptibility to stress, pain and fatigue,[49] muscle wastage and hyperglycemia.[36] Prolonged and elevated expression of cortisol leads to increased serum lipids, endothelial damage and resultant incidence of coronary heart disease (CHD)[50–52] and acute respiratory failure.[46] Hypercortisolaemia has also been shown to cause atopic dermatitis[53] and suppressed skin immunity.[11,54] Other outcomes of excessively high levels of cortisol expression include decreased immunocompetence,[55,56] increased risk of infection, osteoporosis, steroid diabetes, and destruction of hippocampal neurons leading to cell loss, depression and chronic distress.[11,57,58]

In addition (and central to the focus of this paper) ongoing elevation of cortisol can also alter the structure and function of brain regions.[14] These changes can include increased expression of CRH and AVP mRNA in the PVN,[59,60] altered expression of neurotransmitter receptors[61] and increased gamma-aminobutyric acid (GABA) in the hypothalamus.[62] Chronic stress may also lead to increased ACTH and cortisol responses to new stressors, as well as enhanced expression of noradrenaline and increased sensitivity of the *locus coeruleus* to CRH.[14]

Of direct relevance to depression, elevated cortisol has been shown to reduce the density of pyramidal neurons and cell survival in the hippocampus, reducing cognitive processing of stressors,[63] and increase dendritic growth in pyramidal and stellate basolateral amygdala neurons, leading to anxious behaviour.[26] Stress-related increases in cortisol contribute to induce neuropsychiatric disorders such as depression[64] via prolonged glucocorticoid activation due to inhibited glucocorticoid receptor responses in the hippocampus and impaired negative feedback processes there,[65] atrophy and debranching of hippocampal apical dendrites[66–68] and resultant downgrading of hippocampus functioning.[69] Some data suggest that glucocorticoids act within 24 hours to significantly increase the rate of apoptosis in the hippocampus,[70] probably via inhibition of glucose uptake in neurons,[71,72] leading to decreased hippocampal volume and performance.[66] Prolonged stress and elevated cortisol also causes suppression of hippocampal inhibitory neurons to the HPA axis.[73] Some data suggest that this hippocampal degeneration is associated with early-onset depression among elderly persons, arguing for a stress-related causal path that

is distinct from age-related degeneration which may also instigate depression among this group.[74]

Of more importance for impairments in everyday decision-making present in depression,[75] even mild stress can rapidly impair PFC function[76] and structure,[15,77] perhaps via down-regulation of genes which express for synaptic plasticity[78–81] and apical dendritic reorganization in pyramidal neurons in the PFC.[82] These alterations in PCF structure affect perceptual attention, which is impaired in stress-related psychiatric illness.[83] Uncontrollable (but not controllable) stressors cause PFC impairment in animals[84] and humans.[85] In effect, non-stress conditions are marked by dominance of the PFC in decision-making, with influence over the *locus coeruleus* in the brainstem (the source of noradrenergic projections to the rest of the brain) and the *substantia nigra* and *ventral tegmental* areas (where major dopamine projections originate), giving the PFC effective command over catecholamine signals into the brain.[76] However, under chronic stressful conditions, the amygdala overrides PFC control of these functions and activates stress pathways in the hypothalamus and brainstem, thus also increasing levels of noradrenaline and dopamine release.[76] These increased catecholamine levels then strengthen fear conditioning circuits within the amygdala, creating a self-serving circle.[86] By contrast with its apoptotic effects on hippocampal neurons, hypercortisolaemia can increase amygdala structure and function,[26] contributing to emotion-based decision-making during times of chronic stress.[70]

This modification of brain structures by stress begins prenatally[87] and predicts early onset of depression in adolescents.[88] These structural changes to important brain centres reflect a move from thoughtful "top-down" PFC control of behaviour to reflexive and fear-based "bottom-up" emotional amygdala responses,[76] which in turn engenders those behaviours characteristic of anxiety and depression.[75,89] Cortisol has also been shown to have a biphasic effect upon mitochondrial function, with low cortisol levels instigating a neuroprotective effect in the hippocampus and high cortisol decreasing mitochondrial membrane potential, calcium-holding capacity and mitochondrial oxidation, all of which compromise the ability of mitochondria to synthesise ATP.[90] These fundamental influences upon the ability of neurons to grow and function may perhaps explain the mechanism whereby hypercortisolemia inhibits cortical neural plasticity in the PFC and hippocampus.[91]

Hypercortisolemia and major depression

As suggested above, and as a result of the structural and functional changes to the PFC and amygdala, prolonged elevated cortisol that results from chronic stress can be associated with psychological illness such as depression[92] ("depression" is defined here as principally Major Depressive Disorder (MDD)). Impairment of PFC function and reductions in volume and function of the hippocampus, plus amygdala neurogenesis and consequent amygdala-driven hypothalamic hyperactivity, are all possible causal links between elevated cortisol and MDD.[93,94] This hypothesis is further supported by the finding of higher levels of CRH, ACTH and cortisol within depressed patients,[95–98] with Thompson and Craighead[99] reporting that up to 80% of depressed patients have elevated cortisol levels, although this may be more likely with patients suffering from psychotic depression than non-psychotic depression.[96] This is consistent with the finding that more than half of all patients with Cushing's disease develop depressive mood,[33] although this is reversible with anti-cortisol medication. HPA-axis hyperactivation has also been linked to depression in childhood via dampening of the hippocampal glucocorticoid receptor gene Nr3c1 in infant humans who have had adverse nurturing experiences,[100–102] leading to impaired negative feedback to the hypothalamus regarding circulating cortisol.[18] Children whose parents have died have elevated serum cortisol;[103] early and recent aversive experiences predict elevated cortisol responsivity in adolescents;[104] and elevated CRH has also been associated with depression in adults,[105] perhaps via its effect on raphe nuclei that, in turn, influence serotonin activity in the PFC.[106] Depressed suicide victims show elevated CRH in their PFC compared to non-depressed and non-suicide individuals.[107]

As supportive adjunct data to the reported damaging effects of hyper-activation of the HPA axis and elevated cortisol upon cell apoptosis, restructuring and inhibition of network effectiveness within the PFC and the hippocampus, plus excessive neurogenesis in the amygdala, and the downstream effects of these structural and functional changes upon HPA axis hyperactivation which leads to stress-related

depression, several studies of the reversing effects of antidepressants have been reported. For example, Lucassen, Fuchs and Czeh[108] showed that the antidepressant *Tianeptine* reduced hippocampal apoptosis; Crochemore, et al[109] reversed hippocampal neuron apoptosis by activation of the mineralocorticoid agonist aldosterone; and Oomen, Mayer, De Kloet, Joels and Lucassen[110] normalised stress-induced reductions of the hippocampus in rats by applying *mifepristone* dissolved in cream and injected directly into the stomach for only four days. Antidepressant treatments based upon HPA axis function have included antiglucocorticoids to inhibit cortisol synthesis (*aminoglutethimide, ketoconazole, metyrapone*),[111] with supportive data from animal studies[112] and depressed patients.[113–116] Corticotrophin-releasing hormone (CRH) has been targeted by Gold, Licinio, Wong and Croussos,[117] Holsboer[97] and Nemeroff[118] in studies using the CRH-antagonist R121919, which has been shown to reduce major depressive disorder in clinical Phase I studies.[119,120]

One emerging line of research regarding possible mechanisms that cause dysfunction of the HPA axis has focused upon imbalances in the activity of receptors for glucocorticoids (GR) and mineralocorticoids (MR).[65,109] These receptors are complementary and operate to balance the HPA axis actions, with MR normally preventing stress-related disturbances.[65] Two MR genes and six GR genes that determine if an individual is overly stress-responsive have been identified,[121] and it has been shown that elevated expression of these genes is also related to the pathogenesis of depression[122] and related immune and psychiatric illnesses.[123]

Hypocortisolaemia

Although most attention has been paid to the adverse consequence of over-production of cortisol, hyporesponsiveness of the HPA axis is also associated with physical diseases which have concomitant psychopathological states. About one-quarter of patients with stress-related disorders such as chronic pain, fibromyalgia, irritable bowel syndrome, post-traumatic stress disorder and low back pain also suffer from hypocortisolaemia.[49,61] It has been suggested that hypocortisolaemia develops after a prolonged period of hyperactivity of the HPA axis,[124] via (a) reduced biosynthesis or release of CRH, AVP or ACTH or cortisol itself, (b) hypersecretion of one of these, followed by a consequent down regulation of target receptors, (c) increased sensitivity to negative glucorticoid feedback, (d) lowered free cortisol, and (e) decreased effects of cortisol on its receptors and the target cells/tissues.[49] Hypocortisolaemia may also have negative effects upon overall health by inhibiting the negative feedback effect of cortisol on catecholamine synthesis and secretion and by over-activating the immune system by way of absence of the anti-inflammatory effects of cortisol.[49,64]

Both hyper- and hypocortisolaemia can therefore be associated with adverse consequences for the organism. Chrousos[11] listed the comparative effects of each of these dysregulations of cortisol synthesis, arguing that "Malfunction of the stress response might impair growth, development, behavior and metabolism, which might potentially lead to various acute and chronic disorders" (p. 380). These deleterious effects upon general health may also be contributing factors in the development of depression.

Just Disease, or Adaptation Gone Wrong?

Although damaging enough to be classified as physical or psychological diseases, the structural and functional changes mentioned above that happen to selected parts of the brain during chronic stress and resultant hypercortisolemia may also be viewed as an outcome of (extreme) adaptation to the perceived uncontrollable aversive stressful situation in which the organism finds itself, rather than purely pathological.[125–128] That is, one potential benefit of the stress-related reductions in brain function that are present in depression may be to help the depressed individual withdraw from the aversive environment that contains the stressors which is both uncontrollable and ongoing.[129–132] This view is also posited for the remodeling of neural networks that follows exposure to chronic stress,[77] and suggests that, when the individual has no other available respite from the onslaught of uncontrollable aversive stressors, the only recourse for the adaptive individual is to reduce the emotional intensity of that environment via the withdrawal and anhedonic responses that underlie depression.[75] It has been argued that this neural restructure may even be adaptive in a Darwinian sense,[133–135] and Darwin himself commented on this: "But pain or suffering

of any kind, if long continued, causes depression and lessens the power of action; yet it is well adapted to make a creature guard itself against any great or sudden evil",[136] (p. 51).

Some support for the "depression-as-adaptive-withdrawal-from-stress" hypothesis (via the negative side effects of prolonged elevated cortisol) comes from identification of genetic factors which predispose individuals towards higher intensities of the HPA stress response and the unwanted effects of high cortisol.[137] Because HPA-axis dysregulation during adolescence is significantly related to unpleasant prenatal and infancy experiences,[88] those gene vectors which engender this elevated stress response may act to prime the organism for a life environment which is threatening. In this way, the combined effects of stressors and genetic disposition that are seen in hypercortisolaemia and its sequelae may represent an adaptation which has become dysregulated. That dysregulation may lie more appropriately in the field of continuing hyperesponsivity that provided a selective advantage in past environments where high and prolonged SAM and HPA responses might have aided in the conservation of energy, avoidance of dehydration, defeat of adversaries and coping with a hostile environment.[11] In their summary of the evolutionary benefits of the stress response systems, Nesse and Young[10] commented that the selective advantage given to a highly responsive individual "must be substantial in order to outweigh its huge costs" (p. 79), perhaps explaining why the high stress responsivity person remains in modern human gene pools.

Conclusion

The human stress response has obvious advantages in preparing the individual for immediate and decisive action within fight or flight situations. Those advantages have been preserved throughout history, presumably because of their survival benefit, despite entailing some risk of unwanted physiological and psychological illness when the intensity or length of response is extreme.[125] Both of the pathways described here (i.e. SAM and HPA) help in this regard, the first being more immediate than the second and oriented towards different stressors. However, prolonged and uncontrollable stressors may instigate longer-term and potentially damaging response processes within genetically-prone individuals, leading to neurobiological changes which are linked with depression. The hypothetical adaptive nature of these apparently damaging consequences, and the responses which follow them, may explain why they have endured throughout our history and why they represent such a large portion of the total disease burden of the 21st century.

Disclosure

The author reports no conflicts of interest.

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