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Peter Währborg, Panagiota Pervanidou, George P Chrousos

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The Physiology of Stress and Stress Recovery

Peter Währborg[1], Panagiota Pervanidou[2], George P Chrousos[2]

Sahlgrenska Academy, University of Gothenburg, Sweden. Strömstad Academy, Strömstad, Sweden

Corr.address: Peter Währborg, Västerlyckan 16, 423 38 Torslanda, Sweden

Co Authors:

Panagiota Pervanidou, MD and George P Chrousos

Developmental & Behavioral Pediatrics

University of Athens School of Medicine

Aghia Sophia Children's Hospital

Athens, Greece

Abstract

Stress, i.e., the state of threatened homeostasis, is normally associated with adaptive physical and behavioral changes that promote individual survival. The Hypothalamic-Pituitary-Adrenal (HPA) Axis and the Autonomic Nervous System (ANS) are the main components of the "Stress System", through which the brain regulates the complex, adaptive responses of an organism to threatening stimuli. Successful maintenance of homeostasis leads to the state of eustasis, which represents health. On occasion, the organism "learns" from the experience and becomes more resilient to similar stressors in the future. The prolonged, excessive or deficient response of the Stress System to stress, however, may lead to a state of dyshomeostasis or cacostasis, which may lead to physical and mental health problems. Stress exposures during critical periods of development - fetal life, childhood and adolescence- may have permanent negative effects, altering brain structures and functions. Although research has focused on the detrimental effects of stress, only a few studies have been done on positive stress exposure adaptations.

Increased resilience, posttraumatic psychological growth and increased empathy may benefit chronically stressed individuals, enhancing their abilities to cope with distress. Therapeutic efforts in the treatment of short- or long-term stress aims at reducing different aspects of the state; neuroendocrine responses, behavior changes etc. Since there is no patognomonic measure for stress there is neither any consensus on how to monitor stress relief in a reliable way. A number of indirect

measures can be used to indicate stress recovery Community investments and interventions should focus on reducing threats and promoting positive adaptation in people, especially young children, during and after traumatic stress exposures.

Introduction

During the 30's and 40's, Hans Selye, a Hungarian-Canadian endocrinologist, first conceptualized the adaptive response of an organism to external or internal threats, as a process he called "The General Adaptation Syndrome". In 1956, he published the "Stress of Life" (Selye, 1956) presenting the principal features of what he had originally termed the "general adaptation syndrome", to which he also referred as the "stress syndrome" or simply "stress" (Jackson, 2012). "Stress of Life" was his most influential publication of the relations between stress, health and disease and his model remains the basis of our bio-psycho-social understanding stress today (Pervanidou and Chrousos, 2007). Before Selye, Walter Cannon attributed the neuroendocrine response to an injury and the release of catecholamines, as part of the "fight or flight reaction". Selye was the first to describe the crucial role of the pituitary and the adrenal cortex in the physiology of the stress response and he termed the external or internal force causing stress, "stressor". Another one of its major contributions was the distinction between positive "eustress" and negative "distress" (Chrousos and Gold, 1992; Chrousos, 1998).

Selye, however, did not only describe the neuroendocrine processes involved in stress reactions, but also the diseases that are related to stress, such as cardiovascular and inflammatory disorders and peptic ulcer (Szabo, 1998). Furthermore, Selye reflected on the philosophical aspects of stress research: individuals possessed a certain amount of "adaptation energy" that was gradually consumed by the "wear and tear of life", leading to physiological aging and death (Selye, 1956). A longer and healthier life could be achieved by protecting "adaptation energy" by "living wisely in accordance to natural laws". Selye argued that the study of nature would allow people to "derive philosophical lessons": similarly to "biological harmony achieved by intracellular altruism", social harmony and human satisfaction could be enhanced by "interpersonal altruism" (Selye, 1974; Jackson, 2012).

Homeostasis and Stress Physiology

Stress is defined as the state of threatened homeostasis, the complex equilibrium that all living organisms try to maintain (Chrousos and Gold, 1992). Homeostasis is normally challenged by everyday external or internal forces, the stressors. The nature, intensity and duration of stressors, as well as the timing of exposure and the perception of stress are important in stress reactions. When a stressor exceeds a certain threshold, the adaptive homeostatic systems of the organism are compensatory activated, in an innate stereotypic response, to regulate homeostasis and protect the organism during acute stress. These adaptive alterations take place both in the central nervous system (CNS) and the periphery and include facilitation of neural pathways that promote arousal and vigilance, and, simultaneously, inhibition of pathways related to eating, growth and reproduction (Chrousos, 2009). Additional adaptive changes include increased oxygenation of the brain, heart and

skeletal muscles, all essential organs participating in the acute stress response (Chrousos, 2009).

The stress reaction is mainly coordinated by the stress system, consisting by central and peripheral mediators that will be described below. Homeostatic mechanisms exert their effects in a U-shaped curve, where, healthy homeostasis, or eustasis, is achieved in the middle of the curve, and sub-optimal effects may occur on either side of the curve leading to a state of dys-homeostasis, also called allostasis or cacostasis, which may have damaging effects in the short and long term health of the individual (Chrousos and Gold, 1998;Chrousos, 2009).

The activation of the stress system is followed either by return to basal homeostasis (eustasis) or by a state of maladaptive response (inadequate or excessive), and the organism falls into cacostasis. In a third possibility, the organism gains from the experience, and a new, improved homeostatic capacity (hyperstasis) is attained (Figure 1) (Chrousos, 2009).

Perception and Inception of the Stress Reaction

The brain is the integrative center for coordinating the behavioral and neuroendocrine response to challenges, some of which qualify as "stressors". The evolutionary modern mammalian part of the brain, once described as the neocortex (Mac Lean 1990), is certainly involved but also a number of other cortical structures are important actors in the perception and interpretation of potential stressors. The most important of these structures are found in the border zone between the "intellectual brain" (neocortex) and the "emotional brain" (paleocortex). These interconnected structures are often described as the limbic system (Broca 1878) and they are of utmost importance for functions like memory (hippocampus), emotions and emotional reactions (amygdala) and emotional control (cingulate gyrus and prefrontal cortex in the frontal lobes). A significant role in the perception of stress and our reactions to the environment is played by the frontal lobes. During the evolution these important structures have developed an exclusive ability to anticipate threats, and in fact also create potential such, i.e. by worrying for things. In the most frontal part of these lobes the prefrontal cortex is located. They are not only of importance for emotional control but also for integration and evaluation of different stimuli. The prefrontal cortex plays a major role for coordination and activation of behavioral as well as physiological reactions to perceived threats and are closely linked to structures in the limbic system.

However, the brain is not organized in strict hierarchical lines. A number of neural networks are involved in perception as well as in the interpretation of and reaction to stimuli in the outer as well as in the inner world (Ledoux 2003). It is obvious that the human brain has developed to a very complex structure, where simple boundaries for different functions of the brain, repeatedly has to be redefined. Despite this complexity certain areas seems to have more important impact on the diffuse reaction we call stress.

The most explicit, and the first visible reaction to a "stressful" experience, is the emotional adaptation. From an evolutionary point of view the emerging behaviour is aimed at preparing for fight or flight. Hostility, irritation, frustration and anger are common behaviors in such a situation. In exposure to long term stress the behavior more tend to be coined by exhaustion, depressive symptoms, anxiety and more pronounced cognitive difficulties (Währborg 2009).

Amygdala - the Conductor of the Stress Reaction

A crucial part of the limbic system is the almond-shaped amygdala nuclear complex with its thirteen different grains individually enforces different access paths with other parts of the brain. Amygdala deal with both “incoming” and” outgoing” nerve traffic. Incoming information is apprehended from the neocortex and the body via hypothalamus and thalamus. This information is of decisive importance for its conducting of responses to the perceived situation in the outer as well as the inner world of the individual. The coordination is essential for our ability to react on different stimuli and to prepare for proper action that has to be taken in order to avoid or deal with different challenges in our lives.

From the central nuclei in the amygdala complex, neurons to different projection areas are distributed, among them to the paraventricular nucleus in the hypothalamus (Herman et al. 2005). Amygdala is therefore an import actor in setting different stress mediator systems in motion (see Le Doux 1996 for an overview; Davis 1997).

Amygdala as well as the prefrontal cortex is not only executers of stress reactions, but they are also vulnerable victims to its consequences. The latter plays an important role in working memory and executive function and is also involved in extinction of learning. Both these regions are targets of stress hormones, and stress is known to precipitate and exacerbate mood disorders. In long-term depressive illness, the hippocampus and prefrontal cortex undergo atrophy, whereas the amygdala is hyperactive in anxiety and mood disorders and may undergo a biphasic change in structure, increasing in size in acute depression and shrinking on long-term depression. In animal models of acute and chronic stress, neurons in the hippocampus and prefrontal cortex respond to repeated stress by showing atrophy that leads to memory impairment, whereas neurons in amygdala show a growth response that leads to increased anxiety and aggression. Yet, these are not necessarily "damaged" and may be treatable (Vyas 2002; Roozendaal 2009).

Hippocampus, a Vulnerable Master of Memory and an Import Stress Regulator

Stress modulates the brains function and can facilitate or even impair the memory process. Emotionally arousing experiences generally lead to stronger memories than more ordinary events, whereas high stress levels seem to interfere with the retrieval of previously acquired memories. As mentioned, the brain is not only an executer of stress reactions but also a target for its biological consequences. The hippocampus, often called “the gateway to our memory”, was the first brain region (beside the hypothalamus) to be recognized as a target of glucocorticoids. Stress and stress hormones produce both adaptive and maladaptive effects on this brain region throughout the life course. It has been shown that early life events influence life-long patterns of emotionality and stress responsiveness and alter the rate of brain and body aging. The hippocampus as well as amygdala and the prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physiological responses (for an overview see McEwen, 2004 and 2005).

The hippocampal region is located in the medial temporal lobe of the brain and plays a central role for different memory functions. Learning capacity is mainly related to

the anterior parts of the hippocampus formation, whilst recall is related to the posterior parts (Lepage et al 1998; Schacter & Wagner 1999). Interestingly hippocampus is also strongly involved in emotionally contextual memories (Eichenbaum et al 1992; LeDoux 1995; Pugh et al 1997). The hippocampal formation is not only an important structure for different kinds of learning and memory but also for control of autonomic and vegetative functions like adrenocorticotropin (ACTH) secretion via feed-back regulation of the HPA-axis (Jacobson & Sapolsky, 1991). It was shown already in 1968 (McEwen et al.) that hippocampal neurons express receptors for circulating adrenal steroids. Two different receptor types are present in hippocampal neurons, type I (mineralocorticoid) and type II (glucocorticoid). Excitatory amino acids, like N-methyl-D-aspartate (NMDA) receptors, play important roles in the functional and structural changes produced in hippocampus by steroid hormones. There are two different forms of structural plasticity in the hippocampal formation which are affected by stress. Repeated stress in animals causes atrophy of dendrites in a specific region of the hippocampus (CA3). Both acute and chronic stress has further been shown to suppress neurogenesis, i.e. development of "new" granule neurons in the dentate gyrus (for extensive review see McEwen 1999). In has even been suggested that severe long term stress, often described as burnout, is an exponent of stress-mediated decrease in adult neurogenesis leading to decreased ability to cope with stress through decreased hippocampal function possibly involving a disturbed hippocampal regulation of the HPA-axis (Eriksson & Wallin, 2004).

An interesting hypothesis is proposing that decreased glucocorticoid production also might lead to psychopathologies. Haller and co-workers (2007) have shown that aggressiveness can be driven by chronic hypo arousal due to glucocorticoid deficit. This is a situation described and found also in posttraumatic stress disorder, depression and also in burnout patients. A possible theoretical link might be found to serotonergic transmission which seems to lose its impact on aggression. Also, in certain prefrontal areas neurons are weakly activated, whereas the central amygdale acquires important roles.

Mediators of Stress

Based on genetic and epigenetic parameters, stress mediators regulate homeostasis and stress responses to acute or chronic threats. The Hypothalamic Pituitary Adrenal (HPA) Axis and the Sympathetic Nervous System (SNS) are the main components of the Stress System, however, a variety of neurotransmitters, growth factors and cytokines interact with the classic neuroendocrine hormones to maintain homeostasis.

The central mediators of the stress system include the hypothalamic paraventricular nucleus hormones Corticotropin-Releasing- Hormone (CRH) and arginine-vasopressin (AVP), the arcuate nucleus proopiomelanocortin-derived peptides α-melanocyte–stimulating hormone (MSH) and β-endorphin, and the brainstem Norepinephrine (NE) produced in the A1/A2 centers of the Locus Caeruleus (LC) and in the central nuclei of the sympathetic nervous system (SNS). Research has shown that the hypothalamic CRH-AVP and brainstem norepinephrine centers of the stress system mutually innervate and stimulate each other (Chrousos, 1995; Chrousos and Gold, 1992)

In the periphery, the end-effectors of the HPA axis are the glucocorticoids and those of the sympathetic system are the catecholamines epinephrine (E) and norepinephrine (NE). Catecholamines stimulate interleukin (IL)-6 release by immune- and other peripheral cells via β-adrenergic receptors (Papanicolaou et al., 1998).

The targets of these stress mediators are brain structures and functions related to emotion and behavior, as well as peripheral tissues related to metabolism, growth, reproduction, immunity, and cardiovascular function.

Stress-induced metabolic and cardiovascular actions include the increase of heart rate and arterial blood pressure, while increased glucocorticoids and catecholamines induce gluconeogenesis, glycogenolysis, lipolysis and stimulation of hepatic glucose secretion. Stress also affects the immune system, influencing innate and acquired immunity (Chrousos, 1995; Chrousos, 2000). Both the glucocorticoids and the catecholamines suppress the secretion of proinflammatory cytokines (tumor necrosis factor [TNF], IL-1, IL-6, IL-8 and IL-12) and affect trafficking and function of leukocytes and accessory immune cells, whereas both hormone families induce a systemic switch from cellular to humoral immunity (Chrousos, 2009).

Perceived Stress and Trauma –Stress-related Disorders

As previously described, the activation of the stress system by everyday stressors results in adaptive endocrine, metabolic, behavioral and cardiovascular changes with the purpose to maintain homeostasis. However, the experience of intense or longstanding perceived stressors, such as accidents, natural disasters, violent attacks, terrorism, or witnessing such exposures can lead to excessive and prolonged activation of stress mediators or, in a subgroup of individuals, to chronic hypoactivation of the stress system, which is equivalent to a cacostatic state with a variety of psychologic and biological consequences (Pervanidou and Chrousos, 2010;Pervanidou and Chrousos, 2012a).

Stress can lead to both acute or chronic physical conditions and diseases in predisposed individuals (Chrousos and Kino, 2007). For instance, acute or longstanding stress can trigger allergic manifestations, such as asthma or eczema, gastrointestinal symptoms, such as pains or diarrhea, disturbances in arterial pressure, etc. Furthermore, stress-related somatic manifestations often present in clusters and are chronic. The term “Functional Somatic Syndrome” (FSS) refers to a broad cluster of physical symptoms, such as fatigue, abdominal pain, musculoskeletal pain, headache, that cannot be explained by modern medicine. Such symptoms are also named “Medically Unexplained Symptoms” (MUS) (Fischer et al., 2014)

Abnormalities in stress-system mediators have been reported in behavioral and psychiatric disorders, such as anxiety, depression, posttraumatic stress disorder, eating disorders etc (Chrousos, 2009; Gold and Chrousos, 1999; Pervanidou and Chrousos, 2012b). Increased or decreased concentrations of CRH and peripheral stress mediators may be responsible for physical complications and increased morbidity in these populations.

The important role of stress physiology in the pathophysiology of mental health disorders is highlighted in the last revision of the Diagnostic and Statistical Manual for Mental Disorders (DSM), where, a new class appears, the “trauma and stressor-

related disorders" (American Psychiatric Association, 2013), including Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD) that both were previously classified as anxiety disorders.

Posttraumatic Stress Disorder

Posttraumatic Stress Disorder represents the most typical mental disorder linked to chronic distress. Indeed, a large body of evidence supports the crucial role of the stress system in the pathophysiology of PTSD. The concept of "psychic trauma", as an individual's experience of a perceived life threat caused by an external life event is attributed to Sigmund Freud (Freud, 1973; Pervanidou and Chrousos, 2007). Trauma is not simply an extreme form of stress, and both psychological and physiologic aspects of trauma and stress contribute to the understanding of PTSD as an entity of behavioral, emotional and physiologic responses to perceived stress.

The term PTSD describes a syndrome of distress that develops after exposure to death or threatened death, actual or threatened serious injury, actual of threatened sexual violence and by direct exposure, witnessing in person or indirectly, by learning that a close person was exposed to violence or in the course of professional duties (APA, 2013).

The clustering of symptoms, according to DSM-5, includes intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and negativity (APA, 2013).

PTSD has been also associated with dysregulation of the stress system and more precisely with increased CRH centrally (Baker et al., 1999) together with decreased cortisol (Yehuda et al., 1994; Yehuda, 2006; Yehuda, 2001) and elevated catecholamines (Strawn and Geracioti, 2008) in the periphery (Pervanidou and Chrousos, 2010). In a prospective and longitudinal study in children and adolescents experiencing motor vehicle accidents, we (PP and GC) investigated the natural history of neuroendocrine alterations in relation to the development and maintenance (Pervanidou et al., 2007a; Pervanidou et al., 2007b) of PTSD. These children had no previous trauma exposure, and nor current or past psychopathology. Thus, we studied the effects of a single acute and quite common stressor in children from the community. Thirty per cent of the children developed PTSD one month after the event and 15 maintained PTSD six months later.

Evening salivary cortisol and morning serum interleukin-6 in the aftermath of the trauma were both higher in children that later developed PTSD, whereas norepinephrine (NE) was normal. Children with PTSD exhibited gradually greater NE concentrations compared to those experiencing the accident but did not develop PTSD. (Pervanidou et al., 2007a). This study supports an initial elevation of cortisol in individuals exposed to a single acute stressor, followed by a gradual normalization of cortisol, as time passes from the stressor, that might lead to decreased cortisol in the periphery, months or years after the traumatic exposure. At the same time, a progressive elevation of NE is noted in individuals that continue to exhibit PTSD symptoms. It seems that a longitudinal interaction of peripheral measures of the sympathetic systems and the HPA axis characterizes those that develop and maintain the disorder (Pervanidou, 2008)

Early Life Stress and Trauma

The term "early life stress" (ELF) refers to a broad spectrum of negative exposures during fetal life, childhood and adolescence. Commonly studied early life stressors include physical or sexual abuse, neglect, social deprivation, emotional maltreatment, poverty, war, school bullying, but also single stressors, such as natural catastrophes, accidents, terrorism, attacks, or witnessing violence. Evidence has shown that a significant percentage of the population have experienced emotional, physical, and sexual abuse in childhood, and less has experienced emotional and physical neglect. In total, two-thirds of a large epidemiological sample of adults reported at least one adverse childhood experience, whereas, the presence of one stressful experience significantly increased the prevalence of having additional adverse childhood experiences (Dong et al., 2004). Furthermore, extensive research has revealed a strong relation between early life stress and the development of psychiatric disorders, such as depression, anxiety and posttraumatic stress disorder (Infrasca, 2003; Levitan et al., 2003; Pervanidou and Chrousos 2007) as well as a variety of physical health problems in adult life (Brown et al., 2009). There is convincing evidence today that chronic or intense stress during childhood affects developing brain structures and functions and programs the brain to react with more anxiety to new stressors (Lupien et al., 2009).

Indeed, and as discussed earlier in this chapter, animal studies have shown that chronically elevated stress mediators may lead to alterations in brain development through accelerated loss of neurons, delays in myelination, or abnormalities in developmentally appropriate synaptic pruning and/or decreased neurogenesis (Lauder, 1988; Sapolsky, 2000; Huang et al., 2001). Moreover, cortisol hypersecretion in utero alters neuronal development in areas rich in glucocorticoid receptors (GC) (Lauder, 1988). Thus, although cortisol exposure in essential for brain and HPA axis development, studies in animals indicate the substantial and permanent effects of increased stress mediators on brain morphology during prenatal and postnatal brain development.

Studies in humans also confirm the detrimental effects or early life stress in brain morphology. Studies using Magnetic Resonance Imaging (MRI) have suggested that adults having experienced early life stress have smaller hippocampal volumes compared to controls (Bremmer et al., 1997; Bremmer, 2002; Bremmer, 2003). A study in a large sample of adults without history of psychopathology revealed volumetric differences in brain structure in those with a history of childhood trauma, compared to those with minimal ELF. Reductions in brain volumes were apparent in the anterior cingulate cortex (ACC) and caudate nucleus (Cohen et al., 2006). A recent study revealed also that the age of exposure is an important variable determining the effects of stress on brain morphology. Later stress exposures, from age 8 to age 17, was associated with volumetric reductions in the ACC and insula volumes, while ELS experienced between the ages of 1 month and 7 years was not associated with lower brain volumes in these regions (Baker et al., 2013). This study indicates that adolescence is also a vulnerable period for the effects of stress in the brain and that stress might act differentially in specific time windows of brain development. This is also supported by evidence indicating diverse effects of stress during fetal life, dependent also upon sex, when sex-dependent factors have different organizational effects on fetal neural circuits Indeed, females seem to have an increased susceptibility to affective problems, such as anxiety and depression, whereas males are more vulnerable to developmental disorders, such as autism

spectrum disorders and attention deficit and hyperactivity disorders (ADHD). (Davis and Pfaff, 2014).

Positive & Negative Adaptations

Apart from the detrimental effects of traumatic experiences, especially childhood trauma on stress reactivity, stress can also affect resilience. Resilience can be defined as a positive personality characteristic that enhances individual adaptation. A high number of inter-individual differences in stress responses predispose an individual's vulnerability or resilience against environmental challenges. Genetic predisposition is an important factor in the cumulative stress hypothesis of vulnerability or resilience to stress-related mental disorders. According to this hypothesis, in a given context, the accumulation of traumatic stress experiences and the failure to cope with such experiences enhances vulnerability (Mc Ewen, 1998; Taylor, 2010; Daskalakis et al., 2013). Another concept of cumulative stress exposure, the "three hits hypothesis", (Daskalakis et al., 2013), suggests also timing of exposures as a critical point in determining vulnerability or resilience: hit-1, is the genetic predisposition, hit-2 is the early life environment, and hit-3 is the late life environment.

As depicted in figure 2, the acute stress reaction, depending on genetic background and epigenetic influences, is associated with acute activation of stress mediators– hormones, cytokines, growth factors, receptors as well as to epigenetic changes and alterations in gene expression. Stress responses are also dependent on the stressor: acute stressors may act differentially than chronic traumatic experiences. Moreover, convincing evidence supports that timing and intensity, or the exposure are crucial variables determining short and long-term stress-related alterations and conferring either an adaptive advantage or a risk for psychiatric and physical disorders (Baker et al., 2013; Taylor, 2010). Sex and personality traits of the individual, as well as, prior psychiatric symptoms and coping mechanisms are of importance (Davis and Pfaff, 2014; Daskalakis, 2013).

Previous trauma, especially during early life, has received considerable interest in interpreting stress system activity in the sequelae of a traumatic experience, but also in the cumulative stress hypothesis in relation to long-term consequences. According to the cumulative stress hypothesis, if the accumulation of adversities in the life span exceeds a certain threshold, at risk individuals develop psychopathology (Mc Ewen, 1998). However, other theories, such as the predictive-adaptive responses (Gluckman et al.,2009) support that neuroendocrine, metabolic and cardiovascular plasticity associated with early life stress might promote positive adaptations when the individual is exposed to a new stressor, since adaptive changes "predict" an adverse future environment. In this view, exposure to a challenging, however moderate stressor might promote active coping and resilience to future stress exposures (Daskalakis, 2013).

The physiology of stress recovery

Given the behavioral and physiological changes taking place under stress, some described in this chapter, the optimal goal for stress recovery would be to retrieve good health without stress-related symptoms. In a number of recent clinical studies this natural endpoint has been completed with physiological and biochemical

measures of different kind. Apart from clinical status and diagnostic criteria a number of different measures have been used like ECG-based methods (e.g. heart rate variability – to measure sympathetic and parasympathetic tone), neuro imaging techniques (e.g. functional MRI- to detect deviances in visible cortex regions), hemodynamic measures (e.g. blood pressure and heart rate), coagulation measures (e.g. activated blood clotting time) and of course neuroendocrine measures (e.g. cortisol, norepinephrine, testosterone etc.). This kind of studies is also most often supplemented with psychometric instruments in order to capture depression, anxiety, well-being, personality and degree of stress.

Despite the number of methods used to catch the comprehensive concept stress, there is not one single method existing with the reliable capacity to distinguish long term pathological stress from normal stress. An example illustrating this is the measurement of morning awakening cortisol levels. In patients defined as under long term stress ("burnout") both increased (Grossi et al. 2005), decreased (Pruessner et al 1999) and normal levels of cortisol (Mommersteg et al. 2006) has been reported in comparison with control groups. Since there are no single (patognomonic) physiological or biochemical marker to capture long term stress in a reliable manner, there is neither any entirely acceptable method to evaluate spontaneous or therapy-induced recovery. It is indeed possible to feel well and being without cognitive difficulties and at the same time having an overload of measureable neuroendocrine activity.

Another difficulty in evaluating stress recovery is the time courses of the behavioral, physiological and biochemical processes. Most often the premorbid status is unknown for the researcher, and it is also associated with difficulties to follow nervous, cardiovascular and biochemical changes over time, especially if these are taking place at different times in the individual under stress, which most often also is the case. Since stress is such a broad concept and no general marker exists the most fruitful design would be to break down this wide concept to variables possible to define and operationalize., in doing so a number of interventions have been proven valuable. Pharmacological therapy has been shown to improve the regulation of neuroendocrine-autonomic systems as well as metabolism (Ljung 2001). Physical activity has also been shown to improve neuroendocrine function and possibly protect the brain against negative consequences of affective and stress-related disorder (Bjornebekk 2005, Jonsdottir 2006). Also nature-assisted therapy has been proven to increase well-being and reduce the need for health care in patients with stress-related disorders (Annerstedt 2010 and 2011). All therapeutic efforts in the treatment of short- or long-term stress aims at reducing different aspects of the state; neuroendocrine responses, behavior changes etc. Since there is no pathognomonic measure for stress there is neither any consensus on how to monitor stress relief in a reliable way. A number of indirect measures can be used to indicate stress recovery.

Conclusions and Future Suggestions

Advances in neuroscience, endocrinology, molecular biology, genetics and social sciences provide a new eco-bio-developmental framework for understanding the promotion of health and prevention of disease across the lifespan. Genetic predisposition, interacting with environmental factors and perceived positive or negative experiences, determine dynamic brain development and systems of

neuroendocrine adaptation, affecting behavior, cognition, learning and physical health. In contrast to tolerable and mild stress, intense or chronic stress (also called toxic stress), especially in early life, has a critical role in disrupting neural networks in the brain and affecting other regulatory systems of the organism increasing the risk for physical and mental disease.

Preventive societal interventions might include educational efforts, mainly focused on parents and schoolteachers to increase awareness of the effects of stress in health and disease, and community investments on the development of services to reduce sources of stress and to intervene, with collaborative works by mental health professionals and social workers, after adverse exposures. These prevention and intervention strategies might be more effective if applied to young age groups, in the form of early intervention programs.

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Legend for Figures

Figure 1

Following a stressful situation, during which baseline homeostasis is disturbed and the adaptive response is activated, homeostasis is usually successfully regained (eustasis). However, two other states are possible: 1. the individual survives at the expense of the wellbeing of the individual (allostasis or cacostasis) or 2. the organism “learns” and gains from the experience, and a new, improved homeostasis (hyperstasis) at the benefit of wellbeing is attained.

Figure 2

Stress reactions, depending upon individual traits and characteristics, the nature of the stressor and early experiences might lead, in the long term, to either stress recovery or chronic distress. Acute reactions include the activation of stress mediators (hormones, growth factors, cytokines, neurotransmitters), epigenetic effects and alterations in gene expression. Long-term positive or negative effects, through chronic adaptive changes in neuroendocrine networks, affect behavior, emotion and cognition and the physical health of the individual. Positive adaptations might include increased resilience and empathy and posttraumatic growth. Negative adaptations include stress vulnerability and stress-related mental disorders.