The psychobiology of stress

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Introduction

Hans Selye in one of his last books stated that "The great capacity for adaptation is what makes life possible on all levels of complexity. It is the basis of homeostasis and of resistance to stress. Adaptability is probably the most distinctive characteristic of life. Loss of adaptability is death" (Selye, 1976). Also from an evolutionary point of view, adaptation to the continuously changing environmental demands has survival value. Our flexible behavior and physiological system allows us to maintain a certain state of homeostasis, even when the environmental stimulation shows great variation.

Sterling and Eyer (1988) formulated the idea of "allostasis" as the ability to achieve stability (homeostasis) through change. One look at the diagram of blood pressure changes in a person wearing a blood pressure recorder (see Figure 1) reveals that the blood pressure level varies depending on the activities of the person. Those changes sometimes depend on the physical activity, sometimes on the mental activity and sometimes occur just by the anticipation of events. "Homeostasis emphasized that the body's internal environment is held constant by the self-correcting (negative feedback) actions of its constitutient organs. Allostasis emphasizes that the internal milieu varies to meet perceived and anticipated demands. This variation is achieved by multiple, mutually reinforcing neural and neuroendocrine mechanisms that override the homeostatic mechanisms. The allostatic model, in emphasizing the subordination of local feedbacks to control by the brain, provides a strong conceptual framework to explain social and psychological modulation of physiology and pathology." (Sterling & Eyer, 1988, p. 646).

The aim of the present chapter is to make the reader familiar with some basic knowledge about the cardiovascular and endocrine system and their role in the psychobiological stress response. The term stress unfortunately is used in the literature in many different meanings, sometimes resulting in confusion and lack of mutual understanding. Here, we will define stress in a biological way as any threats to the homeostasis. In what follows we will desribe how the body reacts to such threats.

Until recently, the biological stress response was described in terms of Walter Cannon's fight-or-flight reaction, characterized by increased activity of the sympathetic nervous system to produce alertness and energy to prepare the organism for action (e.g. increased arousal and vigilance, increase in heart rate and contraction force of the heart, enhanced blood pressure, dilation of the bronchi, redistribution of the blood from the internal organs to the muscles, increased gluconeogenesis, etc).

Hans Selye developed the notion of the General Adaptation Syndrome (GAS). This "nonspecific response of the body to any demand" has three characteristics: (1) adrenocortical enlargement; (2) thymicolymphatic involution; and (3) intestinal ulcers. Later came the realization that this syndrome actually has three phases: (1) the alarm reaction; (2) the stage of resistance; and (3) the stage of exhaustion. According to Selye, in this final phase there was a total breakdown in the organism, with a complete loss of resistance, giving way to the development of what are called "diseases of adaptation".

The modern view of stress emphasizes the adaptational aspects of the response to any threats to homeostasis. As already said, in the course of the evolution, the development of these reactions may have contributed to the survival of the species, because they were most appropriate to deal with acute threatening situations, in particular the confrontation with predators. However, in modern times we are exposed more to chronic demanding situations (e.g. unemployment, marital problems, the care of parent suffering from Alzheimer, etc), rather than being exposed to the threats of our ancestors, which may be very dramatic and intense, but als rather short in duration. In what follows. We will discuss psychobiological stress responses, emphasizing that the chronic nature of our modern stressors has important consequences for how the stress response develops over time. In addition, we will introduce the concept of "allostasis" and "allostatic load" to describe the process of adaptation and its limitation as a consequence of chronic, long-term exposure to a taxing situation. We further would like to point out that the fight-or-flight reaction also has its counterpart which is characterized by increased activity of the vagal system, which at the behavioral level is accompanied by passivity and lack of motivation to engage in any active behavior. This state can psychologically be described as one in which feelings of disillusionment prevail. Not seldom, this state induces the shedding of tears. A well-known example of this reaction can be seen when soccer players are beaten in the very final phase of a match, laying on the grass or walking slowly with their heads bowed.

Chrousos and Gold (1992) focus in particular on the role of the hypothalamic-pituitary-adrenocortical (HPA) axis and present a model which explains the seeming discrepant findings of both increased and decreased levels of HPA activity. They emphasize that activation of the HPA axis in response to a stressor is meant to be acute or at least of a limited duration, which renders its accompanying catabolic and immunosuppressive effects temporarily beneficial and without any adverse effects for one's health status. However, increased and sustained activation of this system might be related to the pathogenesis of a wide variety of stress-related condition with psychiatric, circulatory, metabolic and immune components (e.g. anorexia nervosa, diabetes mellitus, hyperthyroidism, premenstrual tension syndrome). In addition, these authors provide evidence that the this stress system may also show a decreased function, associated with another group of disorders, such as chronic fatigue syndrome, hypothyroidism, and rheumatoid arthritis.

Stress and allostasis

The quality of our life is entirely dependent upon our ability to adapt. This is how we can live in various environments, various living conditions or seasons. Aging is a process in which our adaptability gradually diminishes. Physiological stress is then defined as allostatic load, referring to the physiological wear and tear on the body that results from individuals' ongoing efforts to adapt to the world around them. It may lead to stress-related disorders due to chronic overactivity or underactivity of allostatic systems. Being in a state of constant activation (as in a chronic fight/flight response to threat)

or in a chronic state of helplessness and giving up, decreases our adaptability (allostasis) and renders us more susceptible to a wide variety of stress related disorders.

As an example, we would refer to the development of essential hypertension. Repeated exposure to stress situations in which blood pressure is elevated leads to a permanent change in set points of baroreceptors which answer for the regulation of blood pressure levels. Such a permanent elevation (a condition called essential hypertension) in turn can lead to increased risk for a catastrophic condition in the blood vessels (stroke, myocardial infarction). Another example is the so-called "metabolic syndrome" in which repeated exposure to stress situations, with little possibility of exerting control, leads to a state of hopelessness and helplessness. In physiological terms, a chronic activation of the HPA axis leads, through cortisol secretion, to an accumulation of fat in central regions (visceral fat) and neck regions. It also affects insulin resistance and may lead to diabetic disease. Blood pressure and blood concentration of fat may be elevated. Simultaneously, testosterone levels decrease, which may enhance the metabolic syndrome even more.

Below we will first summarize recent cardiovascular stress research findings, next we will focus on the endocrine system. Finally, attention will be paid to ways how these sytems may mediate between stressor exposure and pathophysiological states.

The cardiovascular system

The cardiovascular system is the major delivery system of the body with its left and right pump as well as a system of arteries and vessels for the delivery of oxygen and energy, and a system of veins to collect CO_2. Heart rate changes have been observed during experimental mental stress provocations in the laboratory (mental arithmetic, simulated public speaking, cold pressor test or Stroop word-recognition task) or in natural settings (public speaking, exams, medical examination, hospital visits etc. (for a comprehensive review see Herd, 1991). Adaptation to a mild mental stressor involves moderate increases in heart rate and blood pressure. It also includes an increase in cardiac output, and a decrease in vascular resistance in the forearm and calf skeletal muscle. One can also observe an increase in the renal and splanchnic vascular resistance. In the more severe types of stressors which involve lack of control in a threatening situation, a different pattern of response can be observed. There are several examples of psychophysiological experiments showing that difficult tasks, requiring effort produce higher activation than impossible, unavoidable, or inescapable conditions. In addition, situations in which one really feels helpless and sees no opportunities for escape are accompanied by a specific psychobiological response pattern, which involves bradycardia, vasodilatation in the skeletal muscles, decreased arterial blood pressure and eventually, fainting, which may happen during public speech, blood donation, and other situations that are appraised as extremely demanding (Folkow, 1988; Vingerhoets, 1985a; Vingerhoets & Schomaker, 1990).

The dramatic "passivity" response is mediated by an intensive parasympathetic stimulation.

Depressed vagal activity, as assessed by chnages in heart rate variability (HRV), has been shown to be a predictor of sudden cardiac death and myocardial infarction. The depressed HRV, often related to the permanent elevation of heart rate, is among the best predictors of futher cardiac events after myocardial infarction, and has been used as an index of wear and tear of a lifelong exposure to taxing situations (Porges, 1995).

Thus, both in humans and animals, stressor exposure does not always lead to increased cardiovascular activitation. Indeed, impressive examples exist of nearly the opposite reactions, showing a general inhibition of motor activity. Note, however, that there may also be a state in which the organism is tense, concentrating on the forthcoming action, which in sharp contrast to the here described state characterized by unvoluntary weakness.

The endocrine system

The endocrine system consists of ductless glands distributed throughout the body. Most important among them are the pituitary, the thyroid, the adrenal gland, the pancreas, and the gonads. Those endocrine glands that are controlled by the nervous system are also referred to as the neuroendocrine system. The glands of the endocrine system release hormones into the bloodstream. In this way they can exert their influence on their target organs. These targets have specialized receptors which make them sensitive to the effects of specific hormones. These targets either may have a direct effect on bodily processes or they may stimulate the secretion of other hormones (see Figure 1).

The endocrine and nervous system work closely together and they have many similarities in their effects, but there are also some important differences. Generally speaking, one can say that hormones strengthen and/or prolong the effects of stimulation by the autonomous nervous system. The two systems closely work together resulting in integrated adaptive psychobiological reaction pattern to environmental challenges.

Below we will discuss the different glands and the hormones that they release as well as the effects of stressful stimulation on their functioning. In studies of hormonal reactions to stress stimulation one often encounters paradoxical findings. An increased release of a particular hormone may be observed in some situations whereas in others there might be suppression. In order to obtain a better understanding of such differences, it must be stressed that it is in particular the interpretation or appraisal of the stress situation rather than the objective characteristics of it that determines the nature of endocrine and cardiovascular responses (fight/flight or "dejection" response). In addition, the biological state of the individual (e.g., phase of the menstrual cycle, pregnancy, smoking status, physical fitness etc), genetic factors, age, and social support are of further relevance as codeterminants of the biological stress response.

Here we will briefly discuss some recent research findings to illustrate the influences of the psychosocial environment and mood and emotions on these factors. On the other hand, one should also

be aware of the reverse association. There are several examples that disturbed hormonal processes cause mood disturbances and influence behavior, rather then being the consequence. Well-known examples are the depressed mood associated with thyroid dysfunction. In addition, there is still discussion about a possible etiologic role of female sex hormones in post-partum depression and premenstrual syndrome. Post-partum depression refers to an abnormal psychiatric condition that occurs following childbirth, typically from three days to six weeks postpartum. The premenstrual syndrome can best be characterized as a group of psychological (e.g. depression, mood swings, lethargy, irritability etc) and physical symptoms (e.g., abdominal cramps, muscle stiffness, swollen ankles or fingers, skin disorders, etc)that are limited to the week preceding menstruation and which are relieved by the onset of menses.

The pituitary gland

The pituitary or hypophysis - also referred to as the "master gland" because it secretes a number of hormones that affect other glands and stimulates the production of other hormones - is located in the brain just below the hypothalamus (in the forebrain). The hypothalamus sends chemical messages -so called "releasing-" or "inhibiting factors", to the pituitary which control the release of pituitary hormones into the blood. The releasing factors prompt the release of hormones, whereas the inhibiting factors actually inhibit the secretion of hormones. The release of these substances from the hypothalamus is controlled by the structures which together form the emotional brain and is thought to be dependent on the results of appraisal processes of external stimuli, which take place in the cortex as well as the above mentioned other factors.

The pituitary consists of three parts, which are responsible for he production of different hormones. The anterior part or adenohypophysis is most important. The substances released from this structure are the adrenocorticotropic hormone (ACTH), prolactin (PRL), human growth hormone (hGH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and luteinizing hormone (LH). The pars intermedia produces melanophore stimulating hormone (MSH) and endorphins (which are also secreted by the adenohypophysis). The posterior part or the neurohypophysis has as its most imporant products vasopressine or anti-diuretic hormone (ADH) and oxytocine.

Although stress research has focused mainly on only a few pituitary hormones, there is good reason to assume that nearly if not all hormonal factors are under the influence of psychosocial stimulation. ACTH is among the most important hormones seen from the perspective of stress research, because it plays an essential role in the regulation of the psychobiological stress response, more specifically the release of cortisol by the adrenal cortex. Together with the catecholamines (adrenaline and noradrenaline or epinephrine and norepinephrine, see later), cortisol is since the early work of Selye most often used as a biological marker in stress research. The number of human stress studies in which ACTH has been measured is limited, in spite of ots importance for investigating the effects of exposure to chronic stressors.

Other hormones have received less attention in human stress research, although some interesting findings have been reported. For example, research on the effects of psychosocial factors on PRL, of which the biological functions mainly relate to fertility, breast development, and lactation in post-partal women, has yielded a seemingly paradoxical picture. Whereas studies applying typical laboratory stressors (such as mental arithmetic or reaction time tasks) all have shown decreased PRL plasma levels after exposure to these tasks, real life studies with bereaved persons and patient populations generally have found increased levels of plasma PRL. This hormone has been referred to as the hormone that mirrors passivity and helplessness (Theorell, 1992). Interesting in this respect is further the hypothesis that PRL may lower the threshold to cry (Frey, 1985), supporting the relationship between crying and powerlessness. These preliminary data thus suggest that the release of this hormone may either be stimulated or inhibited, dependent on the specific nature and/ or appraisal of the stressor. In other words, exposure to stressors that can be coped with actively, inhibit PRL release, whereas "passive" stressor stimulate the secretion of PRL. Since women in their fertile years have higher PRL levels and their levels are even more increased during pregnancy and just after delivery when starting breast feeding, these sex differences in PRL might partially explain why women cry more often then men.

The major role of hGH is to stimulate protein synthesis. In addition, it decreases the rate of carbohydrate utilization and increased the mobilization of fatty acids and their use for energy. The relatively few human studies focussing on hGH responses to psychosocial stimulation have yielded a confusing pattern. Therefore, we will restrict ourselves to mention briefly the interaction of this axis and the activity of the hypothalamus-pituitary-adrenal cortex (HPA) system, resulting in the adverse effects of stress on growth, resulting from the fact that prolonged activatioon of the HPA axis leads to sepression of hGH and inhibition of several other growth factors (Tsigos & Chrousos, 1996). Generally, one can say that the redirection of nutrients and vital substances to the brain and other areas where they are needed most during states of stress may explain the adverse effects of chronic stress on growth.

Endorphins are important because they probably play a role in what is known as "stress-induced analgesia", which refers to the phenomenon that people under severe stress like soldiers in a battle do not experience pain, when badly wounded. In addition, Panksepp (1998) presents some intriguing findings that these substances play a major role when people are confronted with social losses and losses of attachment figures. His hypothesis is that either exogeneous or endogeneous opioids may replace the social bonds, explaining why addicts consider their opiates as their friends. TSH's target organ is the thyroid gland, controlling the release of thyroxin and thyronin. As an example of the close association between hormones and mood, we would like to refer to studies showing an association between thyroid hormones and depression. Some clinical signs and symptoms of thyroid dysfunction are similar to depression and depression may be provoked by underlying overt hypothyroidism. Depressed inpatients have an increased incidence of (sub)-clinical thyroid dysfunction and women suffering from postpartum depression have higher prevalence rates of elevated TPO-Ab levels, an

important marker of autoimmune thyroid disease. The occurrence of stressful life events (an important determinant of depression) has further shown to be a risk factor for the development of thyroid dysfunction, particularly Graves disease.

The adrenals

Cortisol

Cortisol, among others, acts to conserve stores of carbohydrates, regulates sodium retention and is of particular relevance for students investigating the stress-disease relationship, because of its depressive effects on immune processes. Among the earliest studies investigating the influence of psychosocial stressors on the activity of the HPA-axis were investigations examining the effects of aircraft flights, the preparation for surgical operation, examinations, and combat in Vietnam (see for reviews, Rose 1980, 1984; Vingerhoets, 1985b). It was shown that such dramatic- severe situations caused significant cortisol elevations in humans. However, milder situations such as the admission to a hospital or the confrontation with an unfamiliar environment also appeared to significantly stimulate cortisol release. Other studies showed that reassurance and briefing aimed at reducing feelings of uncertainty in stressful situations lessened the adrenal cortical response. At that time, in the 1970s, there was increasing awareness of the enormous individual differences in reactivity. From then on, the emphasis was more and more on the impact of psychological processes such as appraisal, coping, and defense on biological processes. For instance, in women, who underwent breast tumor biopsy for the determination of potential malignacy and in children during the first day of admission to a hospital, cortisol production could be predicted on the basis of psychological coping measures.

More recently, data have become available suggesting that measures of (un)controllability are more useful as predictors of adrenal cortical activity than more global stress measures. This means that (perceived) control over the environment determines to a large extent the corticosteroid production (see for a review: Brosschot, 1991). Thus, whereas traditionally an increase in the production of cortisol was considered to reflect the biological stress response, more recently one has become aware of the fact that this view needs some correction. First, there came increasing evidence suggesting that cortisol was mainly influenced by the controllability of the situation. Cortisol production was found to be increased after being exposed to uncontrollable stressors, whereas controllable stressors have far less if any effect on cortisol levels. A second important finding was that cortisol also appeared to be lowered in stressful conditions, especially if these were of a chronic nature. This was most elegantly demonstrated in a study with monkeys by Mason and coworkers (1990).

Also in chronically stressed humans relatively low levels of cortisol have been reported (Vingerhoets & Van Heck, 1994). To mention a few examples, patients consulting their general practitioners for tiredness demonstrated low cortisol levels. Our own comparison of endocrine variables

in low- and high-distress subjects also tended to show lower cortisol levels for the high-distress group, whereas the plasma ACTH levels of the latter group did not differ from the low-distress group. Recent data further indicated low cortisol production in Post Traumatic Stress Disorder patients.

Before we already mentioned the interaction of the HPA-axis with the growth axis. For the sake of completeness, it must be added that this axis in a rather similar way interact with the reproductive axis, the thyroid axis, fat, muscle and bone metabolism, as well as gastrointestional function. Finally, the effects of these substances on immune processes must be emphasized, explaining it prominent role as a mediator in stress-induced pathophysiological processes. Cortisol is known for its immunosuppressive effects also resulting in an inhibition of inflammatory processes. This state would lead to an increased susceptibility of the individual to a host of infectious agents or tumors, but increased resistance to autoimmune/inflammatory diseases. In contrast, a decrease of cortisol may stimulate inflammatory reactions, yielding the reverse of the just described susceptibility pattern.

To summarize, after prolonged exposure to stressful conditions, biological processes are set in motion to counteract the elevated plasma cortisol levels. However, which mechanisms are responsible for this phenomenon remains to be established. One hypothesis is that the adrenal system becomes less sensitive and reactive to ACTH and that increasing amounts of ACTH are necessary to stabilize the plasma cortisol levels. Future research should focus directly on these issues in order to increase our insight into the underlying mechanisms.

The catecholamines

The catecholamines (noradrenaline and adrenaline, also called norepinephrine and epinephrine, and dopamine) in the plasma are released by the adrenal medulla (in particular adrenaline or epinephrine), but the major part of noradrenaline originates from the nerve endings of the sympathetic nervous system, in which noradrenaline and dopamine act as neurotransmittors. Adrenaline and noradrenaline both have sympathicomimetic effects, although there are some important differences. Adrenaline has a greater effect on cardiac functions (heart rate and contractility), whereas noradrenaline causes stronger constriction in especially the muscle vessels. Finally, the influence of adrenaline on the metabolic rate of the body is greater, resulting in a more general enhanced activity and excitability of most physiological systems.

Ever since the early work of Cannon there have been examples of studies showing an increase in urinary catecholamine output or metabolites or in plasma levels after exposure to a wide variety of stressful and demanding situations, including overwork, parachute jumping, stressful movies, examinations, etc. However, much the same as for cortisol, this appeared not to be the whole story. Interesting results were obtained, among others, by American investigators who compared behavioral and catecholamine responses of employed and unemployed subjects to an unsolvable task. There was a striking parallel in the behavioral and the endocrine data: Employed and newly unemployed individuals

persisted longer on the task and reacted with increases in catecholamines. In contrast, those who were unemployed for longer periods gave up rather soon and showed a remarkable relative drop in catecholamine levels. A further illustration is given in a study, in which phobic subjects were exposed to their phobic stimulus and self-efficacy or ability to cope with the closeness of the stimulus was assessed. Instead of physical distance as an index of closeness to the stimulus, the focus was on the subjective experience. It was found that difficulties with enduring the situation were associated with sizeable increases in catecholamine levels. However, when the feeling of being overwhelmed dominated, no further increase, but rather a drop in catecholamines was observed. If one can accept that emotional fainting is the ultimate behavioral equivalent of being overwhelmed and feeling helpless, as has been suggested by some studies (see Vingerhoets & Schomaker, 1990) the finding that individuals who just fainted have extremely low catecholamines nicely fits into this view.

To summarize, evidence suggests that the catecholamines responses to stressors also may differ, dependent on the appraisal of them. When one has the feeling that an active approach may help to cope adequately with the stressor, catecholamines increase, whereas hopelessness and inability to respond behaviorally may result in a considerable decrease in catecholamines.

The sex glands

Last, but not least interesting is the behavior of the sex hormones after stressor exposure. In particular for testosteron, it has been shown that the psychosocial context may have a strong influence on its plasma levels. Also for this hormone, both increases and lowered levels have been observed. Generally speaking, a positive mood, feelings of mastery and control, and pride may result in stimulation of testosterone production, whereas a low self-esteem and feeling bad negatively influences the release of this hormone. Both animal work, in particular the levels of dominant and lower subdominants as well as studies with humans (e.g., the comparison of levels of winners and losers in a wrestling match) support this picture (cf. Vingerhoets, 1985b). Animal research further has led Panksepp (1998) to conclude that testosterone plays a major role in the decrease in crying among boys. In addition, there is some evidence that levels of androgen hormones in women correlate rather strongly with empathic ability. To summarize, also for this hormone the picture emerges of a bidirectional relationship between plasma levels of these substances and both external stimulation and mood and behavior.

The development of the biological stress responses

Recent animal research strongly suggests that chronic exposure to intense stressors, resulting in a permanent state of distress, will ultimately lead to the exhaustion of adaptive biological processes. The current lack of longitudinal human studies prevents us from drawing any definitive conclusions whether the same processes occur in men. Whether or not individuals, who react more intensely with

sympathetic arousal and/or slower recovery to baseline, run a higher risk to develop the assumed state of exhaustion as evidenced by a decreased cardiovascular response and low plasma cortisol levels remains to be investigated.

Each of the following five possible different patterns of responding may occur when an existing stressor continues to be present and/or novel environmental demands are placed on an organism ("allostatic load") (see also McEwen, 1998):

(1) Habituation and extinction of physiological arousal

Repeated exposure to the same (neutral) stimulus generally results in a gradual decrease in response amplitude. Moreover, as an organism learns to adapt to ongoing demands, or demands are reappraised as non-threatening, a reduction in stress responding may be expected. For example, paratroopers' adrenal cortical and medullary responses to training were found to subside as they gained more experience and mastery over the situation. In addition, as shown above, some studies have yielded suggestive evidence that chronic stressor exposure may be associated with decreased plasma cortisol levels. However, this should be considered as a different phenomenon. Whereas habituation represents a healthy reaction to repeated stimulation, reflecting a learning proces and increased control over the situation, the decrease in both cortisol and catecholamines after chronic exposure probably indicate very different psychological processes and maladaptation rather than proper adjustment (see later).

(2) Chronic physiologic arousal

The type of apparent habituation described above may not be as likely in some situations, however. Instead, at least for some period of time, the body may keep responding to the perceived demand. For some physiologic systems at least, this responding may continue for a relatively long time. For example, for a subset of subjects living near the damaged nuclear power plant at Three Mile Island, chronic activation of the biological system, as appeared from higher levels of urinary adrenaline, noradrenaline, and cortisol, was evident even years after the actual event. It is tempting to speculate how physiologic responses to new events will be affected by this heightened baseline arousal.

(3) Sensitization of responding

Reactivity to subsequent (in particular novel) events may be exaggerated. In one animal study, exposure to novel challenges following exposure to other stressful conditions resulted in catecholamine elevations greater than if the challenge had occurred without prior stressor exposure. In contrast, repeated exposure to the same stressor showed the usual decline in intensity of reactions (i.e., habituation). Blood pressure responding in humans was also found to be exaggerated among those living in crowded situations when exposed to an acute laboratory challenge. Studies with traumatized patients also showed increased reactivity of several biological systems to trauma-related stimuli. A final example is that children of hypertensice parents have been shown to react more with greater blood

pressure increases to a laboratory stressor than children lacking such a genetic predisposition.

(4) General "muting" of physiological activity

Ongoing demands can alter perceptions of subsequent taxing events leading to decreased responding not only to more or less similar stressors (as in habituation), but also to new events. However, there is also evidence that the resources available for further responding may de depleted because of fatigue or until now unknown mechanisms. For example, it has been shown that the cardiovascular reactions of chronically stressed individuals are decreased, rather than increased in response to laboratory stressors (cf. Vingerhoets & Van Heck, 1994). McEwen (1998) notes that the absence of any adequate responses to a stressor may trigger compensatory increases in other systems, which may make the organism more vulnerable to certain disease states.

(5) Decreased flexibility of the physiologic system

The Swedish researcher Frankenhaeuser has posited the "slow unwinding" hypothesis of stress responding where, in particular, the ability to return to baseline after the event has passed is disrupted. Investigators have reported this pattern of responding among students reporting many stressful life events. No differences were found in baseline blood pressure or heart rate nor in the psychophysiologic reactions to a challenging laboratory task between those with many and those with few life events. However, in the final condition it took longer for study participants with many life events to return to baseline levels than it did for subjects reporting fewer events. This decreased flexibility thus often also implies sustained arousal and, as a consequence, the production of energy, when that energy is not needed to fuel any behavioral efforts.

The five phenomena outlined here are not mutually exclusive. On the contrary, rather, they may reflect different phases in a process. It is hypothesized that the effects of chronic stressful conditions on psychobiologic functioning may show development over time not only as a result of adaptive operation of biological systems, but also depending on the evolution of coping efforts or depletion of social resources. The role of appraisal of events (i.e., how events are subjectively perceived and given meaning to) cannot be overlooked, especially when baseline levels of stress are concerned.

Individual differences

Until now, the role of personality and behavioral habits has not been touched upon. Nevertheless, it is worth mentioning that some behavioral types have in recent years been seen to greatly enhance the stereotyped psychobiological stress responses. The Type A-behavior pattern, which increases the risk of cardivasculr problems, with its hurry sickness and hostility exaggerates the fight/flight response independently of the type of challenge. Another example is the availability of social support, which may

have a strong moderating effect on the biological stress responses. For example, it has been shown that the cardiovascular but also the cortisol responses to laboratory stressors may vary as a function of social support. Kirschbaum, Wolf, and Hellhammer (1998) provide an overview of the sources of the individual differences in adrenocortical responses to psychosocial stressors in humans.

Stress and disease

Beside experimental stress provocations a chronic exposure to stress situations and its effect on cardiovascular and other (e.g. immune related) disease process has been intensively studied. In a study of real life exposure to stress situations one has observed cardiovascular reactions in connection with war situations or an increase in the incidence of acute myocardial infarction in connection to earthquakes. The study of life events, new or past, also show a strong association with cardiovascular and infectious disease. For example, in one such a prospective study an exposure to acute and chronic stress predicted risk for a new infarction in a 3-years follow up. The absence of social support in such adverse situations may increase the risk even more. Social isolation may in itself create a stress situation and lead to an increase in CHD risk. One area which systematically employs the evaluation of cardiovascular function to stress is the "work stress" research. Chronic occupational stress as defined by conditions of high demand/low control or high effort/low return has been shown to be associated with chronic elevation of blood pressure and left ventricle hypertrophy (Karasek & Theorell, 1990).

The risk of CHD is also elevated in the conditions of "job strain" in previously healthy workers. The return to such a work conditions after myocardial infarction is associated with an elevated risk of death in the 5 years follow up. The long exposure to such adverse life conditions like negative life events, social isolation or job strain may in our experience be expressed by negative emotional states. In the recent years concepts like chronic stress, burnout, vital exhaustion or depression have been used to denote such conditions and the cardiovascular risks has been evaluated in such a context. For example, Dutch investigators have been able to show an increased risk for myocardial infarction in 3900 healthy men who before were followed for 4 years reported vital exhaustion. An experience of "perceived stress" predicted cardiovascular events in a large group of men in Gothenburg, followed for a period of 12 years. Stress in this study consisted of experience of tension, anxiety, irritability and sleep problems. Finally, depression has been in numerous studies linked to an increased risk for cardiac events in previously healthy people. In the cardiac patients depression appears to constitute one the biggest danger for adverse development, as important as smoking or elevated lipid levels.

More or less identical examples can be provided for other diseases, although the methodological stronger studies focus on infectious disease, in particular the flu, the common cold, and respiratory problems. Recently, there are also some impressive studies showing the negative effects of stressor exposure on wound healing, illustrating the loss of adaptability. Caretakers of Alzheimer patients showed slower wound healing than a matched control group and the same was shown for

students during examinations in comparison to a more relaxed period. There are thus several examples of studies yielding support for clinically relevant effects of psychosocial factors on pathophysiological processes.

Conclusion

Recent research thus shows there is an association between the duration of the stressor exposure and the degree of controllability, on the one hand, and the specific nature of the psychobiological stress response, on the other hand. In addition, the shifting attention away from the response to acute stressors to the reaction to chronic stressful situations has yielded important new insights, which may better explain some seemingly contrasting clinical phenomena, e.g. that depression may be associated with a lack of appetite or by overeating, by a lack of sleepiness or by increased sleepiness. We have made important progress in our understanding of the complex interactions between the different cardiovascular, neuroendocrine and immunological processes, that all serve to maintain the homeostatic balance. Our understanding of the wear and tear process (allostatic load) which follows the chronic adaptation to a perceived or real stressor, possibly resulting in serious and less severe disease states like metabolic and cardiovascular or infectious disease also rapidly increases. In the near future, studies will unravel the relative contribution of factors, such as genetics, lifestyle, and exposure to physical environmental factors, helping us to acquire a better appreciation of the real clinical importance of these biological stress responses.

Literature

Brosschot, J.F. (1991). *Stress, perceived control, and immune response in man*. Utrecht: University of Utrecht, Unpublished thesis.

Cannon, W. (1915). *Bodily changes in pain, hunger, fear and rage*. New York: D. Appleton and company.

Chrousos, G.P., Torpy, D.J., & Gold, P.W. (1998). Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: Clinical implications. *Annal of Internal medicine, 129,* 229-240.

** Chrousos, G.P., & Gold, P.W. (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA, 267,* 1244-1252.

Chrousos, G.P. (1995). The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *New England Journal of Medicine, 332,* 1351-1361.

** Folkow, B. (1988). Stress, hypothalamic function and neuroendocrine consequences. *Acta Medica Scandinavica, Suppl 723,* 61-69.

Folkow, B. (1993). Physiological organisation of neurohormonal responses to psychosocial stimuli: implications for health and disease. *Annals of Behavior Medicine, 15,* 236-244.

** Henry, J.P., & Stephens, P.M. (1977). *Stress, health, and the social environment: A sociobiologic approach to medicine*. New York: Springer.

Herd (1991).???????????????

** Kirschbaum, C., Wolf, O., & Hellhammer, D. (1998). Adrenocortical responsiveness to psychosocial stress in humans: Sources of interindividual differences. In: D. Krantz & A. Baum (Eds.). *Technology and methods in behavioral medicine*. (pp. 29-45). Mahwah NJ: Erlbaum.

** Mason, J.W., Kosten, T.R., Southwick, S.M., & Giller, E.L. (1990). The use of psychoendocrine strategies in post-traumatic stress disorder. *Journal of Applied Social Psychology, 20*, 1822-1846.

** McEwen, B.S. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338,* 171-179.

** Panksepp, J. (1988). *Affective neuroscience. The foundations of human and animal emotions*. New York: Oxford University Press.

** Porges, S.W. (1995). Cardiac vagal tone. A physiological index of stress. *Neuroscience and Biobehavioral Rev. 19,* 225-233.

** Rose, R.M. (1980). Endocrine response to stressful psychological events. *Psychiatric Clinics of North America, 3*, 251-276.

** Rose, R.M. (1984). Overview of endocrinology of stress. In: G.M. Brown, S.H. Koslow, & S. Reichlin (Eds.), *Neuroendocrinology and psychiatric disorder*. New York: Raven Press, (pp 95-122).

** Selye, H. (1976). *The stress of life (2nd edition)*. New York: McGraw-Hill.

** Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In

S. Fisher & J. Redwin (Eds.), *Handbook of life stress, cognition and health* (pp. 629-649). Plaats: John Wiley and Sons Ltd.

** Tsigos, C., & Chrousos, G.P. (1996). Stress, endocrine manifestations, and diseases. In C.L. Cooper (Ed.). *Handbook of stress, medicine, and health*. Boca Raton FL: CRC Press.

Vingerhoets, A.J.J.M. (1985a). The role of the parasympathetic division of the autonomic nervous system in stress and the emotions. *International Journal of Psychosomatics, 32,* 28-34.

** Vingerhoets, A.J.J.M. (1985a). *Psychosocial stress: An experimental approach. Life events, coping, and psychobiological functioning*. Lisse: Swets & Zeitlinger.

** Vingerhoets, A.J.J.M., & Schomaker, L.R.B. (1989). Emotional fainting: Its physiological and psychological aspects. In: C.D. Spielberger, I.G. Sarason, & J. Strelau, (Eds.), *Stress and anxiety. Vol. 12*. New York: Hemisphere Publishing Corporation, (pp 181-198).

** Vingerhoets, A.J.J.M., & Van Heck, G.L. (1993). The psychobiological aspects of stress and emotions: some alternative views. In: U. Hentschel & E. Eurelings-Bontekoe (Eds.) *Experimental research in psychosomatics*. (pp. 19-36). Leiden: DSWO Press.

Wieck, A. (1989). Endocrine aspects of postnatal mental disorders. *Ballière's Clinical Obstetrics and Gynaecology, 3*, 857-877.