Psychological and physiological responses to stress
Houtveen, J.H.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 2

Human SAM and HPA responses to stress: a dualistic or an integrated system?

Jan H. Houtveen, Paul J. Lucassen, Jos F. Brosschot, & Eco J.C. de Geus

Abstract

The joined responses of the sympathetic adrenal medullary (SAM) axis and the hypothalamic pituitary adreno-cortical (HPA) axis are involved in mediating the effects of psychological stress on health. A popular view of SAM and HPA axes reactivity in response to stressful situations involves a strict dualism in reactivity of these two axes. This view implies that different psychological factors may differentially engage either the SAM or HPA axis. Mental effort has been described as inducing a rapid increase of catecholamine levels mediated through the SAM axis, while perceived distress has been described as triggering additional cortisol responses mediated through the HPA axis. Methodological problems in the studies that support this dualistic view are discussed. Finally, an alternative model is presented that explains the observed SAM and HPA response patterns by variations in the intensity of psychological stress, concurrent muscular activation, and the occupation of glucocorticoid receptors for cortisol. This model may help to better understand the (often paradoxical) effects of hormonal responses to different types of psychological stress as reported in the literature, without introducing a dualism in an obviously integrated physiological response system.
Introduction: the SAM and HPA axes

The physiological response to psychological stress situations encompasses both the sympathetic adrenal medullary (SAM) axis and the hypothalamus pituitary adreno-cortical (HPA) axis (e.g., Cacioppo, 1994; Dienstbier, 1989; Johnson, Kamilaris, Chrousos, & Gold, 1992; Lavallo & Thomas, 2000; Mason, 1968a; Mason, 1968b; Sapolsky, Romero, & Munck, 2000; Stratakis & Chrousos, 1995). These stress-related responses of the SAM and HPA axes are considered important mediators for the effects of psychological stress on health. A popular view states that different psychological factors may preferentially engage either the SAM or HPA axis (e.g., see Lavallo & Thomas, 2000). The current paper evaluates the evidence for this 'dualistic' model of SAM and HPA reactivity in response to different types of stressful situations. An alternative model will be presented that explains the observed SAM and HPA response patterns by variations in the intensity of psychological stress, concurrent muscular activation, and the occupation of the glucocorticoid receptors for cortisol in the brain. This occupation is influenced by circadian rhythms as well as the ongoing level of stress (i.e., the duration of the stressor).

The sympathetic nervous system, as part of the autonomic nervous system, prepares the individual organism for a fast fight or flight response after exposure to a stressor (Cannon, 1915). Following a specific appraisal phase (occurring within seconds) when an organism judges whether the situation is actually threatening, the behavioral response focuses on defensive behavior or, when a challenging other is dominant, flight. Physiologically, this fast response includes all main sympathetic targets (i.e., cardiac, splanchnic, renal, muscle-vascular systems, etc.). The sympathetic nervous system coordinates these responses through release of adrenaline (and to a lesser degree noradrenaline) into the blood by the SAM axis. As a consequence there is a selective increase in blood flow in muscular tissue, an increase in the noradrenergic drive to cardiac muscle and blood vessels, an increase in cardiac output and blood pressure, and an increase in the release of glucose from the liver (Mason, 1968b). The SAM response generates a fast and non-specific state of alarm to meet the special requirements of an emergency situation (Mason, 1968b). In the first phase this response tends to overshoot the actual physiological demand, but in a later stage sympathetic activation is tuned to a level that is just sufficient to maintain homeostasis.

When the intensity and duration of stress are sufficient, an increase is also elicited in the activity of the HPA axis (De La Torre, 1994; Lavallo & Thomas, 2000; Mason, 1968b; Sapolsky et al., 2000; Selye, 1936). HPA activation starts at corticotrophin-releasing factor (CRF) producing neurons in the paraventricular nucleus (PVN) of the hypothalamus. These neurons mainly project to several areas of the brainstem, including the sympathetic control areas, but CRF is also released within seconds after encountering a stressor, acting as a neuropeptide that stimulates adreno-corticotropic hormone (ACTH) release from the anterior
pituitary into the blood (Stratakis & Chrousos, 1995; Kvetnanski et al., 1995; Pacák et al., 1995; Sapolsky et al., 2000). ACTH, in its turn, stimulates the adrenal cortex to release glucocorticoids (cortisol). The central CRF system has a major function in regulating behavioral, autonomic (sympathetic and SAM), and HPA responses to stress (Stratakis & Chrousos, 1995; Kvetnanski et al., 1995; Pacák et al., 1995; Sapolsky et al., 2000). It is controlled and kept within physiological limits by negative feedback that is mediated through cortisol receptors that are present throughout the brain, but concentrated in high densities in the hippocampus, pituitary, and hypothalamus. Together they regulate the amount of CRF released by the PVN. As a result of this complex regulatory system, responsiveness of the HPA axis is considerably slower than responsiveness of the SAM system. Although some relatively fast effects of steroid hormones have been reported by means of rapid second messenger cascade mechanisms (Wehling, 1997), the bulk of the cortisol effects are genomic and do not occur until about several hours after the onset of a stressor (Sapolsky et al., 2000).

Cortisol (in primates) mobilizes energy and enhances metabolism. It stimulates the conversion of fats and proteins into glucose, and it is associated with an increased number of circulating free fatty acids (De La Torre, 1994; Johnson et al., 1992; Munck, Guyre, & Holbrook, 1984). Secondly, cortisol facilitates essential processes by suppressing several less acute, anabolic activities (such as growth, repair, reproduction, digestion, and inflammation) that may be important in the long run, but are not essential for survival under the given emergency conditions (De La Torre, 1994; Munck et al., 1984; Johnson et al., 1992). Thirdly, cortisol may have an enhancing and/or activating (permissive) function in the stress response (e.g., cortisol may increase blood pressure and cardiac output; see Sapolsky et al., 2000). Finally, cortisol may have a protective (suppressive) function. For example, it may protect against excessive or toxic damage exerted by catecholamines released by the sympathetic nervous system (Kapcala, Chautard, & Eskay, 1995; Munck et al., 1984; Sapolsky et al., 2000). The metabolic function of cortisol may have its effects during the initiation phase as well as during continuation of an alarm situation, whereas the slower (genomic) activating and protective functions of cortisol (permissive or suppressive) may have its effects solely during prolonged continuation of an alarm situation. It has been suggested that the permissive and suppressive effects of cortisol complement each other, the former preparing or priming defense mechanisms for action, and the latter limiting the actions of those primary defenses (i.e., to prevent them from overshooting) and to bring about recovery (Munck et al., 1984).

Glucocorticoids (cortisol) are highly lipophilic molecules that easily pass the blood-brain barrier, where they bind to two types of specific receptors in the major HPA feedback-regulation areas located in the brain: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR; De Kloet, Vreugdenhil, Oitzl, & Joels, 1998). Together, both GR and MR receptors control feedback regulation of HPA activity. However, the MR has a tenfold higher affinity for cortisol than the
Consequently, the MR is almost always occupied whereas the GR becomes occupied only during the circadian peak (about 1.5 hours after awakening) or during prolonged stress (De Kloet et al., 1998). The MR is thought to be involved in maintaining basal activity (proactive mode) of the HPA axis, whereas the GR is involved in reactivity (reactive mode) to maintain homeostasis (De Kloet et al., 1998). Most permissive actions of cortisol may be exerted through MR occupation, while suppressive actions may be exerted mainly through GR occupation (Sapolsky et al., 2000).

The SAM and HPA axes may be easily described as separate systems, each with a differential time-scale for the appearance of its major hormones (i.e., adrenaline and cortisol). However, the major point to be made in this paper is that, during stress, they will function as strongly integrated systems. The feedback control areas of the HPA axis (i.e., that regulate the release of cortisol by central GR and MR occupation) are also involved in the release of plasma catecholamines by the SAM axis (Kvetnansky et al., 1995; Munck et al., 1984). These effects of cortisol on the reactivity of the SAM axis may be permissive or, under specific conditions with high GR occupation, suppressive (Sapolsky et al., 2000). Thus, the reactivity of both the SAM and HPA axes is influenced by CRF neurons in the PVN and both systems may be down-regulated through GR occupation. Furthermore, many other reciprocal anatomical connections between the SAM and the HPA control regions have been demonstrated (Stratakis & Chrousos, 1995; Kvetnanski et al., 1995; Pacák et al., 1995).

Peripherally, SAM and HPA regulation also interact. In the adrenal medulla, adrenaline and noradrenaline are secreted by chromaffin cells (McGeer & McGeer, 1980). Haidan and co-workers (1998) demonstrated (in vitro) that chromaffin cells are involved in the release of cortisol as well. Moreover, chromaffin cells are characterized by the presence of phenylethanolamine-N-methyl-transferase (PNMT), which converts noradrenaline into adrenaline. Cortisol is released from the adrenal cortex and delivered preferentially to the medulla via the adrenal portal vascular system, where it induces the synthesis of PNMT in chromaffin cells. Thus, the extent to which adrenaline may be secreted is likely to depend on the amounts of cortisol released. Cortisol may also modify adreno-receptor sensitivity (Kvetnanski et al., 1995). In short, activity of the SAM and HPA axes, and the ensuing release of adrenaline and cortisol, is strongly coupled in the central nervous system as well as in the adrenal medulla and cortex. This coupling is not surprising since the SAM and HPA axes have mutually

1. The results of Kvetnansky and co-workers (1995) demonstrated that the suppressive effects of cortisol on the production of catecholamines reversed when cortisol was continuously administered for 7 days. These results illustrate the fact that the regulating effects of cortisol may be totally different during periods of chronic cortisol elevation (i.e., are truly context dependent).
human SAM and HPA responses to stress

supportive roles in their homeostatic functions (e.g., in glucose-metabolism; Stratakis & Crousos, 1995).

Two separate systems?

In spite of the above, the SAM and HPA axes are traditionally considered as two separate and independently regulated systems. This separation is derived from the classical model of Henry and Stephens (1977), mainly based on animal studies, in which SAM reactivity is thought to occur mainly under fight or flight, active effortful coping conditions (Cannon, 1915; Henry, 1986; Henry, Stephens, & Elly, 1986; Mason, 1968b), whereas reactivity of the HPA axis is thought to be evoked mainly in loss of control, passive conservation-withdrawal conditions (Engel & Schmale, 1972; Henry, 1986; Henry et al., 1986; Mason, 1968a). Thus, the SAM and HPA axes appear to respond differentially when animals are subjected to different situations. Apart from this situational specificity, evidence was found for a dispositional preference for SAM versus HPA reactivity, strongly coupled to the preferred coping style of an animal. Within any group of animals, two extreme ends of the distribution of coping strategies may be discriminated that differ with respect to behavioral, physiological, and central nervous system activities (e.g., see Benus, Bohus, Koolhaas, & van Oortmerssen, 1989). Such within-species differences in coping responses have been related to differences in SAM and HPA responses (e.g., see Fokkema, Smit, VanderGugten, & Koolhaas, 1988).

An example of within-species differences in coping responses is the difference between the short attack latency (SAL) and long attack latency (LAL) mice. These mice are genetically homogeneous but have been interbred for several generations to amplify the individual extremes of aggression and stress responses (Benus, Bohus, Koolhaas, & van Oortmerssen, 1991; Oortmerssen & Busser 1989; Koolhaas et al., 1999). SAL mice show increased aggressive behavior when an intruder is placed in the home cage, whereas LAL mice wait much longer before attacking. These groups may, to some extent, be considered representative for animals or individuals that will predominantly show a fight or flight response versus individuals displaying a preference for the conversation-withdrawal responses respectively (Engel & Schmale 1972). These differences in coping responses are paralleled by a high sympathetic reactivity of the SAL mice, and a preferentially parasympathetic response combined with a strongly enhanced cortisol responses to CRF in the more passive LAL mice (Fokkema et al., 1988). Similar within-species differences in physiological reactivity to stressors were also found between two Wistar rat lines selectively bred for high-anxiety-related behavior (HAB) and low-anxiety-related behavior (LAB; see Liebsch et al., 1998).

Thus, in these strongly inbred animals, many of the predictions on how specific types of animals react to specific stress situations, as described by Henry and Stephens (1977), have been tested and confirmed. Does a dualistic view on
SAM and HPA reactivity also hold for human subjects? The results of a number of situational specificity studies suggest that SAM axis reactivity appears to be triggered predominantly by mental load, effort, or activation (Lovallo, Pincomb, & Wilson, 1986b; Lundberg & Frankenhauser, 1980; Obrist et al., 1978; Peters et al., 1998), while HPA axis reactivity is triggered by perceived novelty (Brandenberger, Follenius, Wittersheim, & Salame, 1980; Wittersheim, Brandenberger, & Follenius, 1985; Davis, Gass, & Bassett, 1981), perceived lack of controllability (Bohlin, Eliasson, Hjemdahl, Klein, & Frankenhauser, 1986; Breier, et al., 1987; Netter, Croes, Merz, & Müller, 1991), or perceived distress (Lovallo, Pincomb, & Wilson, 1986a; Lundberg & Frankenhauser, 1980; Peters et al., 1998). Humans also seem to show evidence of a behavioral disposition that makes either SAM or HPA axis activation the dominant response to most stressors. Specifically, human individual differences in SAM axis hyper-reactivity are ascribed to the cardiovascular ‘disease-prone’ personality (e.g., type A, competitiveness, and hostility; Suls & Wan, 1993), whereas HPA axis hyper-reactivity is ascribed to a disposition for depression and depressive coping (Nemeroff et al., 1984; Gold, Goodwin, & Chrousos, 1988). At first glance, prospective studies on the effects of chronic psychosocial stress on health seem to support this dualism. Subjects with a disposition towards chronic active coping (e.g., related to work stress) and high levels of hostility have a higher risk for cardiovascular disease (Lynch, Krause, Kaplan, Tuomilehto, & Salonen, 1997; Siegman & Smith, 1994), in which sympathetic hyperreactivity is considered to be a major etiological agent. Impaired immune function, in which HPA dysfunction may play a major role, has been found mainly in conditions of chronic passive coping (bereavement, care-taking of ill partner, AIDS) and in subjects with a disposition towards depression (Glaser & Kiecolt-Glaser, 1994). However, it is becoming increasingly clear that immune function is also influenced by SAM activity (e.g., see Schedlowski, Hosch, Oberbeck, & Schmidt, 1994) and that a risk for cardiovascular disease is also influenced by HPA activity (e.g., see Fraser et al., 1999).

Some crucial studies will be discussed in more detail below to test the robustness of the evidence for a situational and dispositional dualism of the reactivity of the SAM and HPA axes in humans. In their classic paper, Lundberg & Frankenhauser (1980) found independent psychological sources of variance for SAM and HPA activation in the effort versus distress dimensions. They designed five different experimental situations (tasks) to induce different degrees of mental effort coupled with either distress or positive affect. After the experimental task (70 minutes) urinary cortisol and catecholamines were measured. A monotonous vigilance task (experienced as both distressing and effort-demanding) resulted in an increase in both cortisol and adrenaline, but not in noradrenaline. However, a self-paced reaction time task (experienced as effort-demanding but not as distressing) produced an increase in both adrenaline and noradrenaline, but a
decrease in cortisol. The authors concluded that effort activates the release of catecholamines, while additional distress was essential for cortisol release.

Two methodological problems may have flawed these conclusions. First, urinary adrenaline may not reliably indicate activity of the SAM axis (Ziegler, Aung, & Kennedy, 1997). Secondly, the different tasks had been performed at different times, which may be considered a confounding factor. Relatively high GR occupation exists during the early morning hours as compared to later hours (De Kloet et al., 1998). The monotonous vigilance task had always been performed relatively short after the early morning circadian peak which thus induced (additionally to MR) relatively high GR occupation (i.e., 8:30 - 9:40 AM), while the self-paced reaction time task had always been performed a few hours later during a situation with much less GR occupation (i.e., 10:50-12:00 AM). Because suppressive actions of cortisol are exerted mainly by GR occupation (Sapolsky et al., 2000), different experimental times may have resulted in differences in permissive versus suppressive actions of this regulatory system. These actions also involve the release of plasma catecholamines by the SAM axis (Munck et al., 1984; Kvetnansky et al., 1995). Thus, the adrenaline response to the early monotonous vigilance task may have been more suppressed than the adrenaline response to the self-paced reaction time task. Additionally, only the monotonous vigilance task may have produced enough (di)stress to result in a cortisol response. Thus, rather than specific task characteristics, the differences in the level of (di)stress combined with differences in (initial) GR occupation as a result of different experimental times may have explained the differential catecholamine and cortisol responses of this study.

Frankenhauser, Lundberg, and Forsman (1980) compared Type A and Type B men and women on a choice-reaction task. They measured urinary adrenaline, noradrenaline, and cortisol at the end of the task. Their results demonstrated an overall increase in the secretion of catecholamines and a decrease in cortisol. The increase in catecholamines was interpreted in terms of the mobilization of effort induced by the task. The decrease in cortisol was interpreted in terms of the high level of personal control (low distress) while performing the task. However, the time of measurement (i.e., 10:50-12:00 AM) was identical to that of the effort demanding/low distress task of the previous experiment (see above). The decrease in cortisol probably resulted from the well-known morning decrease due to the circadian rhythm. Also, a low (initial) GR occupation may very well have been responsible for the relative high catecholamine levels during this low stress task. Although comparison of physiological measures between sexes may be problematic, closer observation of the differences between men and women suggests that the amount of released adrenaline was actually correlated to the amount of released cortisol. Men, as compared to women, reported more effort, secreted more adrenaline, and they had less decrease of cortisol.

Peters and co-workers (1998) used a factorial design in which mental effort was manipulated by a high effort mental arithmetic task versus a low effort key-
press task, while control (and success on the task) was independently manipulated by the amount of controllability and predictability regarding the noise intensity presented to them during the task. They found a main effect of both effort and control on noradrenaline, and only a main (and relatively small) effect of control on cortisol. No meaningful effects were found for adrenaline. Their data would have been more illustrative of a dualistic SAM and HPA reactivity when a main effect of effort was found on adrenaline (high effort should always produce more SAM activation), combined with an effort by control interaction effect on cortisol (increased HPA activation should only be found when high effort is combined with low control). However, such effects were not found.

Lovallo and Thomas (2000) referred to two other studies that (when combined) might suggest differential effects of effort versus distress on SAM and HPA activation. In the first study, a significant rise in both noradrenaline and cortisol secretion was found after 15 minutes of a reaction time task in which subjects had to perform well to avoid noise bursts and electric shocks (Lovallo, Pincomb, & Wilson, 1986a). In the second study, only a significant rise in noradrenaline (no change in cortisol) was found after subjects had performed a nearly identical reaction time task for monetary reward (Lovallo, Pincomb, & Wilson, 1986b). Self-reports showed increases in both effort and distress during the noise bursts and shock avoidance task, but only increases in effort during the monetary reward task. Lovallo and Thomas (2000) concluded that cortisol is preferentially responsive to the subjective states of distress, while catecholamines are responsive to states of ‘activation’, regardless of the emotional valence. However, between-task differences in heart rate and blood pressure responses indicate that the first described task (i.e., the cortisol producing task) may have resulted in an overall higher autonomic activation as compared to the second. The intensity of the stressor may have been sufficient for cortisol release for the first study, but it may not have been sufficient for the second study.

Another main complication in accepting the conclusions of both Peters and co-workers (1998) and Lovallo and Thomas (2000) is that they hinge in part on a differential noradrenaline response. However, noradrenaline levels may not always reliably indicate SAM axis activation. High plasma noradrenaline levels during effortful tasks may also be explained by increased muscle tension. Muscle tension results in reflexogenic local plasma release of noradrenaline from the sympathetic nerve endings that innervate the muscle vasculature (e.g., see Goldstein, 1995). Increases in muscle tension may be more apparent during states of anger and/or defense as compared to states of fear and defeat (Ax, 1953; Henry, Stephens, & Ely, 1986). Thus, noradrenaline responses may falsely suggest a differential psychological effect on SAM reactivity if the tasks used to induce effort versus distress differ in the evoked muscular tension. Goldstein (1995), who reviewed plasma noradrenaline responses, more broadly concluded that this particular measure does not give a valid indication of sympathetic nervous system
activity. Only plasma adrenaline reactivity may be a reliable indicator of SAM axis reactivity to psychological stress.

The studies described above have often been quoted to illustrate that mental effort influences activity of the SAM axis, while perceived psychological distress (as a result of perceived novelty, unpredictability, or lack of control) influences activity of the HPA axis. Although attractive at face value, a strict situational dualism in the reactivity of the SAM and HPA axes in humans did not hold up in our evaluation of the current evidence. The few studies that have tested dispositional differences in the reactivity of the SAM and HPA axes in humans actually contradict a dualism. Cacioppo (1994) demonstrated a significant positive correlation between stress-induced increases in cardiac sympathetic drive and stress-induced changes in plasma cortisol concentrations. Likewise, al’Absi and co-workers (1997) showed a significant correlation between sympathetic reactivity and HPA axis reactivity. They additionally provided evidence that this correlation becomes apparent only during intensive stressors, like public speaking. Finally, Kirschbaum and co-workers (1996) showed that a short term elevation of estradiol levels not only exaggerates the ACTH and cortisol responses to psychosocial stressors, but it also exaggerates noradrenaline and heart rate responses.

**An alternative model**

What has been demonstrated convincingly so far is that increases in plasma adrenaline may occur independently of increases in plasma cortisol, and that neither increases in plasma adrenaline nor cortisol need to occur in parallel to increases in plasma noradrenaline. But do the various possible combinations of reactivity of plasma adrenaline, noradrenaline, and cortisol reflect distinct psychological dimensions of the stressors that evoke them? We will attempt a more parsimonious model that avoids psychological multidimensionality. We propose that variations in the intensity of psychological stressors of all types (e.g., competition with effort, uncontrollability with distress), the amount of muscle tension, and the ongoing central MR and GR occupation may result in several distinct catecholamine-cortisol responses.

Intensity of the stressors is important because activation of the HPA axis is slower and has a higher threshold level (in intensity and/or duration of stress) than activation of the SAM axis (e.g., De La Torre, 1994; Lovallo & Thomas, 2000; Mason, 1968a; Selye, 1936). Results described in Lovallo and Thomas (2000) and the study of al’Absi and co-workers (1997) seem to support the importance of the intensity of the stressor as a determinant of SAM and HPA patterning.

The amount of muscle tension caused by a stressor is important because the levels of plasma noradrenaline may largely depend upon it. A distinction should be
made between an activation dimension (defined here as an increase in action tendency and related muscle tension), and a psychological stress dimension. A high level of activation results in a relatively strong increase in plasma noradrenaline (resulting from increased muscle tension), while a high level of psychological stress results in a relatively strong increase in plasma adrenaline (resulting from activation of the SAM system).

Finally, the ongoing central GR occupation is important, since this may influence the balance in the release of plasma cortisol and adrenaline. Suppressive actions of cortisol are exerted mainly by GR occupation (Sapolsky et al., 2000). These suppressive actions also involve the release of plasma catecholamines by the SAM axis (Munck et al., 1984; Kvetnansky et al., 1995). Thus, regardless of persistent MR occupation, the feedback control loop of the HPA axis is also able to either facilitate (by selective MR occupation) or suppress (by additional GR occupation) the release of adrenaline by the SAM axis. The initial GR occupation, therefore, critically determines the pattern of adrenaline and cortisol responses to stress. Because GR occupation is related to initial cortisol levels, the circadian rhythm is an important determinant of GR occupation (De Kloet et al., 1998). GR occupation is further determined by the duration of the current stressor, or by a history of (chronic) stress (De Kloet et al., 1998).

After a low stress period with low initial GR occupation (i.e., the initial cortisol level was low), relatively moderate levels of plasma adrenaline combined with relatively low levels of cortisol may be found because no suppressive actions are exerted. After a high stress period with initially high GR occupation (i.e., the initial cortisol level was high), relatively moderate levels of plasma adrenaline combined with relatively high levels of cortisol may be found because suppressive actions are exerted. The lowest levels of adrenaline and cortisol may be found after initially high GR occupation combined with low stress, and the highest levels may be found after initially low GR occupation combined with high stress. Finally, muscle tension related to activation may independently contribute to the noradrenaline levels.

An illustration of different predicted catecholamine and cortisol reactivity patterns, as a result of differences in the level of intensity for activation and psychological stress and differences in the GR occupation at the initiation of a stressor, is shown in Table 1. Although the units in this Table are completely arbitrary, the relations between activation levels and suppression rates are illustrative of our alternative model. The mathematical rules used are: (a) the level of released adrenaline by the SAM axis is always four times the level of noradrenaline (i.e., peripheral interactions are ignored); (b) a high intensity stressor, as compared to a low intensity stressor, results in a two-fold increase of SAM responses and an eight-fold increase of HPA responses (based on a higher threshold for stress-related activation of the HPA axis); and (c) an initially high GR occupation results in halving both the SAM and HPA responses. Table 1 illustrates that the catecholamine-cortisol balance may vary without the need for a
distinct psychological source of SAM and HPA axis activation. At the same time, it is fairly easy to project all the findings of previous human studies on this table. For instance, the selective noradrenaline response to reaction time task performance for monetary bonuses (Lovallo et al., 1986b; described in Lovallo and Thomas, 2000) could reflect the two ‘high intensity’ cells of the ‘activation no stress’ column. Additionally, the joint cortisol and noradrenaline responses to the reaction time task to avoid presentation of noise bursts and electric shocks (Lovallo et al., 1986a; described in Lovallo and Thomas, 2000) could reflect the high intensity cells of the ‘activation and stress’ column.

Table 1. Predicted time integrated release (in arbitrary units 1-16) of plasma adrenaline (A), plasma noradrenaline (NA), and cortisol (cort) for two levels of GR receptor occupation at the initiation of the stressor, and two levels of intensity for activation and/or psychological stress.

<table>
<thead>
<tr>
<th>MR/GR occupation</th>
<th>intensity stressor</th>
<th>activation (no stress)</th>
<th>stress (no activation)</th>
<th>activation and stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR/lowGR’</td>
<td>low</td>
<td>+4NA</td>
<td>+2NA</td>
<td>+6NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+8A</td>
<td>+8A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+2cort</td>
<td>+2cort</td>
</tr>
<tr>
<td>MR/lowGR’</td>
<td>high</td>
<td>+8NA</td>
<td>+4NA</td>
<td>+12NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+16A</td>
<td>+16A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+16cort</td>
<td>+16cort</td>
</tr>
<tr>
<td>MR/highGR”</td>
<td>low</td>
<td>+4NA</td>
<td>+1NA</td>
<td>+5NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+4A</td>
<td>+4A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+1cort</td>
<td>+1cort</td>
</tr>
<tr>
<td>MR/highGR”</td>
<td>high</td>
<td>+8NA</td>
<td>+2NA</td>
<td>+10NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+8A</td>
<td>+8A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>+8cort</td>
<td>+8cort</td>
</tr>
</tbody>
</table>

Notes: *Relatively high levels of released catecholamines from the SAM axis may be found as a result of the permissive function exerted through (only) MR occupation. **Relatively low levels of released catecholamines from the SAM axis may be found as a result of the suppressive function exerted through (additional) GR occupation, that may have resulted from previous stress or the circadian rhythm.

Thus, variations in the intensity of psychological stressors combined with variations in the amount of muscle tension and variations in the ongoing central GR occupation may be sufficient to account for all complex (but coordinated) reactivity patterns of the human SAM and HPA axes described in the literature. This alternative model is based on mutual central (and peripheral) interactions.
between the SAM and HPA axes. Plasma adrenaline levels (not noradrenaline) reliably indicate SAM axis reactivity and are predicted to correlate with cortisol. Thus, reactivity in both plasma adrenaline and cortisol may indicate (a high level of) psychological stress.

Recently, the accent has shifted from stress-reactivity studies to a more dynamic view in which the total pattern of reactivity and recovery is observed during psychological stress situations (Linden, Earle, Gerin, & Christenfeld, 1997). This shift is based on new insights showing that in addition to (or even more importantly than) high reactivity, slow recovery or an aberrantly set hormonal balance, might influence the development of a disease process (Dienstbier, 1989; Linden et al., 1997).

A shift in focus towards the temporal patterns of reactivity and recovery of the physiological axes that respond to stress situations, and their inter-relationships, requires abandoning the strict separation of these axes as is now (often implicitly) adopted in the literature. The model presented here may be considered a physiological model of slow recovery, which might influence the development of a disease process or even brain pathology and affective disorders. It would be of great interest to observe individual differences in the reactivity of the SAM and HPA axes in response to moderate and intense stress situations, and under different conditions of (initial) GR occupation as a result of circadian rhythms, previous stressors, or medication. Such an approach is likely to be of great value in the study of specific stress-related disorders and on the effects of stress on health and well being in general.

References


Ax, A.F. The physiological differentiation between fear and anger in humans. *Psychosomatic Medicine, 15*, 433-442.


