



The cortisol awakening response (CAR): Facts and future directions

Eva Fries, Lucia Dettenborn, Clemens Kirschbaum*

Technische Universität Dresden, Faculty of Science, Department of Psychology, Chair of Biopsychology, 01062 Dresden, Germany

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ABSTRACT

In humans, the secretion of cortisol from the adrenal glands follows a diurnal cycle with a profound increase after awakening. This increase after awakening, a phenomenon termed the *cortisol awakening response* (CAR), appears to be a distinct feature of the hypothalamus–pituitary–adrenal (HPA) axis, superimposing the circadian rhythmicity of cortisol secretion. Several studies point towards an important role of the hippocampus and, additionally, other brain structures (e. g. amygdala, prefrontal cortex, suprachiasmatic nucleus) in the regulation of the CAR. There is increasing knowledge that the CAR is influenced by a variety of factors such as gender, health status, and health behavior or stress perception. However, the exact function of the profound cortisol increase after awakening is still not clarified. We hypothesize that the anticipation of the upcoming day is of major relevance for the magnitude of the CAR. The present paper reviews the current knowledge on the neural regulation of the CAR and factors influencing this phenomenon and considerations are addressed concerning the exact function of the CAR.

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1. Introduction

The hypothalamus–pituitary–adrenal (HPA) axis is a major endocrine system adapting the organism to bodily and environmental challenges by inducing behavioral and physiological changes, thus, improving the organism's ability to adjust homeostasis (e. g. Tsigos and Chrousos, 2002). The glucocorticoid cortisol is the hormonal end product of the HPA axis and plays a crucial role in the organism's efforts to adjust to these challenges. Cortisol binds to glucocorticoid receptors that are present in almost every tissue of the body. Consequently, cortisol mediates many metabolic processes ranging from induction of mobilization of energy, increasing cerebral perfusion rates and local glucose utilization, enhancing cardiovascular output and respiration, redistributing blood flow, increasing substrate and energy delivery to the brain and muscles, to modulating immune function (e. g. McEwen and Seeman, 1999).

Cortisol is being released into the blood stream as a result of a hormonal cascade which is initiated in the hypothalamus. More specifically, in the paraventricular nucleus (PVN) of the hypothalamus corticotropin-releasing-hormone (CRH) is synthesized and released into the portal blood circulation at the external layer of the median eminence. In addition to CRH, vasopressin is co-secreted into the portal blood and stimulates synergistically with CRH the secretion of adrenocorticotropic hormone (ACTH) at the level of the anterior pituitary. Via the systemic blood flow, ACTH reaches the adrenal cortex and, subsequently, stimulates the synthesis and secretion of species-

specific glucocorticoids, with cortisol being the main glucocorticoid in humans (Carrasco and van de Kar, 2003; Miller and O'Callaghan, 2002; Habib et al., 2001).

The basal HPA axis activity follows a distinct diurnal rhythm with several secretory episodes of short duration and high amplitude. Under normal conditions, the highest cortisol production occurs in the second half of the night with peak cortisol levels in the early morning hours. Thereafter, cortisol levels steadily decline throughout the day with lowest levels during the first half of the night (Dallman et al., 2000; Tsigos and Chrousos, 2002). In addition to this well-described diurnal cycle, there is a brisk increase of cortisol levels within 20–30 min after awakening in the morning. This phenomenon is termed the cortisol awakening response (CAR). The CAR appears to be a distinct phenomenon superimposing the circadian rhythm of cortisol as it adds a significant incremental effect to the linear trend of increasing cortisol concentrations in the early morning hours (Wilhelm et al., 2007). The CAR is considered a reliable measure for the acute reactivity of the HPA axis (Schmidt-Reinwald et al., 1999) and has been studied extensively over the past two decades, not only in healthy populations, but also in relation to many disorders including cardiovascular, autoimmune, atopic, allergic, and psychiatric diseases, among others (for review see, Wust et al., 2000b; Clow et al., 2004).

In the present review, we provide a detailed description of the CAR and discuss possible brain regions and other mechanisms regulating the CAR. Subsequently, factors influencing the CAR, such as health status, health behavior, or stress perception, are summarized. Since the exact function or teleological relevance of the CAR still awaits to be determined, we will conclude this review with the speculation that the CAR is associated with the anticipation of the upcoming day.

* Corresponding author. Tel.: +49 351 4633 3356; fax: +49 351 4633 7274.
E-mail address: ck@biopsych.tu-dresden.de (C. Kirschbaum).

2. Description of the cortisol awakening response (CAR)

The CAR is characterized by a sharp increase of cortisol release into the blood stream by about 38 to 75% of awakening levels reaching a maximum approximately 30 min after awakening (see Fig. 1, Pruessner et al., 1997). This cortisol surge after awakening is strongly inhibited after intake of a low-dose dexamethasone (Ebrecht et al., 2000), a synthetic glucocorticoid imitating negative feedback signals from circulating cortisol to ACTH-secreting cells of the pituitary, suggesting that the CAR is mainly driven by hormonal release from the pituitary.

The CAR has a relatively high intra-individual stability ($r=.63$ for the area under the curve of two consecutive days, Hucklebridge et al., 2005; Wust et al., 2000b), can be observed in 75% of healthy adults (Wust et al., 2000b) and shows a consistent pattern in school-age children, adolescents, adults and the elderly (Pruessner et al., 1997). A twin study revealed significant genetic impact on the cortisol awakening response with heritability estimates between .40 and .48 for the mean cortisol increase after awakening and the area under the curve, respectively (Wust et al., 2000a).

Recent investigations demonstrate that the CAR is distinct from the diurnal variations in HPA axis activity and is rather an additional phenomenon reflecting specific processes associated with awakening (Wilhelm et al., 2007). More specifically, Wilhelm and colleagues could show through continuous polysomnographical recordings and repeated blood sampling in the sleep laboratory, that the substantial increase in cortisol levels after awakening added a significant incremental effect to the regular linear trend of steadily increasing cortisol concentrations in the early morning hours before awakening. Their well-designed study indicates that this post awakening cortisol increase is linked to the process of awakening possibly through activation of memory representations about the self and orientation in time and space that have the potential to stimulate HPA axis activity. Accordingly, independent research indicates that HPA axis activity is regulated by different brain regions including the hippocampus, a crucial structure implicated in memory processes for facts and spatial information (hippocampus as a cognitive map, O'Keefe and Nadel, 1978; Burgess et al., 2002).

3. Neural regulation of the CAR

HPA axis activity in general is regulated by distinct brain regions including structures of the limbic system (amygdala and hippocampus) and the prefrontal cortex. Previous research indicates that specifically the hippocampus plays a major role in activating and inhibiting HPA axis activity by negative feedback mechanisms (for review see e. g., Herman and Cullinan, 1997; Herman et al., 2005; Jacobson and Sapolsky, 1991). Whether the proposed regulating mechanisms for HPA axis activity in general are identical to the mechanisms regulating the CAR as a distinct

phenomenon of HPA axis activity, is not entirely clear. It is possible that the suprachiasmatic nucleus (biological clock) as an additional structure may be of major importance for the CAR (Clow et al., 2004; Edwards et al., 2001a; Hucklebridge et al., 2005).

3.1. Hippocampus

The hippocampus, a prominent brain structure located within the temporal lobe, has been implicated in the regulation of the hormonal response to psychological and physiological challenges, that is, the HPA axis. Numerous studies describe a mainly inhibitory role of the hippocampus for HPA axis activity (for review see e. g., Herman and Cullinan, 1997; Herman et al., 2005; Jacobson and Sapolsky, 1991). More specifically, the hippocampus seems critically involved in the negative feedback regulation of the HPA axis by glucocorticoids: mineralo- and glucocorticoid receptors are present in abundance in the hippocampus, displaying a target for the negative feedback signals of glucocorticoids on HPA axis activity (de Kloet et al., 1990; Sapolsky et al., 1985). However, there are also some data suggesting a stimulatory role of the hippocampus for HPA axis activity, possibly depending on stressor modality. That is, in animal studies the hippocampus seems to be involved in HPA axis activation in response to ether inhalation or hypoxia, whereas hippocampus-mediated HPA axis inhibition occurs after restraint stress or exposure to novelty (Herman et al., 2005).

Some studies have pointed to the specific role of the hippocampus in the regulation of the CAR showing that, for example, both bilateral and unilateral hippocampus damage was associated with an absent CAR (Buchanan et al., 2004). Similar results were reported by Wolf and colleagues (2005) who showed a lack of a CAR in severely amnesic patients with presumed damage to the temporal lobe. Recently, Pruessner and colleagues (2007) could demonstrate that larger hippocampal volume was associated with a greater CAR. Taken together, these results suggest a central role of the hippocampus in the regulation of the CAR.

3.2. Other brain regions

Besides the central role of the hippocampus, HPA axis activity is regulated by innervations from several other brain regions including hypothalamic subregions, the thalamus, the bed nucleus of the stria terminalis, the nucleus tractus solitarius and the raphe nuclei, all of which directly innervate the PVN of the hypothalamus (detailed reviewed in e. g., Bowers et al., 1998; Herman and Cullinan, 1997; Herman et al., 2003; Herman et al., 2005). Yet, other brain regions mediate HPA axis activity indirectly including amygdala and the prefrontal cortex (Carrasco and van de Kar, 2003; De Kloet et al., 1998; Diorio et al., 1993; Herman et al., 2003; Herman et al., 2005; López

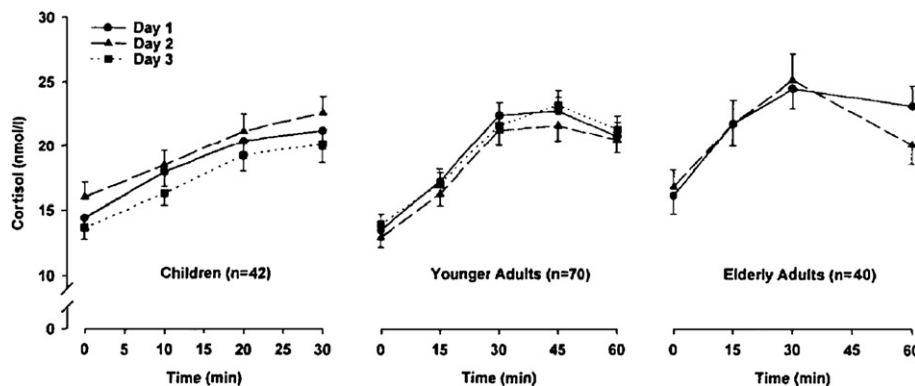


Fig. 1. Mean cortisol levels (\pm standard error) after morning awakening. Subjects studied: children aged 7–14 years, adolescents aged 19–37 years, and elderly adults aged 59–82 years (from Pruessner et al., 1997).

et al., 1999). Some state that the amygdala constitutes a pivotal brain region in the organization of an organism's response to external challenges (e. g. Fanselow and Gale, 2000). There is growing evidence that the amygdala provides excitatory input to the PVN and receives itself excitatory neural signals from the PVN. Additionally, the amygdala serves as a target for peripherally secreted glucocorticoids. Glucocorticoids act on the amygdala via binding to abundant mineralo- and glucocorticoid receptors in the medial and central nucleus of the amygdala (de Kloet et al., 1998), thereby increasing CRH expression within the amygdala (Gray and Bingaman, 1996; Makino et al., 1994; Makino et al., 2002; Cook, 2002).

The prefrontal cortex' role in HPA axis regulation is, similar to the hippocampus, to inhibit the axis' activity. Also, negative feedback processes of glucocorticoids are partially communicated via the prefrontal cortex (Herman et al., 2005; Diorio et al., 1993; Herman and Cullinan, 1997). However, the medial prefrontal cortex seems to be involved only in stress-induced, but not in regulation of basal HPA axis activity (review in e. g., Herman et al., 2005).

Taken together, other brain regions including amygdala and prefrontal cortex, as well as regions that directly innervate the PVN play a role in regulating HPA axis activity in general, however, their specific contribution to the CAR is yet unknown.

3.3. Other mechanisms

Especially for the regulation of the CAR, neural signals from the suprachiasmatic nucleus (SCN), the endogenous biological clock, to the adrenal glands are discussed to be of importance (Clow et al., 2004; Edwards et al., 2001a; Hucklebridge et al., 2005). The SCN is sensitive to light signals from retinal ganglia cells and regulates neuroendocrine activity via different routes. First, the SCN directly enforces its rhythm on the HPA axis via neuronal projections to the PVN (Kalsbeek et al., 2006; Buijs et al., 2003). Second, apart from the classical neuroendocrine control of the adrenal cortex via the hormone cascade of CRH and ACTH release from the hypothalamus and the pituitary, respectively, autonomic projections of the SCN via the sympathetic and parasympathetic branches of the autonomic nervous system determine the daily changes in sensitivity of the adrenal cortex to ACTH (Buijs et al., 2003). More specifically, the adrenal cortex is innervated by the splanchnic nerve and stimulation of this nerve increases the sensitivity of adrenocortical cells for ACTH, thus, resulting in an increased cortisol release in response to ACTH stimulation (Bornstein et al., 1990; Ehrhart-Bornstein et al., 1995). This specific mechanism may also affect the CAR as dissociations between ACTH and cortisol levels during the morning surge have been described (Fehm et al., 1984; Born et al., 1999). Further extrapituitary mechanisms of adrenal regulation have been described: besides ACTH-induced stimulation of cortisol secretion, cortisol release can also follow in response to input from the adrenal medulla or immune signals the adrenal cortex (e. g., Bornstein and Chrousos, 1999; Ehrhart-Bornstein et al., 1998; Engeland and Arnhold, 2005; Pignatelli et al., 1998).

As will be described later, the CAR is sensitive to light exposure, thus, making it plausible that the SCN, the light sensitive biological clock, plays a major role in the regulation of this phenomenon.

4. Factors that influence the CAR

A fair amount of research has been dedicated to investigating demographic and health-related factors with putative influence on the CAR, albeit with some inconsistencies in the results. The factors most studied are 1) age and gender, 2) female reproductive factors such as menstrual cycle phase and oral contraceptive intake, 3) a number of physical and psychological health conditions including cardiovascular, autoimmune, atopic, allergic, and psychiatric diseases, among others, 4) health behaviors such as smoking, and 5) sleep-

related factors including waking time, sleep duration, and sleep quality. Since the HPA axis is a highly stress-sensitive system, stress-related factors have also been studied.

Age: While a number of studies suggest that age does not have a major impact on basal HPA axis activity by showing unchanged circadian rhythms of hormone secretion in relationship to age (review in, Seeman and Robbins, 1994), the influence of age on the CAR is not entirely clear. While two studies described the absence of age effects on the CAR by, e. g., comparing cortisol awakening responses in children (aged 7 to 14 years), young adults (aged 19 to 37 years) and older adults (aged 59 to 82 years, Pruessner et al., 1997; Wust et al., 2000b), a significant association between age and the CAR was found in a sample of individuals between 4 and 64 years (Kudielka and Kirschbaum, 2003). The inconsistency in results may be due to the sample characteristics and analysis techniques of the different studies. While the work by Kudielka and Kirschbaum (2003) is based on a sample of 103 mainly young adults (median age of 23), the work by Pruessner and colleagues (1997) and Wust and colleagues (2000b) encompasses a much larger sample ($n=152$ and 509 , respectively) with a wider and more evenly distributed age range. In summary, it appears that in large studies, age does not have a strong impact on the CAR.

Gender: Sexual dimorphisms in brain structures modulating HPA axis activity and differences in gonadal steroid hormone secretion and corticosteroid binding globulin levels between males and females have shown to influence basal and stress-induced activation of the HPA axis (for review see, Kudielka and Kirschbaum, 2005; Viau, 2002).

Hence, it appears plausible that gender also impacts the CAR. Accordingly, some studies have described sex differences with pre- (Wust et al., 2000b; Pruessner et al., 1997; Pruessner et al., 1999), peri-, and postmenopausal healthy women (Wright and Steptoe, 2005; Kunz-Ebrecht et al., 2004) showing a stronger and prolonged increase of cortisol levels after awakening compared to their male counterparts, at least on workdays. However, other studies did not find support for differences in the CAR between men and premenopausal women (Kudielka and Kirschbaum, 2003; Kirschbaum et al., 1999) or women of a wider age range including pre- and postmenopausal women (Edwards et al., 2001a). It is important to note, that studies that report sex differences in the CAR described very small effect sizes with gender explaining only 1–3% of variability in the CAR (Wust et al., 2000b; Pruessner et al., 1997). In summary, it appears that the impact of gender on the CAR is rather small.

Menstrual Cycle Phase and Oral Contraceptive Intake in Females: In females, gonadal steroid secretion dramatically changes over the course of the menstrual cycle. Considering the impact of gonadal steroids on the HPA axis, these marked changes in hormone concentration may be of importance for the CAR. The results of two studies, however, suggest that the CAR is not influenced by menstrual cycle phase (Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2003). Similarly, oral contraceptive use changes gonadal steroid concentrations. Studies investigating the possible influence of hormonal contraception on the CAR reveal contradictory results: whereas two studies reported a tendency for smaller cortisol increases after awakening in women with oral contraceptive use (Pruessner et al., 1997; Pruessner et al., 1999), another study did not describe such effects (Wust et al., 2000b). Again, the effect size for hormonal contraception on the CAR reported in the study by Pruessner and colleagues (1997) was very small, explaining only 4% of variability in CARs. In summary, effects of gender or gonadal steroids on the CAR seem to be virtually negligible.

Physical/psychiatric conditions: Alterations of HPA axis activity have been well demonstrated for a variety of human disorders and it may be hypothesised that HPA axis alterations play an important, causal role for symptom development (for review see e. g. Chrousos and Gold, 1998; Strohle and Holsboer, 2003; Heim et al., 2000; Fries et al., 2005). As alterations of the CAR may reveal subtle changes in HPA axis

(re-)activity (see also Schmidt-Reinwald et al., 1999), this parameter has been investigated in several patient groups. In many disorders including cardiovascular, autoimmune, atopic, allergic, and psychiatric disease, among others, a blunted CAR has been observed when comparing patients with healthy controls (Kudielka and Kirschbaum, 2003). More specifically, this phenomenon of a reduced CAR has been described for patients with chronic pain (Geiss et al., 1997), patients with systemic hypertension (Wirtz et al., 2007), women with high intima media thickness, an indicator for early, non-symptomatic atherosclerosis (Hurwitz Eller et al., 2001), or patients with functional gastrointestinal disorders (Bohmelt et al., 2005). Additionally, for several psychiatric conditions a reduced CAR was described, such as in posttraumatic stress disorder (Wessa et al., 2006; de Kloet et al., 2007; Rohleder et al., 2004; Neylan et al., 2005), chronic fatigue syndrome (Roberts et al., 2004), or sleep disorder (Backhaus et al., 2004).

Increased cortisol awakening responses, however, were observed in men with visceral obesity (Therrien et al., 2007; Steptoe et al., 2004; Wallerius et al., 2003), in normal weight male offspring of overweight men (Steptoe et al., 2006), or in patients with upper respiratory illnesses (Edwards et al., 2003). Also, for some psychiatric disorders an increased CAR was described: for example in lithium-treated patients with bipolar disorder (Deshauer et al., 2003), in women with borderline personality disorder (Lieb et al., 2004), or in women with fibromyalgia reporting physical or sexual abuse during childhood (Weissbecker et al., 2006).

One large and heterogeneous diagnostic category, depression, has produced conflicting results with regard to the CAR: some studies described a blunted CAR in patients with depression (Stetler and Miller, 2005; Huber et al., 2006), in metastatic breast cancer patients with depression (Giese-Davis et al., 2006) or in subjects with cognitive vulnerability markers of depression (self-focused rumination, Kuehner et al., 2007), and others reported an increased CAR in depressed patients (Bhagwagar et al., 2005) or individuals with self-reported depressive symptoms (Pruessner et al., 2003). As depression is a very heterogeneous diagnostic group, it seems very likely that different subtypes (e. g. atypical vs. melancholic depression) have to be considered separately to obtain consistent results (see also Gold and Chrousos, 2002).

Another symptom cluster with inconsistent results is burnout: findings of an increased (Grossi et al., 2005; De Vente et al., 2003), decreased (Pruessner et al., 1999; Sonnenschein et al., 2007), or normal (Mommersteeg et al., 2006) CAR have been described. For vital exhaustion, a concept relatively close to burnout, one study reported a normal CAR (Nicolson and van Diest, 2000).

In summary, several studies have demonstrated associations between altered cortisol awakening responses and physical and mental symptoms. It is tempting to speculate, that HPA axis alterations not only accompany these symptoms but play a causal role in their development. However, while this assumption finds some support in the antidepressant literature showing that the antidepressant effect of the medication is accompanied by a decrease in cortisol levels (e. g. Aihara et al., 2007) and, interestingly, in this recent study also by alteration of regional glucose metabolism in the hippocampus and parahippocampal gyrus, it still needs confirmation for the different physical and mental symptoms.

Smoking: Acute nicotine consumption associated with e. g. cigarette smoking is a potent stimulator of the HPA axis (Matta et al., 1998). However, basal HPA axis activity is only slightly changed by habitual smoking possibly due to receptor desensitization and additionally, habitual smokers show a decreased responsiveness of the HPA axis to psychosocial stress (for review see e. g. Rohleder et al., 2004). Investigating the impact of smoking on the CAR, conflicting results exist: whereas recent large epidemiological studies described a larger CAR in smokers (Badrick et al., 2007; Steptoe and Ussher, 2006) and a positive association between tobacco use and the morning cortisol rise (Harris et al., 2007), other studies reported an attenuated (Wust et al.,

2000b) or comparable CAR in habitual smokers (Pruessner et al., 1997; Edwards et al., 2001a). In sum, while older studies could not demonstrate an effect of smoking on the CAR, recent large epidemiological studies presented evidence for an increased CAR in habitual smokers. However, the absolute differences in CAR magnitude between smokers and non-smokers are small.

4.1. Sleep-related factors

Results regarding the effects of sleep-related factors including waking time, waking modus, sleep duration, sleep quality, and nightly awakenings on the CAR have been inconsistent. Waking time has been studied repeatedly and, while some studies reported that the CAR was unrelated to waking time (Pruessner et al., 1997; Hucklebridge et al., 1999) others disagreed. For example, Edwards and colleagues (2001b) reported a larger CAR in individuals waking up earlier in the morning. This result was later replicated by Kudielka and Kirschbaum (2003). Additionally, Kudielka and colleagues (2006) described higher cortisol levels in morning compared to evening chronotypes, i. e. in individuals waking up routinely earlier in the morning. Consistent with these results, Federenko and colleagues (2004) showed that very early awakening (between 4:00–5:30 am) in nurses working on the morning shift was associated with a greater and prolonged CAR when compared to waking before the late day shift (between 6:00–9:00 am) or the night shift (between 11:00 am–2:00 pm). Moreover, in the same study, students were asked to take a nap of one to two hours in the early evening hours (range of reported awakening time between 6:45 pm and 8:30 pm). After this short nap, no CAR was observed, suggesting that the CAR is associated with longer periods of nocturnal sleep. Recently, Williams et al. (2005) could replicate findings of a higher CAR in individuals waking up for an early work shift compared to waking up for a later work shift or on leisure days. Interestingly, though, this difference disappeared when controlling for higher stress perception and impaired sleep quality before an early work shift.

Whether the individual's knowledge about a certain waking time influences hormone increases before and after awakening was studied by Born and colleagues (1999). They studied individuals in the sleep laboratory with blood sampling for determination of ACTH and cortisol every 15 min. By manipulating forced wake up to be expected or unexpected, they could show that with the expectation that sleep would end at a specified time, ACTH already increased in the hour before this expected wake up time. This apparently preparatory hormonal process was not present in unexpected wake up which was followed but not preceded by marked ACTH and cortisol increases.

In a slightly different vein, Wust and colleagues (2000b) were interested in whether waking modus, that is, spontaneous waking versus forced wake up by alarm clock, had an impact on the CAR. They found, that the CAR did not differ on days where subjects woke up spontaneously or used the alarm clock.

The possible impact of sleep duration on the cortisol rise after awakening was investigated by Pruessner and colleagues (1997) who reported no relation between self-reported hours of sleep during the previous night and the CAR. In contrast, another study described a significantly larger CAR in subjects reporting short sleep duration. However, the respective effect size revealed that sleep duration explained less than 1% of variability in the cortisol awakening response, so that the effect was too small to interpret it (Wust et al., 2000b). As self-reported sleep duration is subject to large biases, it appears inevitable to conduct polysomnography studies on the possible impact of sleep quality on CARs.

Considering the role of nightly awakenings for the CAR in the morning, Backhaus and colleagues (2004) showed that insomniac participants with a higher frequency of nightly awakenings had lower awakening cortisol values in the morning. The authors speculate that the lower morning values could be the result of more nightly cortisol activation due to more awakenings after sleep onset. This hypothesis

could not be supported in experimental studies. Here, comparable CARs were measured after undisturbed and disturbed nights, with subjects being woken up once (Hucklebridge et al., 2000) or repeatedly (Dettenborn et al., 2007). Furthermore, the latter study showed that nightly awakenings, especially during the first half of the night, were not accompanied by significant cortisol rises, a finding consistent with earlier work by Born and colleagues (1988). Backhaus and colleagues' (2004) findings of attenuated CARs after sleep-disturbed nights were based on insomniac patients rather than healthy individuals, which may explain the contradictory results.

Last, a less well-studied factor related to sleep and the CAR is light exposure during awakening. Although cortisol levels rise after awakening when waking up in total darkness, the CAR is more pronounced when subjects are exposed to light (Scheer and Buijs, 1999). This result was confirmed by a later study (Thorn et al., 2004). Also, noise exposure during the night appears to have an impact on the CAR, such that there is no cortisol rise after nights with low frequency noise exposure (Waye et al., 2003).

In sum, most studies reported that early awakening was associated with a larger CAR, albeit with conflicting results. In contrast, sleep duration or nightly awakening seems to be unrelated to the CAR. As a single study by Born and colleagues (1999) demonstrated, the expectation of wake up seems to be of major importance for the CAR. However, more studies are needed using the gold standard method of polysomnography for the assessment of objective sleep parameters and their association with the CAR.

4.2. Stress-related factors

The HPA axis is a highly stress-responsive system and it is widely discussed that chronic stress induces persistent changes in HPA axis activity (e. g. Fries et al., 2005; Chrousos and Gold, 1992; McEwen and Stellar, 1993; McEwen, 2001). In association with chronic stress, alterations of the CAR have been reported. For example, an altered CAR was observed in individuals caring for a chronically ill close relative, a circumstance associated with increased stress and burden (Buchanan et al., 2004; de Vugt et al., 2005). Another circumstance, which is likewise supposed to be associated with increased burden, is low socioeconomic status. Growing evidence shows an inverse association between the CAR and socioeconomic status (Wright and Steptoe, 2005; Kunz-Ebrecht et al., 2004), a relationship, which may be mediated by material hardship, associated with low socioeconomic status (Ranjit et al., 2005).

Focusing on the importance of perceived stress for the CAR, there is growing evidence of an increased CAR in individuals reporting chronic stress and worrying (Schlotz et al., 2004; Wust et al., 2000a), work overload (Schulz et al., 1998; Steptoe et al., 2000), social stress and lack of social recognition (Wust et al., 2000a), or increased stress early in the day (Williams et al., 2005), albeit with exceptions. For example, Thorn and colleagues (2006) reported a decreased CAR in individuals with high perceived stress and Harris and colleagues (2007) found no effect of self-reported job stress or workload on the CAR in a healthy sample of female health care workers. However, effects of stress-related factors on the CAR may vary with the duration of stressful conditions. Whereas chronic stress is initially associated with an increased HPA axis activity, it is hypothesized, that some individuals develop a hypoactive HPA axis when chronic stress persists over a long period of time (Hellhammer and Wade, 1993; Fries et al., 2005). This may account for conflicting results regarding stress-related factors and the CAR.

Contrary to reported studies focussing on the association of chronic stress and the magnitude of the CAR, a first study conducted by Rohleder and colleagues (2007) investigated the importance of a single, temporary stressor for the cortisol rise after awakening. In this study, participants of a competitive ballroom dance tournament, a highly social-evaluative event, showed an increased CAR in the

morning of a day with a tournament later the same day, whereas the CAR on a non-competition day was within the normal range. This observation suggests that alterations of the CAR are not only a consequence of chronic stress but rather occur in anticipation of upcoming demands.

5. What is the function of the CAR?

Despite well over 100 published studies on the CAR, the exact function of the sharp cortisol increase after awakening is still unknown. We hypothesize, that the cortisol rise after awakening may accompany an activation of prospective memory representations at awakening enabling individual's orientation about the self in time and space as well as anticipation of demands of the upcoming day. According to anticipated demands, the magnitude of cortisol secretion may vary. Several lines of results support the hypothesis of an association between the CAR and the anticipation of upcoming demands:

First, we observed that the CAR is only mounted in the morning following the individual getting out of bed and starting the daily routine. Waking up the same individuals in the middle of the night, no CAR occurred (Dettenborn et al., 2007). Consistently, it was described that there was no CAR after a short nap (duration 1–2 h) in the early evening hours (Federenko et al., 2004). We interpret these results such that the CAR only emerges when the organism is confronted with a series of upcoming demands as is the case after awakening in the morning, but not after awakening during the night or in the early evening.

Second, an increased CAR was observed in subjects facing elevated burden, again, supporting the hypothesis on the special importance of daily demands for the cortisol secretion after awakening. For example, an increased CAR was described for workdays in comparison to work-free weekend days (Schlotz et al., 2004; Thorn et al., 2006; Kunz-Ebrecht et al., 2004) or in subjects reporting chronic stress and worrying (Schlotz et al., 2004; Wust et al., 2000a), work overload (Schulz et al., 1998; Steptoe et al., 2000), social stress and lack of social recognition (Wust et al., 2000a), or increased stress early in the day (Williams et al., 2005). Whereas these studies do not clearly disentangle whether alterations of the CAR are a consequence of chronic stress or occur in anticipation of upcoming demands the study by Rohleder and colleagues (2007) highly supports our hypothesis. In the study, participants of a competitive ballroom dance tournament showed an increased CAR on the day of the competition, whereas the CAR on a regular, non-competition day was within the normal range. These results clearly demonstrate a modulation of the CAR in dependence of demands of the upcoming day.

Third, the assumption of an adaptation of the CAR depending on daily burden is supported by analyses applying structural equation models to disentangle state and trait components of the CAR. These analyses revealed that the area under the curve for the CAR on a single day is determined to a great extent by situational factors (occasion specificity between 40% and 63%) and to a lesser extent by trait factors (Hellhammer et al., 2007). This supports the assumption on the situation-dependent adaptation of the CAR depending on daily hassles and stress load.

Accordingly, it is tempting to speculate that for the CAR, anticipation of these upcoming demands may be essential in regulating the CAR magnitude for the particular day. The hippocampus is, besides its established role in long-term memory consolidation (e. g. Martin and Morris, 2002), involved in the formation of a cohesive construct and representation of the outside world within the central nervous system processing information about space, time and relationships of environmental cues (Sweatt, 2004; O'Keefe and Nadel, 1978; Burgess et al., 2002). This puts the hippocampus in a pivotal position for the regulation of the CAR. Hippocampal volume highly correlates with the magnitude of the CAR (Pruessner et al., 2007) and subjects with lesions of the hippocampal formation do not show an increase of

cortisol after awakening (Buchanan et al., 2004). Likewise, subjects suffering from retrograde amnesia do not mount a CAR (Wolf et al., 2005). Interestingly, these subjects do not show orientation regarding time, space or relationships of environmental cues, either. These data point to a major role of the hippocampus for the CAR. Innovative methods and study protocols are now needed to define the specific role of the hippocampus in the development and regulation of the CAR more precisely. It is quite likely that such experiments will provide important clues to the source and nature of this endocrine response pattern.

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