The cortisol awakening response: More than a measure of HPA axis function

Abstract

In most healthy people morning awakening is associated with a burst of cortisol secretion: the cortisol awakening response (CAR). It is argued that the CAR is subject to a range physiological regulatory influences that facilitate this rapid increase in cortisol secretion. Evidence is presented for reduced adrenal sensitivity to rising levels of ACTH in the pre-awakening period, mediated by an extra-pituitary pathway to the adrenal from the suprachiasmatic nucleus (SCN). A role for the hippocampus in this pre-awakening regulation of cortisol secretion is considered. Attainment of consciousness is associated with 'flip-flop' switching of regional brain activation, which, it is argued, initiates a combination of processes: (1) activation of the hypothalamic pituitary adrenal (HPA) axis; (2) release of pre-awakening reduced adrenal sensitivity to ACTH; (3) increased post-awakening adrenal sensitivity to ACTH in response to light, mediated by a SCN extra-pituitary pathway. An association between the CAR and the ending of sleep inertia is discussed.

Keywords

Cortisol awakening response; CAR; Suprachiasmatic nucleus; Adrenal sensitivity to ACTH; Hippocampus; Sleep inertia; Flip-flop switching

Introduction

The cortisol awakening response (CAR), the rapid increase in cortisol levels following morning awakening, was first described in the mid 1990s (Pruessner et al., 1997). Since then, research into this aspect of the circadian cortisol cycle in humans has flourished although findings regarding associations with the CAR have frequently been inconsistent (see Clow et al., 2004, Fries et al., 2009, for reviews). A high proportion of research in this area has been approached from a psychological perspective, i.e. exploration of the CAR in relation to a spectrum of individual difference measures. Although there is some level of understanding, there has been less research from a physiological perspective, i.e. systematic exploration into the regulation of the CAR in order to illuminate meaning and functional significance and the impact of dysregulation in terms of pathology. This paper describes some potentially interconnected physiological processes that occur during the immediate pre- and post-awakening period and attempts, sometimes speculatively, to relate these to available evidence about the regulation of the CAR. The overall purpose is to try to make sense of interacting physiological influences at the same time as identifying gaps in understanding that warrant further investigation. It is hoped that this overview of physiological processes will facilitate a fuller understanding of CAR regulation and enlighten its contribution to biopsychosocial research.

Section snippets

The transition from sleep to awakening

The cortisol awakening response is what the name implies: a physiological response to awakening (Wilhelm et al., 2007). It is a discreet and distinct component of the cortisol circadian cycle, with characteristics unrelated to those of cortisol secretion throughout the rest of the day (see Clow et al., 2004, Fries et al., 2009). In order to gain insight into potential regulatory influences it seems appropriate to examine the CAR in relation to other physiological processes also initiated by the …

Pre-awakening influences on cortisol secretion

Circadian influences on physiological systems are mainly transmitted via the body's endogenous central pacemaker: the suprachiasmatic nucleus (SCN). The circadian rhythm of the HPA axis is largely controlled by the SCN, which influences adrenocortical activity via input to the paraventricular nuclei of the hypothalamus (Buijs et al., 2003, Dickmeis, 2009, Kalsbeek et al., 2006, Krout et al., 2002). These patterns of cortisol secretion result from changes in an underlying much faster ultradian…

Post-awakening influences on cortisol secretion: the CAR

In one of the few human studies that measured patterns of neuroendocrine function pre- and post-awakening, ACTH and cortisol both exhibited a response to awakening (Wilhelm et al., 2007). Furthermore the same study demonstrated that the maximum concentration of cortisol shortly after waking was positively related to levels of ACTH, confirming the importance ACTH signalling (and hence the HPA axis) for the CAR. However, there is evidence for additional extra-pituitary input to the CAR, again …

Relationship between patterns of awakening and post-awakening cortisol secretion

As most studies of the CAR are undertaken in the domestic setting there is limited direct evidence of the relationship between patterns of pre- and post-awakening cortisol secretion. A notable exception is the Wilhelm study of 2007, which has already been described in some detail. This study reported that high nocturnal levels of cortisol secretion were significantly associated with an attenuated incremental post-awakening increase. Furthermore, and in line with these effects, a significant …

Sleep inertia and the CAR

The period between regaining consciousness (i.e. awakening) but before attainment of full alertness is described as ‘sleep inertia’: a transitory period of impaired arousal and behavioral performance lasting between 15 and 60min (Ferrara et al., 2006, Ikeda and Hayashi, 2008). Sleep inertia is associated with measurable physiological processes. For example, following morning awakening it takes about 30min to reach global cerebral blood flow velocity values corresponding to the waking state of …

Measurement of the CAR

It is hoped that the evidence presented here for a potential combination of regulatory mechanisms will encourage publication of the key determinants of the CAR: the first waking sample (an indicator of pre-awakening cortisol secretion) as well as the dynamic of the increase. Ideally, each of these component parts could be subject to statistical investigation. Without this information the task of unravelling associations with the host of physiological and psychosocial variables of interest will …

Conclusion

It is hoped that this paper has highlighted that the CAR is subject to a range of influences, both pre- and post-awakening. It seems that extra-pituitary input from the SCN serves to 'fine tune' HPA axis functioning in the pre- and post-awakening period. It may not be surprising that the CAR literature is so inconsistent with regard to associations with trait psychosocial and health measures. Putting aside issues related to participant non-adherence to protocol (which undoubtedly severely …