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EFFECTS OF STRESS ON BEHAVIOR AND SLEEP. CORTISOL: A STRESS HORMONE AND A WAKE HORMONE?

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This review is dedicated to the role of cortisol in behavior and sleep grounded on evidence-based information that acute and chronic stress (in particular the stress-induced release of glucocorticoids), induce changes in glutamate neurotransmission in prefrontal cortex and hippocampus, and influence cognitive processing. Dysfunction of glutamatergic neurotransmission is indeed more considered pivotal in stress-related neuropsychiatric disorders. Sleep is important for memory consolidation. Recently new data has shown the multifaceted nature of sleep-related motor memory consolidation. Intriguingly, motor learning does not alone take place during the actual task but also between training sessions including periods of sleep. Knowing that sleep may increase performance of motor tasks in subsequent retests, an effect specific to the sleep towards the end of the sleep cycle, when receptor occupancies will change. That cortisol profiles show individual diurnal rhythms warrants further appreciation of the pivotal role of cortisol in sleep-wake physiology and behavioural performance. It is safe to conclude that cortisol is a hormone during wake and during sleep.

ВПЛИВ СТРЕСУ НА ПОВЕДІНКУ І СОН. КОРТИЗОЛ: ГОРМОН СТРЕСУ ЧИ ГОРМОН ПРОБУДЖЕННЯ?

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Ключові слова: стресс, сон, поведінка, кортизол

Цей огляд, присвячений ролі кортизолу в поведінці та в сні, ґрунтується на доказовій інформації про те, що гострий і хронічний стрес (зокрема, стрес-індуковане вивільнення глюкокортикоїдів), ініціюють зміни в нейромедіаторному впливі глутамату в префронтальній корі та гіпокампі, що впливає на обробку когнітивної інформації. Дисфункція глутаматергічної нейротрансмісії насправді більше розглядається як ключова у разі стресових нейропсихіатричних розладів. Сон важливий для консолідації пам'яті. Останнім часом нові дані показали багатогранний характер консолідації моторної пам'яті, пов'язаної із сном. Інтригує те, що навчання на моторних магістральних машинах відбувається не тільки під час виконання завдання, але й між тренувальними заняттями, включаючи періоди сну. Знаючи, що сон може збільшити продуктивність виконання моторних завдань під час подальшого повторного тестування, та викликати ефект, специфічний для сну, у кінці циклу сну, коли змінюється

кількість зайнятих рецепторів. Такі кортизолові профілі показують, що існують індивідуальні добові ритми, які підтверджує необхідність подальшої оцінки основної ролі кортизолу у фізіології та поведінкових станах, після сну. Сучасні дані дозволяють вважати кортизол гормоном пробудження та під час сну.

Cortisol is a truly pleiotropic steroid hormone. It is probably best known for its role in stress physiology. Many call cortisol the stress hormone. This notion may require a revisit as will be discussed. During stress responses a cortisol surge is normally preceded by an adrenalin response. In fact adrenalin, released immediately, in seconds following perception of a stressor, is the true stress hormone. It frees glucose (energy) rapidly from glycogen stores to prepare the organism for fight or flight. Cortisol comes in next and also frees energy (glucose, fatty acids) to allow the organism to adapt to stressful conditions and initiate recovery from disturbances. In sleep-wake physiology cortisol is often referred to as the wake hormone. Preceding from the notion that cortisol redistributes energy in the organism to cope with novel stress conditions or with recurring conditions of altered energy needs, for instance the activities of the day to come, requires a re-appreciation of cortisol. Cortisol is not merely a stress hormone; it is first of all an 'energy expenditure hormone' in 'normal' life and an adaptation hormone following stressful events.

In healthy humans plasma cortisol levels exhibit a circadian profile, in accordance with varying production and secretion to cover needs. The maximum in plasma cortisol levels 30 to 45 minutes after waking is called the 'cortisol awakening response' (CAR). Following this maximum, cortisol levels decline throughout the day with lowest levels during the late afternoon and early night (the circadian trough). Feeding events during the day (peaks around 12.30 and 18.00 hrs in Figure 1) coincide with milder peaks in plasma cortisol, again to handle and redistribute energy taken in. In the night to come cortisol secretion will again abruptly rise, reaching the maximum just after waking (Figure 1). This rise which occurs normally during sleep seems specifically linked to the awakening event. The CAR is assumed to supply energy to prepare the body for the coming day, both for physical and mental activities, not in the least for vigilance and alertness, conditions and behaviors with key survival value.

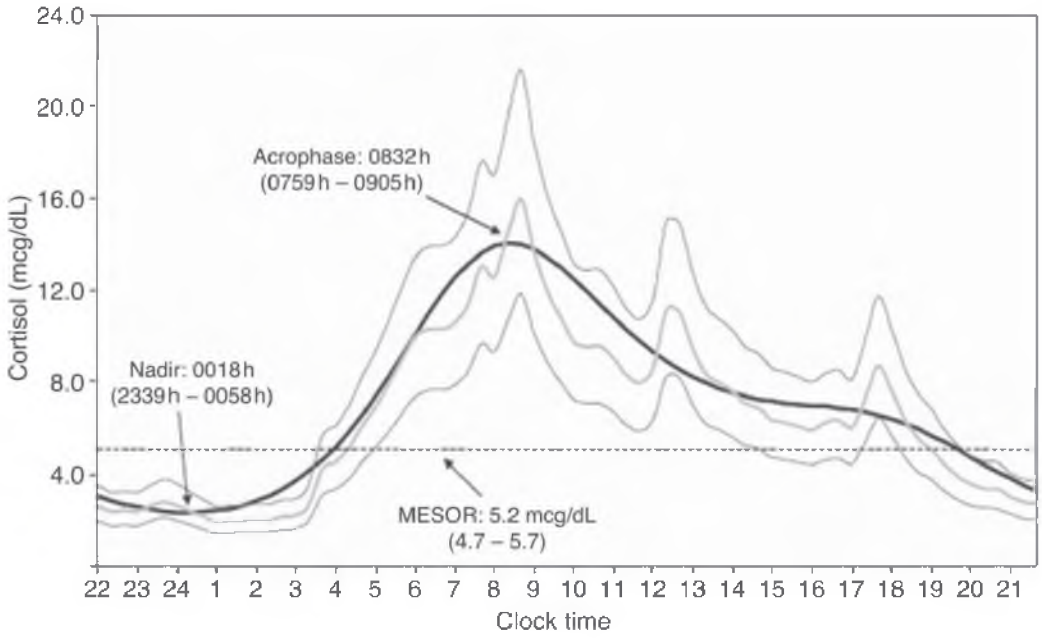

Figure 1. Circadian rhythm of plasma cortisol in humans. Peak cortisol levels (acrophase) are reached around 08:30; the trough (nadir) in cortisol levels is around midnight. Smaller cortisol peaks at 12.30 and 18:00 represent meal-induced cortisol secretions. (After Chan and Debono, 2010).

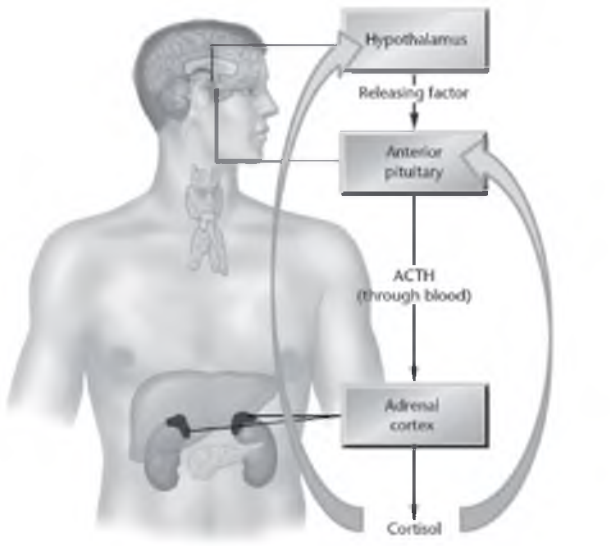

Figure 2. The hypothalamus-pituitary-adrenal cortex (HPA) axis, the endocrine cascade controlling cortisol levels in the blood. Note the negative feedback loops of cortisol on hypothalamus and pituitary gland. Cortisol also feeds back on the adrenal cortex (not shown in figure).

In stress physiology cortisol is generally referred to as *the* stress hormone. In a situation interpreted as stressful, the hypothalamus-pituitary-adrenal (HPA) axis is activated. Hypothalamic neurons on which stress-information is conveyed, enhance release of corticotrophin releasing factor (CRF), which stimulates secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH travels to the adrenals to trigger secretion of the glucocorticoid cortisol from the zona fasciculata of the adrenal cortex (Figure 1). In parallel, but preceding in time, neural pathways induce release of fast acting catecholamines (adrenaline and noradrenaline) from the adrenal medulla (not shown). These two hormones prepare the body to cope with the demands of stress, they make up the fast adrenergic fight-or-flight stress response and the slower cortisol-mediated redistribution of energy to adapt to the stressful condition and energy requirements of adaptation to novel conditions evoked by the stressor. The availability of energy for brain and body mediated by cortisol allows for an optimal adaptation to the stressful situation. Thus, cortisol is not a genuine stress hormone, nor it is a wake hormone, but rather an 'adaptation hormone'. Both during stress and under basal non-stressful conditions, cortisol supports brain and body with access to energy needs, fitting to the circumstances.

The notion put forward above that cortisol is in fact an adaptation hormone (and adrenalin *the* stress hormone) requires a rethinking on its role in normal, in stress, and in sleep-wake physiology. In normal non-stressful conditions it appears that behavioral performance seems best when cortisol levels are moderate, *i.e.* in the normal, basal range (0-20 ng/ml plasma) and the same seems true for cognitive processing and the influence of cortisol thereupon. It is well known that under stress behavioral performances, including cognitive performances, are impeded. In particular chronic stress leading to elevated basal levels of cortisol, correlates with poor learning. Also other vital domains of bodily physiology including growth, reproduction and immune competence become compromised under chronic stress. Yet, the association between circulating levels of cortisol and its effects on general performance and cognition is far from straightforward. The relationship(s) between cortisol and human functioning are difficult to unravel; experiments addressing this relation suffer too often from many confounders and are complicated by technical (*e.g.* how to assess basal cortisol levels ?), individual, psychological and socioeconomic factors. However, a main line in the overwhelming literature on this topic is that hypercortisolemia is more associated with adverse effects and is a risk factor in proper cognitive performance.

Already in 1908 psychologists Yerkes and Dodson described the inverted-U shaped relationship between arousal and performance. When the level of vigilance heightens, performance improves, but further arousal (due to increasing stress levels), may lead to impaired cognitive efficiency. Indeed, moderate levels of cortisol seem to have positive effects on memory consolidation, too high cortisol levels may have detrimental effects on memory formation (Lupien et al., 2007; Roozendaal, 2002). Indeed such differential concentration dependent effects of cortisol on memory and learning agree with the above described adaptive role of cortisol in normal physiology. But how to explain such differential actions? Is this just a matter of concentration of the hormone? It appears that we get a far better view on cortisol actions if we consider its targets: the mineralocorticoid and glucocorticoid receptors, members of the nuclear receptor superfamily. Cortisol receptors are expressed in essentially every cell of the body, albeit in

different concentrations and ratios. The receptors for cortisol are ligand-dependent transcription factors, which, upon binding cortisol in the cytosol and associating with a variety other proteins, migrate to the nucleus and lead to transactivation or transrepression of genes carrying specific steroid responsive elements. In addition, association of the steroid-receptor complex with other transcription factors may occur expanding its actions in regulatory pathways beyond the cortisol pathway proper. Further, the presence of a large cohort of receptor isoforms with dedicated expression, different gene regulatory actions and varied functional profiles deepens our insight and views on the potentials of cortisol in (cell) physiology tremendously. Cortisol binds to two receptor subtypes: the mineralocorticoid (type I; MR) receptor and the glucocorticoid (type II; GR) receptor (Reul and De Kloet, 1985). As indicated above, GR subtypes following alternative splicing of the receptor gene and alternative translation initiation mechanisms expand the receptor landscape significantly; post-translational modifications of receptor isoforms adds further to this and helps to understand the great diversity of glucocorticoid responses (Oakley and Cidlowski, 2013).

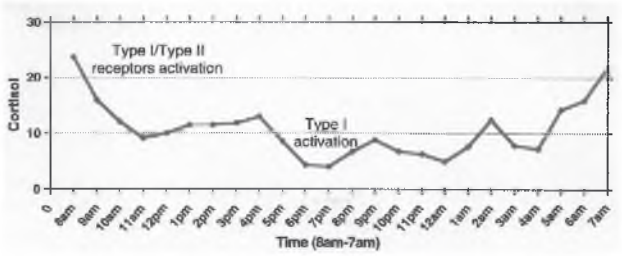

Figure 3. At the time of the peak in the circadian cortisol rhythm, there is activation of both type I and type II glucocorticoid receptors, while at the time of the cortisol trough in evening and early night there is mainly activation of the high affinity type I glucocorticoid receptors (after: Lupien et al. 2007).

When considering just the MR and GR class of receptors, there is a main intrinsic difference between these: MRs (Type I) bind cortisol with a high affinity, roughly 5 to 10 times higher than the affinity for cortisol of GRs (type II). If we address the distribution of cortisol receptors in the brain, another important difference shows up, *viz.* the location in the brain. The MRs shows a high abundance in the hippocampus and limbic structures, and GRs are also present in these structures and are, additionally, prominent in frontal cortical areas. The difference in affinity of the two receptor classes results in major differences in the occupation of the receptors under different conditions and in time of day. Reul and de Kloet (1985) reason that during the circadian nadir (the trough in evening and early night) cortisol occupies more than 90% of the high affinity type I receptors and only 10% of the low affinity type II receptors. During the high cortisol level in the acrophase and during stress, the high affinity type I receptors become saturated and then there is occupation of approximately 70% of the low affinity type II receptors (schematized in Figure 3). The presence of two receptor classes for cortisol with defined anatomical and differential expression profiles may explain some poorly understood stress phenomena and the multiple actions of the steroid in growth, reproduction and immunity. Regarding general and cognitive performance, de Kloet et al. (1999) formulated the type I/ type II glucocorticoid hypothesis to explain the link between cortisolemia and memory performance (Figure 4). When type I cortisol receptors are completely saturated and there is only partial occupancy of type II receptors, maximum performance of memory is observed. On the other hand when both type I and type II receptors are equally occupied, i.e. in stress conditions or at peaks in the diurnal rhythm, memory function may become impaired.

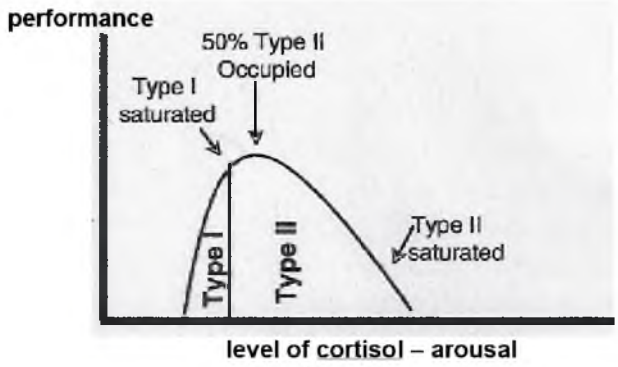

Figure 4. The hypothetical association between the arousal level expressed by the amount of circulating cortisol and behavioral performance, as indicated by the 'Yerkes-Dodson law of arousal'. The hypothetical occupancy of the glucocorticoid receptors as given by de Kloet et al. (1999) and Lupien et al. (2007) is indicated. When type I receptors are saturated there is a maximum of performance, but when type II receptors become occupied performance becomes impaired (after: Lupien et al., 20017).

An inverted U-shaped relationship between arousal and performance as originally described by Yerkes and Dodson (Yerkes and Dod-

son, 1908) might be explained in the same way as the relation between hypercortisolemia and cognitive performance: when type I receptors are occupied this gives rise to enhancement of behavioral performance, but when both type I and type II receptors are activated the performance becomes affected. Thus the inverted U-shaped function between circulating levels of glucocorticoids and cognitive and behavioral performance can be explained through differential activities of the cortisol receptor classes, which differ greatly in terms of brain localization and in their affinity for cortisol. Whether the balance in receptor occupation between the two classes plays a role in the negative effects, or simply the occupancy of the type II receptors with their prominence in cortical areas, is a matter of future research.

And what about a similar role of cortisol in aspects of sleep-wake physiology? Interestingly, predominant MR activation is known to enhance declarative memory consolidation via sleep-dependent reactivation of hippocampal memories (in which cortisol-controlled synaptic plasticity plays a key role). However, this positive 'high affinity' (MR) effect is counteracted by 'low affinity' GR activation at high cortisol levels and this may explain mnemonic impairment in stress-induced pathologies (Groch et al., 2013). Evidence is accruing that acute and chronic stress (in particular the stress-induced release of glucocorticoids), induce changes in glutamate neurotransmission in prefrontal cortex and hippocampus, and influence cognitive processing. Dysfunction of glutamatergic neurotransmission is indeed more and more considered pivotal in stress-related neuropsychiatric disorders (Popoli et al., 2011). Sleep is important for memory consolidation. King and colleagues (King et al., 2017) address in a seminal review the multifaceted nature of sleep-related motor memory consolidation. Intriguingly, motor learning does not alone take place during the actual task but also between training sessions including periods of sleep. Knowing that sleep may increase performance of motor tasks in subsequent retests, an effect specific to the sleep towards the end of the sleep cycle (Plihal and Born, 1997), when receptor occupancies will change. That cortisol profiles show individual diurnal rhythms warrants further appreciation of the pivotal role of cortisol in sleep-wake physiology and behavioural performance. It is safe to conclude that cortisol is a hormone during wake and during sleep.

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