



Fitzsimons, C. P., Herbert, J., Schouten, M., Meijer, O. C., Lucassen, P. J., & Lightman, S. (2016). Circadian and Ultradian Glucocorticoid Rhythmicity: Implications for the Effects of Glucocorticoids on Neural Stem Cells and Adult Hippocampal Neurogenesis. *Frontiers in Neuroendocrinology*, *41*, 44-58. <https://doi.org/10.1016/j.yfrne.2016.05.001>

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Link to published version (if available):
[10.1016/j.yfrne.2016.05.001](https://doi.org/10.1016/j.yfrne.2016.05.001)

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Manuscript for Frontiers in Neuroendocrinology, Special Issue on Adult Neurogenesis, Guest Editor Liisa Galea.

Author's version

Title

Circadian and Ultradian Glucocorticoid Rhythmicity: Implications for the Effects of Glucocorticoids on Neural Stem Cells and Adult Hippocampal Neurogenesis.

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Abstract

Psychosocial stress, and within the neuroendocrine reaction to stress specifically the glucocorticoid hormones, are well-characterized inhibitors of neural stem/progenitor cell proliferation in the adult hippocampus, resulting in a marked reduction in the production of new neurons in this brain area relevant for learning and memory. However, the mechanisms by which stress, and particularly glucocorticoids inhibit neural stem/progenitor cell proliferation remain unclear and under debate.

Here we review the literature on the topic and discuss the evidence for direct and indirect effects of glucocorticoids on neural stem/progenitor cell proliferation and adult neurogenesis. Further, we discuss the hypothesis that glucocorticoid rhythmicity and oscillations originating from the activity of the hypothalamus-pituitary-adrenal axis, may be crucial for the regulation of neural stem/progenitor cells in the hippocampus, as well as the implications of this hypothesis for pathophysiological conditions in which glucocorticoid oscillations are affected.

Keywords

Adult hippocampal Neurogenesis, stress, glucocorticoid oscillations, neural stem cells, ultradian.

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1. Stress and GCs: regulation of adult hippocampal neurogenesis (AHN).

1.1. The stress response

The term stress refers to the stereotyped response to a challenging stimulus that requires acute or chronic adaptive readjustment (Selye, 1971). Stress represents an essential alarm system that is activated when there is a substantial mismatch between a most favorable state, whether physiological, psychological or social, and that in which an individual is at any given moment in time. Stress can be (un)predictable, (un)controllable and diverse in its duration or intensity; it can be psychological in nature, such as during relational problems (Ursin and Eriksen, 2004), or involve more biological changes such as those occurring during an infection. Stress is subjective as the experience of stress depends on the perception or evaluation by the individual: a situation that may seem threatening to one person may not seem so to another. Exposure to any stress generally elicits a stress response that in most cases enables the individual to respond appropriately and thereby adapt, regain homeostasis and ultimately promote survival. The 'stress response' is coordinated by various limbic and hypothalamic brain structures that integrate several cognitive, neuroendocrine and autonomic inputs and determine the magnitude and duration of the organism's response to stress which involves numerous bodily and mental responses to a perceived threat.

One convenient way to assess stress is to measure the associated neuroendocrine response. This response fulfills an important component of coping and adaptation to the stressor, and acts as an essential ingredient for the restoration of homeostasis or successful adaptation to new conditions. Even though the definition of 'stress' is complex, and the endocrine reaction is only one component, the overall endocrine and neural responses to stress are well-defined and allow a given event to be can be classified as a stressor.

The interpretation of what constitutes a stressor, as well as the magnitude of an individual's response to a given stressful situation, largely depends on factors like genetic background, sex,

personality and (early) life history (Joels et al., 2007, Koolhaas et al., 2011, Joels et al., 2012). The physiological responses to stress can be divided into a fast and a more delayed response (Joels and Baram, 2009, Joels et al., 2012). While the first phase involves a rapid activation of the autonomic nervous system (ANS), that induces epinephrine (adrenaline) and norepinephrine (noradrenaline) release, the second, slower and more sustained response to stress involves activation of the hypothalamic-pituitary-adrenal (HPA) axis and results in the release of glucocorticoid (GC) hormones from the adrenal (corticosterone in rodents and cortisol in humans, a mixture on some other species) herewith abbreviated as CORT. Upon their release in the periphery, GCs affect numerous important functions such as energy balance, inflammation and lipid metabolism. GCs generally may act in a faster non-genomic, cell-membrane-dependent phase, and later in a genomic phase as ligand-induced transcription factors, which has been associated to a sustained response or recovery from the first phase (Joels et al., 2012).

1.2. HPA axis and stress regulation

Activation of the hypothalamic-pituitary-adrenal (HPA) axis is triggered by corticotropin-releasing hormone (CRH) released from the paraventricular nucleus (PVN), that in turn induces adrenocorticotrophic hormone (ACTH) secretion from the pituitary, which causes adrenal GC release. GC plasma levels are under strict circadian and ultradian control (Qian et al., 2012, Liston et al., 2013), as will be discussed in detail in subsequent sections. GCs, through glucocorticoid and mineralocorticoid receptors (GR and MR), are a major factor determining an individual's sensitivity and responsiveness to stress (Sousa et al., 2008, Pruessner et al., 2010, Harris et al., 2013, Medina et al., 2013). Negative feedback regulation of the activity of the HPA axis occurs through GCs binding to high-affinity MR and lower affinity GR (Kretz et al., 1999, de Kloet et al., 2005, Erdmann et al., 2008). Although these features are characteristic of the HPA axis in the adult individual, the HPA axis matures postnatally and it is fully functional only after weaning in rodents (Allen and Kendall, 1967, Schmidt et al., 2003) and after puberty in humans (Panagiotakopoulos

and Neigh, 2014). Interestingly, another of the features that develops at later stages is the characteristic circadian rhythmicity of hypothalamic CRF and plasma CORT release (Allen and Kendall, 1967, Ader, 1969, Hiroshige and Sato, 1970, Honma and Hiroshige, 1977, Hiroshige et al., 1982).

Whereas the response to an acute stressor is generally thought to be adaptive, exposure to chronic stress may alter HPA feedback regulation, GR levels and/or stress responsiveness in a way that can result in (prolonged) overexposure of the brain and body to GCs, though this, as for other features of the stress response, may vary between individuals and within a given individual across time and may be non-adaptive (Herbert et al., 2006, Lucassen et al., 2014, McEwen et al., 2016). It is relevant that aberrant GR expression, or an MR/GR imbalance has been implicated in hypercortisolism, stress resistance, anxiety and depression (de Kloet et al., 2005, Ridder et al., 2005, Wei et al., 2007, Harris et al., 2013).

1.3. Stress effects on the hippocampus

The presence of the GR in the rodent and human hippocampus make this brain structure, together with the hypothalamic PVN, very sensitive to the action of GCs and key to the regulation of the stress response (de Kloet et al., 2005, Wang et al., 2013). The GR is central in the regulation of the stress response and other situation where GC levels are elevated, which is in keeping with its lower affinity for CORT compared to mineralocorticoids such as aldosterone (Sapolsky, 2000, de Kloet et al., 2005, ter Heegde et al., 2015), since basal levels of CORT will not occupy all the receptors, leaving some vacant for signaling the response to stress. In functional terms, it is well known that stress can modify excitability of the hippocampal network, long-term potentiation and hippocampal (i.e. episodic or spatial) memory - effects that notably depend on timing, type and controllability of the stressor (Joels et al., 2007, Joels et al., 2012). The consequences of chronic stress on structural plasticity in the hippocampus commonly include reductions in hippocampal volume, atrophy of the dendrites of hippocampal pyramidal neurons and decreased adult

neurogenesis in the dentate gyrus (Cameron and Gould, 1994, Lucassen et al., 2014, McEwen et al., 2016).

1.4. Stress and AHN

AHN refers to neural stem/progenitor cells (NSPCs) that are present in the hippocampal dentate gyrus where they continue to produce new neurons during adulthood in many species, including human (Eriksson et al., 1998, van Praag et al., 2002, Spalding et al., 2013). New neurons in the adult hippocampus have been implicated in various hippocampus-related functions and disorders, such as spatial learning and memory, pattern separation, epilepsy, anxiety, depression and dementia (Clelland et al., 2009, Jessberger et al., 2009, Aimone et al., 2011, Bielefeld et al., 2014, Jessberger and Gage, 2014, Oomen et al., 2014, Abrous and Wojtowicz, 2015, Cho et al., 2015, Dery et al., 2015, Richetin et al., 2015), but the evidence is, in most cases, still debated. Recent reports further indicate that the new neurons also play an important role in HPA axis feedback regulation after stress. Mice that lack new neurons in the hippocampal dentate gyrus, show CORT levels that follow a slower recovery to baseline after stress. Other measures indicate that hippocampal newborn neurons play an important role in stress regulation; and increasing AHN, e.g. by antidepressants, improves behavior and the regulation of the stress response (Santarelli et al., 2003, Snyder et al., 2011, Surget et al., 2011, Anacker and Pariante, 2012, Lucassen et al., 2013a, Lucassen et al., 2013b).

NSPCs in the hippocampus go through progressive stages of activation, proliferation, fate specification, selection, migration and neuronal differentiation before newborn neurons integrate functionally into the pre-existing adult hippocampal network (Kempermann et al., 2004, Zhao et al., 2008, Jessberger and Gage, 2014, Opendak and Gould, 2015), a progression that resembles that of the rest of CNS during embryogenesis. This process of AHP is further regulated by environmental factors, including stress, environmental enrichment, physical activity, systemic factors various hormones and growth factors that change with age and by drugs used as

antidepressants (i.e. acting on serotonin and, possibly, norepinephrine), drugs of abuse (dopamine and opioid acting), (Gould et al., 1997b, Lemaire et al., 2000, Montaron et al., 2003, Heine et al., 2004, Wong and Herbert, 2004, Conboy et al., 2005, Wong and Herbert, 2005, Eisch and Petrik, 2012, Schouten et al., 2012, Anacker et al., 2013, Lehmann et al., 2013, Lucassen et al., 2013a, Schoenfeld and Gould, 2013, Dery et al., 2015, Opendak and Gould, 2015).

Both acute and chronic stress can suppress one or more phases of AHN (Czeh et al., 2001, Czeh et al., 2002, Mirescu and Gould, 2006). For example, predator stress (the presence or odor of a predator) rapidly raises GC levels, which cause significant reductions in hippocampal NSPC proliferation (Czeh et al., 2001, Lucassen et al., 2014, Czeh et al., 2016). Many other psychosocial (Gould et al., 1997a, Czeh et al., 2002) and physical stressors (Malberg and Duman, 2003, Pham et al., 2003, Vollmayr et al., 2003), including physical restraint, social defeat, inescapable foot shock, sleep deprivation and inflammation, also suppress proliferation and/or decrease the numbers of newborn neurons (Gould et al., 1997a, Czeh et al., 2002, Pham et al., 2003, Heine et al., 2004, Dageyte et al., 2009, Lucassen et al., 2010, Van Bokhoven et al., 2011, Hulshof et al., 2012, Schoenfeld and Gould, 2013).

While many, if not all, of these effects are generally attributed to increased GC levels, a simple interpretation of the effects of CORT on the regulation of AHN is difficult to provide and it is important to realize that many other variables can influence AHN and the way GCs regulate it (Holmes et al., 2004, Ehninger and Kempermann, 2006, Mirescu and Gould, 2006). An interesting example of this context-dependent effect of GCs on AHN is provided by the observation that physical exercise increases CORT levels but at the same time promotes AHN, however, this may be a concentration-dependent effect since long-term mild, rather than intense, exercise enhances AHN (Inoue et al., 2015). The response to stress can also alter other parameters, such as glutamate release, and this may alter AHN via activation of NMDA receptors present on NSPCs (Gould et al., 1997a, Gould et al., 1997b, Nacher and McEwen, 2006, Mu et al., 2015), or GABA, a key regulator for the recruitment and activation of hippocampal neural stem cells (Ge et al., 2006, Ge et al., 2007,

Song et al., 2012). Stress further affects various neurotransmitter systems implicated in the regulation of AHN, such as serotonin (Djavadian, 2004), noradrenaline (Joca et al., 2007), acetylcholine (Bruel-Jungerman et al., 2011), dopamine (Dominguez-Escriba et al., 2006, Takamura et al., 2014), cannabinoids and opioids (Galea et al., 2008, Balu and Lucki, 2009). So the reactions of the endocrine system to stress, and the results of that activation on neuronal function, are modulated by other events and may vary in complex ways. The sum total of this pattern determines how a given stressor alters AHN in a given individual at any one time.

In general, when the stressor is unpredictable and its nature is severe and chronic, this will activate the HPA axis and reductions in AHN are commonly seen. Multiple stages of the neurogenic process are affected, including proliferation, as well as subsequent neuronal differentiation, connections to output pathways (e.g. CA3) and dendritic growth. Stress not only reduces NSPC proliferation and AHN, it may also control subsequent NSPC fate specification and differentiation through the action of the GR (Fitzsimons et al., 2013, Chetty et al., 2014), which has important consequences for hippocampal network connectivity and function and influences behavior (Fitzsimons et al., 2013). Specifically, direct effects of CORT on NSPCs have been demonstrated in the absence of known stressors, showing that the GR plays a central role in mediating the direct effect of CORT on hippocampal NSPCs, since a reduction of GR expression selectively in the newborn cells resulted in strong alterations in AHN and affected AHN-dependent behaviors (Fitzsimons et al., 2013).

1.5. GCs and AHN

One of the implications of stress involving the activation of many different brain regions and transmitter systems is that an endogenous stress state differs markedly from the condition of a brain that is otherwise 'at rest' but exposed to high GC levels. Indeed, several conditions that robustly elevate GC levels, such as physical exercise, mating, enriched environmental housing or

intracranial self-stimulation, promote AHN (van Praag et al., 1999b, Takahashi et al., 2009, Galea et al., 2013, Kim et al., 2013, Yau et al., 2014a, Yau et al., 2014b, Opendak and Gould, 2015). This apparent paradox has been tested in experimental models employing, for example, repeated injections with exogenous GCs to imitate hypercortisolism. Notably, such artificial conditions exert negative feedback at the level of the pituitary, thereby inhibiting the endogenous production of GCs by the adrenal. As a result, ACTH and CRH levels are very low in GC-treated rodents, a condition which is in contrast to the endogenous HPA axis activation, seen in chronically stressed animals and people, where CRH, ACTH as well as GCs are elevated, that is, the feedback set-point has been altered. Another possible explanation is that very stressful situations, which generally impair AHN, could be associated with alterations in the rhythmic release pattern of CORT from the adrenals. This hypothesis will be further presented and discussed in this review. It is clear that GCs operate on the background provided by many other factors, some of which represent the basal state of the individual and others that are features of that individual's response to a given stressor.

Despite these considerations, exogenous GC administration exerts effects on cell proliferation, differentiation and cell survival that are in many ways similar to those of stress per se. Interestingly, the reduced AHN after chronic stress or GC application can be prevented by blocking GC release, or by CRH or GR antagonists and a short treatment for 1 or 3 days with the GR antagonist mifepristone (Alonso et al., 2004, Joels et al., 2007, Oomen et al., 2007, Datson et al., 2012, Zalachoras et al., 2013).

1.6. The GC 'milieu' and AHN.

In rodents, a normal rhythmic release of CORT levels restrains the rate of mitosis in the hippocampal progenitor cells throughout the day (Figure 1) and below its maximum ceiling. This becomes evident from the increased rate of mitosis seen after bilateral adrenalectomy (ADX), a procedure that depletes CORT, and the subsequent replacement with CORT, not dexamethasone, to levels observed in the intact animal, which reduce it to the normal basal state (Sloviter et al.,

1989, Sloviter et al., 1995, Hu et al., 1997a, Hu et al., 1997b). Furthermore, stress and elevated GC levels slow down neuronal differentiation (Heine et al., 2004), effects that may be indirectly mediated via neurotrophins, including brain derived neurotrophic factor (BDNF) or vascular endothelial growth factor (VEGF)(Heine et al., 2005, Schmidt and Duman, 2007). NSPC express the GR and cell-specific mechanisms regulating its activity at the level of intracellular trafficking, suggesting an important biological function for the GR in NSPC (Garcia et al., 2004, Fitzsimons et al., 2008). Consistent with a role in NSPC differentiation, knocking down GR expression in the newborn cells results in increased NSPC differentiation (Fitzsimons et al., 2013), demonstrating that direct effects of CORT on these cells via the GR exist as well.

In some psychosocial stress models, the GC 'milieu' is altered; GC levels escape circadian regulation and remain elevated for prolonged periods of time, a condition that resembles human hypercortisolism which appears to have even stronger inhibitory effects on AHN (Figure 2) than severe, but predictable, physical transient stressors, like restraint stress, which may lead to habituation (Wong and Herbert, 2004). A proportion of individuals with major depression show a flattened diurnal cortisol rhythm (Sachar et al., 1973). The question is whether disruption of the corticoid diurnal rhythm itself has an effect on AHN: that is, does the nature of the diurnal rhythm have signaling properties as far as the hippocampus is concerned? The progenitor cells of the hippocampus are so sensitive to GCs that there is a diurnal rhythm in the rate of mitosis that reflects that in GC secretion and is abolished if this rhythm is flattened. Several examples exist of a persistent and lasting inhibition of AHN after exposure to an initial stressor, despite the later normalization of GC levels (Czeh et al., 2002, Mirescu and Gould, 2006, Schoenfeld and Gould, 2013). In contrast, GC levels can remain persistently elevated after the onset of a first, often psychosocial stressor, and result in a lasting suppression of AHN for prolonged periods of time. Together, these observations suggest that while GCs are involved in the initial suppression of proliferation, other processes may be responsible for the maintenance of this effect. Alternatively,

GCs could have long lasting effects at the level of gene expression that result in a prolonged inhibition or adaptation of the NSPC proliferation rate, to new environmental conditions.

Serotonin, whose activity is the basis of many drugs used as anti-depressants, has a major role in the milieu in which corticoids act on AHN. The 5HT1A receptor may contribute to sex differences in stress responses (Goel et al., 2014). Deletion of the serotonin transporter (5HTT) alters the way that early life stress accentuated stress responses later in life (van der Doelen et al., 2014). There are also reverse interactions: for example, GCs regulate the diurnal changes in tryptophan hydroxylase type 2 gene expression, a major controller of serotonin synthesis in the brain (Nexon et al., 2011). There is a rich serotonergic innervation of the suprachiasmatic nucleus, so altered serotonin activity will impinge both directly and indirectly on the diurnal corticoid rhythm. Furthermore, since the action of corticosterone on adult neurogenesis in the rat's hippocampus is moderated by serotonin (Huang and Herbert, 2005), changes in this activity will have direct effects on the sensitivity of the progenitor cells or their subsequent maturation process to corticoids and the way their diurnal rhythm is expressed.

2. Pulsatile GC release and its implications for physiopathology.

2.1. Ontogeny of rhythmic HPA axis activity

Normal endocrine functioning, including HPA axis activity is in many cases characterized by the presence of daily rhythms in hormone release. In most cases these circadian rhythms originate from endogenous “clock” mechanisms and are synchronized by environmental signals such as the daily light cycle, feeding behavior and physical activity, and other cues. Interestingly, the circadian rhythm of the HPA axis is not present at birth and develops in time, to reach full maturity around adolescence in rodents and humans. For example, the 24-hr light-synchronized rhythm in plasma levels of CORT is first observed in experimentally naive rats only after the first month of life (Allen and Kendall, 1967, Hiroshige et al., 1982). Although circadian CORT rhythms

are less well-characterized in mice, HPA axis activity and its response to stress is not fully developed until at least three weeks after birth (Schmidt et al., 2003) and in humans until puberty (Panagiotakopoulos and Neigh, 2014), suggesting that the detailed observations made in the rat could be extrapolated to other mammals. Interestingly, circadian rhythmicity of hypothalamic CRF expression starts in rats around the third week after birth (Hiroshige and Sato, 1970, Honma and Hiroshige, 1977), suggesting that maturation of the central nervous system, i.e. hypothalamic areas, may be necessary to trigger rhythmic plasma CORT release. Indeed, the central nervous system's ability to regulate rhythmic ACTH secretion is delayed well beyond the time when the pituitary is capable of secreting ACTH and when the adrenal cortex can secrete CORT (Allen and Kendall, 1967). Early postnatal environmental stimulation of the rat, e.g. by handling in the first week of life, accelerates maturation of the 24-hour rhythm of CORT secretion. Daily exposure to stressors like electric shock stimulation, speeded up the onset of CORT rhythms to the second week of age (Ader, 1969). This indicates a dissociation between the developmental onset of the circadian rhythm and stress-induced changes in HPA activity (Hiroshige and Sato, 1970), that can be modulated by environmental factors.

The generation of episodic pulses of GC secretion was thought to be mediated by a pulse generator in the hypothalamus. Indeed, Mershon et al., (Mershon et al., 1992) did detect an episodic release of CRH from macaque hypothalamic explants while rapid changes in CRH levels were detected both from the median eminence of rat (Ixart et al., 1991) and portal blood from the sheep (Caraty et al., 1998). There was however, no clear relationship between the rapid CRH pulses as they were detected in these systems and the much slower hourly ultradian rhythm detected for CORT. Engler (Engler et al., 1990) showed that even after a disconnection of the hypothalamic portal input to the pituitary, ACTH and cortisol pulsatility was maintained. It has therefore been hypothesised that there must be a sub-hypothalamic oscillator that emerges as a consequence of the interaction between the pituitary corticotrophs and adrenal fasciculate (GC-producing) cells. Due to their lipophilic nature, GCs cannot be stored in granules and must be newly synthesised following

activation of adrenal MC2 receptors by ACTH. This implies that there must be a systematic delay between any increase in ACTH and the subsequent release of CORT, as has been clearly demonstrated both in rat and in man (Carnes et al., 1989, Henley et al., 2009). The other end of this feedback loop is the inhibitory effect of CORT on pituitary corticotrophs – and the very rapid effects of CORT on the inhibition of ACTH release, as have indeed been shown both in rat and man (Jones et al., 1972, Rotsztein et al., 1975).

This combination of a feedforward and feedback interaction with a built-in delay in at least one part of the loop, results in a system that – mathematically – must show intrinsic oscillatory activity. Based on this idea a mathematical model was generated, that predicted that even in the presence of a constant input of CRH, there should be a resultant self-sustained oscillation of both ACTH and CORT occurring at the same frequency as that found under normal physiological conditions (Walker et al., 2010). The model was tested experimentally by studying male rats in the morning – a time of very low endogenous CRH. In keeping with this mathematical model, a constant infusion of CRH indeed resulted in ultradian oscillations of ACTH and CORT with a normal physiological pulse frequency (Walker et al., 2013). Interestingly, following publication of this data, others have been able to confirm that rapid and non-genomic effects of classic GR mediate rapid and reversible GC feedback inhibition on pituitary corticotrophs consistent with the proposed mechanism for ultradian adrenocortical pulse generation (Deng et al., 2015).

2.2 Intra-Adrenal Feedback

The adrenal can convert cholesterol to CORT in such rapid bursts that even without the ability to store CORT in granules, it can still generate pulses of hormone in the plasma. The signal cascade begins with the binding of ACTH to the melanocortin-2 receptor, resulting in the activation of adenylyl cyclase and PKA induced genomic and non-genomic steroidogenic pathways. The rate-limiting step of steroidogenesis is the transport of cholesterol into the mitochondria by StAR which is transcriptionally regulated by CREB and enhanced by both the binding of positive regulators

(Caron et al., 1997, Conkright et al., 2003, Sugawara et al., 2006, Takemori et al., 2007), and inhibition of the negative regulator DAX-1 (Song et al., 2004). PKA also has rapid non-transcriptional effects, activating steroidogenic proteins by phosphorylation of StAR (Arakane et al., 1997) and of hormone sensitive lipases, which are needed to increase intracellular cholesterol (Kraemer et al., 2002).

The adrenal clearly consists of several activating and inhibitory steroidogenic systems. When ACTH is given in a pulsatile manner, these systems complement each other to result in extremely well organised pulses of CORT. On the other hand, when the adrenal is exposed to a non-physiological, constant infusion of exactly the same amount of ACTH, it fails to respond – suggesting, among other effects, a disruption of normal steroidogenic mechanisms (Spiga et al., 2011a, Spiga et al., 2011b). The reason for this is not clear, but when *in vivo* data is integrated with mathematical modelling of adrenal responses, this analysis shows that rapid intra-adrenal inhibition must be an important factor sensitising the adrenals ultradian oscillatory activity (Walker et al., 2015). These mechanisms now need to be investigated using dynamic studies of fasciculata cell activation.

The status of the adrenal insensitivity to ACTH is also an important part of the HPA homeostatic response. As well as the well-characterised circadian changes that are mediated through the autonomic nervous system (Ulrich-Lai et al., 2006), adrenal sensitivity increases in response to inflammatory stress, both in man and the rat (Gibbison et al., 2015) which provides a mechanism by which homeostatic responses can be activated via increased pulsatile CORT secretion during periods of acute inflammatory stress.

2.3 Biological significance of GC pulsatile release.

As discussed before, in the absence of stressors (i.e. under basal conditions), diurnal CORT secretion is not constant, but is characterized by a circadian release pattern, with hormone levels highest during the active phase and lowest during the inactive phase of the light cycle. Importantly,

CORT levels start to gradually increase towards the end of the inactive phase of the circadian cycle and peak around the beginning of the active phase, to finally reach their nadir around the beginning of the inactive phase, effectively following a phase response curve, characteristic of most circadian rhythms, both in rodents and human (Weitzman et al., 1971, Dallman et al., 1978) Furthermore, CORT levels during the day are released from the adrenal gland (Jasper and Engeland, 1991, 1994) in a dynamic pattern resulting in an ultradian pulsatile rhythm in blood (Windle et al., 1998) as well as in target tissues like the brain (Droste et al., 2009). The circadian changes of CORT result from changes in the activity of an underlying ultradian rhythm system, as discussed in the previous section, and changes in ultradian pulse amplitude, and to a lesser extent their frequency, make up the circadian rhythm. Thus, ultradian and circadian CORT rhythms are intrinsically linked and ultradian pulses are a necessary component of circadian oscillations (Walker et al., 2010) (Figure 1 and 2). This ultradian CORT rhythm influences glutamatergic transmission and synaptic plasticity in the hippocampus (Sarabdjitsingh et al., 2014, Sarabdjitsingh et al., 2016) and is an important factor in determining behavioral, neuroendocrine and genomic response to stress (reviewed in (Spiga et al., 2014)) and is crucial for an optimal transcriptional response of GC-responsive genes (Stavreva et al., 2009). This point will be further discussed in the next sections of this review.

Another level of regulation imposed by GC pulses takes place at the level of GC-carrier proteins present in the blood. The main GC carrier protein is CBG, a member of the serpin family of proteins. Under normal conditions, 95% of the circulating GCs is not bioavailable to target cells because it is bound to CBG, which becomes saturated at GC concentrations only slightly below those reached during ultradian peaks. This therefore significantly increases the percentage of bioavailable GCs at times of peak secretion (Cameron et al., 2010). In this way, GC effects on target tissues correlate better to free bio-available steroid at the ultradian peak, rather than to the level of total GC levels measured in circulating blood (Lightman and Conway-Campbell, 2010).

GC pulsatility has important implications for stress-induced GC release. At stress-equivalent levels of (constant) CRH, both ACTH and CORT oscillations are dampened, which

results in a steady-state response in hormone secretion. This is important for our understanding of several conditions where pulsatile GC patterns are altered, such as chronic inflammation and e.g. chronic exposure to constant light in the rat (Windle et al., 2001, Waite et al., 2012), chronic illnesses in humans, like rheumatoid arthritis, asthma, depression and chronic fatigue syndrome (Webster et al., 2002), sleep apnea (Henley et al., 2009) and the recovery from major surgery and critical illness (reviewed in (Henley et al., 2009)). Cardiac surgery is a condition associated with strong inflammation, CORT elevation and an increased risk of post-traumatic stress disorder (Schelling et al., 2006, Porhomayon et al., 2014) and has also been associated with a disruption in CORT pulsatile secretion, with high CORT levels observed during the post-surgical period (Gibbison et al., 2015). The hormonal response in rats administered with lipopolysaccharide (LPS), a well-established animal model of critical illness and associated chronic inflammatory response, is similar to that observed in humans undergoing cardiac surgery (Boonen and Van den Berghe, 2015, Gibbison et al., 2015), suggesting that inflammatory factors are responsible for the adrenal sensitivity observed both in clinical situations and experimental models. Importantly, major depression is also associated with a chronic inflammatory response, cell-mediated immunity and further activation of the compensatory anti-inflammatory reflex system (CIRS) that results in the induction of negative immunoregulatory processes with most common triggers of this response being stressors and trauma (Berk et al., 2013).

In the brain, GC responsiveness to stressors varies over the ultradian GC cycle in a brain-region-specific manner, indicating GC ultradian pulsatility is important for the coordination of the stress response and for the maintenance of normal physiological reactivity to a stressor (Sarabdjitsingh et al., 2010a). This interaction between two GC-mediated release mechanisms is not trivial since in general, circadian and ultradian rhythms have likely evolved to adapt to predictable changes in environmental factors (i.e. the earth rotation), while the stress response has evolved to adapt to unpredictable environmental factors (i.e. stressors) and thus presents an excellent example of the integrative and dynamic adaptive function of the HPA axis.

3. Molecular and cellular effects of GC rhythmicity, regulation of gene expression.

One of the central concepts emerging from recent observations on the role of GC ultradian pulsatility is that pulsatile release is important for the prolonged induction of GR-dependent transcriptional activity without inducing desensitization, leading to the concept of continuous dynamic equilibration as a key function of GC pulsatility (Lightman and Conway-Campbell, 2010). This mechanism seems to be relevant for several tissues, including the brain, where the interruption of GC rhythmicity attenuates gene expression responsiveness to (changes in) GC signaling (Sarabdjitsingh et al., 2010b). This indicates that it is crucial to maintain normal responsiveness to GCs in the brain. In the following section we will analyze this hypothesis in more detail.

3.1 Ultradian hormone stimulation induces GR-mediated pulses of gene transcription.

Recent pioneering observations have demonstrated that GR signaling and transcriptional activity have been optimized for a prompt and timely response to the fluctuations in hormone levels. Hence, GC pulsatility encodes biologically unique information for target cells (Stavreva et al., 2009, McMaster et al., 2011). Interestingly, ultradian hormone patterns induce cyclic GR-mediated transcriptional regulation, or "gene pulsing", both in cultured cells and in animal models, which is driven by a rapid exchange of GR at DNA response elements and by intranuclear GR recycling through the chaperone machinery (Stavreva et al., 2009). Thus, pulsatile, as opposed to constant, hormone release patterns induce unique sets of gene and regulatory element activation in a brain area and cell-type specific fashion (Conway-Campbell et al., 2010, Stavreva et al., 2015).

These experiments provide a possible integrative explanation regarding the coordination of GC circadian and ultradian rhythms. At lower hormone concentration, as may be the case during the nadir of the circadian rhythm, the GR is considered to reside in the cytoplasmic compartment, where ligand binding occurs first. Following binding of the ligand, the activated GR translocates to the nucleus to bind DNA. However, exposure of cell lines to ultradian GC patterns induces complete

GR translocation into the nucleus after the first pulse and the GR then remains nuclear as long as the cells are exposed to this pulsatile pattern, as may occur at times surrounding the circadian peak *in vivo* (Stavreva et al., 2009). Importantly, although the GR remained intranuclear during pulsatile exposure, during hormone-free periods, that modeled lower hormone concentration in ultradian interpeak intervals, the GR was unliganded and did not bind chromatin. Furthermore, GR was reactivated in the nuclear compartment after a next pulse of ligand, resulting in the re-association of GR with chromatin. These observations are important for the regulation of AHN by GCs and gene expression in NSPCs, which we will discuss in next sections, because hippocampal NSPCs express specific cytoskeletal proteins that tightly control the nuclear/cytosolic localization of the GR, and indicate that regulation of GR intracellular localization is a relevant mechanism in these cells (Fitzsimons et al., 2008).

Overall, these results support previous observations made in several other target cell types, showing that the same dose of GCs delivered in a pulsatile or in a constant manner results in different patterns of gene regulation, suggesting that ultradian pulse pattern is not simply a decomposed circadian pattern, but has signaling properties of its own. This indicates that the temporal pattern of endogenous GC secretion acts through the GR to control and maintain normal transcriptional responsiveness of target genes. With respect to the brain, and particularly the hippocampus, this seems to be a crucial mechanism because the discrete GC pulses present in circulating blood readily access the hippocampus (Droste et al., 2008). Interestingly, some of the genes regulated by GC ultradian pulsatility in the hippocampus are components of the circadian clock systems (Conway-Campbell et al., 2010). These observations and their implications for the regulation of adult hippocampal stem cells in healthy and disease states will be discussed in the next sections.

4. Basic molecular organization of the circadian system in mammals.

The circadian clock system is a temporal interface that organizes and synchronizes physiology and behavior to dynamic, external and predictable environmental cues (Frank et al., 2013). In mammals, the circadian system is composed of three main modules: the input signaling pathways, the main pacemaker (or central oscillator) and the output signaling pathways (Fuhr et al., 2015). The input pathways convey environmental signals to the central oscillator. These signals are termed 'zeitgeibers' and include external signals such as the day-night light cycle, food, exercise and temperature, among others. The central oscillator is formed by two small groups of neurons located in the Suprachiasmatic Nucleus (SCN) of the hypothalamus. There, upon the reception of a signal input, the central oscillator generates and maintains rhythms that are subsequently conveyed to the peripheral organs via both neuronal afferents of the autonomic nervous system and humoral factors. In this respect, GCs play a central role in the coordination of the circadian timing system (Nader et al., 2010, Son et al., 2011) and GR-mediated pulses of gene transcription induced by ultradian hormone release may thus be of particular physiological relevance (Figure 2C and 2F). In the following section, we will focus on the hippocampus, a well-characterized GC target in the brain.

4.1 Regulation of clock genes in the hippocampus by GC rhythmicity

Genes implicated in the molecular clock are widely expressed across the brain and play important roles in brain functions relevant for mood disorders, sleep, emotional control, dopamine receptor responsiveness and synaptic plasticity (Andretic and Hirsh, 2000, McClung et al., 2005, Frank et al., 2013). This biological clock is regulated by transcriptional events involving CLOCK and BMAL1, which through a feedback loop, activate the Period and Cryptochrome genes, which in turn repress their own transcription. However, recent observations suggest that the posttranscriptional regulation of messenger RNA levels of specific clock genes also plays a role in circadian regulation (Doherty and Kay, 2012, Koike et al., 2012, Morf et al., 2012).

The period circadian protein homolog 1 (Per1) gene is a key component of the molecular clock and it is rhythmically expressed in the SCN, the primary circadian pacemaker in the mammalian brain. Per1 is a stress and GC-regulated gene in many mouse peripheral tissues by a specific mechanism involving the GR and GC-responsive elements (GREs) present in the Per1 promoter (Yamamoto et al., 2005). This suggests that GCs can regulate Per1 in brain areas with high GR expression such as the hippocampus, but not in the SNC itself (Conway-Campbell et al., 2010). Indeed, in ADX rats replaced with pulses of CORT to determine the transcriptional effects of ultradian pulses in the hippocampus, each GC pulse resulted in a transient GR activation in hippocampal neurons and a 'burst' of Per1 transcription (Figure 2C). As suggested by previous studies in cell lines (Stavreva et al., 2009), Per1 levels reach a plateau throughout the time course of pulsatile exposure, thus indicating that GC pulsatility optimizes a steady state of Per1 expression in hippocampal neurons. Interestingly, Per1 expression is sensitive to much lower GC levels, as compared to other responsive genes, which may position Per1 in regulatory range by diurnal changes in GC levels (Reddy et al., 2009). With respect to the regulation of AHN, there is a diurnal rhythm in the number of mitotic NSPC in the dentate gyrus in adult male per1-luciferase rats, approximately 6 h out of phase with the plasma CORT rhythm and the per1 rhythm in the dentate gyrus, but not the SCN, was suppressed by clamping the plasma CORT rhythm, suggesting that Per1 expression may be linked to the regulatory effects of CORT on cell proliferation (Figure 2) (Gilhooley et al., 2011). Suggestively, the canonical clock genes BMAL1(ARNTL), PER1-2-3, NR1D1 (REV-ERBa), DBP, BHLHE40 (DEC1), and BHLHE41(DEC2) were found to be rhythmically expressed in the brain of healthy human subjects, while the cyclic patterns were much weaker in the brains of patients with MDD (Li et al., 2013), although distinguishing between arrhythmicity and desynchrony can be difficult from data obtained from multiple individuals (Silver and Rainbow, 2013). Although not directly demonstrated in the hippocampus yet, in peripheral organs GC influence the expression of other genes of the clock system, such as PER2-3 and BMAL1 (Cuesta et al., 2015). The functional interaction between CLOCK/BMAL1 repression and GR-

induced transcriptional activation (Nader et al., 2009) suggests a bidirectional regulation in gene expression. Thus, any perturbation to GC pulse frequency or duration could have rapid quantitative effects on the levels of clock genes such as *Per1*, which could affect hippocampal function, especially circadian related memory and learning processes (Conway-Campbell et al., 2010). This indicates that brain areas expressing GR are responsive to ultradian GC rhythmicity in vivo, which may affect the expression of components of the clock system. As GC pulses control the *Per1* transcription independently of clock-regulated feedback loops or light cycle cues, *Per1* expression could hence optimize the interaction between GC ultradian pulsatility and circadian activity in the hippocampus, and link clock gene products to the regulation of cognitive functions, while alterations in them could be associated with pathological states (Conway-Campbell et al., 2010) as we will discuss below.

5. Clock gene expression in adult hippocampal NSPCs, implications for the regulation of AHN.

Several clock genes, including *Per1*, *Per2* and *Bmal1* are expressed in a rhythmic manner in the hippocampus and their role in hippocampal NSPCs is now beginning to be understood. *Per1*, *Per2* and *Bmal1* play important roles in controlling NSPC proliferation and the survival of their progeny, and some studies have demonstrated a circadian rhythm of NSPC proliferation in the hippocampus (Figure 1) (Holmes et al., 2004, Gibson et al., 2010, Bouchard-Cannon et al., 2013). Furthermore, in several paradigms of sleep deprivation AHN was impaired (Guzman-Marin et al., 2005, Guzman-Marin et al., 2008, Mueller et al., 2008). However, one other study found that inhibition of AHN by sleep deprivation is independent of circadian disruption and melatonin suppression, and in this study the authors could not detect a daily rhythm in proliferation (Mueller et al., 2011). Thus, the relationship between sleep and AHN remains controversial, but evidence suggests that sleep loss impairs AHN by the associated presence of wake-dependent factors, rather than by the absence of sleep-specific processes (Mueller et al., 2015). Crucially, experiments

performed in *per1*-luciferase rats have demonstrated that there is a diurnal rhythm in the number of mitotic NSPC in the DG, and that this rhythm is 6h out-of-phase with CORT circadian rhythm (Gilhooley et al., 2011). Studying the role of the circadian clock in timing cell-cycle events in NSPC, *Per1*, *Per2* and *Bmal1* were found to have a rhythmic expression in a pool of quiescent NSPCs, indicating the existence of a functional circadian clock in these cells (Bouchard-Cannon et al., 2013). Moreover, *Per2* and *Bmal1* are critical for cell cycle control in quiescent NSPCs as deletion of *Per2* abolished the gating of cell-cycle entrance, while deletion of *Bmal1* resulted in an increased proliferation and delayed cell-cycle exit. This suggests that *Per2* and *Bmal1* are critical for establishing a temporal window that restricts the expansion of rapidly dividing neural precursors. In addition, *Bmal1* controls the number of cell divisions that neural precursors undergo before permanently exiting the cell-cycle, and plays an important role in the survival of the new neurons generated from these precursors that thus may be important for controlling the (over)production of new neurons in the dentate gyrus. Consistent with these extended functions of *Bmal1*, homozygous *Bmal1* knockout mice display impaired cognitive functions in hippocampus dependent tasks associated with AHN, such as pattern separation (Bouchard-Cannon et al., 2013). However, others found no significant difference in the cellular proliferation in *Bmal1* knockout mice, yet survival of proliferating cells, was significantly greater in *Bmal1* knockout animals (Rakai et al., 2014).

Altogether, these observations suggest that while a functional circadian clock may not be indispensable for normal proliferation of NSPCs, the survival and total number of newly generated neurons in the hippocampus does require the expression of functional circadian clock genes in the NSPCs. Similarly, NSPCs in other neurogenic areas of the adult brain, like the subventricular zone of the lateral ventricle, also express clock genes and these, and specifically *Bmal1*, are involved in the neuronal differentiation of adult NSPCs (Kimiwada et al., 2009), pointing towards a conserved mechanism across different NSPC populations of the adult brain.

Several studies have further demonstrated the importance of a functional circadian molecular clock for the regulation of NSPC in the dentate gyrus and AHN. For example, analysis of a mutant mouse line affecting *Per2* (*Per2^{Brdm}*), has revealed a higher density of dividing neural progenitors and increased numbers of immature newborn neurons. However, the lack of a functional *mPer2* is compensated by an increase in neuronal cell death and thus does not change the total amount of mature adult-generated granule neurons (Borgs et al., 2009). Furthermore, deletion of the nuclear receptor *Rev-erb α* (*Nr1d1*) in the brain, which plays a role in the molecular circadian clock system, resulted in increased proliferation of NSPC in the hippocampus and was associated with alterations in memory and mood related behaviors (Schnell et al., 2014).

Physiological and environmental factors, like ageing and physical activity have been associated with changes in the (circadian) regulation of AHN. Proliferation of NSPCs is e.g. enhanced in *Bmal1* knockout mice, resulting in a premature aging of the hippocampal neurogenic niche in aged animals, as characterized by a reduced pool of NSPC, a scattered distribution, enhanced survival and increased differentiation of neural progenitors into the astrocytic lineage, notably at the expense of the neuronal progeny. This phenotype was associated with disrupted regulation of ROS balance, overall accelerated aging, neurodegeneration and cognitive deficits in *Bmal1* knockout mice (Ali et al., 2015). On the other hand, physical activity (running) increases proliferation and AHN in the hippocampus (van Praag et al., 1999a, van Praag et al., 1999b) and is associated with a reduced risk of cognitive impairment and dementia with age in man (Laurin et al., 2001). Importantly, the influence of physical activity on cell proliferation and AHN in mice is modulated by the circadian light cycle, with maximal effects on animals exercising at the middle of the dark (active) period of the cycle (Holmes et al., 2004). Interestingly, this phase corresponds with the lowest blood CORT levels during the circadian CORT oscillatory rhythm in mice, which suggests that GCs may play a role in the regulation of the circadian effects of physical exercise on AHN (Kochman et al., 2006).

Further strengthening the connection between circadian regulation of NSPC and GCs, the rhythmic expression of *per1* in the dentate gyrus is suppressed by corticosterone (Gilhooley et al., 2011). This shows that there is a diurnal rhythm in the number of mitotic progenitor cells in the dentate gyrus of the hippocampus in adult male rats, approximately 6 h out of phase with the plasma CORT rhythm. This rhythm is suppressed by clamping the daily CORT levels by a subcutaneous implant of CORT, which results in a parallel inhibition of *per1* rhythmic expression in the dentate gyrus, but not the SCN and demonstrates that daily oscillations in CORT control both proliferation and function of the circadian clock in the hippocampus (Gilhooley et al., 2011). Similarly, others have shown that persistently high GC levels but not the normal circadian fluctuation in GCs inhibit cell proliferation in the hippocampus (Ambrogini et al., 2002).

Overall, these studies demonstrate the expression of clock gene and a circadian molecular clock in adult hippocampal NSPCs and its implications for the regulation of AHN. Some of them indicate that GCs, and specially their rhythmic release from the adrenal gland, play a role in this regulation, which has implications for diseases associated with alterations in GC rhythmicity, as we discuss in the next section.

6. CORT pulsatility and its implications for neuropathology.

Frequency encoding, mediated by the ultradian pulsatile release of hormones, is a common feature among many hormonal axes. For example, ultradian release is crucial for gonadotropin-releasing hormone (GnRH) regulation of the hypothalamic–pituitary–gonadal axis (Belchetz et al., 1978), for normal physiological function of a leutinizing hormone (LH) (Knobil et al., 1980) and insulin (Matthews et al., 1983) and for sexually dimorphic gene expression induced by growth hormone (GH) in the liver (Waxman et al., 1995). Similarly, several mediators of the HPA axis including corticotrophin releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and GCs show a well-characterized ultradian pulsatile release in all mammalian species studied, as discussed in previous sections.

The ultradian pulsatile release of GC forms the basis of their typical circadian rhythm (Lightman et al., 2008). Interestingly, the ultradian pulsatile GC release only develops in adults, as discussed, and is remarkably plastic and adapts to physiological changes such as pregnancy, lactation and ageing, the latter e.g. affecting the diurnal variation but not the pulse occurrence (Lightman et al., 2000). These characteristic features suggest a role for GC pulsatility in the internal circadian regulation, as GCs represent entraining signals for many peripheral circadian oscillators (Pezuk et al., 2012). Therefore, it is not surprising that alterations in glucocorticoid pulsatility are associated with several diseases that are accompanied by circadian rhythm disturbances. For an overview, we refer to some excellent reviews (Lightman et al., 2008, Nader et al., 2010, Son et al., 2011) and in this section, we will focus on the possible role of GC pulsatility in the regulation of cell proliferation in adult hippocampal NSPC in relation to diseases associated with AHN changes, a well-characterized function in many other cell types and tissues (Dickmeis and Foulkes, 2011). For this hypothesis to make sense, it is important to realize that CORT exhibits an ultradian rhythmicity within discrete brain structures, including the hippocampus in freely behaving rats (Droste et al., 2008, Qian et al., 2012).

The relationship between stress and GC pulsatility is complex. With respect to the timing of an acute stressor, the phase of the endogenous ultradian CORT pulses can determine the eventual physiological response. For instance, animals exposed to a stressor while in the rising phase of an endogenous CORT pulse will respond with additional CORT release, while those exposed to the stressor during the falling phase of a pulse, typically longer than the rising phase, will display very little additional changes in CORT release (Windle et al., 1998). In contrast, in models of stress associated with prolonged inflammation and chronic disease, chronic stress results in marked increases in pulse frequency leading directly to an elevation of the average level of circulating CORT levels (Shanks et al., 2000, Windle et al., 2001), and thus to an increased probability of an additional stressor to occur during the non-responsive, falling phase of an endogenous CORT pulse.

As a result, responsiveness to an additional stressor is significantly smaller in chronically stressed animals (Windle et al., 2001).

Thus, chronic stress is associated with clear alterations in GC rhythmicity, such as a flattened diurnal GC secretion, elevated basal GC levels and a reduced GC response to additional stressors. This pattern reflects to a certain extent the flattening of the diurnal rhythm of cortisol secretion seen in patients with depression (Gibbons, 1964, Yehuda et al., 1996, Deuschle et al., 1997, Wong et al., 2000). Interestingly, in comparable models of chronic stress associated with prolonged inflammation and chronic disease, depression-like behaviors are associated with reduced AHN (Kubera et al., 2011, Lin and Wang, 2014), and these reductions can be rescued by treatment e.g. with the antidepressant fluoxetine (Santarelli et al., 2003), which targets NSPC in the adult brain (Encinas et al., 2006). Ageing is the most relevant risk factor for the development of neurodegenerative disorders, such as Alzheimer's disease, and associated cognitive impairment and dementias, and stress is associated with increased risk (McEwen et al., 1999). Importantly, in rats, the HPA axis is desensitized to both fast and delayed feedback inhibition by GCs, and progressive degeneration in the aged hippocampus might be the cause of this dampened sensitivity to feedback inhibition (Sapolsky et al., 1986). In man, increasing age is commonly associated with an elevation of evening cortisol levels, and a relative flattening of GC daily rhythms (Van Cauter et al., 2000). Thus, the brain is exposed to high levels of cortisol at older age (Guazzo et al., 1996). In terms of the effects on AHN, it seems to be slowed by high levels of corticosteroids present in aged rats, since removal of the adrenal glands restores the rate of cell proliferation in the hippocampus (Cameron and McKay, 1999), however, this effects may be mediated by inhibition of GC actions at many levels and may, thus, be indirect. Indeed, other studies have found diverging effects of ADX on AHN, highlighting once again the complex relationship between circulating GC levels and AHN (Brunson et al., 2005, Montaron et al., 2006). These diverging findings may arise from different ADX conditions in different studies. ADX, when performed correctly, removes the whole adrenal glands and thus suppresses the production of GC, but also mineralocorticoids and

catecholamines, resulting in a general poor health condition in ADX animals. As an attempt to correct for this, in many studies addressing the effects of ADX on AHN animals are administered NaCl solutions and a low concentration of CORT, typically 20mg/L, enough to tonically stimulate the MR (Montaron et al., 2006, Krugers et al., 2007). However, these low CORT are insufficient to stimulate the GR, which gets fully occupied only at CORT concentrations around the circadian peak. Thus, the beneficial effect of CORT supplementation has been attributed to the tonic MR stimulation (Krugers et al., 2007), in the absence of GR stimulation, which is commonly associated with inhibition of AHN (Fitzsimons et al., 2013). Importantly, suppression of glucocorticoids secretion from midlife to the rest of the animals' life increases AHN in old animals and prevents the emergence of age-related memory disorders (Montaron et al., 2006). These findings may have interesting implications for age associated cognitive decline in humans too, since recent findings indicate that high levels of perceived stress are associated with a 30% greater risk of amnesic mild cognitive impairment in healthy aged individuals (Katz et al., 2015). Highlighting the relevance of endogenous GC rhythms for AHN, stimulation of AHN in the hippocampus by fluoxetine requires the presence of the endogenous rhythmic changes in CORT, since the proliferative response of hippocampal NSPC to fluoxetine is ablated if CORT levels are clamped to a fixed value using subcutaneous CORT pellets (Huang and Herbert, 2006). Finally, we should mention that patients suffering of the chronic inflammation-associated disorders are commonly treated with high and constant doses of synthetic GCs like dexamethasone, which lead to a strong negative feedback on the HPA axis and an ablation of its characteristic pulsatile patterns of GC release. Therefore the current and future understanding of the endogenous ultradian GC rhythms requires a substantial re-evaluation of therapeutic rationales, even at the simplest therapeutic level — the replacement of GCs in patients with GC deficiency — in order to prevent the occurrence of significant side-effects associated with GC therapy, which include well-known alterations in behavior and brain function.

7. Conclusions and future perspectives.

We have reviewed existing literature evaluating the physiological roles of GC rhythmicity, its implications for human disease. We have discussed the possibility that GC pulsatility may be crucial for the maintenance of AHN and the adaptation of NSPC proliferation levels to environmental changes, that may possibly impact on the regulation of key components of the molecular circadian clock system. Future experiments should aim to characterize the biological signals that GC oscillations convey to NSPC, the molecular mechanisms involved in these signals, as well as their implications for pathophysiological conditions in which GC oscillations are affected.

Acknowledgements

This work has been financed by grants from the Innovational Research Incentives Scheme VIDI 864.09.016 from The Netherlands organization for Scientific Research (NWO) and The International Foundation for Alzheimer's Research (ISAO) to CPF. P.J.L. is supported by ISAO, Alzheimer Nederland and NWO.

Figure legends

Figure 1 - Circadian effects of GC on levels of proliferating and quiescent NSPC.

(A) Schematic depiction of the adult rodent hippocampus displaying the neurogenic cascade, its main phenotypical phases and the associated cells. The boxed area highlights the main cell-types that determine AHN levels.

(B) Illustration showing the circadian nadir of GC in rodents.

(C) Schematic images displaying amongst others that mitotically active NSPC can mostly be found during the circadian nadir.

(D) Illustration showing the circadian peak of GC in rodents.

(E) Schematic images displaying amongst others that quiescent (non proliferative) NSPC can mostly be found during the circadian peak.

(A, C and E) A lighter color shade indicates a lower abundance of this cell-type. Arrows toward other cell-types indicate possible transitions between cells of the neurogenic progeny originating from Type-1 cells and arrows toward the same cell indicate self-renewal potential. Thicker arrows indicate induction and dashed ones inhibition of cell transition/proliferation.

Figure 2 - Circadian GC levels are dictated by ultradian GC peaks and balance the levels of proliferating and quiescent NSPC.

(A) Plot displaying the daily GC oscillations in a rodent to follow a circadian rhythm (dotted green line), superimposed by discrete ultradian (red line) GC pulses. Adapted from Walker et al (Walker et al., 2010).

(B) Schematic plot displaying the daily ultradian GC oscillations in a rodent.

(C) Zoomed in from boxed area in (B) schematic plots of the ultradian pulses of GC (red line) resulting in pulses of *Per* nascent RNA (nRNA; green line) and concomitant homeostatically balanced levels of *Per* protein (blue line).

(D) Schematic images displaying amongst others that the homeostatically balanced levels of *Per* protein might results in balanced levels of NSPC mitotic activity and quiescence during the inactive phase.

(E) Schematic plot displaying the disruption of daily ultradian GC oscillations in a rodent often seen after subcutaneous GC pellet implantation or hypercortisolemia in humans.

(F) Zoomed in from boxed area in (E) schematic plots of the constant GC (red line) resulting in accumulation of *Per* nascent RNA (nRNA; green line) and concomitant accumulated levels of *Per* protein (blue line).

(G) Schematic images displaying amongst others that the accumulated *Per* protein might results in disrupt the balanced levels of NSPC mitotic activity and quiescence.

(D and G) A lighter color shade indicates a lower abundance of this cell-type. Arrows toward other cell-types indicate possible transitions between cells of the neurogenic progeny originating from

Type-1 cells and arrows toward the same cell indicate self-renewal potential. Thicker arrows indicate induction and dashed ones inhibition of cell transition/proliferation.

(H) Schematic plot displaying the normal physiological daily ultradian GC oscillations in a human.

(I) Schematic plot displaying patho-physiological disruptions of daily ultradian (red line) GC oscillations in seen in some cohorts of aged, depressed or chronically stressed humans. Also systemic administration of exogenous synthetic GC can result in abnormal patterns (green line) of GC exposure.

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