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STRESS & SLEEP: A RELATIONSHIP LASTING A LIFETIME

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ABSTRACT

Stress is an adaptative response aimed at restoring body homeostasis. The classical neuroendocrine stress response involving the activation of the hypothalamic-pituitary-adrenal (HPA) axis modulates many physiological aspects, such as the wake-sleep cycle. In the present review, we will first report a series of human and rodent studies showing that each actor of the HPA axis has the potential to interfere with sleep homeostasis and, then, we will highlight how acute or chronic stress differently modulates the wake-sleep cycle. Moreover, we will present new and interesting studies dealing with the relationship between sleep and stress on a different (longer) time scale. Particularly, we will discuss how the exposure to perinatal stress, probably through epigenetic modulations, is sufficient to cause persistent sleep derangements during adult life. In light of this evidence, the main message of the present review is that the complex relationship between sleep and stress changes dramatically on the basis of the time scale considered and, consequently, "time" should be considered as a critical factor when facing this topic.

KEYWORDS

Stress, Sleep, Chronic, Acute, Epigenetics, Cortisol, Hippocampus, HPA, insomnia.

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1. INTRODUCTION

It has been well established that stress and sleep are intimately connected. This bidirectional relationship plays an important role among the mechanisms that allow the maintenance of body homeostasis in response to internal or external challenges (McEwen and Karatsoreos, 2015). Several animal and human studies have demonstrated that stress-inducing factors may significantly impact on the wake-sleep cycle in a variety of ways, mainly depending on type of stressors and duration of exposition (acute or chronic), as well as on interindividual differences (Koolhaas et al., 1997; Meerlo et al., 2002; Sanford et al., 2015; Kim and Dimsdale, 2007; Germain et al., 2003). On the other hand, it is well known that sleep disorders can deeply impact on several biological pathways, stress responses and, eventually, on quality of life. Even few days of sleep deprivation or circadian misalignment are enough to increase appetite, caloric intake, pro-inflammatory cytokines, blood pressure, insulin and blood glucose. Moreover, sleep deprivation alters the physiological neuroendocrine stress response by increasing the sympathetic tone and cortisol levels (McEwen and Karatsoreos, 2015). Chronic circadian disruption and reduced sleep time can even make this scenario worse, significantly increasing the risk of developing cardiovascular and metabolic disorders (diabetes and obesity) (Tobaldini et al., 2017).

Stress responses are also critically linked to temporal dynamics. This notion was already proposed several years ago to indicate that a relatively brief (acute) exposure to a stressor may increase later vulnerability to stress pathology in animals (Koolhaas et al., 1997). In recent years, a growing number of evidences highlights a new aspect of stress temporal dynamics, relevant in mediating the effects of the interaction with sleep: the moment of life in which stress is acting. In particular, it has been shown that stress exposure during the early stages of life can have an effect on adult sleep (Palagini et al., 2015). Therefore, in this manuscript, in which we aim to review the connection between stress and sleep, "time" will be emphasized as the central element of the equation. First, the mechanisms of response to stress will be examined, focusing on the epigenetic mechanisms that can mediate the long-term effects of stress acting in the early stages of life. Subsequently, we will describe the effects of acute and chronic stress on sleep, and the long-term effects of perinatal stress on adult sleep. Finally, the theoretical bases of a possible new therapeutic approach to adult sleep disorders based on the pharmacological manipulation of epigenetic mechanisms activated by perinatal stress will be discussed.

2. MECHANISMS OF THE STRESS RESPONSE

First, we will discuss some of the mechanisms by which stress may impact on the wake-sleep cycle. Stress is an adaptative response with the purpose of restoring body homeostasis and facing ambient challenges. To this aim, it modulates many different physiological functions, with different interactions occurring at multiple levels, from the molecular (gene transcription regulation) to the more integrated (brain activity and behavior) levels. The regulation of the wake-sleep cycle involves a widely distributed neural network, multiple neurotransmitter systems, excitatory and inhibitory amino acids, peptides, purines, and neuronal and non-neuronal humoral modulators. Many of the same circuits, neurotransmitters, and neuromodulators are also influenced by and/or mediate the effects of stress and are likely to be involved in the effects of stress on sleep (Sanford et al., 2015).

2.1. Stress activates the hypothalamic-pituitary-adrenal axis

In this review, we will mainly focus on the activation of the classical neuroendocrine stress response. Essential to this response are neurons in the paraventricular nucleus of the hypothalamus, which express corticotropin-releasing hormone (CRH), vasopressin (VP), and other neuropeptides driving the activity of the sympatho-adrenomedullary and the hypothalamic-pituitary-adrenal (HPA) systems. These two systems exert control over each other’s activity, with the HPA system being slower and more persistent in its actions involving hormones secreted by the adrenals (cortisol in humans or corticosterone in rodents) (De Kloet et al., 1998). CRH and VP secretion leads to pituitary release of adrenocorticotropin (ACTH) and adrenal gland activation, with release of glucocorticoids. HPA axis activity exhibits a clearly established circadian rhythmicity that roughly parallels the activity cycle. Plasma corticosteroid levels are typically highest before wakening (i.e., cortisol awakening response) and lowest before sleep, corresponding in humans to early morning and late evening, respectively (the reverse in rodents, which are nocturnally active). HPA axis activity also increases in response to stress. While short periods of controllable stress may be beneficial to emotion and health, a lack of control and uncertainty can produce a chronic state of distress, which is believed to enhance vulnerability to disease. Both the stress-induced activation and the circadian rhythmicity of the HPA axis are inhibited by glucocorticoid negative feedback (Jacobson and Sapolsky, 1991). This control is exerted both at the hypothalamic and pituitary level where glucocorticoids inhibit the release of CRH and ACTH, respectively (Figure 1).

Corticosteroids exert their actions by binding intracellular receptors and, consequently, modulating gene expression. These receptors are part of a multiprotein complex consisting of one receptor molecule and several heat shock proteins. Molecular and biochemical studies have shown the existence of 2 receptor subtypes with different affinity for aldosterone and cortisol (or corticosterone), respectively known as mineralcorticoid (MR) and glucocorticoid receptor (GR). GRs are expressed everywhere in the brain, but they are particularly abundant in the hypothalamic CRH neurons and pituitary corticotropes. Historically, MRs have rarely been related to the stress response, since the control of the sodium balance through actions in the kidney and hypothalamus was considered their unique homeostatic function (De Kloet et al., 1998). However, the highest expression of MRs in the brain takes place outside the hypothalamus, specifically in the hippocampus, a structure that is mainly involved in learning and memory processes. Interestingly, MR selectivity for aldosterone is lost in the hippocampus, thus, in this structure, cortisol (or corticosterone) activates 2 different pathways via MRs and GRs (Reul and de Kloet, 1985). Another peculiar and often underestimated feature of the hippocampus is that this structure plays a key role in the regulation of HPA axis activity (Figure 1). In particular, the hippocampus exerts an inhibitory effect on hypothalamic CRH release (Jacobson and Sapolsky, 1991), thus participating in the restraint (negative feedback) of the stress response and in the dampening of HPA rhythmicity (primarily by raising the nadir corticosteroid level toward that of the peak). So, the hippocampus can be considered a functional component of the HPA axis. In the hippocampus, corticosterone binds to MRs with a 10-fold higher affinity than to GRs (Veldhuis et al., 1982). The MRs are substantially occupied even at basal levels of HPA axis activity, suggesting that these receptors are implicated in the maintenance of basal activity of the stress system. High concentrations of corticosteroids progressively saturate GRs, implying that the suppression of stress induced HPA activity occurs, in particular, through GRs (De Kloet et al., 1998).

2.1.1. Early-life stress and long-term HPA axis alterations

Glucocorticoids are essential for life, influencing virtually every tissue and affecting a wide range of physiological functions such as metabolism, blood pressure, breathing, immune system, and behavior. Both acute and chronic stress condition may alter the response of the HPA axis (including the negative feedback loop exerted by the hippocampus), entailing increased levels of circulating corticosteroids which predispose the body to cope in an emergency. However, the period of life when the stress is faced can exert a specific impact on the duration and intensity of HPA axis activation. There is now convincing evidence that early life experience can cause changes in the stress response system that persist into adulthood. Indeed, it has been proposed (Reynolds, 2013) that some factors acting during critical windows of development may lead to permanent changes in the fetus which initially promote survival, but then predispose the individual to later life disease. The term "factors" includes a batch of different conditions such as alteration in maternal care, depression, abuse, malnutrition (either pre- or post-natal), and traumatic events; these have been identified by an increasing number of studies performed in recent years (Lucassen et al., 2013). It is important to note, however, that not all the early-life events necessary negatively impacts on adult phenotype. For instance, several studies

(Lehmann et al., 2000) suggest that neonatal handling and/or maternal separation may have almost opposite effects depending on their duration (i.e., 5-15 min per day versus several hours per day). These events can differently impact on the HPA axis either increasing or decreasing its activity. Whether or not such HPA axis modulations will have good or bad outcomes during adulthood depends on the nature of the factor (quality and quantity) as well as the nature of the individual (genes and gender) and the interaction with the environment. However, for the purposes of the present review, we will focus on the negative correlation between early-life events and adult phenotypes.

Different aspects of maternal behavior (feeding, passive contact or non-nutritive sucking, licking and grooming) might affect HPA axis regulation in newborns. It is likely that these maternal behaviors act in concert to limit and prevent stress hormones from exceeding their optimal level (Levine, 2001). It has been shown that disruption in the mother–infant relationship is enough to exert several negative consequences. Indeed, lack of maternal behavior impacts on hippocampal neurogenesis (Meaney, 2001; Oomen et al., 2009) and neuronal plasticity increasing vulnerability to aging and psychopathology (Cirulli et al., 2003). Naturally occurring variations in maternal care alter the expression of genes involved in behavioral and endocrine responses to stress (Meaney, 2001; Plotsky et al., 2005); moreover, it negatively impacts on energy metabolism (Pankevich et al., 2009) and the cardiovascular system in adults (Matthews et al., 2011). Interestingly, some of these studies also highlighted gender-dependent outcomes. For instance, cross-fostering produced increased abdominal adiposity and increased values of systolic blood pressure only in adult male but not in female mice (Matthews et al., 2011). Likewise, hippocampal neurogenesis has been found to increase in male and to decrease in female mice after maternal deprivation (Oomen et al., 2009).

Besides maternal behavior, it is widely accepted that maternal diet and adiposity have an impact on the offspring's development. There is a clearly established relationship between maternal obesity and offspring obesity and the children of obese mothers are more likely to develop metabolic complications such as diabetes later in life (Pankevich et al., 2009). On the other hand, severe prenatal malnutrition is proved to affect HPA axis activity and feeding circuitry, resulting in adult obesity and comorbidities (Spencer, 2013). Similarly, the incidence of psychiatric disorders and cognitive impairment is highly increased in subjects who experienced, during their childhood, maternal depression, sexual abuse, or catastrophic events (Lucassen et al., 2013). Finally, early life stress, induced by behavioral stressors or adverse childhood experiences, is highly correlated with ischemic heart disease in adulthood, more so than the traditional risk factors (Loria et al., 2014).

Numerous studies have tried to understand how early-life stress can impact on adult life. The hippocampus, among the other brain regions, seems the most fitting candidate to be permanently modulated by stress conditions. Indeed, the hippocampus is particularly sensitive to the early-life environment because it has a high degree of structural and synaptic plasticity, it undergoes dynamic changes in neuronal connectivity (Lucassen et al., 2013), and it is rich in stress-hormone receptors (GRs and MRs). This high receptor concentration makes the hippocampus a key structure in the regulation of the physiological stress response. Indeed, the activation of the hippocampus through these receptors has the ultimate effect to inhibit the release of CRH from the hypothalamus (Jacobson and Sapolsky, 1991). Finally, the human hippocampus develops between the last trimester of gestation and 16 years of age (Arnold and Trojanowski, 1996); in rodents this occurs between embryonic day 18 and postnatal weeks 2–3 (Altman and Bayer, 1990). Therefore, in offspring hippocampus modulation may occur both in utero and during the post-natal period, invariably entailing HPA axis derangements that can be responsible for adult predisposition to numerous diseases (Figure 1). Levels of cortisol in pregnant women naturally increase during the last trimester of gestation (Reynolds, 2013). However, even if lipophilic steroids easily cross the placenta, fetal glucocorticoid levels are much lower than maternal levels (Seckl, 2004). In fact, the 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which catalyzes the rapid conversion of active physiological glucocorticoids (cortisol and corticosterone) to inert 11-keto forms (cortisone and 11-dehydrocorticosterone), is highly expressed in the placenta. Nevertheless, conditions of stress during pregnancy can increase maternal cortisol level beyond the limit of action of 11β-HSD2, thus overexposing the fetus to glucocorticoids. The large amount of steroids in the fetus, probably through epigenetic modifications (cf. paragraph 2.1.2), downregulates hippocampal GR expression eventually reducing the inhibiting role that this structure exercises on the HPA axis activity (i.e. hyperactivating the HPA axis) (Pankevich et al., 2009; Seckl, 2004). Similarly, the lack of maternal care and sensory stimulation (van Oers et al., 1999) as well as under or over nutrition (Laus et al., 2011; Schmidt et al., 2006) in the early postnatal period is sufficient to increase cortisol levels in newborns, possibly affecting the HPA axis development (Figure 1).

2.1.2. Role of epigenetic mechanisms in long-term effects of early-life stress

The stress-related cortisol increase in fetuses or newborns impacts on HPA development possibly through epigenetic modulation of CRH, GR, and MR expression, particularly in the hippocampus (please refer to Table 1 for more detail on epigenetic inheritance systems). Different studies performed in rats highlighted the relevance of GR exon I_7 (in the gene promoter region) for later life consequences and its potential as a target for reversal of early-life effects (Weaver et al., 2004; Weaver et al., 2005). In particular, the investigators showed that poor maternal care was responsible for the hypermethylation of GR promoter and the consequent decrease in the number of hippocampal GRs in the offspring (Weaver et al., 2004). Since the hippocampus plays a key role in the negative feedback regulation of the HPA axis, a low number of GRs in this area reduces hippocampal inhibition of the HPA axis. Consequently, poor maternal care reduces hippocampal GRs in the offspring, eventually leading to exacerbated HPA axis activity and increased corticosteroid levels in adults. Rescue experiments showed that in perinatally stressed adult rats the increased corticosterone levels normalize after demethylation of the hippocampal GR promoter (Weaver et al., 2004; Weaver et al., 2005), further suggesting epigenetic involvement in HPA axis alterations. Epigenetic modifications resulting from perinatal stress conditions also included demethylation of hypothalamic CRH and VP promoter (Chen et al., 2012; Murgatroyd et al., 2009) and consequently, increased CRH and VP levels in adults.

3. EFFECTS OF STRESS ON SLEEP

Stressful conditions entail a plethora of body responses involving molecular, hormonal, neurochemical, and behavioral changes aimed at coping with external challenges and maintaining internal homeostasis. Stress response largely varies according to the characteristics of the stressor applied (e.g., duration, intensity, controllability, and predictability) and of the subject experiencing stress (e.g., individual stress coping strategies, relative resilience, and vulnerability) (Sanford et al., 2015). Modulation of the HPA axis activity plays a central role in these processes, and the various actors of this axis can exert a deep impact on sleep function. This may have important consequences on the health of subjects. In fact, it is a shared experience that a good night's sleep improves physical and cognitive performance, while lack of sleep worsens our performance in daily activities. This subjective experience is supported by scientific evidence (review in Goel et al., 2013): human subjects with reduced sleep duration (less than 6 hours / night) (Gildner et al., 2014) or with disturbed sleep, as patients with sleep apnea (Yaffe et al., 2011), have a significant reduction in memory performance and cognitive assessment. Studies on animal models (Karatsoreos et al., 2011; Kwon et al., 2015) also led to similar conclusions. Emerging evidence suggests that sleep deprivation and circadian rhythm disruption may increase the risk for the development of Alzheimer’s disease and other neurodegenerative brain pathologies, mainly by interfering with the glymphatic-vascular-lymphatic clearance of brain macromolecules and by increasing oxidative stress (Wu et al., 2019). Finally, sleep deprivation itself can represent a stress, enhancer of other stressors that have negative consequences for the brain and many body systems (McEwen & Karatsoreos, 2015). A growing body of evidences correlates a reduction of duration and/or quality of sleep with alterations in endocrine and metabolic function, favoring the development of obesity and type 2 diabetes (Van Cauter & Tasali, 2013). Sleep deprivation can decrease parasympathetic tone, increase corticosteroids and metabolic hormones when they should be low (flattening of rhythms), and increase level of proinflammatory cytokines

(Spiegel et al., 2004; Vgontzas et al., 2004). However, since the outcome of this approach is to evaluate the sleep phenotype after application of stressors, sleep deprivation or sleep derangements are not included in the list of stress-inducing factors in order to prevent circular discussion. Therefore, in this section we will discuss first the mechanisms through which the activation of the HPA axis produced by stress can modify sleep and, then, the specific effects on sleep exerted by acute or chronic stress, or a stress applied in the early stages of life.

3.1. Effects of HPA stress mediators on sleep

There are significant overlaps between neural networks and neurochemistry underlying the stress response and that regulating arousal and sleep. In fact, the regulation of the wake-sleep cycle involves multiple neurotransmitters and neuromodulators, most of which plays also a role in the stress response. In the following paragraphs, we will discuss the effect exerted by the stress mediators of the HPA axis on the wake-sleep cycle either directly or indirectly through the modulation of circadian rhythms. Even if it is generally accepted that the products of the HPA axis exert a sleep-reducing effect by stimulating waking, experimental evidence shows that the mechanisms of action of the different mediators and the timing of their effects are quite different.

3.1.1. CRH

CRH receptors are densely distributed in the basal prosencephalic areas, thalamus, hypothalamus, mesencephalus, brainstem, and pons (De Souza, 1987). All these areas are involved in cerebral activation and waking maintenance, thus suggesting an involvement of CRH in wakefulness regulation. There are three related CRH receptor subtypes, CRH-R1, CRH-R2α, and CRH-R2β, that differ from each other in anatomical distribution as well as in pharmacological profile. CRH-R1 is widespread in the brain and is also found in the anterior and intermediate lobes of the pituitary gland, whereas CRH-R2 is confined to subcortical structures in the brain, and is either undetectable or only detected in scattered cells in the pituitary gland (Chang and Opp, 1999). A series of studies documented that intracerebroventricular (ICV) administration of CRH in rats produced many of the signs associated with anxiety in humans, including increased wakefulness (Chang and Opp, 1998) and, simmetrically, decreased non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep (Romanowski et al., 2010) (Table 2), altered locomotor activity, and an exaggerated startle response (Swerdlow et al., 1986). The major impact of CRH on wakefulness and NREM sleep regulation seemed to be exerted by central CRH-R1 (Romanowski et al., 2010). However, studies using non-selective CRH receptor antagonists such as α-helical ovine CRH_{9_41} (αh-CRH) and astressin reported conflicting results. In one study the ICV administration of either αh-CRH or astressin to rats at dark onset reduced the amount of time spent awake immediately after the injection or with a longer delay, respectively (Chang and Opp, 1999). Interestingly, when these compounds were administered at the beginning of the light period (resting phase in rodents), they failed to affect wakefulness, which supports the view that CRH contributes to the regulation of physiological waking periods. Similarly, CRH antisense oligodeoxynucleotides reduced spontaneous wakefulness during the dark period, but not during the light period (Chang and Opp, 2004). On the contrary, another study found that αh-CRH injections at dark onset exerted no effect on spontaneous sleep-wake behavior (Gonzalez and Valatx, 1997), whereas REM sleep induced by immobilization stress appeared to be abolished and the rebound of REM sleep after sleep-deprivation was reduced (Gonzalez and Valatx, 1997). Accordingly, mice with overexpression of CRH showed an increased basal level of REM sleep compared to controls and enhanced recovery REM sleep after 6h sleep deprivation (Kimura et al., 2010).

In a study in humans, the pulsatile intravenous administration of CRH prompted a decrease in stage N3 of NREM sleep, an increase in intermittent wakefulness and an increase in the time spent in REM sleep during the first third of the night (Steiger et al., 2013). On the contrary, 4 weeks of infusion of the CRH-R1 antagonist R121919 increased the amount of NREM sleep, while decreasing the number of awakenings and REM density (Held et al., 2004).

In conclusion, while it is well consolidated that CRH promotes wakefulness and, consequently, reduces NREM sleep both in humans and rodents (Table 2), its action on REM sleep has not been totally clarify yet and, most likely, it diverges between species (Table 2).

3.1.2. ACTH

In a rat study, the ICV injection of ACTH promoted wakefulness, whereas injections of its derivatives, desacetyl-alpha-melanocyte stimulating hormone and corticotropin-like intermediate lobe peptide, increased NREM sleep and REM sleep, respectively (Chastrette et al., 1990). In young male volunteers, sleep electroencephalographic (EEG) activity changes occurred after pulsatile intravenous administration of ebiratide, an ACTH analog. Specifically, in these subjects NREM sleep decreased whereas sleep latency and wakefulness increased during the first third of the night (Steiger et al., 1991). In intact cats, ACTH infusions suppressed REM sleep (Koranyi et al., 1971) and, in rats, it significantly increased sleep latency and wake time while decreasing NREM sleep time (Tsutsui et al., 2015). Since sleep disturbances in depressive patients are characterized by an increase in sleep latency and a decrease in NREM sleep time (Holshoe, 2009), it has been proposed that chronic administration of ACTH in rats might represent a valid animal model for human depression (Tsutsui et al., 2015) (Table 2).

Similar to CRH, available evidence from humans and animals indicates that ACTH stimulates wakefulness at the expenses of NREM sleep (Table 2). Even in this case, the picture concerning the effects of ACTH on REM sleep is still incomplete.

3.1.3. Cortisol (and corticosterone)

Large doses of corticosterone in adrenalectomized rats decreased the amount of NREM sleep (Bradbury et al., 1998). On the other hand, lower doses of corticosterone in intact rats seemed to have a biphasic effect (Table 2), first increasing and then decreasing wakefulness. The initial alerting effect of corticosterone was also accompanied by a slight decrease in NREM sleep while REM sleep was not affected (Vazquez-Palacios et al., 2001).

In young men, it has been reported that cortisol administration reduced REM sleep and slightly increased NREM sleep (Born et al., 1991). Accordingly, REM sleep decreased and NREM sleep increased in a similar study performed in elderly men (Bohlhalter et al., 1997). Since CRH and cortisol seem to exert opposite effects on NREM sleep, at least in humans, it is reasonable to suppose that these effects do not depend on cortisol itself but are mainly due to the negative feedback inhibition exerted by cortisol on endogenous CRH production. On the other hand, because CRH, ACTH, and cortisol diminish REM sleep, this effect seems to be mediated by cortisol itself after the administration of each of these hormones (Steiger, 2007) (Table 2).

Altogether, while it is well known that HPA axis perturbations affect the wake-sleep cycle, the exact role exerted by cortisol (and corticosterone) in this context is still controversial (Table 2). Indeed, rodent and human studies failed to provide a conclusive picture of the effects of cortisol (corticosterone) on wakefulness or REM sleep while they even showed contrasting consequences on NREM sleep.

Finally, it is important to highlight that at least some of the contrasting findings shown in Table 2 might be due to experimental conditions rather than the real actions of stress mediators. Indeed, most of the above-mentioned studies have been performed via exogenous administration of CRH/ACTH/cortisol or their analogous/antagonists. Under real physiological conditions, however, it is likely that the actions of stress modulators on the wake-sleep cycle is highly dependent not only on the amount of each circulating molecule but also on how they differentially interact with their receptor subtypes in different brain structures.

3.1.4. Possible effects of glucocorticoids on sleep through the modulation of circadian clocks

It is important to note that besides the direct effect they exert on sleep, glucocorticoids might also modulate sleep indirectly through their influence on circadian clocks. Consequently, in this paragraph we will briefly introduce the circadian clock system and then we will illustrate its potential modulation by glucocorticoids.

The 24-hour rotation of the earth strongly affects animal physiology, biology and behavior (such as wake-sleep cycle rhythmicity). Evolution has equipped almost all organisms with an elaborate intrinsic timing system, the so-called clock system which creates internal circadian rhythmicity, in order to deal with these recurring changes. A primary role of the circadian clock is to entrain the organism to environmental cues, so that an animal can anticipate fluctuations in the environment and determine key issues such as food availability, predator risk, and the likelihood of reproductive success. Furthermore, the circadian system is critical to the synchronization and relative phasing of various internal physiological processes that are essential for the optimization of responses to environmental fluctuations and for the strengthening of homeostatic control mechanisms (Kalsbeek et al., 2012).

The hypothalamic suprachiasmatic nucleus (SCN) represents the central master clock of the circadian clock system. SCN is under the strong influence of light/dark input from the eyes, whereas the peripheral clocks behave as subordinates, being subjugated by the former through mechanisms which remain still unclear (Charmandari et al., 2011). At the molecular level, circadian clock rhythms are based on autoregulatory feedback loops involving clock genes that cycle with a period of about 24 h. These genes include the Circadian Locomotor Output Cycle Kaput (CLOCK), its heterodimer partner Brain Muscle-Arnt-Like protein 1 (BMAL1) and other essential negative regulators, such as the Periods (PER1-3) and the nuclear hormone receptors RevErbα (Takahashi et al., 2008). Besides the strong influence exerted by the SCN, peripheral clocks are also set to external time by different regulatory (neural, hormonal, temperature, metabolic control) pathways. Among others, steroids can directly or indirectly modulate clock gene expressions through GR binding. Since the SCN lacks GRs, glucocorticoids cannot directly modulate central rhythms (Balsalobre et al., 2000). On the other hand, they strongly influence peripheral rhythmicity. Unbound GRs reside in the cytoplasm, and once the glucocorticoid binds to the GR, the complex travels towards the nucleus where it can bind the glucocorticoid response element (GRE) in the promotor region of target genes, thereby positively (as for Per1) or negatively (as for RevErbα) regulating gene expression. Alternatively, the glucocorticoid-GR complex can physically interact with other transcriptional factors, altering the activities of the latter on their own responsive genes (Chrousos and Kino, 2005; Gross and Cidlowski, 2008). Glucocorticoids acutely induced Per1 gene expression in rodent (Balsalobre et al., 2000), canine (Ohmori et al., 2013), and human (Fukuoka et al., 2005) peripheral blood mononucleate cells and affect rhythmic Per1 (Balsalobre et al., 2000; Mongrain et al., 2010; Yamamoto et al., 2005) and Per2 (Curie et al., 2015; Segall and Amir, 2010) expression in rodent peripheral clocks. Accordingly, adrenalectomy modulated circadian clock gene mRNA abundance with a tissue-dependent effect. In mice the elimination of plasma corticosterone and its rhythmicity resulted in significant inhibition of Per1 mRNA in the visceral adipose tissue, liver, jejunum, and splenocytes but not in the kidney, as well as a decrease in the mRNA levels of some other clock genes (Sotak et al., 2016). The effect of glucocorticoids on Per1 appeared to occur directly through the GRE in the Per1 gene (Yamamoto et al., 2005), and, since transcription of clock genes is regulated via mutual feedback regulation by other clock gene products (Takahashi et al., 2008; Yamamoto et al., 2005), changes in the accumulation of the PER1 protein are likely to influence the expression of other clock genes. Similarly, in humans, the intravenous administration of hydrocortisone strongly affected Per1 and partially Per3 expression whereas it did not affect Per2 expression (Yurtsever et al., 2016).

Besides entraining peripheral clocks at a molecular level, glucocorticoids seems to be also involved in the entrainment of behavioral rhythmicity such as wake-sleep cycle rhythmicity. Adrenalectomized rats showed an accelerated rate of re-entrainment to a shifted light-dark cycle (Sage et al., 2004). In adrenal-specific clock knockdown mice kept under constant darkness conditions, the amplitude of plasma corticosterone rhythm as well as their behavioral rhythm was severely dampened (Son et al., 2008). This indicated that in the absence of light as a timekeeping cue, the rhythm in corticosterone was an important factor driving locomotor activity (Kalsbeek et al., 2012). Indeed, inhibiting corticosterone production in mice resulted either in advanced or delayed behavioral resynchronization, depending on the time of injection and the direction of the phase change (Kiessling et al., 2010). Taken together, these findings indicate that, as well as entraining peripheral clocks at the molecular level, corticosterone acts as a regulator of behavioral adaptation to phase shifts, possibly through an indirect feedback to the SCN (Kalsbeek et al., 2012).

3.2. Effects of acute stress on sleep

In animal studies, a variety of protocols have been developed to investigate the consequences of acute stress on hypnic phenotype. Due to the large variety of responses reported in these studies, it is not possible to draw a unifying causal mechanism linking acute stress and hypnic derangements. Indeed, even if it is well known that acute stress invariably entails sleep loss in rodents, the following sleep rebound may vary depending on the type/duration of the applied stressor with considerable interindividual differences (possibly linked to the level of activation of the HPA axis).

A widely used protocol to produce stress in rodents is *immobilization* because it does not entail physical pain and can be considered as only a psychological stress. As a rule of thumb, acute immobilization, which is usually performed for 1 or 2 hours, produces a sleep debt in both rats and mice. Generally, this sleep debt is paid off by increasing the time spent asleep during the following hours. This sleep rebound mainly concerns REM sleep (Bouyer et al., 1998; Marinesco et al., 1999; Meerlo et al., 2001b; Pawlyk et al., 2008; Descamps and Cespuglio, 2010). Conversely, restraint stress does not appear to have a major effect on the period or phase of the activity period (Meerlo et al., 2002) indicating that this protocol probably does not affect SCN activity.

The exposure of rodents to intermittent brief *electrical shocks* represents another widely used acute stress protocol. In this case, of course, the procedure also includes pain that must be considered in subsequent analyses as a potential source of interindividual variability. However, contrary to restraint, electrical shock is usually associated with a decrease in the animals' subsequent total sleep time and, particularly, in REM sleep time (Pawlyk et al., 2008). Similarly, fear conditioning procedures entail a REM decrease during both the stimulus application (shock training) and cue exposure (Sanford et al., 2003) in different mouse strains.

Several studies have shown that *social conflicts* are one of the most potent stressors in terms of classical indicators of the stress response such as secretion of catecholamines and corticosterone. Moreover, this paradigm is probably the best way to mimic a stress-inducing condition which can be physiologically encountered in everyday life by rodents. Several studies in rats have shown that social stress may result in severely disturbed physiological and behavioral rhythms that can last for several days, up to weeks, after the conflict, particularly concerning activity patterns, body temperature, and heart rate. Regarding locomotor activity, the amplitude reduction is mainly due to a decrease in activity during the animal's activity phase. As far as body temperature is concerned, the amplitude decrease is caused by an increase in temperature during the resting phase. Also, the amplitude of the daily heart rate rhythm is reduced, but this effect may be due to both an increase during the resting phase as well as a decrease during the active phase (Meerlo et al., 2002). Despite this evidence, the social conflict does not affect the endogenous pacemaker's sensitivity to light, and the reduction of the temperature and activity amplitude do not appear to reflect a reduction in amplitude of the SCN activity (Meerlo et al., 2002).

Social defeat has also been found to have immediate effects on subsequent sleep: rats (Meerlo et al., 2001a; Meerlo et al., 1997) and mice (Meerlo and Turek, 2001) showed increased amounts of NREM sleep and/or increased NREM sleep intensity, as reflected in elevated EEG slow wave activity (SWA), and a strong reduction in REM sleep in the first couple of hours after the conflict (Kamphuis et al., 2015). The SWA increase was not explained by sleep loss per se, as it was significantly higher than in animals that had been sleep deprived through gentle stimulation for the same duration. Interestingly, the increase in NREM sleep SWA, as well as REM sleep suppression, was not different between animals that had won and animals that had lost the conflict, which indicates that these alterations were caused by the conflict per se and not by the outcome. Similarly, the peak response in blood pressure, heart rate, and corticosterone, were similar between winners and losers, but these alterations persisted longer in the losers (Kamphuis et al., 2015).

Altogether, social conflict may represent an intense form of wakefulness that requires more intense recovery sleep. Indeed, the SWA increase after the conflict agrees with the synaptic homeostasis hypothesis which states that intense wakefulness is associated with large synaptic potentiation and, as a result, with a higher synchronous NREM sleep and slow waves of higher amplitude (Tononi and Cirelli, 2006).

In humans, the effects of acute stress on the wake-sleep cycle have only marginally been investigated. Moreover, except for Post-Traumatic Stress Disorder (PTSD) patients, only few studies were performed with replicated designs on groups of participants exposed to specific types of stressors (Germain et al., 2003; Kim and Dimsdale, 2007). However, one of the most recurrent finding is that the exposure of healthy subjects to acute experimental psychological stress (e.g. telling them before bedtime that the next morning they would have given a speech) produces REM sleep alterations more frequently than NREM sleep alterations (Kim and Dimsdale, 2007; Cartwright, 1983; Pillar et al., 2000; Reynolds et al., 1993). Interestingly, this finding is in line with what has been reported in rodents exposed to immobilization protocol, a paradigm of psychological stress (Bouyer et al., 1998; Marinesco et al., 1999; Meerlo et al., 2001b; Pawlyk et al., 2008; Descamps and Cespuglio, 2010). In humans not only the nature and length of the stressor, but most importantly, the individual psychophisiological reactivity and the capacity to cope with stressful situations may determine the sleep outcome. It has been postulated that an attenuation of REM sleep phasic activity after experimental stress exposure may reflect adaptive regulation of waking emotional arousal system of the individual (Germain et al., 2003). More generally, negative emotions triggered by unfamiliar environments (such as sleep laboratories) entail lower sleep efficiency (percentage of total sleep time during the recording time), frequent awakenings, decreased REM and NREM sleep (Kim and Dimsdale, 2007). Apart from laboratory conditions, investigators have also examined several daily life stressors including acute stressful events such as bereavement (for an overview see Kim and Dimsdale, 2007). Results suggest that daily life stressors may produce several changes in sleep architecture including reduced REM sleep latency, increased time spent in REM sleep, and reduced time spent in NREM sleep (Kim and Dimsdale, 2007). Another common category of stressors is that characterized by traumatic events. Similar to acute laboratory adaptation test, life-threatening injury reduces total sleep time also increasing the number of awakenings, it increases REM sleep latency while reducing time spent in REM sleep and in NREM sleep (Kim and Dimsdale, 2007). These comparable changes in sleep pattern might indicate that the effects of stressor exposure may have similar time course (i.e., immediate effects of stress on sleep) regardless of the intensity of the stressor. Traumatized patients without PTSD whose wake-sleep cycle was recorded in within 1 month from injury showed reduced total sleep time, increased number of awakenings, and increased REM sleep density (frequency of eye movements during REM sleep) when compared to healthy controls (Mellman et al., 2002). During the subsequent follow-up, patients that developed PTSD showed an increased number of REM sleep episodes with a shorter average duration compared to patients that did not develop PTSD (Mellman et al., 2002).

It is interesting to notice that one of the most diffused models of insomnia, the 3P model (based on the interaction of Predisposing, Precipitating, and Perpetuating factors), has been built considering the effect of acute stress on sleep (Spielman et al., 1987). According to this model, predisposed individuals may develop acute/transient insomnia after a precipitating factor, such as an acute stress, while perpetuating psychological and behavioral factors may contribute to the development of chronic insomnia forms. Similar to rodents exposed to electrical shock or to social conflict protocols, insomnia patients presents a moderate but significant reduction in REM sleep time and also a reduction in NREM sleep time. These data are consistent with the hypothesis that insomnia symptoms may be due to physiological cognitive and somatic hyperarousal related to the hyperactivation of the stress system, including the HPA axis and inflammatory system (Riemann et al., 2015; Riemann et al., 2010). Indeed, subjects with elevated stress-related sleep reactivity (degree to which the person is vulnerable to sleep disturbance when exposed to stress) are more prone to develop chronic insomnia (Kalmbach et al., 2018) suggesting that, in humans, dysregulation of the stress response rather than general hyperarousal may be a more pertinent marker of risk to develop sleep disturbances after an acute stress (Kalmbach et al., 2018).

Despite significant inter-study and inter-species differences, REM sleep deregulation seems the most common hypnic feature affected by acute stress both in rodents and humans, particularly in PTSD patients.

3.3. Effects of chronic stress on sleep

Chronic stress has been reported to disrupt sleep in a variety of situations. Several experimental studies in laboratory rodents have applied different kinds of stimuli for periods up to several weeks, with the effects on sleep and circadian rhythmicity then being investigated. For instance, in the same study rats were exposed for 4 consecutive days either to 22 h/day of *immobilization*, *forced swimming*, or *footshock* stress protocol (Papale et al., 2005). Each kind of stress promoted changes in a differential fashion; during the diurnal phase, while immobilization and forced swimming led to a reduction in sleep efficiency during all 4 days, immobilization was the only stressor that resulted in a significant decrease in sleep efficiency and a decrease in NREM and REM sleep throughout the entire period of recording. Forced swimming produced a reduction in NREM sleep and augmented REM sleep only during the first day of stress exposure. Footshock produced alterations in sleep efficiency and a decrease in NREM and REM sleep only on the two last days (Papale et al., 2005). Footshock entailed a reduction in total sleep and REM sleep in rats only during the first day, even when the protocol was protracted up to 14 days (Kant et al., 1995). This limited effect might be linked to the fact that stress predictability, as well as stress controllability, can influence the perception of the stressor and modulate the direction of its effects on sleep (Sanford et al., 2015).

Similarly, repeated exposure to a *cued fear conditioning procedure* specifically reduced REM sleep in both rats (Sanford et al., 2001) and mice (Sanford et al., 2003). In the rat study (Sanford et al., 2001), sleep was recorded immediately after the fear conditioning procedure. In the mouse study (Sanford et al., 2003), which utilized 15 tone-shock pairings, sleep was recorded up to 24 h after training, immediately after the presentation of 15 tones. These similar findings in different species suggested that the reduction in REM may be a fundamental response of organisms to stress.

Once again, *repeated fighting and/or being defeated in a social interaction* may represent a more naturally occurring stressor in social species such as rats and mice. This technique involves an ethological form of stress related to territorial aggression in rodents and has numerous advantages when attempting to understand the ways in which behavioral and molecular adaptations develop over time in response to stressful experiences. One advantage is that key behavioral endpoints that are altered by chronic social conflict (e.g., social interaction) are sensitive to chronic but not acute treatment with standard antidepressants and acute treatment with ketamine, both of which resemble the time courses of therapeutic drug actions in humans. In addition, chronic social conflict can reveal separate “susceptible” and “resilient” populations, potentially modeling individual differences in stress susceptibility in humans. Chronic social conflict effects can endure beyond the termination of the stressor, making it a particularly appealing method with which to study some of the persistent characteristics of stress-related psychiatric illnesses as they occur in clinical settings (Wells et al., 2017). In rats, this paradigm of chronic stress entails long-lasting consequences also on daily rhythms of heart rate, blood pressure and body temperature in rats that do not depend on the physical intensity of the fight but largely on how the subjects deal with the conflict (Meerlo et al., 1999). In mice, it has been shown that chronic social conflict profoundly impacts on the wake-sleep cycle. Particularly, it increases the time spent in REM sleep and the number of REM sleep bouts; it also increases the time spent in NREM sleep, and conversely it decreases the amount of time spent in wakefulness (Wells et al., 2017). Some of these effects can be reversed by the cessation of chronic social conflict, while others persisted through the recovery period, in which reductions in circadian amplitude of body temperature and motor activity, and increases in time spent in NREM sleep, were present (Wells et al., 2017). A brief increase in REM sleep time after 10 days of social conflict was also independently reported by another experiment in which, contrary to what has been described for acute protocols (Kamphuis et al., 2015), no change in SWA was detected (Olini et al., 2017).

As expected, chronic stressors deeply impact also human sleep architecture as it has been reported in cases of marital separation (Cartwright and Wood, 1991), shift works (Kim and Dimsdale, 2007), burnout patients (Armon et al., 2008), or people who experienced lack of social support in the work environment (Gadinger et al., 2009; Nomura et al., 2009). In particular, marital separation in non-depressed persons resulted in the reduction of time spent in NREM sleep and the increase of the time spent in REM sleep, accompanied by a decreased of REM sleep latency (Cartwright and Wood, 1991). Similarly, studies on shift workers reported that these subjects had longer NREM sleep latency, decreased amount of NREM sleep, increased amount of REM sleep, and shorter REM sleep latency, compared to students (Goncharenko, 1979). A reduction of time spent in NREM sleep was also recorded in those subjects worried about going to work the next morning (Kecklund and Akerstedt, 2004; Soderstrom et al., 2004).

One of the dominating models in the field of psychosocial work (chronic) stress is the Job–Demand–Control–Support (JDCS) model (Johnson et al., 1989). The central tenet of the JDCS model is an increasing likelihood of mental and physical impairment with increasing job demands and decreasing job control and social support. Thus, the most adverse health outcomes can be expected in high-demand jobs with low job control and poor social support (isolated high-strain jobs). Indeed, a cross-sectional study in German-speaking executives conducted on 348 male and 76 female executives and managers from Germany, Austria and Switzerland showed that lack of social support, and job demands were related to poor sleep quality especially in females (Gadinger et al., 2009). A similar study conducted on 1209 male workers confirmed these data highlighting independent effects of job strain and job control on insomnia development (Nomura et al., 2009).

Burnout represents a negative affective state that comprises feelings of emotional exhaustion, physical fatigue, and cognitive weariness, and denotes depletion of energetic resources resulting from cumulative exposure to chronic work and chronic life stresses. There is compelling evidence, based on both questionnaire data and objective polysomnographic recordings, pointing to an association between burnout and sleep disturbances, particularly chronic insomnia (Ekstedt et al., 2006; Melamed et al., 1999). Moreover, both burnout and insomnia are closely associated with chronic stress. These 3 elements seem to be chasing each other on a vicious circle. For example, insomnia can cause non-refreshing sleep and waking up exhausted (Riemann et al., 2012) in individuals who are also exposed to work and life stresses reducing their resources for coping with stress, thus, exacerbating symptoms of mental and physical fatigue and, ultimately, sustaining burnout or the development of new cases of burnout (Armon et al., 2008).

In conclusion, since many different chronic stress protocols have been used in rodent experiments and many different types of stressors can be encountered in everyday life by humans, it is complicated to draw a unifying picture on the effects of chronic stress on sleep architecture. This is probably due to the fact that, besides the type of stressors, temporal dimension (how many times and for how long a stressor has been applied?) has a critical role in the stress responses and, thus, it must be carefully considered. However, a reduction in NREM sleep time seems to be a distinctive tract of chronic stress exposure in humans as well as in several experimental protocols applied to rodents (Papale et al., 2005).

3.4. Long-term effects of early-life stress on sleep

Stress responses are critically linked to temporal dynamics. For example, the exposure to a brief session of inescapable and unpredictable footshock (Miller et al., 1975) has a proactive effect, and the reactivity to a minor stressor increases progressively during period after the stress experience (Van Dijken et al., 1992). The importance of the temporal dynamics in terms of hours, days and weeks of a wide variety of stress parameters after the termination of the stressor itself has been discussed several years ago by Koolhaas et al. (Koolhaas et al., 1997). At that time, little was known about the mechanisms involved in these long-term effects of stress. Today, we start to unravel the cascade of neurobiological processes induced by stress. Each of these processes may have a different time course, ranging from milliseconds in the case of direct signal transduction processes, to minutes, hours and days when modulatory processes are involved at the level of DNA transcription and peptide synthesis. This cascade may lead ultimately to permanent alterations at the level of neuronal morphology and fine tuning of neurochemical signal transduction mechanisms. Moreover, repeated (chronic) exposure to stressors likely entails differential additive effects depending on the time interval between stressors (Koolhaas et al., 1997). Considering these concepts, in this section we will extend the hypothesis of the time-dependent consequences of stress response to a different (longer) time scale. In particular, we will deal with the long-term effects produced by perinatal stress on sleep phenotype.

The number of studies focusing on the possible relationship between perinatal stress exposure and adult sleep derangements is rapidly increasing. As expected, due to numerous possible confounders, performing these studies in humans is very complex. Thus, animal studies in which it is possible to limit confounders such as genetic variability, pharmacological therapies, different lifestyles, and so on, might represent a very useful tool in the understanding of the long-term effects of early-life stress. Several methods to induce early-life stress have been used in animal models, either before (prenatal stress) or immediately after (postnatal stress) birth. Applied prenatal stressors include maternal restraining (Dugovic et al., 1999; Rao et al., 1999), malnutrition (Datta et al., 2000; Duran et al., 2006), exposure to various stimuli (bright light (Koehl et al., 1999), or hypoxia (Joseph et al., 2002), whereas cross-fostering (Santangeli et al., 2016) and, particularly, maternal separation (Feng et al., 2007; Perez-Morales et al., 2014; Sampath et al., 2014; Tiba et al., 2003; Tiba et al., 2004, 2008) have been used as protocols for postnatal stress.

In the following sections, we will discuss the long-term effects exerted by either prenatal or postnatal stress on adult sleep phenotype. In both cases we will provide a comprehensive review of both animal and human studies so far performed.

3.4.1. Prenatal Stress

In one of the first works exploring the relationship between prenatal stress and adult sleep phenotype in rodents (Dugovic et al., 1999), pregnant rats were restrained 3 times a day during the last week of gestation and then the offspring's phenotype was evaluated at 3-4 months of age. Prenatally stressed rats showed sleep fragmentation, a slight decrease in NREM sleep during the active (dark) phase and an increased amount of REM sleep. An increased amount of time spent in REM sleep, positively correlated to plasma corticosterone levels, was found by another study, in which the authors also reported a phase advance in hormonal/behavioral circadian rhythms of adult rats that had been prenatally stressed (Mairesse et al., 2015). A decrease in time spent in NREM sleep, together with prolonged REM sleep latency, was also described in another preliminary report using a similar stress protocol (Rao et al., 1999).

There is evidence that protein malnutrition experienced at a time when the nervous system is developing rapidly significantly impacts the development of the central nervous system and affects both the circadian rhythm and homeostatic processes involved in the wake-sleep cycle regulation. In particular, prenatal manipulations in nutritional status induce alterations in hippocampal neurogenesis, as well as reduce granular cell size, dendritic complexity, and synaptic spine density. When tested shortly after weaning, prenatally malnourished rats exhibited a phase shift in the occurrence of both wakefulness and REM sleep, and during adulthood they showed increased levels of corticosterone after restraining (Duran et al., 2006). However, discordant results have been reported concerning their wake-sleep cycle alteration. In one case it was reported that prenatally malnourished rats spent more time in NREM sleep and less time in REM sleep than controls (Datta et al., 2000), whereas the opposite was shown in a later published study (Duran et al., 2006).

In another prenatal stress protocol (Koehl et al., 1999), in which pregnant rats were exposed to bright light during the last week of gestation, circadian rhythmicity of the HPA axis was evaluated in adult offspring. Interestingly, the authors reported that prenatal stress induced long-term changes in the circadian rhythm of corticosterone secretion but not in ACTH rhythmicity. Particularly, in both males and females, prenatal stress induced modifications in the temporal pattern of daily corticosterone secretion reflected by increased levels during the light period. In females, an increased secretion of corticosterone over the entire 24-h period was observed. Finally, hippocampal MRs were constantly downregulated throughout the 24-h period both in male and female rats, whereas hippocampal GRs were downregulated only in male rats and only during the light (resting) period.

Prenatal exposure of pregnant rats to hypoxia induced, in the adult offspring, marked alterations of the functional organization of the circadian rhythm of activity associated with decreased sensitivity of the biological clock to light. Under a regular light-dark cycle, these rats showed a phase advance of the onset of activity and were less active than controls. Even this prenatal stress protocol was enough to entail hyperresponsiveness of the HPA axis (i.e., increased corticosterone levels) to acute restraining in the adult offspring. Thus, it is fascinating to speculate that these HPA axis derangements, possibly through the modulation of clock genes (i.e., Per1-3), were responsible for the altered circadian rhythmicity in this rodent model of early-life stress. Unfortunately, in this study gene clock expression was not evaluated, thus leaving this hypothesis an open question.

Surprisingly, it has been documented that prenatal stress exposure may impact on fathers' spermatogenesis and, particularly, on microRNA composition (Rodgers et al., 2015). In this case, however, rats exposed to chronic stress showed a specific microRNA pattern (Table 1), entailing a reduction in the HPA axis activity in adult offspring. Thus, contrary to what happens in the mothers, perinatal stress exposure in the fathers seems to entail, through sperm microRNAs, a protective role against HPA hyperactivation in the offspring. However, since this is a completely new field of research, no evidence is yet available concerning the possible consequences of paternal prenatal stress on offspring sleep phenotype.

As already mentioned, clinical studies exploring the link between prenatal stress and long-term derangement of adult sleep phenotype are difficult to perform. Most human studies in this field is predominantly descriptive and only measures sleep in young infants, without observing what happens to them during subsequent developmental stages. Thus, in the following paragraph, we will report the scientific literature highlighting long-lasting effects of prenatal stress on sleep architecture in newborns.

Field et al. (Field et al., 2002) analyzed 106 women, dividing them into 2 groups according to their anger levels during the second trimester of pregnancy. The high-anger women showed higher cortisol and adrenaline and low dopamine and serotonin levels compared to low-anger pregnant women. Accordingly, infants of high-anger women resulted to have higher cortisol and lower dopamine levels compared to infants of low-anger women. The high-anger mothers and infants were also similar regarding their relative right frontal EEG activation and their low vagal tone. Finally, the newborns of high-anger mothers had disorganized sleep patterns (greater indeterminate sleep and more state changes). A second study by the same group (Field et al., 2007) was performed on 253 pregnant women during their second and third trimester of gestation who were assigned to depressed and non-depressed groups. Depressed women self-reported more sleep disturbances, higher depression, anxiety, and anger scores, and showed higher norepinephrine and cortisol urine levels than controls. Newborns of depressed mothers were more active, cried more, and had more sleep disturbances, including less time in deep sleep and more time in disorganized sleep. The relationship between prenatal maternal anxiety/depression and sleep alteration in newborns was also investigated by two more studies. The first was a large longitudinal study conducted on more than 10,000 pregnancies and extended up to 30 months after delivery (O'Connor et al., 2007); the second was a study by Nevarez et al. (Nevarez et al., 2010) that was performed on 1676 mother-infant pairs in a pre-birth cohort study. In both these studies, the investigators found that babies of depressed pregnant women were more prone to disturbed sleep with frequent nocturnal awakenings and reduced sleep duration (O'Connor et al., 2007; Nevarez et al., 2010). The exact mechanism linking maternal prenatal depression and infant sleep alterations has yet to be fully understood but available evidence suggests that this mood condition can be considered as a sufficient psychological stress to elevate glucocorticoid secretion, thus potentially perturbing fetal HPA axis activity.

Altogether, human and animal studies strongly suggest that physical and psychological stress factors acting during pregnancy might have a key role in the development of long-term sleep disturbances both in newborns and adults (Figure 2).

3.4.2. Postnatal Stress

One of the most common protocols used in animal research to evaluate the long-term effects of postnatal stress is maternal separation. Of course, this protocol may vary across laboratories concerning the duration of each single separation or the number of days in which the protocol was applied. However, a large body of data has shown that this protocol leads to long-lasting behavioral, physiological, and molecular alterations that include elevated activation of the HPA axis. Behaviorally, rats which undergo maternal separation were more sensitive to stressful stimulation and showed increased anxiety. Moreover, they had increased brain CRH, plasma ACTH, and corticosterone both at baseline and in response to stressful stimulations (Feng et al., 2007; Plotsky et al., 2005). Concerning the sleep phenotype, it has been reported that these rats had difficulty falling asleep and/or difficulty staying asleep, particularly during the resting period. Indeed, they showed increased total wake time and decreased total sleep time compared to controls (Feng et al., 2007; Perez-Morales et al., 2014). Increased time spent in REM sleep in rats that had been maternally deprived during the early-life period was also reported (Sampath et al., 2014; Tiba et al., 2004). Some studies explored the sleep rebound in these adult rats after acute cold exposure or restraint, highlighting that male rats showed a decrease in sleep efficiency (Tiba et al., 2003; Tiba et al., 2004) whereas female rats (Tiba et al., 2008) showed an increase.

Finally, in a more recent rat study, changing pups between mothers at an early age (cross-fostering) was used as a model of mild postnatal stress (Santangeli et al., 2016). Despite the less severe stress protocol, even in this case, adult rats (both males and females) exhibited increased number of REM sleep onsets during spontaneous sleep. Moreover, the total amount of time spent in REM and NREM sleep during the light period was elevated in cross-fostered rats, reflected as a decrease in waking. The total amount of NREM sleep was also slightly increased during the dark period (Santangeli et al., 2016).

Stressful events occurring in the postnatal period or in infancy may contribute to the onset or maintenance of stress system alterations even in adult humans (Davidson and McEwen, 2012; Heim and Binder, 2012; Teicher et al., 2003). Several studies documented the prominent role of childhood stress such as sexual, physical, or emotional abuse, emotional or physical neglect, or parental loss, in the pathogenesis of stress-related disorders including mood disorders and insomnia (Carr et al., 2013; Wilkinson and Goodyer, 2011). Inconsistencies in the literature (i.e., evidence of global vs. specific effects) are likely to reflect several methodological differences across studies, including the characteristics of the examined population (e.g., psychiatric vs. community samples; age range; gender composition), the specific type of sleep disturbance assessed (e.g., trauma-related nightmares, disruptive nocturnal behaviors, general sleep problems) and the type of analysis used (e.g., categorical vs. continuous approaches). Despite these limitations, several studies demonstrated that exposure to family conflicts or adversity during childhood must be considered risk factors and predictors for sleep disorders, such as primary insomnia, later in life. (Bader et al., 2007a; Bader et al., 2007b; Bernert et al., 2007; Chapman et al., 2011; Gregory et al., 2006; Noll et al., 2006). Koskenvuo et al. (Koskenvuo et al., 2010) emphasized the relationship between the child-parent relationship and the poor quality of sleep in a population study of 26,000 Finns. In this case, the risk of poor quality of sleep was considerably increased among those with both poor relationships with parents and multiple childhood adversities. Those with poor child-mother relationships and multiple adversities reported poor sleep 10 times more often than those with good relationships and no adversities (Koskenvuo et al., 2010). Similarly, it has been shown that physical, emotional, and sexual abuse are all critical risk factors for the development of sleep disturbances and poor sleep quality in adults (Bader et al., 2013; Chapman et al., 2013; Greenfield et al., 2011; Ramsawh et al., 2011).

All these stressful events experienced during sensitive periods of development might fundamentally alter the neuroendocrine system that regulates both the stress system and wake-sleep cycle, leading to chronic sleep problems (Figure 2). Hypervigilance (i.e., hyperarousal) has been described to be a characteristic of subjects with adverse early life experiences, and it can persist for many years and may never fully remit. Hypervigilance in traumatized individuals may reflect the promptness and preparation to deal with potentially negative events. In other words, it may be considered an adaptive process of the organism resulting from the persistence of stress-related neurophysiologic patterns, e.g., chronically elevated levels of catecholamines (Otte et al., 2005), and of HPA axis activity (Perry and Pollard, 1998). Dysregulation of the HPA axis may thus be the link between adverse childhood experiences and adult insomnia (Bader et al., 2013; Bader et al., 2007a; Bader et al., 2007b; Chapman et al., 2013; Chapman et al., 2011; Koskenvuo et al., 2010).

Few studies have investigated whether gender affects the relationship between early trauma and sleep disturbances (Calhoun et al., 2014; Steine et al., 2012). Early life events and adult sleep disorders in women are of particular interest because females are more frequently victims of sexual abuse. Consequently, females abused during childhood are more prone to develop several types of physical and psychological alterations, among which sleep problems (e.g., difficulty maintaining sleep and excessive daytime sleepiness) are often reported (Elliott and Briere, 1992; Hulme, 2000; Kelly, 2010; Noll et al., 2006). In particular, a couple of studies (Lind et al., 2016; Noll et al., 2006) showed that childhood abuse represents an important predictor of sleep disturbances up to 25-30 years after the stressful event and that the occurrence of these hypnic disturbances was higher in females than in males.

Altogether, human and animal studies sustain the hypothesis of the latency model. The essence of the latency model is that specific biological factors (e.g., low birth weight) or developmental opportunities (e.g., adequate exposure to spoken language) at critical/sensitive periods in (early) life have a lifelong impact on health and well-being, regardless of subsequent life circumstances. In line with this theory, most of the crucial elements of emotional control, peer social skills, and language development has critical periods in the first five years of human life (Hertzman, 1999). Since early-life events may entail multiple sleep disorders and disturbances later in life, the correct development of the wake-sleep cycle can also be included in the latency model (Koskenvuo et al., 2010). Therefore, sleep may be thought of as an important mediator of the association between childhood trauma and poorer health outcomes.

4. EPIGENETICS AS A TARGET FOR THE CURE OF LONG-TERM SLEEP DISTURBANCES

The studies so far discussed suggest that early-life stress can be related to the development of insomnia and other sleep derangements in newborns and later in adult life (Palagini et al., 2015), producing long-lasting amplifications in stress reactivity through an alteration of HPA axis activation. In this respect, negative life events could activate arousal-regulating systems inducing a condition of "hyperarousal" that leads to the development of sleep disturbances with an evolution to chronic insomnia. As stated above, epigenetic mechanisms may have a crucial role in connecting prenatal stress, HPA dysfunction, and adult phenotype alterations (Figure 2 and Table 1). Thus, considering that the reversibility of epigenetic modifications affecting HPA axis activity (e.g., through modulation of hippocampal GR expression) has been proved (Weaver et al., 2004; Weaver et al., 2005), it might be possible to speculate that the injection of drugs acting on epigenetic machinery (epidrugs) could repristinate the normal HPA axis activity in adults, eventually restoring a normal sleep pattern.

A general classification of epidrugs is to consider them as either broad reprogrammers or targeted therapies. Among these, there are DNA methyltransferases (DNMT), bromodomain and extra terminal (BET), and histone deacetylase (HDAC) inhibitors. These agents have wide and dramatic effects on gene expression and effectively alter the epigenetic cell signature. Nowadays, potential applications for epidrugs arise in cancer, cardiovascular, neurological, and metabolic diseases, which tend to have complex phenotypes and epigenetic dysregulations (Naveja and Medina-Franco, 2017). For instance, BET inhibitors have already been tested in preclinical studies against heart failure, inflammatory processes, and HIV reactivation, with promising results. Furthermore, HDAC inhibitors showed promising results in murine models of Alzheimer's disease. Concerning metabolic diseases, some advances have resulted from studying epigenetic targets for diabetes and obesity treatments, particularly HDACs, histone acetyltransferases (HATs), DNMTs, and protein arginine methyltransferase (PRMTs) (Naveja and Medina-Franco, 2017).

So far, no epidrugs for treatment of sleep disorders have yet been proposed or tested.

An alternative strategy to prevent or reduce sleep disturbances may be to reinforce the capacity to regulate stress responses, specifically in expectant mothers. Some studies have already suggested to adopt psychological interventions to reduce stress during pregnancy or breastfeeding time in order to reduce the risk of developing psychopathology or other negative medical outcomes. Among others, mindfulness-based, music, or psychological and support intervention represent strategies experimentally proved to reduce stress, anxiety and depression in pregnant women (Corbijn van Willenswaard et al., 2017; San Lazaro Campillo et al., 2017; Vieten et al., 2018). Unfortunately, no information is currently available on possible long-term effects of these strategies on adult sleep phenotype of offspring.

5. SUMMARY

Stress is an adaptative response aimed at restoring body homeostasis and facing ambient challenges. The classical neuroendocrine stress response involving the activation of the HPA axis produces a plethora of different physiological effects, with different interactions occurring at multiple levels. Among others, the wake-sleep cycle and circadian rhythmicity are two physiological aspects that are intimately linked to stress levels. Indeed, it is known that each actor of the HPA axis (CRH, ACTH and cortisol) can interfere with the physiological wake-sleep cycle either directly or indirectly through the modulation of endogenous circadian rhythmicity. In the present review we first reported a series of studies performed on humans and rodents showing the different sleep effects exerted by each component of the HPA axis and, then, we highlighted how acute or chronic HPA axis activation differently modulates the wake-sleep cycle. In addition to these well-characterized aspects, a new and interesting research field deals with the relationship between sleep and stress on a different (longer) time scale. A growing body of evidence shows that the exposure to perinatal stress, probably through epigenetic modulations, is sufficient to cause persistent sleep derangements during adult life. In light of this evidence, the main message of the present review is that the complex relationship between sleep and stress changes dramatically on the basis of the time scale considered and, consequently, “time” should be considered as a critical factor when facing this topic.

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FIGURE CAPTIONS

Figure 1. Effects of perinatal stress on development and activity of the hypothalamic-pituitary-adrenal axis. (NO COLOR)

The diagram highlights the link between early-life stress exposure (in utero life and lactation period) and the developmental alteration of the hypothalamic-pituitary-adrenal (HPA) axis in newborns. The most interesting hypothesis about this relationship is that increased maternal cortisol levels produce downregulation of glucocorticoid receptors (GRs) in the infant hippocampus. The persistent low level of GRs in the stressed hippocampus limits the physiological negative feedback role (thin dotted line) that this brain structure exerts on the HPA axis. Because of this interrupted negative feedback regulation, the HPA axis of newborns that have been perinatally exposed to stress results persistently hyperactivated and the level of circulating cortisol is abnormally elevated.

Figure 2. Early-life stress exposure and adult sleep disorders. (NO COLOR)

Graphical representation of the hypothesis linking perinatal (in utero life and lactation period) stress exposure to sleep disorders in adult life. According to available data, one possible explanation for these long-term effects of stress is that perinatal stress, through the epigenetic downregulation of glucocorticoid receptors (GRs) in the newborn hippocampus, deregulates the hypothalamic-pituitary-adrenal (HPA) axis activity (Figure 1). The epigenetic modulation of hippocampal GRs and, consequently, the HPA axis alteration may persist until adulthood thus predisposing the subject to develop sleep disorders such as insomnia.

Table 1. Epigenetic inheritance systems

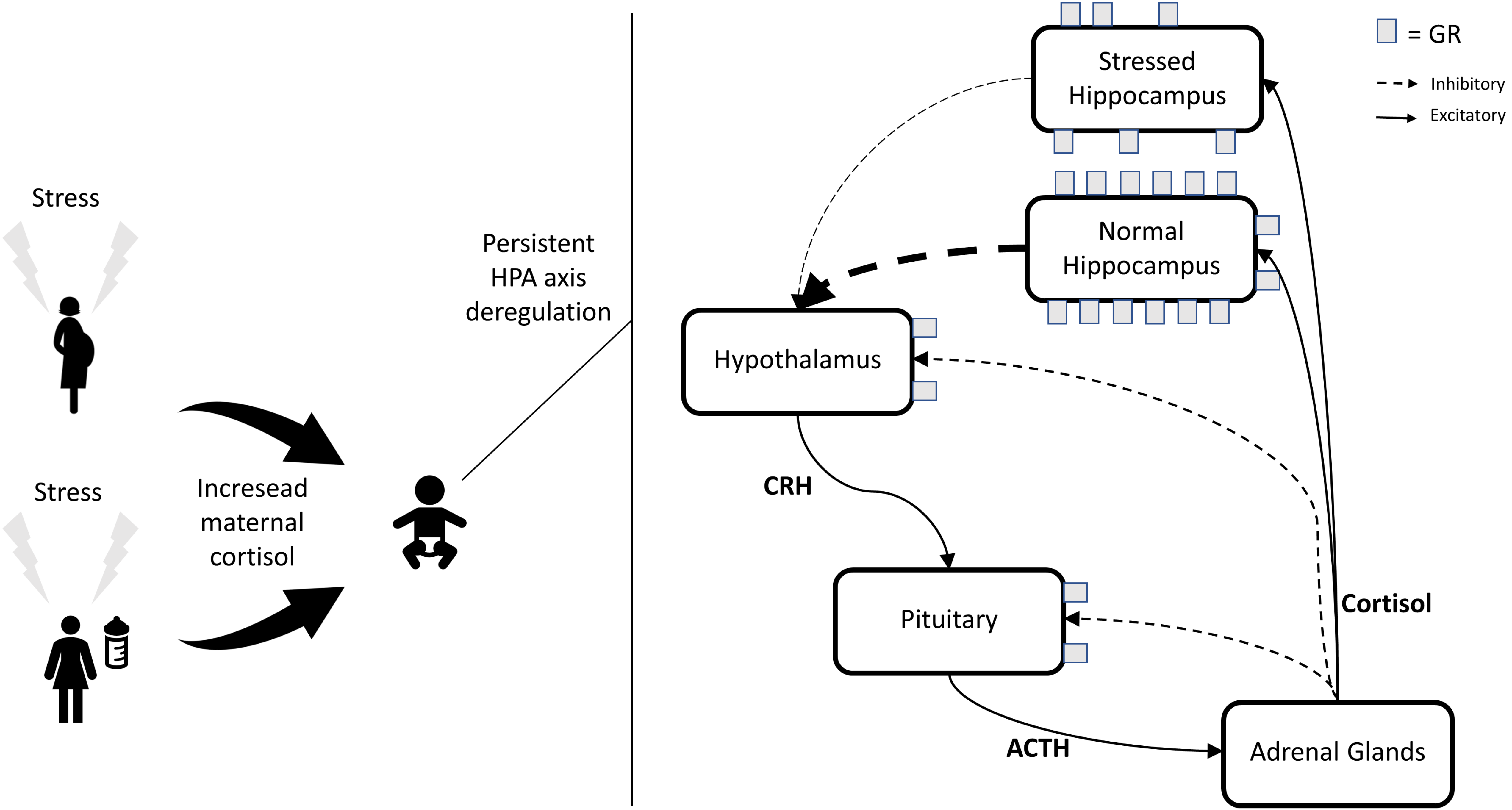
Mechanisms	Level of Action	Way of Action
DNA Methylation and Demethylation	Chromatin Remodelling	Addition or Removal of Methyl (CH3) groups to specific DNA sites. The DNA methylation (or demethylation) increases (or decreases) gene expression
Histon Acetylation and Deacetylation	Chromatin Remodelling	Addition or Removal of acetyl (COCH3) groups to histons. Histon deacetylation (or acetylation) decreases (or increases) gene expression through DNA rolling (or unrolling)
Non-Coding RNAs (such as miRNA and siRNA)	Chromatin Remodelling + Post-Transcriptional Level	Direct modulation of proteins involved in DNA (de)methylation and histon (de)acetylation systems *or* Downregulation of gene expression inhibiting specific complementary mRNA

The table shows a brief description of the level and way of action of the main epigenetic mechanisms modulating gene expression in human and rodent cells.

Table 2. Effect of hypothalamic-pituitary-adrenal axis mediators on the wake-sleep cycle.

Substance	Species	Wakefulness	NREM sleep	REM sleep
CRH	*Humans*	↑	↓	↑
	Rodents	↑	↓	↓
ACTH	*Humans*	↑	↓	=
	Rodents, Cats and Rabbits	↑	↓	↓
CORTISOL / CORTICOSTERONE	*Humans*	=	↑	↓
	Rodents	↑↓	↓	=

The table summarizes the effect (increased, decreased or unchanged amount, respectively ↑, ↓. =) on wakefulness, non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep exerted by corticotropin releasing hormone (CRH), adrenocorticotropin hormone (ACTH) and cortisol (or corticosterone for rodents).


Stress
Stress
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maternal
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Persistent
HPA axis
deregulation
= GR
Inhibitory
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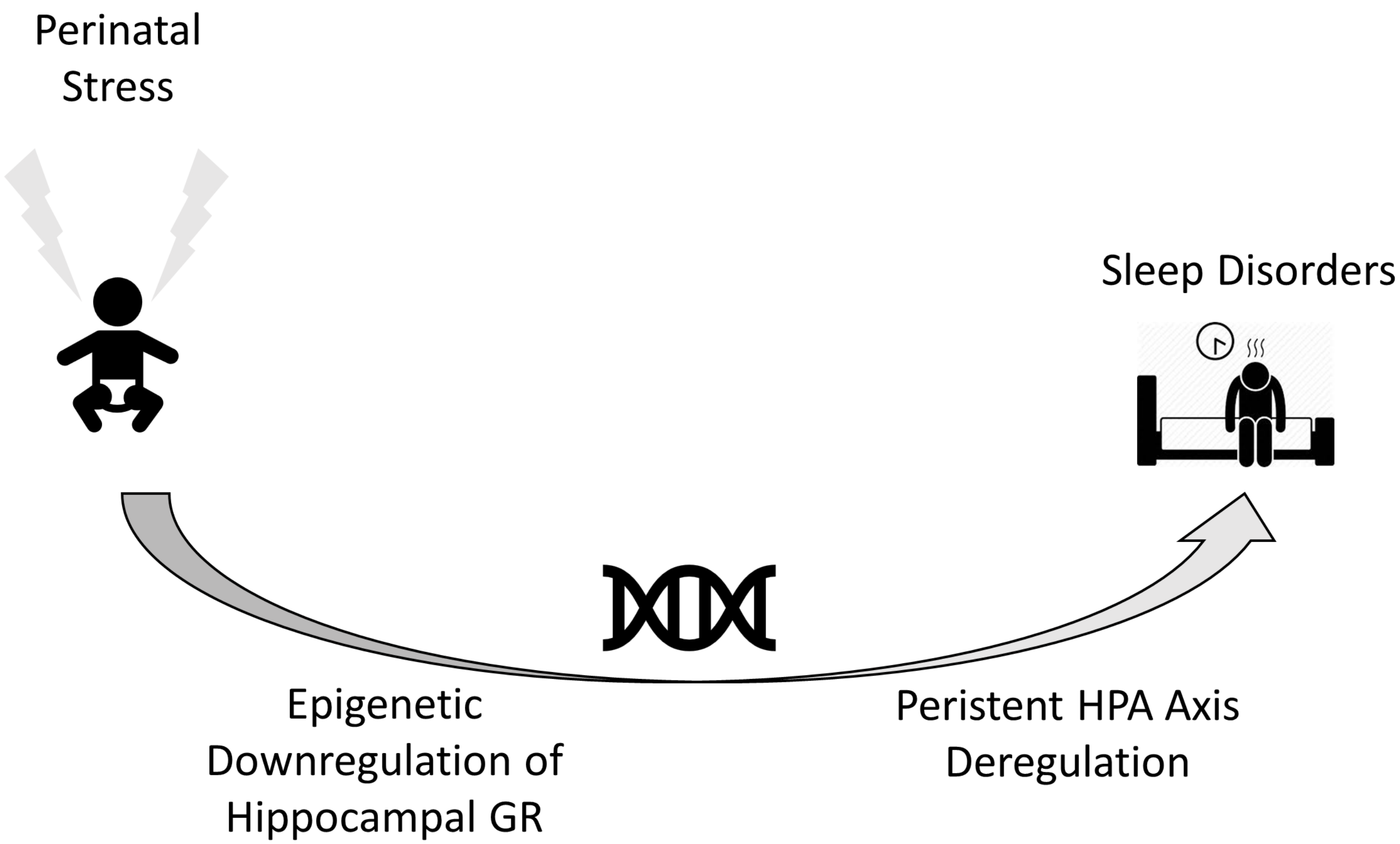
Stressed
Hippocampus
Normal
Hippocampus
Hypothalamus
CRH
Pituitary
ACTH
Adrenal Glands
Cortisol



Perinatal Stress
Sleep Disorders
Epigenetic Downregulation of Hippocampal GR
Peristent HPA Axis Deregulation