Research report

Novel environment induced inhibition of corticosterone secretion: physiological evidence for a suprachiasmatic nucleus mediated neuronal hypothalamo-adrenal cortex pathway

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Abstract

Basal plasma ACTH and corticosterone levels are controlled by the suprachiasmatic nucleus (SCN), the site of the circadian pacemaker, resulting in a daily peak in plasma corticosterone and ACTH. The present study was carried out to investigate the mechanisms employed by the biological clock to control these hormones. Novel environment induced changes in plasma ACTH and corticosterone in intact and SCN-lesioned animals were employed as experimental approach. Placing intact animals in a new environment results in different plasma corticosterone and ACTH responses depending on the clock time of the stimulus. (1) Novel environment (2 h after onset of darkness (ZT14)) results in a fast decrease followed by an increase in corticosterone. This changing pattern in corticosterone secretion was not accompanied by any change in plasma ACTH, suggesting a direct neuronal control of the adrenal cortex. (2) In contrast, novel environment at 2 h after light onset (ZT2) results in a rapid increase in plasma ACTH. Regression analysis of the relation ACTH-corticosterone before and after stress shows a changed pattern at ZT2, although at that time still no significant correlation between ACTH and corticosterone was detected. AT ZT14 this correlation was only present after stress. (3) SCN lesioning results in low basal ACTH at all circadian times combined with elevated corticosterone levels. Here, a new environment results in an immediate increase in corticosterone without inhibition; ACTH also increases rapidly, but attains lower levels than at ZT2 in intact animals. (4) The present results therefore demonstrate SCN modulating corticosterone secretion by affecting ACTH secretion and changing the sensitivity of the adrenal cortex by means of a neuronal input.

Keywords: Corticosterone; ACTH; Suprachiasmatic nucleus; Adrenal cortex; Circadian; Stress; Paraventricular nucleus

1. Introduction

The suprachiasmatic nucleus (SCN) is responsible for a circadian variation in plasma ACTH and corticosterone levels [28,29,35]. Only recently have we begun to understand the anatomical pathways, transmitters and mechanisms that serve this function [5,21,40]. With regard to the control of the hypothalmo-pituitary-adrenal-axis (HPA), recent studies have uncovered that the SCN has both a strong inhibitory action on corticosterone secretion mediated by vasopressin, and a subtle stimulatory role, which is only apparent during the diurnal surge of plasma corticosterone [4,6,20,22,23]. Furthermore, circadian changes in the sensitivity of the rat adrenal cortex to ACTH were already described more than a decade ago [1,10,12,25]. These early studies indicated that the adrenal is more sensitive to adrenocorticotropin hormone (ACTH) at the end of the inactive period [2,11,24,25]. Studies on calves have also indicated that stimulation of the splanchnic nerve, which provides the adrenal with sympathetic information, only results in cortisol secretion if a basal level of ACTH is present [10]. Recently, Dijkstra et al. [9] and Jasper and Engelbert et al. [19] provided evidence that the diurnal pattern of high corticosterone secretion is at least partly due to a CNS influence on the adrenal cortex, mediated by the splanchnic nerve. The highest sensitivity of the adrenal cortex coincides with the diurnal elevation of plasma ACTH. In the experiments of Dijkstra et al. [9], for which a splanchnic nerve transection was used, the adrenal cortex sensitivity hypothesis is challenged. They proposed a diurnal drive by the CNS upon the adrenal cortex; together, the increased ACTH level and the CNS
influence on the adrenal would result in a diurnal surge of plasma corticosterone at the end of the inactive period. However, stress-induced secretion of ACTH is more pronounced when basal levels of ACTH and corticosterone are at an absolute minimum in the early inactive (light) period, which seems to contradict the setting of the adrenal [2,8,17,30]. In the present study, we showed that the processing of this stress input by the SCN is responsible for this discrepancy. Here, we utilized intact, SCN-lesioned and adrenalectomized animals which were subjected to a novel environment as a mild (psychological) stress at different moments of the light–dark cycle.

2. Material and methods

Male Wistar rats of 150–200 g housed individually in humidity- and temperature-controlled 12:12 h light–dark L/D rooms had food and water available ad libitum. All of the following animal experiments were conducted under the approval of the Animal Care Committee.

A bilateral lesion of the SCN was carried out under Hypnorm anesthesia (Duphar 0.4 ml/kg i.m.). The animals were mounted in a David Kopf stereotact (tooth bar +5) and sustained an SCN lesion using bilateral lesion electrodes, 0.2 mm diam, with temperature set at 85°C for 1 min (lesion generator, Radiotronics). This temperature was found empirically to result in lesions large enough to eliminate the SCN bilaterally, but small enough to leave the surrounding tissue and PVN intact [4]. For the control group, intact animals were used that underwent the same surgery without heating the electrodes. After the surgery the animals received an i.m. injection of buprenorphine to relieve post-operative pain. In the following 3–5 weeks, the effectiveness of the lesion was checked continuously by measuring water intake and activity during the light vs. dark period. If the animals drank between 40 and 60% of their daily water consumption for 8 h during the 12 h light period, and if they showed complete arrhythmia of activity under L/D conditions, they were considered to be SCN-lesioned animals and were used for further study. Typically intact animals drank between 0–5% of their daily water consumption during the light period. Having reached a weight of 300 g, intact and arrhythmic animals were implanted with a permanent silicone catheter in the jugular vein, again under Hypnorm anesthesia. After this operation the animals were handled daily for 5 days a week until the end of the experiment. Once a week the animals were routinely transferred to a clean cage. For adrenalectomy the animals were anesthetized with a combination of hypnorm and valium. Together with the bilateral adrenalectomy the animals received the jugular vein catheter. Adrenalectomized animals had free access to fresh water and to 0.9% saline to compensate for the loss of minerals. All experiments started 1–2 weeks after the last operation and were conducted once or twice a week with an interval of at least 3 days between each experiment up to a total of four experiments per animal. During the experimental weeks the animals were continuously connected to a swivel that allowed remote blood withdrawal without touching the animal but did not hinder the animal in its movements. At the beginning of the experiment (4 h before (ZT20), 2 h after light on (ZT2), or 2 h after light off (ZT14)), the animal was removed from its home cage (25 × 25 × 30 CM) and transferred to an identical clean experimental cage, the only difference being that there was no sawdust on the floor. A blood sample (0.2 ml) was taken before (t = 0) and 5, 15, 30 and 60 min after the animal had been taken from its home cage and placed in the experimental cage. The same amount of saline solution (0.2 ml) was replaced intravenously each time after blood withdrawal, to make up for the loss of volume.

Blood samples were collected in heparinized tubes placed on ice and centrifuged, and plasma was stored at −20°C until assay. Plasma ACTH and corticosterone was measured directly without extraction using a radioimmunoassay from ICN Biomedicals (Costa Mesa, CA) with iodinated ACTH or corticosterone. The interassay coefficient of variation for corticosterone was 10.2% and for ACTH 11.7%. The detection limit for ACTH is 10 pg/ml ED50 = 60 pg/ml and ED80 = 15 pg/ml for Cort 10 pg/ml, 60 pg/ml and 12 pg/ml, respectively.

After the completion of the experiment, SCN-lesioned animals were perfused intracardially under deep pentobarbital anesthesia with 4% paraformaldehyde. After 48–72 h post-fixation, the hypothalamus was sectioned on a Vibratome, and 50-μm sections were stained for vasoressin (VP) or vasoactive intestinal peptide (VIP) alternatingly. All antibodies were raised in the Netherlands Institute for Brain Research and the immunocytochemical staining procedure was already described in detail previously [4,5]. VP and VIP staining was examined in the SCN area and the region of the paraventricular nucleus of the hypothalamus in dorsomedial nucleus of the hypothalamus (PVN-DMH). If the animals had cell bodies that stained positively for either VP or VIP in the region of the SCN or around the border of the lesion, they were considered partial SCN lesions.

All results are expressed as mean ± S.E.M. Multivariate analysis of variance (MANOVA) with repeated measurement design was used to determine the effect of the new environment stress at the various time periods and of the SCN lesions. When MANOVA detected a significant effect, this was followed by a Student Newman–Keuls posthoc procedure to assess the specific time points of the difference. The significance of the new environment induced variation in plasma corticosterone and ACTH values (time dependency) was assessed using a one-way ANOVA with repeated measures. If significant, ANOVA was followed by Student’s paired t-test. For multiple comparisons the Bonferroni correction was used. P = 0.05 was accepted as the level of significance.
3. Results

Only nine animals of the 25 that had sustained a lesion of the SCN appeared to have a complete SCN lesion, as was evident from lack of diurnal variation in (a) their water consumption, i.e. 40–60% during 8 h in the 12 h light period, (b) their activity as assessed by infrared movement detection [22] remained completely disrupted, also under L/D conditions 6 weeks after the lesion, and (c) the absence of VP or VIP immunocytochemical staining of the SCN area after the experiment was finished (see [4]). The activity recordings appeared to have an accurate predictive value for the determination of the completeness of the lesion. Only one case, a lesion that had spared a small rostral part of the SCN, was not detected by the activity record as an incomplete one. The data of this animal were not used for further analysis. With respect to the corticosterone curves, MANOVA indicated clear effects of group (F(5,48) = 6.94, P < 0.001), time (F(4,192) = 48.65, P < 0.001) and ‘group × time’ (F(20,192) = 6.01, P < 0.001). For ACTH, MANOVA also indicated clear effects of group (F(4,40) = 6.18, P < 0.001), time (F(4,160) = 22.12, P < 0.001) and the interaction of ‘group × time’ (F(16,160) = 6.39, P < 0.001). Further details of the tests of significance are given in the legends of Figs. 1–7.

Placing animals in a new environment generally resulted in the same kind of behavior irrespective of the moment of the light–dark cycle. All animals reared on their hind paws and moved around actively in their new cage for ≈10–15 min. At ZT2 intact animals resumed their sleeping position, while at ZT14 the activity turned back to normal basal levels. Only ADX animals defecated several times after their move to a new cage. SCN-lesioned animals, in contrast, remained active during the whole 60 min of the duration of the experiments.

After exposure to the new cage, plasma corticosterone increased in all animals and reached a maximum at 30 min. In all animals, this maximum differed significantly from the level at t = 0 min. At ZT2 the new environment resulted in plasma corticosterone levels reaching significantly higher levels than at ZT14 and at ZT20 (Fig. 1A). At no moment of the light–dark cycle did any of the intact animals show an increase in plasma corticosterone during the first 5 min (Fig. 1A). In fact, when basal corticosterone levels were elevated (at ZT14), placing the animals in a new environment at that time resulted in a highly significant decrease of plasma corticosterone within 5 min after their transfer (Fig. 1A). Experiments conducted at ZT20 also showed a similar decrease, but this decrease did not reach statistical significance, probably because of lower basal levels at that time point (Fig. 1A).

The pattern of ACTH secretion as a response to a new environment showed quite different profiles. At ZT14, no significant change whatsoever could be detected in the ACTH profile (Fig. 1B). At ZT20, only t = 15 was significantly different from t = 0 (P < 0.0125), while at ZT2 a clear increase in ACTH could already be demonstrated after 5 min in a new cage (Fig. 1B) (P < 0.025) (see for significance also the legends to the figures). Basal plasma corticosterone levels of SCN-X animals were significantly elevated as compared to intact animals at ZT2, but were at approximately the same level as those of the intact animals at ZT14 (Fig. 2A). Interestingly, basal ACTH levels of SCN-X animals as determined at t = 0 were significantly below ZT14 and at the same level as ZT2 ACTH (Fig. 2B). In contrast to intact animals at ZT14, SCN-X animals showed an increase in ACTH secretion, but much less so at t = 15 and t = 30 than at ZT2 (Fig. 2B). SCN-X animals were tested at ZT14 but showed the same response when they were tested at ZT2 (data not shown; see also [4]). SCN-X animals showed an increase in seven of the

![Graph A](image1.png)  
**Fig. 1. A,B:** plasma corticosterone (A) and ACTH (B) values after intact rats were placed in a new cage at three different circadian times. 2 h after light onset (ZT2, n = 8), 2 h after dark (ZT14, n = 15) and 4 h before lights on (ZT20, n = 8). Single-factor ANOVA revealed time-dependent significant effects for all curves P < 0.001, except for ACTH release during a ZT14 new environment exposure P > 0.52. A: Student-Newman-Keuls indicated significant differences at t = 0 between ZT2 and ZT14. The paired Student’s t-test indicated a significant difference between t = 0 and t = 5 only at ZT14 when the new cage resulted in a highly significant decrease in plasma corticosterone values (P < 0.0025) (see also Fig. 3). At t = 15 ZT2 and ZT20 differed significantly from 0, t = 30 differed significantly from t = 0 at all circadian time points. B: for the plasma ACTH values the paired Student’s t-test revealed no differences at ZT14; at ZT20 only t = 15 differed significantly from t = 0, P < 0.0125. At ZT2 all time periods differed significantly from t = 0, P < 0.0025.
nine animals 5 min after placement in a new environment (Fig. 3). In contrast to this is the small but highly significant decrease of plasma corticosterone in intact animals at ZT14, as demonstrated by the individual values (Fig. 3), which illustrates that the responses following SCN lesioning show a much greater variability. Control blood sam-

Fig. 3. The presentation of paired samples of intact ($n = 18$) or SCN-lesioned animals ($n = 9$) subjected to a novel cage at ZT14. Of the intact animals 16 show a decrease, one an increase, and one remains stable. Note that also when the plasma level is already low, still a decrease can be observed. In contrast, only two of the nine SCN-lesioned show a decrease.

Fig. 4. Plasma corticosterone values after SCN-lesioned rats had been placed in a new cage at $t = 0$ (SCN-X new), as compared to intact animals (intact crtr) ($n = 10$) and SCN-X (SCN-X crtr) animals ($n = 9$) that were only subjected to the blood sampling protocol. The circadian time of the experiment was at ZT14. When analyzed by a single-factor ANOVA, only the SCN-lesioned animals in a new environment showed significant time-dependent changes ($P < 0.001$).

Fig. 5. Illustrates the lack of habituation of intact animals for the novel cage with corticosterone values at ZT2 (A) and ZT14 (B). It compares the curves of intact animals that received the protocol of blood sampling and a novel environment for the first time to those of intact animals that already been exposed twice or more to this protocol. A: MANOVA did not find any significant differences between the animals that were tested for the first time ($n = 8$) and those that had been tested repeatedly ($n = 10$). B: MANOVA detected no significant difference between the newly ($n = 10$) and repeatedly tested animals ($n = 8$). However, the interaction effect (group vs. time) did reach significance, due to the first and last value. If animals are tested closer to the circadian peak, it is obvious that this affects especially the first and the last value. Both curves, however, show a highly significant decrease at $t = 5$, which is again illustrative of the novel cage induced inhibition.
Fig. 6. Illustrates the relationship between the influence of the new environment at ZT14 on ACTH levels in adrenalectomized animals (ADX) as compared to control blood sampling without new cage. Single-factor ANOVA to reveal time-dependent changes revealed no significant effects in either of the two groups: ADX-new $F(4,20) = 1.79, P = 1.71$; ADX-ctr $F(4,20) = 0.40, P = 0.81$. This figure also emphasizes that if anything happens to ACTH values at $t = 5$, it is an increase, as opposed to the decrease in corticosterone that can be seen in intact animals.

Fig. 7. Diagram illustrating regression lines of the relationship between corticosterone and the log of ACTH at ZT2 and ZT14 at $t = 0$ and $t = 15$. These regression lines show a completely different relationship between corticosterone and ACTH at these two different circadian time points, which is evident at basal level, but also after the stress induced increase of these hormones. Illustrative of the absence of correlation at ZT2 between ACTH and corticosterone in the negative correlation at $t = 0$, $r = -0.4002, P = 0.05$, and the absence of correlation at $t = 15$, $r = 0.2987, P > 0.05$. The only regression lines which reached significance were at ZT14 at $t = 15, r = 0.8055 P < 0.005$ and $t = 30, r = 0.830 P < 0.005; t = 60, r = 0.635 P < 0.01$. The presence of nearly horizontal lines at ZT2, $t = 0$, indicated a strong suppressed release of corticosterone under basal conditions, while at ZT14 the nearly vertical line suggests a strongly facilitated release.

4. Discussion

Placing animals in a new environment appears to be a very reliable and reproducible natural stress procedure. Probably because animals are routinely exposed to a change of cages, this response is already habituated to the present level as is illustrated by the identical response after first and repeated new environment. The return within 15 min to their previous behavior of intact animals also illustrates their acquaintance with the procedure. That SCN-X animals show a much longer activation is illustrative for the fact that the SCN modulates the activity of intact animals. It is clear that with regard to the corticosterone and ACTH response, the patterns differ completely, depending on the moment in the circadian cycle that the animals are introduced to a new environment, which is illustrative of the separate control of the SCN on ACTH and corticosterone secretion.

Basal plasma levels of corticosterone and ACTH at different times of the L/D cycle in the present study show, as expected [8,22–24], a clear circadian difference. Both ACTH and corticosterone are elevated at ZT14, which confirms the circadian peak of these hormones just before the beginning of the dark period. High basal corticosterone and low ACTH levels of the SCN-X group indicate the differential influence of the SCN on corticosterone and
ACTH: an inhibitory role of the SCN on corticosterone secretion and a permissive role on ACTH secretion. This observation confirms seemingly conflicting previous conclusions that the SCN stimulates ACTH secretion [6], whereas, on the other hand, it inhibits corticosterone secretion [4,20]. The fact that plasma corticosterone levels in SCN-x animals drop as rapidly as in intact animals indicates that the clearance of corticosterone is not changed by SCN lesion.

A direct influence of stress on the adrenal cortex, thus bypassing ACTH secretion, is demonstrated by the present surprising finding that at ZT14 corticosterone levels after new environment stress rapidly decrease. This brief fall in corticosterone is accompanied by stable or even slightly increased ACTH levels. Consequently the most likely explanation for this phenomenon is that an acute inhibition of corticosterone secretion takes place at the level of the adrenal, resulting in an immediate drop in plasma corticosterone. To our knowledge, this is the first time that such an acute decrease in plasma corticosterone has been reported after a stressful stimulus. Other studies indicated a decrease in corticosterone after food or water deprivation [16,41]. However, this fall in corticosterone also coincided with a decrease in plasma ACTH. Since blood flow changes increased corticosterone levels within the order of minutes, but never resulted in a decrease in corticosterone (see [3]), volume redistribution or volume changes can hardly be the cause of these changes. Also, half-life time of corticosterone in blood is relatively short (1–2 min) [13] (see also [41]) and may account for the decrease in corticosterone with stable or even slightly increased ACTH levels. The fact that also at ZT20, 5 min after the change to a new cage, there is a small decrease and that ZT2 shows a steady low level of corticosterone during the first 5 min, indicates that this inhibition may occur at all time points. This corticosterone decrease as result of a new environment is entirely absent in SCN-lesioned animals which show an increase instead. This further emphasizes that this decrease is not the result of possible volume redistributions by the minute blood samples and illustrates that the SCN is implicated in this inhibition. The clear-cut inhibition apparent within 5 min. also warrants a direct central nervous system impact on the adrenal cortex. Descending hypothalamic input to the pre-ganglionic neurons in the spinal cord is the most likely pathway to influence the adrenal by the splanchnic nerve [11,18,36,37]. The high corticosterone and low basal ACTH levels in SCN-lesioned animals also indicate that the reported inhibition of the SCN on corticosterone secretion is outside the HPA axis. The difference in the regression lines showing the changing relation between ACTH and corticosterone at ZT2 compared to ZT14 shows that this inhibition is most strong at ZT2, which is in agreement with recent studies of Kalsbeek et al. [22,23]. A direct inhibitory influence of the CNS on corticosterone secretion was reported by Jasper and Engeland [19], who demonstrated that corticosterone secretion from the adrenal is increased during the diurnal trough after the splanchnic nerve is cut. Consequently, these observations provide physiological evidence for a (multisynaptic) SCN-adrenal cortex pathway comparable to the SCN-pineal pathway (Fig. 8).

The involvement of the SCN in mediating stress input can also be inferred from the fact that switching animals to a new environment is a stimulus which influences the SCN. At CT6 this becomes visible as an immediate phase advance of the circadian rhythm [14,27]. We now demonstrate that this new environment results in a direct, but

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Fig. 8. Diagram with the proposed relationship between the SCN and the dorsal hypothalamus, with special emphasis on the paraventricular nucleus (PVN), subPVN and dorsomedial nucleus of the hypothalamus (DMH). Following this diagram, the SCN is able to modulate corticosterone secretion in three different ways: (1) a direct innervation of spinal cord projecting neurons in the PVN (mainly resulting in an inhibition of corticosterone secretion), (2) a direct innervation of CRH producing neurons (mainly resulting in stimulation of CRH release). The balance between these two pathways will determine the circadian peak and trough in corticosterone secretion. Furthermore, (3) an indirect projection to CRH neurons is proposed. This pathway is able to modulate incoming stress input. The sign indicates the pathways that provide the circadian information to the system. The open arrows indicate the pathways that are activated by a new environment stress. A new environment stress will activate the areas in the dorsal hypothalamus via the brain stem (A1 and A2 area) and amygdala. This stress input will activate CRH neurons directly or indirectly via neurons in the DMH and subPVN. The present study demonstrated that stress also directly activates the adrenal cortex. Stress will also affect the SCN in such a way that, depending on the state of the pacemaker, the result will be an activation of the CRH neurons at ZT2, a modulation of other input to the PVN at ZT14 or a transient activation of the SCN projection to PVN autonomous neurons, resulting in an inhibition of corticosterone secretion. (See for papers that relate to the anatomical and functional connections in this region [5,7,15,32–34,39]).
brief inhibition of corticosterone secretion, which is dependent on the presence of the SCN. Therefore, the present results also illustrate that a novel environment not only affects the pacemaker system of the SCN [27], but also its output. It is likely that information from olfactory bulb, optic system and brain stem conveying new environment information to the SCN plays a major part in this stress, but exact knowledge of the pathways that bring about this change in the SCN is still limited.

In addition to this multisynaptic SCN-adrenal cortex pathway, the present results also demonstrate that the SCN not only is able to set the diurnal peak and trough of plasma ACTH, but also interferes with the stress-induced ACTH response. Basal ACTH levels are increased at ZT14, but in spite of this there is no detectable response to new environment. This pattern agrees with data from several previous studies [2, 17, 30], using other stressors. Yet, the relationship between ACTH and corticosterone at ZT14 results in a highly significant regression line with a very steep angle, indicating that with minimal excursions of ACTH, a high level of corticosterone can be obtained. Thus we are confronted with the paradoxical finding that while at ZT14 basal ACTH levels are elevated, indicating a higher stimulatory input to CRH neurons, the ACTH response to novel environment is not detectable. At ZT2 more or less the reverse is observed, i.e. basal ACTH release is low, but there is a significant increase after stress. This part of the study also confirms earlier data of Bradbury et al. [2], who, as in the present study, showed this lack of ACTH response at ZT14 to be independent of the feedback of corticosterone. In fact, our data on SCN-lesioned animals show that in spite of their sustained high corticosterone level these animals still respond to mild stress with increased ACTH and corticosterone. We therefore propose that in addition to the SCN pathway, which increases ACTH at the end of the inactive period, a second SCN pathway should be present, able to interfere with ascending or descending stress input to the PVN. Such a connection should suppress this stress input to the HPA axis at ZT14 and enhance it at ZT2 (see Fig. 8). These observations argue for an elaborate control mechanism regulating the circadian pattern in ACTH and corticosterone secretion and the way the levels of these hormones respond to stress. We propose that this control mechanism consists of at least three components.

1. An excitatory input from the SCN to (the dendrites of) the CRH neurons [15] for the circadian setting of the basal ACTH level, which can be activated by novelty stress only at ZT2.

2. An input from the SCN to spinal cord-projecting neurons in the PVN for the circadian setting of the responsiveness of the adrenal cortex. This pathway is also activated by novelty stress. This input results in an inhibition of corticosterone secretion. Both the CRH and the spinal cord-projecting neurons can also be indirectly activated by an input from neurons around the PVN.

3. SCN inputs to neurons receiving a stress input in and around the PVN which serves to modulate the stress input to PVN neurons.

The balance obtained by this system is not only influenced by stress, but also by many other environmental and endogenous factors, such as water and food intake, light, time of the day, and glucocorticoid feedback. The present study demonstrates that the SCN is one of the structures through which these factors may reach their effect. It also puts the SCN in the position of integrator between the periphery and the CNS, adding the time of the day information to this incoming peripheral information. Together with its multisynaptic pathway to the adrenal cortex, this integrative function of the SCN may form the basis for an explanation of phenomena, such as discrepancies in ACTH and cortisol levels and failing dexamethasone suppression tests during mental depression and Alzheimer’s disease [26, 31], of which in the latter disease a clear-cut deterioration of the SCN is present [38].

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References


