The stress system in depression and neurodegeneration: Focus on the human hypothalamus

A.-M. Baoa,⁎, G. Meynena,b, D.F. Swaab

aNetherlands Institute for Neuroscience, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands
bGGZ Buitenamstel, Hogguerstraat 1183, 1164 EK Amsterdam, The Netherlands

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ABSTRACT

The stress response is mediated by the hypothalamic-pituitary-adrenal (HPA) system. Activity of the corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) forms the basis of the activity of the HPA-axis. The CRH neurons induce adrenocorticotropin (ACTH) release from the pituitary, which subsequently causes cortisol release from the adrenal cortex. The CRH neurons co-express vasopressin (AVP) which potentiates the CRH effects. CRH neurons project not only to the median eminence but also into brain areas where they, e.g., regulate the adrenal innervation of the autonomic system and affect mood. The hypothalamo-neurohypophysial system is also involved in stress response. It releases AVP from the PVN and the supraoptic nucleus (SON) and oxytocin (OXT) from the PVN via the neurohypophysis into the bloodstream. The suprachiasmatic nucleus (SCN), the hypothalamic clock, is responsible for the rhythmic changes of the stress system. Both centrally released CRH and increased levels of cortisol contribute to the signs and symptoms of depression. Symptoms of depression can be induced in experimental animals by intracerebroventricular injection of CRH. Depression is also a frequent side effect of glucocorticoid treatment and of the symptoms of Cushing’s syndrome. The AVP neurons in the hypothalamic PVN and SON are also activated in depression, which contributes to the increased release of ACTH from the pituitary. Increased levels of circulating AVP are also associated with the risk for suicide. The prevalence, incidence and morbidity risk for depression are higher in females than in males and fluctuations in sex hormone levels are considered to be involved in the etiology. About 40% of the activated CRH neurons in mood disorders co-express nuclear estrogen receptor (ER)-α in the PVN, while estrogen-responsive elements have been found in the CRH gene promoter region, and estrogens stimulate CRH production. An androgen-responsive element in the CRH gene promoter region initiates a suppressing effect on CRH expression. The decreased activity of the SCN is the basis for the disturbances of circadian and circannual fluctuations in mood, sleep and hormonal rhythms found in depression. Neuronal loss was also reported in the hippocampus of stressed or corticosteroid-treated rodents and primates. Because of the inhibitory control of the hippocampus on the HPA-axis, damage to this structure was expected to disinhibit the HPA-axis, and to cause a positive feedforward cascade of increasing glucocorticoid levels over...
time. This ‘glucocorticoid cascade hypothesis’ of stress and hippocampal damage was proposed to be causally involved in age-related accumulation of hippocampal damage in disorders like Alzheimer’s disease and depression. However, in postmortem studies we could not find the presumed hippocampal damage of steroid overexposure in either depressed patients or in patients treated with synthetic steroids.

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1. Introduction

1.1. The stress system

1.1.1. The HPA-axis

As pointed out for the first time by Hans Selye in Nature in 1936 (Selye, 1998), stress or ‘noxious agents’ initiate a reaction in the body, which he called the ‘general adaptation syndrome’ (GAS). Selye distinguished three stages that the body passes when responding to stress in the GAS: 1) the first stage is an ‘alarm reaction’, in which the body prepares itself for ‘fight or flight’; 2) the second stage of adaptation (provided the organism survives the first stage), is one in which a resistance to the stress is built; and 3) finally, if the duration of the stress is sufficiently long, the body enters a stage of exhaustion, a sort of aging, due to ‘wear and tear’. Although the stress response of the body is meant to maintain stability or homeostasis, long-term activation of the stress system can have a hazardous or even lethal effect on the body, increasing the risk of obesity, heart disease, depression, and a variety of other illnesses.

The hypothalamo–pituitary–adrenal (HPA) system is the final common pathway in the mediation of the stress response. Briefly, the hypothalamus releases corticotropin-releasing hormone (CRH) in response to a stressor, CRH acts on the pituitary gland, triggering the release of adrenocorticotropic (ACTH) into the bloodstream, which subsequently causes the hormonal end-product of the HPA-axis, corticosteroid release from the adrenal cortex (mainly cortisol in humans). Cortisol normally exerts a negative feedback effect to shut down the stress response after the threat has passed, acting upon the levels of the pituitary and hypothalamus. Cortisol is a major stress hormone that acts on many organs and brain areas through two types of receptors, i.e. the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), which have a specific and selective distribution in the brain (Reul and de Kloet, 1985). GRs have been found in multiple brain regions such as the hippocampus, amygdala and prefrontal cortex, which are relevant to cognition. These regions are also actively involved in feedback regulation of the HPA-axis. Moreover, stimulation by corticosteroids can be exerted at the level of the amygdala, the prefrontal cortex and the brain stem (locus coeruleus), interfering with HPA activity and stress effects on memory (Quirarte et al., 1997; Roozendaal, 2002; Fuchs et al., 2004). CRH-expressing neurons in the hypothalamic PVN project not only to the median eminence but also to other brain areas, where they regulate the adrenal innervation and thus the sensitivity of the adrenal for ACTH via the autonomic system (Buijs and Kalsbeek, 2001). Besides the role of a crucial neuropeptide which regulates the HPA-axis, CRH also shows
central effects, including cardiovascular regulation, respiration, appetite control, stress-related behavior and mood, cerebral blood flow regulation and stress-induced analgesia (for review see [Swaab, 2003]). Part of the CRH neurons in the hypothalamic PVN co-express arginine vasopressin (AVP). When released together into the portal capillaries, AVP strongly potentiates the ACTH-releasing activity (Gillies et al., 1982; Rivier and Vale, 1983). In addition, circulating AVP from the supraoptic nucleus (SON) may induce ACTH release from the pituitary (Gispen-de Wied et al., 1992).

CRH and AVP mediate ACTH release via different second messenger systems (Won and Orth, 1990; Won et al., 1993, 1990). CRH activates G protein-linked adenylate cyclase, leading to cAMP formation and protein-kinase-A activation. AVP works through a specific AVP receptor subtype termed V1b or V3, which is almost exclusively expressed by pituitary corticortrophs (Rene et al., 2000), and activates only phospholipase C. The V3 receptor is required for a normal pituitary and adrenal response to some acute stressful stimuli, and is necessary for a normal ACTH response during chronic stress (Lolait et al., 2006). The number of CRH and AVP-colocalizing neurons is increased during activation, such as in multiple sclerosis (MS) (Erkut et al., 1995), depression and during the course of aging—at least in males (Radsheer et al., 1993, 1994b; Bao and Swaab, 2007). V3 receptor mRNA levels and coupling of the receptor to phospholipase C are stimulated by glucocorticoids. Consequently, AVP up-regulation may be critical for sustaining the corticotrophic responsiveness in the presence of high circulating glucocorticoid levels during chronic stress or depression (Aguilera and Rabadan-Diehl, 2000). Oxytocin (OXT), on the other hand, inhibits ACTH release, a finding that has been confirmed in humans (Legros, 2001) and that provides an example of the various opposite actions of AVP and OXT. Following different types of corticosteroid treatment in different disorders or during the presence of high levels of endogenous corticosteroids produced by a tumor, we found, in postmortem tissue, not only that CRH-expressing neurons are hard to detect, but also that AVP expression in the SON and PVN is strongly decreased. OXT neurons were not affected, which further illustrates that, in the human brain, selective negative-feedback of cortisol is present in the CRH cells and in cells that co-express AVP (Erkut et al., 2004, 1998). The glucocorticoid-induced suppression of AVP-synthesis has been proposed to occur at the posttranscriptional level (Erkut et al., 1998, 2002b).

1.1.2. HPA–HPG-axis interaction

Stress suppresses the reproductive system at various levels: CRH prevents the release of the hypothalamic luteinizing hormone-releasing hormone (LHRH=GnRH) which signals a cascade of hormones that direct reproduction and sexual behavior. Cortisol and related glucocorticoid hormones not only inhibit the release of LHRH, but also inhibit LH-induced ovulation and sperm release. In addition, glucocorticoids inhibit the testes and ovaries directly, hindering production of the male and female sex hormones (Swaab, 2003). CRH fibers from the PVN do not only run to the portal capillaries but also innervate LHRH neurons in the infundibular nucleus, which may be one of the substrates for CRH control of reproductive functions (Dudas and Merchenthaler, 2003). On the other hand, the hypothalamic-pituitary–gonadal (HPG) axis also exerts extensive effects on the HPA-axis. Sex hormones partially control CRH gene expression. Both the nuclear estrogen receptor (ERα) (Bao et al., 2005) and the nuclear androgen receptor (AR) (Bao et al., 2006) are found to be colocalized with CRH neurons in the human hypothalamic PVN. In addition, an up-regulation of CRH and nuclear ERα was observed in mood disorders, both in males and females (Bao et al., 2005). There are five perfect half-palindromic estrogen-responsive elements (EREs) in the human CRH gene region, which may confer direct estrogenic regulation of human CRH gene expression (Vamvakopoulos and Chrousos, 1993). An androgen-responsive-element (ARE) that initiates a repressing effect of AR on CRH gene expression in the human CRH gene promoter region has also been localized recently (Bao et al., 2006).

Ovarian steroids have been found to increase HPA-axis activity, enhance the HPA-axis response to psychological stress, and sensitize the HPG-axis to stress-induced inhibition in human and rhesus monkey (Kirschbaum et al., 1996; Roy et al., 1999).

1.2. Sex and age differences in the stress system

Sex-related differences in the stress response are well-known from the animal experimental literature, but in humans the findings seemed inconsistent, probably, at least partly, due to the different methods used to stimulate the HPA-axis and to the age of the subjects. Gender-related differences in sex hormone levels further confound the specific role of the gender in HPA-axisresponsivity. Over the past decade, however, the situation has become much clearer as a result of the development of psychological tests that generate adequate HPA-axis responses, for example the Trier Social Stress Test (Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Kudielka and Kirschbaum, 2005). The conclusion of these studies is that sex differences in the basal, unstressed state are subtle but become greatly pronounced following a psychological stressor. Although there are exceptions, in general between puberty and menopause, the HPA-axis and autonomic responses tend to be lower in women compared to men of the same age (Kajantie and Phillips, 2006). Recently, Rocca et al. have found that, compared with age-matched women, young to middle-aged (18–45 years) men showed increased stimulated ACTH and cortisol, to either pharmacological (CRH) or physiological (exercise) stressors during pharmacological suppression of the gonadal axis. In addition, the secretion of cortisol after exercise and the initial secretion (0–30 min) of ACTH to either of the stressors were significantly larger in men compared to women. These data demonstrate that sex differences in the HPA-axis exist even in the absence of characteristic sex differences in reproductive steroids (Rocca et al., 2005).

It has also been found that elderly men activate the HPA-axis to a greater extent than women in response to psychological stress (Traustadottir et al., 2003; Kudielka et al., 1998; Uhart et al., 2006). Our group has also recently found gender differences in the number of CRH expressing neurons in the human hypothalamic PVN, namely: 1) there is a significant age-related increase of CRH neurons in men, but not in women; and 2) men have significant more CRH neurons than women from the age of 24 years onward (Fig. 1). We also showed that an abnormal hormone status, induced by castration, ovarioectomy or sex hormone-producing tumor, was accompanied by changes in CRH neuron number (Fig. 2) (Bao and Swaab, 2007). The increased number of CRH neurons in the human PVN may be interpreted as a sign of activation of the CRH neurons, because
in situ hybridization of CRH mRNA analyzed in the same patients gave the same results under such varied chronic circumstances as depression, hypertension and MS (Huitinga et al., 2004; Goncharuk et al., 2002; Raadsheer et al., 1995). Moreover, during aging, cortisol levels in the cerebral spinal fluid (CSF) and in plasma are found to increase progressively between the ages of 20 and 80 years (Laughlin and Barrett-Connor, 2000).

Age-related activation of CRH neurons could be due to a series of factors, such as a decreased function of the hippocampus, which suppresses the activity of the HPA-axis and which is more sensitive to the process of aging than the PVN (Giordano et al., 2005; Miller and O’Callaghan, 2005)(see below). In this respect, it is of interest that a sex difference has also been reported in hippocampal aging, e.g., a significant age-related decline of hippocampal volume was found in men but not in women (Bouix et al., 2005; Pruessner et al., 2001). Increasing insensitivity of the HPA-axis to the feedback of cortisol may be another factor involved in the activation of the HPA-axis during aging (Concharova and Lapin, 2002). Baseline AVP levels were found to be significantly higher in elderly subjects compared with young subjects (Rubin et al., 2002), which may also stimulate the HPA-axis. In addition, a sex difference was reported in AVP plasma levels. Men have higher AVP levels than women (van Londen et al., 1997; Asplund and Aberg, 1991), which agrees with the observation that the posterior lobe of the pituitary, where AVP and OXT are released into the circulation, is larger in boys than in girls (Takano et al., 1999). These sex differences are explained by the higher metabolic activity we found in AVP neurons in the SON in young men as compared to women, as determined by the size of the Golgi apparatus (Ishunina et al., 1999).

1.3. Circadian fluctuations

The stress response is strongly influenced by the time of day. The hypothalamic suprachiasmatic nucleus (SCN), the biological clock, is responsible for the rhythmic changes of the stress system. The

Fig. 1 – The total number of corticotropin-releasing hormone (CRH)-immunoreactive neurons in the hypothalamic paraventricular nucleus (PVN) of control males and females. The control males had significantly (p = 0.004) more CRH neurons than control females from age 24 onwards and showed a significantly positive correlation (the solid line) between age and the total number of CRH neurons. The control female group did not show significant correlation (the dashed line) between age and the total number of CRH neurons. (From Bao and Swaab, 2007, Fig. 2, with permission.)

Fig. 2 – The total number of corticotropin-releasing hormone (CRH)-immunoreactive neurons in the hypothalamic paraventricular nucleus (PVN) of control males and subjects with abnormal sex hormone status. Values of control-male-group (△, solid line), castrated-male-group (◇, dashed line), and ‘extended group’, i.e. the castrated-male-group (◇) plus an ovariectomized female-to-male (F–M) transsexual (○, dashed line), are delineated by a minimum convex polygon, respectively. Note that the total number of CRH neurons in the PVN of the 5 castrated males (n = 5, age = 67) is significantly (p = 0.008) lower than that of the matched old control males (n = 5, age = 66). Such a significant difference remained (p = 0.009) when the ovariectomized F–M transsexual was included in the ‘extended group’ (n = 6, age = 51) compared with the matched control males (n = 6, age = 50). The total numbers of CRH neurons in the three M–F castrated-with-estrogen-replacement M–F transsexuals (○) were significantly larger than those in the castration group (p = 0.036) and the ‘extended group’ (p = 0.024), while there was no significant difference when compared with age-matched control males (age 50–70, n = 6, p = 0.905; or age 50–78, n = 5, p = 1.000). The 31-year-old male with an estrogen-producing adrenal tumor (□) had a very high total number (16832) of CRH neurons in the PVN. M–F transsexual: male-to-female transsexual; F–M transsexual: female-to-male transsexual; Feminizing tumor: estrogen-producing adrenal tumor. (From Bao and Swaab, 2007, Fig. 3, with permission.)
SCN innervates brain areas in the human hypothalamic region (Dai et al., 1997, 1998a,b) imposing its rhythm also onto the body via three different routes of communication: 1) Via the secretion of hormones; 2) via the parasympathetic autonomous nervous system and 3) via the sympathetic autonomous nervous system. The SCN uses separate connections via either the sympathetic or the parasympathetic system, not only to prepare the body for the impending change in activity cycle but also to sensitize the body and its organs for the hormones that are associated with such a change (Buijs et al., 2006). We have also found CRH fibers in the area of the SCN (Bao et al., 2005; Bao and Swaab, 2007), which suggests the existence of a bi-directional direct anatomical connection between the SCN and the PVN. The function of such an anatomical connection in health and disease deserves further study.

### 2. Depression

#### 2.1. The stress system in depression

The HPA-axis is considered to be the ‘final common pathway’ for a major part of the depressive symptomatology. A large part of the environmental and genetic risk factors for depression appear to correlate with increased HPA-axis activity in adulthood. When patients or animals in models for depression are treated with antidepressants, electroconvulsive therapy, or when patients show spontaneous remission, the HPA-axis function returns to normal (Nemeroff, 1996). Stressful life events such as child abuse and early maternal separation form risk factors for later depression and anxiety disorder (for review see Swaab et al., 2005). Prenatal environmental stressors of a chemical nature, such as nicotine exposure due to smoking of the pregnant mother, may sensitize a subject for developing depression in later life, especially children who were either light or heavy at birth (Clark et al., 1996; Clark, 1998). Childhood abuse is an early stressor that may predispose individuals to adult onset depression accompanied by a permanent hyperactivity of the HPA system (Tarullo and Gunnar, 2006). In addition, small size at birth is associated with an alteration in the set-point of the HPA-axis and an increased cortisol responsiveness and risk of depression in adulthood (Phillips, 2001; Thompson et al., 2001).

In addition to these robust and well-established indications for a hypothalamic hyperdrive, there are various other measures that point to a causal and primary role for an increased HPA-axis activity in depression (Pariente, 2003). First, it is generally known that stressful life events are among the most potent factors that can trigger depressive episodes (Kendler et al., 1999; Paykel, 2001). Second, elevated plasma and salivary cortisol and cortisone levels, increased urinary free cortisol excretion, disturbed dexamethasone suppression, decreased corticosteroid receptor function, an enhanced adrenal response to ACTH, a blunted pituitary ACTH response to CRH as well as adrenal and pituitary enlargement have been found in patients suffering from depression (Scott and Dinan, 1998; Krishnan et al., 1991b; O’Brien et al., 1996; Rubin et al., 1996; Modell et al., 1997; Maes et al., 1998; Weber et al., 2000; Holsboer, 2000). The combined dexamethasone/CRH test does not only identify, with high sensitivity, a dysfunction of the HPA-axis in depression; the elevated cortisol response in the test also correlates with a 4–6-fold higher risk for relapse compared to individuals who had a depression but subsequently showed a normal cortisol response (Zobel et al., 2001). Moreover, studies in high-risk probands of patients with major depression have shown that abnormalities in HPA-axis function already exist prior to the onset of the clinical symptoms, suggesting that such abnormalities not only correlate but can, in fact, also precipitate depressive episodes (Holsboer, 2000). Increased ACTH secretion occurred in depressed in-patients regardless of cortisolemic status, confirming central HPA-axis overdrive in severe depres-

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<th>CRH hypothesis</th>
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<tr>
<td>* CRH neuron number in PVN increased (Raadsheer et al., 1994a; Bao et al., 2005).</td>
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<td>* AVP colocalization in CRH neurons in PVN increased (Raadsheer et al., 1994a).</td>
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<td>* CRH mRNA in the PVN increased (Raadsheer et al., 1995).</td>
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<td>* CRH in CSF increased (Banki et al., 1992).</td>
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<td>* CRH-R1 SNP (Liu et al., 2006b).</td>
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<td>* Anti-depressants decrease CSF CRH (Heuser et al., 1998).</td>
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<td>* CRH-R1 antagonists: anti-depressants (O’Brien et al., 2001a; Keck and Holsboer, 2001).</td>
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<td>* CRH i.c.v. in rat induces symptoms (Holsboer, 2001).</td>
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<td>* Transgenic mouse overproducing CRH: anxious (Stenzel-Poore et al., 1994).</td>
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**Vasopressin hypothesis**

- AVP and OXT neuron numbers increased (Purba et al., 1996).
- AVP mRNA increased in SON, and in melancholic depression in both PVN and SON (Meynen et al., 2006).
- Elevated AVP plasma levels in depression (van Londen et al., 1997), normalizing when patients improve (van Londen, 2003).
- Colocalization of AVP and CRH increased (Raadsheer et al., 1994a).
- Depressed patients who attempted suicide had higher plasma AVP levels compared to those who did not (Inder et al., 1997).
- Anxious-retarded (melancholic) depression: relation with plasma AVP and cortisol (de Winter et al., 2003).
- Animal model: after antidepressant, decrease of elevated AVP mRNA in PVN (Keck et al., 2003).
- SNP in AVP V1b receptor protects against recurrent MD (van West et al., 2004).
- AVP-deficient Brattleboro rats: AVP involved in development of depression-like behavior (Mlynarik et al., 2006).

**Glucocorticoid hypothesis**

- Increased level of corticosteroids and decreased level of CRH in atypical depression (Gold et al., 1995; Gold and Chrousos, 2002).
- Atypical depression found in a large proportion of Cushing’s syndrome (Gold et al., 1995; Dorn et al., 1995).
- SNPs GR gene NR3C1 (van West et al., 2006).
- Inhibitors of cortisol production (metyrapone, aminglutethamide, ketoconazole): anti-depressants (Reus et al., 1997; Murphy, 1997).
- GR-antagonist (mifepristone (RU486)) for psychotic depression (Gold et al., 2002; Belanoff et al., 2002).

AVP: arginine vasopressin/vasopressin; CRH: corticotropin-releasing hormone; CRH-R: CRH receptor; CSF: cerebral spinal fluid; GR: glucocorticoid receptor; NR3C1: Nuclear Receptor Subfamily 3, Group C, Member 1; OXT: oxytocin; PVN: paraventricular nucleus; SNPs: single-nucleotide polymorphisms; SON: supraoptic nucleus.
sion (Carroll et al., 2007). Recent studies in patients with psychotic depression also support the concept that treatment aimed directly at interfering with the consequences of HPA-axis abnormalities, such as treatment with high doses of GR-antagonist, would reverse the clinical symptoms (Belanoff et al., 2002).

2.1.1. The CRH hypothesis of depression

Several findings have pointed towards a central role of CRH in the neurobiology of depression. CRH neurons are strongly activated in depression. First, a fourfold increase in the number of CRH neurons in the PVN has been found. Second, the number of CRH neurons co-expressing AVP is increased, and third, the amount of CRH mRNA in the PVN is increased in depressed subjects compared to controls (Raadsheer et al., 1994a, 1995) (see Table 1; Figs. 3 and 4). The central effects of increased amounts of CRH may be responsible for at least some of the signs and symptoms of depression. The observation that a significant improvement in mood occurred in patients with treatment-resistant depression who received dexamethasone while remaining on their antidepressant (sertraline or fluoxetine) treatment supports the concept of hyperactive CRH neurons playing a causal role in the symptomatology of depression (Dinan et al., 1997). An important argument for a crucial role for central effects of CRH in depression is that similar symptoms such as decreased food intake, decreased sexual activity, disturbed sleep and motor behavior, and increased anxiety can all be induced in experimental animals by intracerebroventricular injection of CRH (Holsboer, 2001). The recently found single-nucleotide polymorphisms (SNPs) in CRH receptor1 (CRHR1) gene, associated with increased susceptibility to major depression (Liu et al., 2006b), is an argument for the direct involvement of CRH in the symptomatology of depression. Antidepressant drugs attenuate the synthesis of CRH by stimulation and/or upregulation of corticosteroid receptor expression (Barden, 1996). In addition, the CRH concentrations in CSF in healthy volunteers and depressed patients decrease due to antidepressant drugs (Heuser et al., 1998), although it should be noted that CSF-CRH is also derived from other brain areas, such as the cortex (see below). Moreover, a transgenic mouse model with an overproduction of CRH appeared to have increased anxiogenic behavior, i.e. symptoms that are usually related with major depression, that could be counteracted by injection of a CRH antagonist (Stenzel-Poore et al., 1994). Lastly, CRH-receptor antagonists may be effective in the treatment of depression (Grammatopoulos and Chrousos, 2002; Keck and Holsboer, 2001). Together, the arguments mentioned above have led to the CRH-hypothesis of depression, i.e., hyperactivity of CRH neurons, and thus of the HPA-axis, induce the symptoms of depression.

Although some negative neuroendocrine findings seem to suggest that CRH might not be involved in the pathogenesis of depression.
of depression, we should realize that the endocrine measurements leading to these findings relate to the CRH neurons that project to the periphery. Actually, the CRH-hypothesis of depression may still hold for these cases, since this hypothesis includes the idea that a subgroup of CRH neurons that project to brain areas other than the median eminence are activated in depression and induce the symptoms. These subgroup CRH neurons are not monitored endocrinologically in the periphery.

2.1.2. AVP hypothesis of depression

Other neuropeptides involved in the symptoms of depression are AVP and OXT. In the PVN of patients with major depression, AVP and OXT neurons are activated as well (Purba et al., 1996), which may have functional consequences for HPA-axis reactivity (Table 1). There is also an enhanced pituitary AVP responsivity in depression (Dinan et al., 1999). It is important to note that, whereas in acute stress CRH is the main cause of increased ACTH release, animal experiments show that in chronic stress there is a switch from CRH to AVP stimulation of ACTH release (Scott and Dinan, 1998). Since depression is, by definition, a state that lasts for weeks at a minimum, these observations could indicate that HPA-axis hyperactivity in depression may be AVP-driven rather than CRH-driven.

Interestingly, the SON also shows enhanced AVP mRNA production in depression (Meynen et al., 2006) (Fig. 5). This may be related to the increased plasma levels of AVP (van Londen et al., 1997, 1998, 2001) and to an enhanced suicide risk (Inder et al., 1997). Considering the possibility that AVP produced in the SON may not only be the source of increased AVP plasma levels, but may also be responsible for the HPA-axis hyperdrive in depression, two points are of relevance. First, animal studies show that the release of magnocellular AVP, originating in the PVN or SON, might also take place in the median eminence and thus in the portal system, where it might potentiate ACTH release (Antoni, 1993; Wotjak et al., 1996). Second, it is possible that an increased AVP release from the SON into the systemic circulation contributes to the increased ACTH release from the pituitary. A clear indication that AVP in the systemic circulation might play a role in HPA-axis regulation is provided by the finding of (Gispen-de Wied et al., 1992), that intravenous administration of AVP results in increased levels of ACTH and cortisol in both controls and depressed subjects. Another indication is the finding that plasma AVP levels are positively correlated with cortisol levels in depression as observed in different studies (Brunner et al., 2002; de Winter et al., 2003; Inder et al., 1997). Furthermore, there might be a feedback mechanism between the HPA-axis and the SON and PVN: GRs are present in both the PVN and SON in rats (Morimoto et al., 1996), as well as in rhesus monkeys (Sanchez et al., 2000). In humans we have found that AVP is not only reduced in the PVN but also in the SON in response to increased glucocorticoid plasma levels (Erkut et al., 1998). A recent study on AVP-deficient Brattleboro rats has shown that AVP is involved in the development of depression-like behavior, in particular of the coping style and anhedonia. Moreover, behavioral and endocrine responses were found to be dissociated. It is suggested that brain vasopressinergic circuits other than from those regulating the HPA-axis are involved in generating depression-like behavior (Mlynarik et al., 2006), a finding which deserves further study in human. A major SNP haplotype of the AVP V1b receptor has been found to protect against recurrent major depression (van West et al., 2004), supporting the possibility of a direct involvement of AVP in depression.

The parallel activation of OXT neurons has been connected with decreased appetite and weight loss in depression due to the central effects of this neuropeptide as a satiety hormone (Gimpl and Fahrenholz, 2001; Purba et al., 1996; Meynen et al., 2007a). Loss of weight is one of the features of melancholic type depression. Interestingly, it was found recently that OXT mRNA is increased in melancholic type depressed patients compared to non-
melancholic type depressed patients. In addition, in the group studied, the highest amount of OXT mRNA was found in a melancholic type depressed subject who had lost 16 kg during a depressive episode in the last year of her life (Meynen et al., 2007a) (Fig. 6).

2.1.3. Glucocorticoids in depression

There are also observations that point to a causal role for glucocorticoids in depression. Using a whole gene-based association analysis of SNPs, genetic variations in the GR gene (Nuclear Receptor Subfamily 3, Group C, Member 1; NR3C1) have been examined and the data suggest that polymorphisms in the 5' region of the NR3C1 gene may play a role in the genetic vulnerability for major depression (van West et al., 2006). A few studies have reported that glucocorticoid (receptor) antagonists may be effective in the treatment of major depression (Murphy, 1997; Wolkowitz et al., 1999), supporting the idea of an involvement of glucocorticoids in depression. Inhibitors of cortisol production such as metyrapone, aminoglutethamide or ketoconazole, may result in clinical success in depressed patients, which is not to be expected if an increase in CRH itself would be the cause of all the symptoms (Reus et al., 1997; Murphy, 1997). The GR antagonist mifepristone (RU486) is effective in treating psychotic depression, producing clinically relevant responses at high dosages in considerable numbers of patients within a few days of treatment (Gold et al., 2002; Belanoff et al., 2002). This is in clear contrast with most classic antidepressants that generally need at least weeks to take effect. Unfortunately, these compounds induce many unspecific effects (Holsboer and Barden, 1996).

It is proposed that the severe, ‘melancholic type of depression’, characterized by symptoms such as loss of pleasure in all (or almost all) activities, lack of mood reactivity to usually pleasurable stimuli, worse mood in the morning, early morning awakening and significant anorexia or weight loss, would be due to a hyperactivity of CRH neurons (Gold and Chrousos, 2002). In contrast, ‘atypical depression’, a state of hyperphagia, hyperomnia, enhanced affected responsiveness to external stimuli, lethargy and fatigue would be based upon increased levels of corticosteroids and decreased levels of CRH (Gold et al., 1995; Gold and Chrousos, 2002). Indeed, CRH receptor antagonists, cortisol synthesis inhibitors, and corticosteroid receptor antagonists have all been reported effective in some depressed patients (Holsboer, 2000; Gold et al., 2002). In addition, a well-known side effect of glucocorticoid treatment is depression, while one-third of the patients who are receiving glucocorticoids experience significant mood disturbances (Mitchell and O’Keane, 1998). Moreover, atypical depression is found in a large proportion of Cushing’s syndrome patients, especially those with longer duration (Gold et al., 1995; Dorn et al., 1995), which indicates that an elevated level of cortisol, rather than of CRH, causes this type of depression. This conclusion is supported by a small study that showed that depression can be treated with ketoconazole, an antiglucocorticoid (Wolkowitz et al., 1999), and by the observation that metyrapone successfully treats depression in Cushing patients (Checkley, 1996) (Table 1). However, it should be noted that after correction of the hypercortisolism in Cushing’s syndrome, atypical depression frequently continues to be present and suicidal ideation and panic may even increase (Dorn et al., 1997).

2.2. Causes of HPA-axis hyperactivity

The increase in HPA-axis activity in many depressed cases raises the question of the possible underlying pathogenic mechanisms. So far, an imbalance in the ratio between MR and GR has been shown in depressed patients (Young et al., 2003) but it is not clear whether this should be considered cause or effect. Impaired negative feedback control of the HPA-axis and adrenocorticotrophic hormone are commonly found in a subgroup of depressed patients (Checkley, 1996; Modell et al., 1997). They coincide with episodes of depression and reverse, at least partially, after recovery. Some observations suggest that the impaired negative corticosteroid feedback on the HPA-axis in a number of healthy probands at risk for affective disorder is caused by a disturbed corticosteroid receptor function, indicating a genetically transmitted risk factor (Holsboer et al., 1995; Holsboer, 2000). Genetic variations (polymorphisms) of the GR may explain why only some 50% of the depressed patients show hypercortisolaemia and why considerable variation in their symptoms occurs (Checkley, 1996; Holsboer, 2000).

An alternative possibility involves changes during early development that can induce altered feedback control of the HPA-axis that may persist into adulthood, and could lead to acquired GR resistance in some specific feedback areas (Brommgard et al., 1996; De Bellis et al., 1999; De Kloet et al., 1997) and GR hypersensitivity in other brain regions (Nemeroff, 1996). Depression and anxiety have been found to be more frequent in the sons and daughters of women who had been treated with DES during pregnancy (Vessey et al., 1983; Brown et al., 1995) and in children of mothers who were pregnant during the ‘hunger winter’ in the Netherlands during the Second World War (Susser and Lin, 1992; Susser et al., 1996). However, so far, the HPA-axis has not been investigated in these patients.

2.3. Sex differences and reproductive stages

Unipolar depression and dysthymia are twice as common in women as they are in men (Seeman, 1997; Piccinelli and Wilkinson, 2000). During the reproductive years, a woman is exposed to monthly fluctuations of circulating estradiol and progesterone that accompany the menstrual cycles, which are expected to influence the secretion of hypothalamic CRH and catecholamines until menopause. Premenstrual syndrome or premenstrual dysphoric disorder is characterized by feelings of depression, anxiety and mood swings during the last week of the luteal phase, with decreased secretion of CRH and an increased incidence of suicides and enhanced vulnerability to autoimmune and allergic inflammatory phenomena (Rabin et al., 1990; Fourestie et al., 1986; Skobeloff et al., 1996; Hayward et al., 1997). It has been found that the time of the maximum emotional disturbance coincides with the decrease of plasma estradiol levels during the latter part of the luteal phase of the cycle when plasma progesterone levels are still elevated (Hayward et al., 1997). Other studies have suggested that the period of peak estradiol secretion in the state immediately before ovulation is associated with elevations in mood, a phenomenon that might contribute to fecundity (Blum et al., 2004; Davydov et al., 2004; Endicott, 1993; Henderson and Whissell, 1997). Premenstrual dysphoric syndrome is characterized by
disturbances in circadian rhythms and the response to critically timed light administration. Interventions with bright light improve mood in these patients (Parry and Newton, 2001). Although at present there is no conclusive evidence that premenstrual dysphoric disorder is indeed associated with abnormalities in the levels of sex hormones, both suppression of ovarian function by an LHRH agonists and ovariectomy are effective treatments for this type of mood disorder (Steiner, 1996; Rubinow et al., 1998a). The fluid retention in the premenstrual syndrome has been proposed to be related with the increased AVP levels (Reid and Yen, 1981; Ishunina and Swaab, 1999; Ishunina et al., 1999), which indeed show fluctuation during the menstrual cycle, although the relationship between these fluctuations and psychological symptoms of the premenstrual syndrome remains unclear at present.

Antepartum depression is found in some 5% of pregnant women (Campagne, 2004). This condition may be a risk factor for the development of preeclampsia (Kurki et al., 2000) and is the strongest predictor of postpartum depression (Graf et al., 1991). Maternal depressive symptoms during pregnancy may lead to behavioral changes in the child (Oren et al., 2002). Pharmacological treatment of depression of pregnant women is complicated because of the possible behavioral-teratological effects (Swaab and Boer, 2001). It is therefore of great practical interest that an open trial has shown that morning light therapy may be effective as an antidepressant during pregnancy (Oren et al., 2002). A randomized controlled trial should confirm these promising data. The latter half of human pregnancy is associated with hypercortisolism. Indeed, the levels of free plasma cortisol and 24-h urinary free cortisol excretion in pregnancy overlap with levels in patients with mild Cushing syndrome (Nolten et al., 1980). Placental CRH is the cause of this hypercortisolism (Chrousos et al., 1998).

The postpartum period is characterized by an increased incidence of psychiatric disturbances. The ‘postpartum blues’, transient depressed feelings, occur in 60% to 70% of women, while a postpartum depression affects about 10% and very severe postpartum psychosis affects about 1 in 1000 (Affonso and Newton, 1998). Maternal depressive symptoms during pregnancy may lead to behavioral changes in the child (Oren et al., 2002). Pharmacological treatment of depression of pregnant women is complicated because of the possible behavioral-teratological effects (Swaab and Boer, 2001). It is therefore of great practical interest that an open trial has shown that morning light therapy may be effective as an antidepressant during pregnancy (Oren et al., 2002). A randomized controlled trial should confirm these promising data. The latter half of human pregnancy is associated with hypercortisolism. Indeed, the levels of free plasma cortisol and 24-h urinary free cortisol excretion in pregnancy overlap with levels in patients with mild Cushing syndrome (Nolten et al., 1980). Placental CRH is the cause of this hypercortisolism (Chrousos et al., 1998).

The postpartum period is characterized by an increased incidence of psychiatric disturbances. The ‘postpartum blues’, transient depressed feelings, occur in 60% to 70% of women, while a postpartum depression affects about 10% and very severe postpartum psychosis affects about 1 in 1000 (Affonso and Domino, 1984). The postpartum estrogen withdrawal state has often been held responsible for this disorder. However, available studies show a lack of evidence that serum sex hormones account for mood disturbances in these women. Yet there is evidence that estradiol might be effective in its treatment (Gregoire et al., 1996; Sichel et al., 1995). Clinical implications of placental CRH extend beyond pregnancy, labor, and delivery (McLean et al., 1995; Magiakou et al., 1996b). There is evidence showing that the postpartum period might be associated with low hypothalamic CRH secretion, which would predispose patients to atypical depression (Magiakou et al., 1996a). It is supposed that in the postpartum state the placenta, the major source of CRH and estrogen during pregnancy, is no longer present, whereas the hypothalamic CRH neuron is probably suppressed as a result of previous exposure to high levels of cortisol and concurrent after-birth estrogen deficiency. High-dose estrogen has a marked antidepressant effect during this period, possibly because it reestablishes normal stress system secretion of CRH and norepinephrine (Gregoire et al., 1996). Postpartum women are also at risk for hypothalamic–pituitary–thyroid (HPT) axis dysfunction, which may increase their vulnerability to affective disorders (Sichel et al., 1995; Wisner and Stowe, 1997).

Depressive symptoms are also common during the transition to menopause, and there are suggestive data that estrogen deficiency may increase the susceptibility for depression (Birkhauser, 2002). However, although perimenopause may be a period of risk for mood disturbances, it generally does not lead to major depression. According to some studies (Banger, 2002) depressive disorders do not occur more frequently during perimenopause, although perimenopausal women with both estrogen and hence CRH withdrawal states indeed show mood improvements with estrogen therapy (Soares et al., 2001). Estrogen replacement therapy also improves mood in postmenopausal women and estrogens may improve the effect of some antidepressants in postmenopausal women (Birkhauser, 2002).

2.4. Sex hormone level fluctuations

It was found in males that testosterone levels were lower in severely depressed patients (Heuser, 2002) and older men with lower bioavailable testosterone levels were more frequently depressed (Barrett-Connor et al., 1999). Low testosterone levels were also found in men with dysthymic disorder (Seidman et al., 2002). Both the testosterone level and AR polymorphism are related to the risk for middle-aged men to become depressed. Men who have low total testosterone levels and a shorter CAG codon repeat length in the AR have a greater likelihood of becoming depressed (Seidman, 2001). It is of interest that the testosterone levels of bodybuilders who take supraphysiological doses of testosterone had a strong negative correlation with depression scores (Dickerman and McConathy, 1997). Studies in anabolic androgenic steroid users show that some of them develop manic or aggressive reactions to these drugs. Supraphysiological doses of testosterone indeed increased ratings of manic symptoms in normal men (Pope et al., 2000).

Based upon the observations mentioned above, that 1) men show higher HPA-axis activity than women (Uhart et al., 2006; Vierhapper et al., 1998; Shamim et al., 2000; Traustadottir et al., 2003; Kudielka et al., 1998; Roca et al., 2005; Bao and Swaab, 2007), while 2) the lifetime prevalence of major depression is twice as high in women as in men (Lehtinen and Joukamaa, 1994; Pearlstein et al., 1997); and 3) the prevalence of mood disorders increases during the reproductive years, especially during times of change in gonadal hormone levels, e.g., the premenstrual and postpartum periods and the transition to menopause (Lehtinen and Joukamaa, 1994; Pearlstein et al., 1997; Young and Korszun, 2002), it could be speculated that the changes of sex hormone levels may play a more important role in the vulnerability to mood disorders than the basal absolute levels. In this respect it is of interest to see that depressed female patients had significantly higher amplitudes of diurnal estradiol rhythms than controls (Bao et al., 2004). Moreover, it is unknown whether a different local production e.g., of estrogens, involving aromatase and adrenal or brain-derived androgens due to the changes of circulating sex steroids, may act as a ligand and regulate sex hormone receptors in the brain (Kroboth et al., 1999), or whether the regulation of sex hormone receptors is modulated by neurotransmitters, such as norepinephrine, dopamine or serotonin (Asberg et al., 1976; Blaustein et al., 1986), and this deserves further study in relation to depression.
Not only sexual function but also mood improved in hypogonadal men who received testosterone replacement (Fink et al., 1999; Seidman and Walsh, 1999; Wang et al., 1996; Fink et al., 1998; Wong et al., 2000). Although this is a promising observation, there are not enough controlled studies at present that prove that testosterone administration is indeed effective in mood disorders (Sternbach, 1998). Estrogen replacement therapy (ERT) may make women with Alzheimer’s disease (AD) less vulnerable to depression (Carlson et al., 2000) and may augment the fluoxetine response in elderly depressed patients (Schneider et al., 1997). On the other hand, it should be noted that estrogen substitution in postmenopausal women with depressive symptoms was effective in some studies but not in others (Rubinow et al., 1998b; Rasgon et al., 2001). Progestins during sequential hormonal replacement therapy cause negative mood and physical symptoms that are accentuated by increasing the estrogen dose (Bjorn et al., 2003).

2.5. The circadian system

The SCN that induces circadian and circannual variations in neuronal activity (Hofman and Swaab, 1992, 1993) is supposed also to be related to circadian and circannual fluctuations in mood and to sleeping disturbances in depression (van Londen et al., 2001). A polymorphism in the clock gene NPAS2 appeared to be associated with seasonal affective disorder (Johansson et al., 2003), indicating that the SCN may also play a causal role in this type of depression. A disorder of SCN function, characterized by an increased number of AVP-expressing neurons, a decreased amount of AVP mRNA in this nucleus, and diminished circadian fluctuation of AVP mRNA has been found in depressed patients (Zhou et al., 2001) (Fig. 7). Decreased activity of the SCN in depression is presumed to be at least partly due to the increased circulating plasma cortisol levels that are known to inhibit SCN function (Liu et al., 2006a). Light therapy is found to be effective, not only for the seasonal subtype but also for major depression, while morning light, as an adjuvant to conventional antidepressants in unipolar patients, or lithium in bipolar patients, hastens and potentiates the antidepressant response (Wirz-Justice et al., 2005). Animal data have shown that AVP neurons of the SCN exert an inhibitory influence on CRH neurons in the PVN (Kalsbeek et al., 1992). It is thus logical to propose that in depressed patients, stress results in a disproportionately high activity of the HPA-axis because of a deficient cortisol feedback effect due to the presence of glucocorticoid resistance. Meanwhile AVP neurons in the SCN react to the increased cortisol levels and subsequently fail to inhibit sufficiently the CRH neurons in the PVN of depressed patients. Such an impaired negative feedback mechanism may lead to a further increase in the activity of the HPA-axis in depression. Both high CRH and cortisol levels contribute to the symptoms of depression (see above) (Swaab et al., 2005), while light therapy may activate the SCN, directly inducing an increased synthesis and release of AVP that will inhibit the CRH neurons (Fig. 8). However, it should be noted that human beings are diurnal creatures that might hold a different mode of interaction between SCN–AVP neurons and the PVN–CRH neurons, as is the case in the nocturnal rat. It can also be hypothesized that the diminished AVP activity in the SCN in depression is due to inhibition by hyperactive CRH neurons in the PVN that project to the SCN. This possibility deserves further study.

2.6. Influence of the cortex

Depression is also commonly observed after stroke. The severity of the mood disorder in this condition is increased particularly in

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**Fig. 7** - The number of arginine vasopressin-immunoreactive (AVP-IR) neurons (A) and the mask area of silver grains of the AVP mRNA (B) in the suprachiasmatic nucleus (SCN) in control subjects (n = 11) and depressed subjects (n = 11). The error bars indicate the S.D. Note the change in the balance between the presence of more AVP and less AVP mRNA in depression. There is probably a disorder of the transport of AVP that leads to accumulation of the peptide, in spite of the decreased production rate. (From Zhou et al., 2001, Fig. 2, with permission.)
patients with left prefrontal cortex lesions or with right posterior–dorsal lesions (Robinson et al., 1984; Iacoboni et al., 1995). Postmortem studies have further provided morphological evidence for the involvement of the prefrontal cortex in depression; cell loss takes place in the prefrontal cortex, while cell atrophy occurs in the dorsolateral and orbitofrontal cortex (Rajkowska, 2000). PET and SPECT studies have further shown that bilateral hypometabolism occurs in the orbital–inferior prefrontal lobe of most types of depression (George et al., 1993; Mayberg, 1994; Morris et al., 1996; Galynker et al., 1998). Whether these metabolic changes in the cortex of depressed patients are cause or effect of the disorder remains a matter of debate. Increased glucocorticoid levels are known to inhibit prefrontal cortex metabolism (Brunetti et al., 1998; Fulham et al., 1995). In addition, glucocorticoid receptor dysregulation is found in the neocortex and hippocampus of patients with depression (Webster et al., 2002; Pariante and Miller, 2001). Furthermore, the prefrontal cortex inhibits the HPA-axis, as is clear from lesion studies, particularly of the left prefrontal cortex; a lesion in that area appears to go together with symptoms of depression and hypercortisolism. On the other hand, the hypercortisolism that occurs in depression will inhibit prefrontal cortex activity. Together, these two effects might even reinforce each other (Swaab et al., 2000). In depression pathogenesis, a changed interaction between the prefrontal cortex and the HPA-axis may therefore be crucial.

3. Alzheimer’s disease (AD)

3.1. The stress system in AD

AD is a multifactorial disease and ‘aging’ is its major risk factor. The presence of apolipoprotein E (ApoE) e4 alleles is responsible for some 17% of the cases. Mutations in the amyloid precursor protein presenilin 1 and 2 genes contribute less than 1% to the prevalence of AD (Tol et al., 1999). Additional possible risk factors for AD are being female, lack of sex hormones, smoking, low degree of education and cardiovascular disorders (Swaab, 2004).

The HPA-axis shows extensive changes in AD. We observed a hyperactivation of CRH neurons with age, which is significantly present in men (Raadsheer et al., 1993, 1994b; Bao and Swaab, 2007) (Fig. 1). This finding is in full agreement with hormone assays that indicate a general activation of various HPA-axis parameters during the course of human aging. Cortisol plasma levels are increased in AD (Umegaki et al., 2000; Murialdo et al., 2000a; de Bruin et al., 2002; Rasmuson et al., 2002) and may occur in an early stage, relating to cognitive decline (Umegaki et al., 2000). The salivary cortisol levels are found to be correlated with severity of disease, as measured by the mini-mental state examination and the global deterioration scale (Di Giubilei et al., 2001). Hypercortisolemia in AD appears to be related to the clinical progression but not to aging or length of survival (Weiner et al., 2000).

**Fig. 8** – Depression; schematic illustration of an impaired interaction between the decreased activity of vasopressin neurons (AVP) in the suprachiasmatic nucleus (SCN) and the increased activity of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN). The hypothalamo–pituitary–adrenal (HPA) system is activated in depression and affects mood, via CRH and cortisol. We found a decreased amount of vasopressin (AVP) mRNA of the SCN in depression. The decreased activity of AVP neurons in the SCN of depressed patients is the basis of the impaired circadian regulation of the HPA system in depression. Moreover, animal data have shown that AVP neurons of the SCN exert an inhibitory influence on CRH neurons in the PVN. Increased levels of circulating glucocorticoids decrease AVP mRNA in the SCN, which will result in smaller inhibition of the CRH neurons. In the light of our data we propose the following hypothesis for the pathogenesis of depression. In depressed patients, stress acting on the HPA system results in a disproportional high activity of the HPA system because of a deficient cortisol feedback effect due to the presence of glucocorticoid resistance. The glucocorticoid resistance may either be caused by a polymorphism of corticosteroid receptor or by a developmental disorder. Also AVP neurons in the SCN react to the increased cortisol levels and subsequently fail to inhibit sufficiently the CRH neurons in the PVN of depressed patients. Such an impaired negative feedback mechanism may lead to a further increase in the activity of the HPA system in depression. Both high CRH and cortisol levels contribute to the symptoms of depression. Light therapy activates the SCN, directly inducing an increased synthesis and release of AVP that will inhibit the CRH neurons. Antidepressant medication generally inhibits the activity of CRH neurons in the PVN. ACTH, corticotropin.
1997). There is a linear relationship between plasma and CSF cortisol levels (Erkut et al., 2002a) and indeed we have found CSF cortisol levels also to be increased in AD (Swaab et al., 1994; Erkut et al., 2004; Hoogendijk et al., 2006). Moreover, the presence of 1 or 2 alleles of ApoE-ε4 is accompanied by higher cortisol CSF levels in both AD patients and controls (Peskind et al., 2001). CRH mRNA was found to be increased in the hypothalamic PVN, causing hyperactivity of the HPA-axis in Alzheimer patients (Raadsheer et al., 1995) (Fig. 4). There is a very high prevalence of depression in AD, affecting up to 50% of the patients (Zubenko et al., 2003; Lyketsos and Lee, 2004). Recently, we found a positive correlation between the Cornell scale for Depression in Dementia and the number of CRH neurons in the PVN, suggesting that depressive disorder and depression in AD share, at least partly, their pathogenesis (Meynen et al., 2007b). In demented patients with delirium, HPA-axis feedback was found to be disturbed (Robertson et al., 2001). The AVP-producing neurons in the SON and PVN generally remain intact in AD (Van der Woude et al., 1995) and the AVP neurons even appear to be activated in the course of aging (see above). Yet some studies report changes in circulating AVP and OXT levels in AD, although these data are somewhat equivocal. The AVP CSF levels do not change in dementia according to some authors (Jolkken et al., 1989; Gottfries et al., 1995) whereas others say they are increased (Tsui et al., 1981) or reduced (Mazurek et al., 1986; Gottfries et al., 1995). The fact that the type of dementia is often not specified in these papers may be part of the reason for the discrepancies.

A decreased number of neurons expressing AVP, neurotensin and vasoactive intestinal peptide (VIP) in the SCN has been found in AD patients (Swaab et al., 1985; Zhou et al., 2001, 1995; Stopa et al., 1999). In addition, it is clear from the neurofibrillary changes, from the increased number of GFAP-positive astrocytes (Swaab et al., 1992; Stopa et al., 1999; van de Nes et al., 1998) and from the 3 times lower amount of AVP mRNA in the SCN of Alzheimer patients (Jiu et al., 2000) that the SCN is affected in AD. The SCN is strongly affected from the earliest AD stages onwards (Wu et al., in press). Alterations observed in the SCN are accompanied by a disruption of circadian rhythms, nightly restlessness, and a phase delay in body temperature rhythm (Harper et al., 2001). Indeed, stimulation of the SCN by light improves circadian rhythmicity, decreases behavioral disturbances such as nightly restlessness (Van Someren et al., 1999) and can even improve cognitive performance (Yamadera et al., 2000; Graf et al., 2001).

3.2. AD and sex hormones

Diminishment of sex hormones, i.e. of estrogens in menopause and of testosterone in aging men, is considered to be a risk factor for AD (Atwood et al., 2005). According to some studies, the prevalence of AD is higher in women than in men (Bachman et al., 1992; Brayne et al., 1995; Fratiglioni et al., 1997; Launer et al., 1999; Letenneur et al., 2000), although other researchers did not find an association between AD and gender (Hebert et al., 2001; Lindsay et al., 2002; Gatz et al., 2003) and suggested that the larger number of women with AD is only due to the longerlife expectancy of women rather than to any specific risk factors for the disease (Hebert et al., 2001). Our observation of an increased number of nucleus basalis of Meynert neurons containing AD-pathology, i.e. hyperphosphorylated tau, in women as compared to age-matched men (Salehi et al., 2000), and the association found between AD and a locus on the X-chromosome (Zubenko et al., 1998), support, however, the presence of sex differences in AD. In addition, ERα polymorphisms PvuII and XbaI are associated with the risk of developing cognitive impairment (Yaffe et al., 2002) and CAG-repeat polymorphism of AR is also associated with AD in men (Lehmann et al., 2003). Moreover, an interaction between ERα and ERβ polymorphisms and the risk of developing AD has also been recognized (Lambert et al., 2001).

Various studies suggest a relationship between sex hormone levels and cognitive performance and AD. Lower endogenous estradiol levels are correlated with poor cognitive, behavioral and functional status in older but undemented individuals (Farrag et al., 2002; Senanarong et al., 2002). In women, higher estradiol levels as well as higher testosterone levels are associated with better verbal memory. Moreover, estradiol is associated with a diminished susceptibility to interference (Wolf and Kirschbaum, 2002). In elderly, non-demented men, higher free testosterone levels are associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning, and with a reduced rate of longitudinal decline in visual memory (Wolf and Kirschbaum, 2002; Moffat et al., 2002). Several studies have reinforced the idea that the postmenopausal decrease in estrogen levels may be an important factor in triggering the pathogenesis of AD, since women with high serum concentrations of bioavailable estradiol are less likely to develop cognitive impairment than women with low concentrations (Inestrosa et al., 1998; Manly et al., 2000; Yaffe et al., 2000). In old men, endogenous testosterone levels are not associated with risk for cognitive decline and AD, whereas higher estrogen levels increase this risk (Geerlings et al., 2006). An interesting relationship has been observed between CSF levels of estradiol and AD-pathology β-amyloid. Estradiol CSF levels are lower in AD patients than in controls, and within the Alzheimer group the estradiol levels are inversely correlated with ApoE-ε4 concentration. This observation has been interpreted as corresponding to the beneficial effects of estrogen replacement therapy on AD (Schonknecht et al., 2001).

ERT as a preventive measure for AD is becoming increasingly controversial. Epidemiological evidence, randomized controlled trials, and cross-sectional and longitudinal studies have indeed indicated that ERT in postmenopausal women is effective in protecting against a decline in verbal memory in healthy postmenopausal women and in preventing and delaying the onset of AD (Henderson et al., 1996; Stephenson, 1996; Sherwin, 2002; van Duijn, 1999). However, other studies reported no effect on cognition was observed after 4 years of hormone therapy (Grady et al., 2002). It has also been found that estrogen plus progestin did not improve cognitive function when compared with placebo; what is more, there was even a small increased risk of clinically meaningful cognitive decline that occurred in the estrogen plus progestin group (Rapp et al., 2003). At least part of the controversial literature on the possible positive effects of sex hormones in AD may be based upon the different effects that different sex hormones may have on different brain areas, depending on, e.g. age and ApoE genotype. There is a need for more long-term, randomized controlled trials with estrogens, starting immediately in the postmenopausal
period in mentally unaffected women, in order to get more information on the possible prevention of AD.

3.3 Hippocampal damage in AD and depression: is the glucocorticoid cascade hypothesis valid

The hippocampus is strongly affected in AD. Also the sensitivity for estrogens in the hippocampus is changed in AD, possibly because of the changes in the ratio of the various splice variants and isoforms of the ERα (Ishunina et al., in press). Neuronal loss was reported in the hippocampus of stressed or corticosteroid-treated rodents and primates. On the basis of earlier animal experiments, overexposure of the brain to glucocorticoids during prolonged periods of stress was expected to be damaging to the brain, especially in aged animals, and particularly affecting the hippocampus (Sapolsky, 1985, 1996; Landfield et al., 1978). Since, under normal conditions, the hippocampus inhibits the HPA-axis activity, the damage to the hippocampus was proposed to cause a disinhibition of the HPA-axis, which would lead to its further activation, and to subsequent rises in glucocorticoid levels and thus to accumulating damage to the hippocampus. This hypothesized feed-forward cascade became known as the ‘glucocorticoid cascade hypothesis’ and was proposed to be a major pathogenetic mechanism also in human neurodegenerative diseases associated with HPA-axis alterations such as depression and AD (Sapolsky et al., 1986). The excessive, repetitive hypersecretion of cortisol, and possibly even the increased basal levels of the hormone, were supposed to accelerate the course of hippocampal damage in Alzheimer patients (Sapolsky et al., 1986). Increased cortisol levels would not only cause hippocampal neuronal damage but was also proposed to potentiate amyloid toxicity, while DHEA and DHEAS are believed to exert a neuroprotective action (Murialdo et al., 2000b).

It has been hypothesized that in various cases the ‘glucocorticoid cascade’ might be involved in the pathogenesis of the disorder (Sapolsky et al., 1986). Glucocorticoid treatment causes memory disturbances in the absence of concomitant stress exposure (Lupien and McEwen, 1997; Lupien et al., 1998; Wolf, 2003). Depressed patients who did not suppress cortisol when given dexamethasone made more mistakes in a verbal memory task (Wolkowitz et al., 1990). A considerable percentage of Alzheimer patients indeed presents with a non-suppression of plasma cortisol following dexamethasone administration (O’Brien et al., 1996; Swaab et al., 1994), while the degree of HPA-axis hyperactivity generally correlates with the severity of cognitive impairment and hippocampal atrophy (Gurevich et al., 1990; de Leon et al., 1988; Weiner et al., 1993; Lupien et al., 1998). Several studies have found a reduced hippocampal volume in patients with unipolar depression, although there are discrepancies. Meta-analyses of hippocampal volumetric studies in patients with mood disorders revealed that although such studies were highly heterogeneous regarding age and gender distribution, age at onset of the disorder, average number of episodes, and responsiveness to treatment, the hippocampal volume was reduced in patients with unipolar depression, possibly as a consequence of repeated periods of major depressive disorder (Videbech and Ravnkilde, 2004), especially when the hippocampus was measured as a discrete structure (Campbell et al., 2004). However, it should be noted that a reduced hippocampal volume does not prove cell loss (see below); the hypercortisolaemic state in depressed patients might cause a change in water content, as indicated by the shortened T1 relaxation times in the hippocampus of depressed patients, especially in the elderly (Krishnan et al., 1991a). In addition, it should be studied whether a small hippocampal volume may predispose for depression.

There are, however, also quite a number of observations that do not support the possible importance of the ‘glucocorticoid cascade hypothesis’ in the pathogenesis of AD. In contrast to the often claimed association between elevated cortisol levels and impaired declarative memory performance, subjects with a remarkably high cortisol increase in response to psychological stress appeared to show improved memory performance (Domes et al., 2002). The activation of the HPA-axis and the impaired cognition in AD may both be explained by the ongoing Alzheimer process in the hippocampus, without cortisol playing a crucial causal role. Although some papers reported baseline levels of cortisol to be elevated in plasma and urine of Alzheimer patients (Davis et al., 1986; Maeda et al., 1991; Umegaki et al., 2000) others failed to do so (Ferrier et al., 1988). One study indicated that, as a group, Alzheimer patients have a mildly increased HPA-axis activity, but the increased baseline cortisol levels were not stable longitudinally and did not increase with follow-up, which is not consistent with the ‘glucocorticoid cascade hypothesis’ (Swanwick et al., 1998). In presenile patients the postmortem CSF levels were found to be 5 times higher than in controls. However, due to the increasing cortisol levels in the course of normal aging, significant differences in postmortem CSF cortisol levels were no longer found between senile Alzheimer patients and controls. Increased basal plasma and CSF cortisol levels thus do not seem to be necessary for the development of AD pathogenesis (Swaab et al., 1994). In addition, the lumbar puncture CSF levels of cortisol were found to be increased in AD in an ApoE genotype-dependent way. ApoE-e4 went together with higher cortisol levels (Peskind et al., 2001). However, this observation may be explained by the stronger Alzheimer changes in the hippocampus of ApoE-e4-positive subjects, which would cause a stronger disinhibition of the HPA-axis. One of the strongest arguments, so far, against the causal involvement of the ‘glucocorticoid cascade hypothesis’ in AD is that no Alzheimer or other neuropathological changes are present in the hippocampus of depressed patients, nor in patients with Cushing’s disease (Trethowan and Cobb, 1952), multi-infarct dementia (Maeda et al., 1991), multiple sclerosis (Purba et al., 1995; Erkut et al., 1995) or in patients treated with glucocorticoids (Lucassen et al., 2001; Müller et al., 2001; O’Brien et al., 2001b), despite a much stronger activation of the CRH neurons in depression than in AD (Raadsheer et al., 1995).

Although cell death is often presumed to be the mechanism behind cerebral atrophy following prednisone administration, such a phenomenon could not be observed by histological and neuropathological examination of the hippocampus of patients exposed to synthetic corticosteroids or who had a long history of depression and were therefore likely to have higher cortisol levels (Lucassen et al., 2001; Müller et al., 2001) (Figs. 9 and 10). Moreover, hippocampal volume reductions in Cushing’s disease were shown to be reversible after a decrease or cessation of the steroid exposure, which is in accordance with the general clinical
experience with depressive or Cushing’s patients that treatment or operation can relieve the depressive symptoms, the HPA-axis alterations and even the hippocampal atrophy (Starkman et al., 1999; Müller et al., 2001; Lucassen et al., 2001). Changes in water content of the hippocampus have been proposed as an alternative explanation for hippocampal atrophy in depression (Lucassen et al., 2001; Müller et al., 2001; Krishnan et al., 1991a), while alterations in neuronal components or glial cells in the adult hippocampal dentate gyrus subareas may be alternative mechanisms (Czeh and Lucassen, in press). A number of studies reported atrophy of the hippocampus in Vietnam-combat-veterans with posttraumatic stress disorder as another example of the ‘glucocorticoid cascade hypothesis’, but no hypercortisolism is found in these patients. On the contrary, this disorder is associated with decreased HPA-axis activity and steroid feedback supersensitivity, often for decades after the initial trauma (Bremner et al., 1995; Yehuda et al., 1995). An increased sensitivity or upregulation of GR in PTSD and a pre-existing smaller hippocampal volume thus seems, at present, the best explanation for these data (Bremner, 1999; Rasmusson et al., 2001).

4. Conclusions

Stress plays a major role in various (patho)physiological processes associated with mood disorders and neurodegenerative
diseases. In principle, stress has the potency to exert either ameliorating or detrimental effects. The specific outcome depends on multiple variables. A crucial factor seems to be time: effects that are beneficial to an organism in the short term may have detrimental effects in the long-term. HPA-axis hyperactivity is present in a possibly large subpopulation of depressed subjects. There are two main hypotheses concerning the HPA-axis-hyperdrive and depression, i.e. 1) the CRH-hypothesis, according to which CRH not only causes the neuroendocrine-hyperdrive, but is also responsible for depressive signs and symptoms via CRH innervation of brain areas; and 2) the glucocorticoid hypothesis, which states that increased cortisol plasma levels are causal to the development for depressive symptoms. More recently, attention has been drawn to the role of AVP on HPA-axis activation in depression. A clear sex difference has been indicated in the stress response and in the susceptibility, progress, and

Fig. 10 – In situ end-labeling (ISEL) results. (A) Positive labeling in the CA-4 area of depressed patient 94-112, showing necrotic morphology (upper arrow) as indicated by the comparable size of an intact, neighboring neuron (arrowhead) without chromatin reorganization or apoptotic bodies being visible. Also seen is a labeled apoptotic cell as evidenced by its pycnotic appearance, strong condensation and brown DAB precipitate (horizontal arrow). (B) ISEL-positive neuron (arrow) just outside the CA1 cell layer of depressed patient 90-001 with clear apoptotic morphology, i.e. a reduced size as compared to unstained, healthy-looking neurons (triangle), and apoptotic bodies clearly visible. (C) ISEL-positive, apoptotic cell (arrow) with a pycnotic, condensed appearance adjacent to a nonstained large cell (arrowhead). CA1 of depressed patient 94-094. (D) Apoptotic neuron (arrow) in the subiculum of depressed patient 94-032 with three clear apoptotic bodies visible. (E) Frequent, granular morphology (arrows) suggestive of chromatolytic processes, adjacent to normal-looking neurons in CA3 of depressed patient 90-001. (F) Normal-appearing neurons in CA1 of control subject 94-123. Also, one granular, chromatolytic-like structure is visible (arrow). Scale bars: 34 μm (A, B, E and F) and 15 μm (C and D). Please note that in the absence of any major pyramid cell loss (Müller et al., 2001 and Fig. 9) and the rare occurrence of apoptosis that notably was absent from areas at risk for glucocorticoid damage such as CA3, apoptosis most probably only contributes to a minor extent to the hippocampal volume changes in depression. (From Lucassen et al., 2001; Fig. 1 with permission.)
actual outcome of depression. The hippocampus shows no Alzheimer neuropathological changes or massive cell loss in depressed patients despite a possibly reduced hippocampal volume. The latter does, however, not imply cell loss and can alternatively be ascribed e.g. to changes in water content, in neuronal components or in glial cells. On the other hand, the hippocampus in AD shows a very pronounced and early cell loss that may account for severe clinical disabilities such as memory loss. The HPA-axis is only moderately activated in AD pathogenesis. However, CRH and cortisol seem to be causally involved in the development of depression. Although there is no evidence for any major damage in the human hippocampus in depression or following glucocorticoid treatment, subtle changes can, of course, at present not be excluded.

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