General introduction

Preface
This thesis aims at identifying the neurobiological features that characterize major depressive disorder (MDD) and depression in Alzheimer’s disease (AD). The underlying question is to what extent does depression in AD share its biological characteristics with MDD?

Depression is a common occurrence. It is estimated that the life-time prevalence of depression is about 12-20% (Sadock et al., 2000; Bloom, 2004). In AD, 25-50% of the patients suffer from a form of depression at some point in the disease process (Lyketsos et al., 2002; Lyketsos et al., 2004), while the average disease duration in the population of a brain bank was found to be 8.5 years (Jost et al., 1995). In both the non-AD- and AD-population, the occurrence of depression has important consequences regarding social and daily life activities and cognitive functioning (Ustun et al., 2004; Starkstein et al., 2005).

The pathophysiology of MDD is not known, nor of depression in AD. However, there are a number of hypotheses about the pathophysiology of MDD, mainly concerning (a decrease in) the availability of neurotransmitters like noradrenaline and serotonin (Owens, 2004). These hypotheses are supported by the effects of the medication that influences the noradrenergic and serotonergic system (Owens, 2004).

Another hypothesis concerns the hyperactivity of the hypothalamic-pituitary-adrenal (HPA)-axis (Nemeroff et al., 2004; Antonijevic, 2006). Both antidepressant medication and light have an attenuating effect on the HPA-axis, while medication specifically directed at components of the HPA-axis is now becoming available: such compounds are in the pipeline of several pharmaceutical companies (Nemeroff et al., 2005; Bosker et al., 2004). The hypothesis concerning HPA-axis hyperactivity is one of the best-studied. The HPA-axis is an endocrine axis and this enables researchers to investigate it by measurements in the peripheral blood, for instance in MDD patients and in depressed AD patients. However, whether the peripheral levels fully reflect the central effects of, e.g., corticotropin-releasing hormone (CRH) is doubtful (Swaab, 2003). While the HPA-axis ultimately releases cortisol in the blood, its starting point is the paraventricular nucleus.
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(PVN) of the hypothalamus, more particularly the CRH neurons located in this nucleus. With our aim of testing the HPA-axis hypothesis in depression and answering the question whether MDD shares any neurobiological characteristics with depression in AD, the human brain, especially the hypothalamus, is of course the first place to look.

For this reason we conducted a series of post mortem studies, using hypothalami of depressed subjects, AD patients and control subjects provided by the Netherlands Brain Bank. The AD patients were studied during their lives as part of a longitudinal study of depression in AD. Prospectively obtained clinical information concerning depression is therefore available from this group of AD patients (for detailed information on this cohort, see Chapter 5).

The hypothalamic-pituitary-adrenal (HPA)-axis

Anatomy

Starting point of the HPA-axis is the hypothalamus, a small (4 cm³) and complex structure in the midline of the brain (Swaab, 2003). It contains more than ten nuclei, one of which is the paraventricular nucleus (PVN), located on either side of the third ventricle, and another is the supraoptic nucleus (SON), located on top of the optic chiasm. The PVN has a volume of only 6 mm³ (Goudsmit et al., 1990), and has a rich capillary bed, indicating the high activity of this nucleus. According to Morton it consists of about 56,000 neurons (Morton, 1969), of which some 25,000 neurons contain oxytocin (OXT) (Wierda et al., 1991; Purba et al., 1993) and 21,000 express vasopressin (AVP) (Van der Woude et al., 1995). Part of the PVN neuronal population consists of smaller neurons, called parvocellular neurons (Latin: parvus=small), that project to the median eminence or to other brain areas. A major part of the PVN and all the SON neurons have a larger cell size (magnocellular neurons) and most magnocellular neurons of these two nuclei project to the neurohypophysis (Swaab, 2003). However, an estimate of the exact neuron numbers in the PVN and SON turns out to depend strongly on the methods used (Harding et al., 1995).

While some of the PVN axons project to the neurohypophysis, the posterior lobe of the pituitary, where they release neuropeptides such as AVP and OXT into the general circulation, others terminate on the capillaries of the portal system. From these capillaries neuropeptides such as CRH are transported to the anterior part of the pituitary (Swaab, 2003). The nonapeptides AVP and OXT are synthesized in magnocellular neurons of the PVN and SON. In the PVN a rostrocaudal gradient in the ratio between OXT and AVP cells is present. The ratio AVP: OXT cells in the PVN starts below 20% and in the caudal half it goes
up to 60%, after which the ratio decreases again (Swaab, 2003). AVP neurons from the PVN project to different brain areas, among which the parabrachial nuclei, the locus coerules and the spinal cord (Fliers et al., 1986; Fodor et al., 1992; Van Zwieten et al., 1994). Unlike the rat brain, the human PVN does not allow determination of which OXT and AVP-expressing neurons will project to the median eminence or neurohypophysis and are therefore of a neuroendocrine nature, and which neurons project to other parts of the brain where they act as neurotransmitters or neuromodulators (Swaab, 2003).

CRH is produced in the parvocellular neurons which are scattered throughout the PVN, with relatively few present in the rostral part (Koutcherov et al., 2000). Fibers from these neurons do not only project to the median eminence, but also to other parts of the brain (Raadsheer et al., 1993). The biological actions of CRH are mediated via binding to two G protein-coupled receptors (GPCRs), the CRH receptor types 1 and 2 (CRHR1 and CRHR2) (Hsu et al., 2001). CRHR1 expression is very high in the cerebral cortex, amygdala, pituitary and septal region (Swaab, 2003) and this receptor mediates the “fight or flight” response, characterized by the release and production of adrenocorticotropic hormone (ACTH) by the pituitary, and consequently by the release of cortisol by the adrenal gland. The expression of CRHR2 mediates the stress-coping response during the recovery phase of stress and is confined to subcortical structures such as the PVN and SON (Swaab, 2003).

**Physiology**

The CRH peptide, consisting of 41 amino acids, is released from the parvocellular neurons in the PVN into the capillary bed of the median eminence and plays a key role in the response to stress (Vale et al., 1981; Swaab, 2003). It causes the corticotropic neurons of the anterior pituitary to release ACTH, which in turn will cause the adrenal gland to release cortisol, also called the ‘stress hormone’. This cascade is called the hypothalamic-pituitary-adrenal (HPA)-axis or ‘stress’-axis. Besides its role in the HPA-axis, CRH administered into the cerebrospinal fluid of animals leads to signs and symptoms of depression, such as loss of appetite, decreased libido, and psychomotor symptoms (Holsboer, 2001). Notably, the ACTH-releasing effect of CRH on the pituitary is strongly potentiated by AVP (Rivier et al., 1983; Gillies et al., 1982; Aguilera et al., 2000). CRH and AVP are colocalized in neurons of the PVN and increased activity of CRH neurons is accompanied by a higher proportion of CRH neurons that express AVP (Raadsheer et al., 1993; Raadsheer et al., 1994a; Raadsheer, 1994; Raadsheer et al., 1994b).

AVP, synthesized in the PVN and SON, acts as an anti-diuretic hormone (ADH)
on the kidney (Ring, 2005) and is released after dehydration (Husain et al., 1973) and other types of osmotic stimulation (Vallotton et al., 1983; Pedersen et al., 2001). AVP exerts its antidiuretic effect by increasing the readsorption of solute free water in the distal and collecting tubules of the kidney (Robertson, 2001). In the pituitary, AVP triggers ACTH release through a specific receptor subtype termed V1b or V3, which is almost exclusively expressed by pituitary corticotrops (Rene et al., 2000). There is evidence that, while CRH is important in acute stress situations, AVP becomes more prominent in chronic HPA-axis activation (Volpi et al., 2004).

AVP and OXT are produced in two kinds of neurons (Hoogendijk et al., 1985), and while in the SON the vasopressinergic neurons are obviously larger, in the PVN the two cell types show considerable variation. Still, here, too, the vasopressinergic neurons are generally larger (Dierickx et al., 1977). The observation that, under extreme forms of stimulation, neurons may produce both peptides in the rat (Mezey et al., 1991), has not yet been made in humans (Swaab, 2003). OXT is only two amino-acids away from AVP. OXT is a neuropeptide with many effects on reproduction and social interactions (Gimpl et al., 2001). While AVP has a potentiating effect on hypophyseal ACTH release, the inhibiting effect of OXT on ACTH release has now been confirmed in various species (Legros, 2001).

**Major depressive disorder**

Depression is the number four cause of disease burden and causes the largest non-fatal burden, accounting for almost 12% of all total years lived with disability worldwide (Ustun et al., 2004). The lifetime risk of MDD among Americans is 17 percent, with as many as 5-10 percent suffering from MDD in any 1-year period (Bloom, 2004; Kessler et al., 2003). Several criteria must be met when classifying MDD. The first requirement is a depressive episode. This is a period of at least two weeks with either depressed mood or loss of interest or pleasure in almost all activities, together with other symptoms, such as appetite disturbances, change in weight, sleep disturbances, psychomotor agitation or retardation, decrease of energy, feelings of (inappropriate) guilt or worthlessness, difficulties in concentration, and thoughts of death, suicidal ideations or a suicide attempt. In total at least five symptoms should be present (American Psychiatric Association, 1994).

Not only the severity of the depression may vary, there are also various subtypes (American Psychiatric Association, 1994). Melancholic-type depression, for instance, which is relevant for the studies we performed in depressed subjects, is associated with specific symptoms like worse mood in the morning (fluctuation
over the day), early morning awakening, or significant anorexia and/or weight loss. Generally, this type of depression is a severe mood disturbance and it has been related to changes in AVP plasma level (Van Londen et al., 1997). This is why in our study of hypothalamic AVP gene expression we distinguished patients with this melancholic-type depression from the patients that did not meet the criteria for melancholic-type depression. In the past, melancholic-type depression was thought to be more ‘somatic’, originating from ‘within’, ‘endogenous’ (Peselow et al., 1992), distinct from ‘exogenous’ depression which was thought to be originating externally, e.g. from social circumstances. It was thought that an endogenous type of depression would respond better to ‘somatic’ therapy, i.e. medication. In the DSM-III-R a good response to medication was considered to be related to melancholic-type of depression (American Psychiatric Association, 1987). DSM-IV, however, has dropped this characteristic, and, in general, the concept of ‘endogenous’ depression as an etiologic category has become obsolete. Today also ‘exogenous’ depression is considered to have a representation in the brain (Sadock et al., 2000).

A major question at present is whether the hyperactivity of the HPA-axis contributes to the pathogenesis of depression, or whether its activation is no more than a ‘final common pathway’ of a response to a medical (psychiatric) disorder. The ‘final common pathway’-hypothesis is supported by the fact that changes in the HPA-axis have been found in various psychiatric illnesses such as schizophrenia (Altamura et al., 1999) and panic disorder (Risbrough et al., 2006). The focus of recent research has therefore been to show the specificity of the HPA-axis disturbances with regard to the vulnerability for and relapse of depression (Zobel et al., 1999; Appelhof et al., 2006; Lauer et al., 1998).

**Alzheimer’s disease**

A hundred years ago, Alois Alzheimer first described the neuropathological hallmarks of a disease that would later be known as Alzheimer’s disease (Jellinger, 2006; Graeber et al., 1999). These hallmarks consist of plaques and tangles (Graeber et al., 1999). It is estimated that at this moment about 180,000 people in the Netherlands are suffering from dementia (RIVM, 2006), and the larger part of these demented patients will suffer from AD. The most important risk factor for AD is age. As a general rule, the prevalence of AD doubles every 5 years after the age of 65 (McDowell, 2001).

AD is a progressive disease for which no treatment is available at the moment (Jellinger, 2006). In spite of enormous efforts to unravel the pathogenesis, this so far remains unclear for the major, sporadic, form (95% of the cases) (Turner,
There are at present three major hypotheses concerning the etiology of AD: 1) The starting point of the disease is the depositing of amyloid in plaques (Jacobsen et al., 2005). 2) The ‘tangle’ or the tau-pathology is the starting point of the disease (Gold, 2002). 3) There is an underlying factor that constitutes the essence of the process, with plaques and tangles following from this process. The underlying factor could be a decrease in neuronal metabolism, leading to formation of plaques and tangles (Swaab et al., 1998).

Since animal research offers so many advantages, transgenic mice models have been created (Games et al., 2006). Each of these models exhibits at least one of the features of AD, but a ‘perfect’ model for AD accounting for all relevant aspects of the disease is not available at this moment (Van Dam et al., 2006).

**Depression in Alzheimer’s disease**

AD is considered to be primarily a disturbance of cognition (Grossberg, 2003). Until the DSM-IV, the central feature of AD is cognitive impairment, as the A-criterion is: “The development of multiple cognitive deficits manifested by both memory impairment and one or more of the following: aphasia, apraxia, agnosia, and disturbances in executive functioning” and the B criterion is: “The cognitive deficits represent as decline from previous functioning and cause significant impairment in social or occupational functioning” (American Psychiatric Association, 1994). However, in addition, up to 90% of the AD patients exhibit psychiatric symptoms during the course of the disease process (Lyketsos et al., 2002; Grossberg, 2003), such as delusions, hallucinations, depression, mania, aggression, wandering and apathy (Lyketsos et al., 2002). Also, the patient first described as “AD patient” by Alois Alzheimer, Auguste D., exhibited delusions (Cummings et al., 1992). Sleep disturbances, in addition, are a major problem for many patients, with nighttime sleep severely fragmented and daytime activity disrupted by multiple napping episodes (Dowling et al., 2005). Delusions and hallucinations are very common in AD and predict cognitive and functional decline (Scarmeas et al., 2005). The presence of hallucinations is also associated with institutionalization and increased mortality (Scarmeas et al., 2005).

Depression is one of the most frequent psychiatric complications in AD. It affects up to 50% of the AD patients during some period of the disease (Lyketsos et al., 2002). When AD patients become depressed, this has major clinical consequences, since it distresses the patient (Burns, 1991), and results in decreased daily activities (Fitz et al., 1994), decreased cognitive functioning and a higher mortality rate (Burns, 1991; Burns et al., 1991). In addition, the burden to caregivers is increased (Rabins et al., 1982), as well as the likelihood of being
admitted to a nursing home (Steele et al., 1990). Given the large and growing population of AD patients in the community, depression in AD constitutes a significant public health problem (Lyketsos et al., 2002). Depressive symptoms may also occur in the period of time before a person is diagnosed as “AD patient”. It appears that these depressive symptoms are early manifestations, rather than predictors of AD (Chen et al., 1999). Diagnosing depression in AD is of practical clinical relevance, since depressive symptoms in AD patients can be successfully treated with selective serotonin re-uptake inhibitors (SSRIs) (Lyketsos et al., 2002; Sadock et al., 2000), whereas there is no effective treatment available for AD proper.

However, diagnosing depressive disorder in AD patients is complicated due to a profound overlap of symptoms between depression and AD, e.g. loss of interest, decreased energy, difficulty in thinking or concentrating, and psychomotor agitation or retardation (Burke et al., 1988). When using, for instance, the DSM-IV criteria to diagnose depression in AD, it remains unclear whether the observed symptoms are due to depression or whether they are in fact symptoms of AD (Alexopoulos et al., 1988). Therefore, a question to which research in this field is vulnerable is whether the DSM-IV really measures depression symptoms, or in fact symptoms of AD. Another, more formal point is that according to the DSM-IIIR (and DSM-IV), depression complicating AD should not be classified as major depression (or major depressive disorder), because it occurs during the course of a neurodegenerative disease (American Psychiatric Association, 1987; American Psychiatric Association, 1994). In our research we had to deal with the problem of overlap between AD and depressive symptomatology. To overcome this confounding factor we implemented the Cornell scale for depression in dementia (Alexopoulos et al., 1988) in addition to the DSM classification. The Cornell scale is a 19-item clinician-administered instrument that uses information from interviews with both the patient and a nursing staff member, a method suitable for demented patients.

There are several hypotheses about the high prevalence of depression in AD. It has been hypothesized that depression occurs as a psychological reaction to the disease, but so far no clear association has been found between the retention of insight into the dementia process and the occurrence of depression (Ott et al., 1992; Verhey et al., 1993). As far as biological hypotheses are concerned, both the Alzheimer process and depression could be effects of a common underlying pathogenetic factor, for instance, decreased cortical metabolism (Swaab et al., 2002). Alternatively, the destruction of the cortical integrity, especially in the hippocampus, could lead to disinhibition of the HPA-axis, since under physiological circumstances the hippocampus is an inhibitor of HPA-axis activity (Swaab et al., 2005).
Scope of this thesis

The central question of this thesis, i.e. to which extent does depression in AD share its neurobiological characteristics with MDD, will be answered within the framework of the HPA-axis hypothesis of depression. Different components of the HPA-axis are studied both in depressed subjects (AVP and OXT) and in AD patients with and without depression (cortisol, AVP and OXT). In addition, the relationship between the neuropathological hallmarks of AD, plaques and tangles, and depressive symptomatology is determined.

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