Manipulating serotonin function in depression

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Introduction

Major depressive disorder

Depressive disorder is one of the most disabling diseases in the world (Üstün et al., 2004). Lifetime prevalence rates of major depressive disorder are about 17% in the USA; one in six persons will have a diagnosable depression at some point in their lives (Blazer et al., 1994). However numbers may differ between countries (Hammen, 1997). More women than men are affected by depressive disorders worldwide (with a ratio of 2:1). The rates of onset and current depression are highest in late adolescence and early twenties (Hammen, 1997). The core symptoms of depression are low mood and anhedonia (the inability to gain pleasure from normally pleasurable experiences). Other symptoms may include a decreased appetite, difficulties sleeping, fatigue, feelings of worthlessness, diminished ability to concentrate and thoughts of death or suicide. Table 1 represents the diagnostic criteria for a Major Depressive Episode, as stated by the Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 1994).

The most effective treatments for depression are antidepressant medication, structured forms of psychotherapy (eg. cognitive behavioural therapy), or a combination of both. Selective serotonin reuptake inhibitors (SSRIs) form the most widely used pharmacological treatment for depression (Petersen et al., 2002).

Since rates of relapse and recurrence in depressive disorder are high (Judd, 1997), extensive research is done on the mechanisms that may play a role in the development and maintenance of depressive disorder. Vulnerability to depression may include cognitive, biological, psycho-social and genetic factors (Hammen, 1997). In terms of biological vulnerability to depression, neurotransmitter dysfunction (serotonin, dopamine, norepinephrine) is thought to play an important role (Maes & Meltzer, 1995). This thesis focuses on the

role that the neurotransmitter serotonin (5- hydroxy-triptamine; 5-HT) plays in depression, especially in mood and cognitive processing. The link between serotonin and two biological vulnerability factors (the cortisol response to stress and heart rate variability) associated with depression will also be investigated.

The role of serotonin in depressive disorder

The notion that a dysfunctional serotonergic system is involved in the pathophysiology of depression is supported by a wide range of experimental studies (Delgado et al., 1990; Maes & Meltzer, 1995). Abnormalities in the 5-HT system can occur at different levels: availability of the serotonin precursor tryptophan (Cowen et al., 1989), serotonin synthesis, release, reuptake or metabolism, or at the pre- or postsynaptic receptors (Cleare et al., 1998; Maes & Meltzer, 1995). This 'serotonergic vulnerability' may be caused by a variety of factors such as innate factors (genetic factors, family history, personality, gender, sex hormones); environmental factors (stress, immune system and cytokines, drug use), and bio-psychological interactions (Jans et al., 2007).

Some serotonin abnormalities are not only found in acutely depressed but also in remitted depressed patients and subjects with a family history of depression (Bhagwagar et al., 2006; Flory et al., 1998). This suggests that either a dysfunctional serotonin system or an increased sensitivity of the serotonin system is a trait abnormality in depression. However, not all depressed patients show all abnormalities in 5-HT function (Van Praag, 2004).

Table 1. The diagnostic criteria for Major Depressive Episode according to the DSM-IV

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)

(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

The neurobiological basis of depression has been linked to the mechanism of action of antidepressant medication: serotonergic antidepressants increase brain serotonin function by inhibiting the re-uptake of the neurotransmitter serotonin (Blier & de Montigny, 1994; Delgado, 2000).

Since a direct measurement of serotonin in humans is problematic, research into serotonin function is based on indirect methods. Experimentally manipulating serotonin levels in humans makes it possible to study the role of serotonin function in depression and antidepressant action. In this thesis, two different interventions are used to manipulate serotonin activity in humans: acute tryptophan depletion and a diet enriched with the milk-whey alpha-lactalbumin.

Manipulations of serotonin

Tryptophan depletion

Serotonin synthesis depends on dietary intake of its precursor, the essential amino acid tryptophan. At the blood-brain barrier, tryptophan has to compete for entry with the other large neutral amino acids (LNAAs; tyrosine, phenylalanine, leucine, isoleucine and valine). Once tryptophan has entered the brain, it is synthesized in a rate limiting step by tryptophan-hydroxylase into 5-hydroxytryptophan (5-HTP) and then into serotonin. See Figure 1.

Acute tryptophan depletion (ATD) is a method to experimentally lower serotonin function by depleting the brain from its precursor tryptophan. This is done through administration of an amino-acid mixture devoid of tryptophan (Young et al., 1985). The most common ATD method involves a low-tryptophan diet during the 24 hours before the test session, followed by an overnight fast. In the morning of the test day, subjects are asked to consume a drink containing a 100g load of 15 amino-acids that does not contain

tryptophan (Bell et al., 2001), mostly mixed with water and artificial flavour. After five to six hours, ATD results in peak reductions of plasma tryptophan levels (+/- 70%) and ratio tryptophan/LNAA, which is an index of central 5-HT turnover, (+/- 90%). Therefore, ATD is a useful tool to investigate the effects of lowered serotonin function in humans. ATD results in significant behavioural effects, including a lowering of mood (Young et al., 1985), changes in cognitive performance (Park et al., 1994; Schmitt et al., 2000), increased impulsive behaviour (Young, 1986) and changes in sleep architecture (Bhatti et al., 1998). It is important to note that differential effects of ATD are found in healthy vs. depression vulnerable subjects. Mood effects of ATD are only found in remitted depressed patients taking SSRIs (Booij et al., 2002; Delgado et al., 1990) and in healthy subjects with a family history of depressive disorders (Benkelfat et al., 1994; Klaassen et al., 1999). Some of the other effects (on cognition, sleep) are not restricted to these groups, but may also occur in healthy volunteers.

The effects of ATD are usually compared to an amino acid mixture with tryptophan (Murphy et al., 2002; Park et al., 1994; Rubinsztein et al., 2001). This 'control' mixture generally results in a considerable but highly variable increase in plasma tryptophan and the tryptophan/LNAA ratio, thereby forming an active control condition instead of a placebo condition. This is especially undesirable when investigating subtle effects. An alternative was developed by Krahn et al. (1996): a quarter-strength amino acid mixture containing the same amino acids as the ATD mixture, again without tryptophan. The alternative was necessary because tryptophan was banned from the US market for several years after 1990. This mixture is also not a neutral control condition, but results in a predictable moderate reduction of the plasma tryptophan/LNAA ratio. Since this 'low-dose' mixture has been

found not to affect mood (e.g. Booij et al., 2005a), it allows for an investigation of the dose-response effects of lowered serotonin function and thus seems to be a better control condition for some research questions. Recently, different studies (Hayward et al., 2005; Munafò et al., 2006) have reported effects of a different low-dose tryptophan depletion method, using a mixture containing eight amino acids instead of the regular fifteen amino acids. The low-dose tryptophan depletion method is further discussed in Chapter 5.

Dietary interventions

Carbohydrate-rich diets have been found to increase the tryptophan/LNAA ratio and thus increase central serotonin function. This is due to a carbohydrate induced insulin response that stimulates the uptake of LNAA in skeletal muscles with the exception of tryptophan (Fernstrom & Wurtman, 1971). However, these increases are only found under rather extreme dieting conditions (Yokogoshi & Wurtman, 1986). Carbohydrate-rich, protein-poor diets have been found to increase the tryptophan/LNAA ratio by 42% compared to a control diet (Markus et al., 1998) and to prevent stress induced deterioration of mood and cortisol response but only in stress-vulnerable subjects (Markus et al., 1998). Also, carbohydrate intake improves cognitive performance of stress-vulnerable subjects under controllable laboratory stress (Markus et al., 1999). Overall, the effects of carbohydrate-rich diet seem to depend on factors such as the time of day, the type of task and the vulnerability of the population (Dye et al., 2000).

Another way to manipulate tryptophan levels is a diet rich in the milk-whey alpha-lactalbumin (Heine et al., 1996). Diet rich in alpha-lactalbumin leads to an increase in plasma tryptophan/LNAA ratio of 48% compared to a casein (placebo) diet (Markus et al., 2000), thereby raising brain serotonin

activity. Diet enriched with alpha-lactalbumin has been found to prevent stress-induced cortisol and mood response (Markus et al., 2000) and to improve cognitive performance (Markus et al., 2002), but again only in stress-vulnerable individuals.

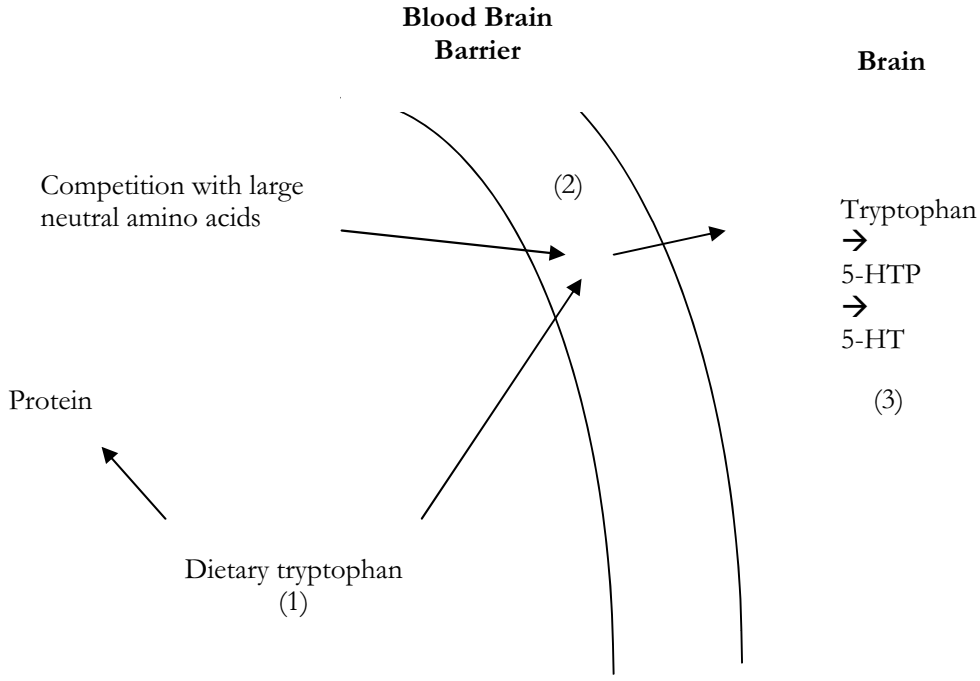
Cognitive and biological vulnerability to depression

Cognitive function

Problems concentrating and making decisions are part of the diagnostic criteria of Major Depressive Disorder (American Psychiatric Association, 1994). Experimental research has shown that memory, learning, attention, motor function and problem solving may also be affected in depressed patients (Austin et al., 2001; Elliott, 1998; Weiland-Fiedler et al., 2004). In terms of impairments in emotional (as opposed to neutral) information processing, the recognition of facial expressions of emotions has been found to be affected in depressed patients (Bouhuys et al., 1999; Gur et al., 1992). Also an increased attentional bias for negative information (Williams et al., 1996) and an increased level of dysfunctional attitudes (Ingram et al., 1998) are found compared to healthy controls.

Some of these cognitive impairments persist into the euthymic phase; however research on cognitive impairments in recovered depressed patients has shown conflicting results (Paelecke-Habermann et al., 2005; Paradiso et al., 1997; Weiland-Fiedler et al., 2004). Recently, evidence indicates that persisting impairments may exist in the specificity of autobiographical memory (Spinhoven et al., 2006), the recognition of facial emotions (Bouhuys et al., 1999) and attentional bias (Williams et al., 1996).

Figure 1. Manipulating serotonin synthesis



Serotonin synthesis can be influenced at three levels: by restricting the dietary intake of tryptophan (1); by increasing the competition with the other large neutral amino acids (2); and by inhibition of tryptophan-hydroxylase which synthesizes tryptophan into 5-HTP (3). The ATD method described in this thesis is based on (1) and (2).

Some of these impairments are also related to risk of relapse (Bouhuys et al., 1999; Williams et al., 1996), suggesting that some aspects of emotional information processing may be vulnerability markers for depression.

Evidence from animal and human studies has linked serotonin to cognitive function, especially learning and memory (McEntee & Crook, 1991; Sirviö et al., 1995). ATD studies have supported these findings. In healthy volunteers, ATD selectively impairs learning (Park et al., 1994), memory retrieval and consolidation (Klaassen et al., 2002; Park et al., 1994; Riedel et al., 1999) and ATD improves attention in healthy samples (Schmitt et al., 2000) and patients (Booij et al., 2005a). Recently, interest has been paid to the effects of ATD on emotional information processing; ATD impaired the recognition of facial expressions of fear in female healthy volunteers (Harmer et al., 2003c) and increases emotional interference in both healthy and recovered depressed patients (Hayward et al., 2005; Munafò et al., 2006).

Research on the effects of antidepressant medication also supports the link between serotonin and cognition (Amado-Boccara et al., 1995; Harmer et al., 2003b; Thompson, 1991). Very brief (one day or one week) treatment with a serotonergic antidepressant causes selective changes in emotional information processing, in particular in the recognition of facial expressions of emotions, in both healthy volunteers and recovered depressed women (Bhagwagar et al., 2004; Harmer et al., 2003a; Harmer et al., 2004; Harmer et al., 2006a).

Stress and cortisol

Depressive episodes are often preceded by stressful life events (Brown et al., 1987; Kendler et al., 1999). Elevated cortisol levels, caused by stressful life events, may lower brain serotonin function and in turn lead to a depressed

state (Cowen, 2002). High cortisol levels may initially cause higher central nervous system turnover; however during continuous or frequent stress the availability of brain tryptophan and serotonin may diminish and vulnerability to depression may increase (Markus, 2003).

This makes cortisol an important biological mediator through which stress lowers serotonin function and thereby causes depression in vulnerable individuals. Cortisol is controlled by the hypothalamo-pituitary-adrenal (HPA) axis with which the central serotonergic system interacts. The finding of HPA-axis hyperactivity in depression appears to be consistent, although it is not found in all patients (Jans et al., 2007).

To study neuroendocrine dysfunction in depression, neuroendocrine challenge tests are used, such as d-fenfluramine (Cleare et al., 1998) or the dexamethasone/ corticotrophin releasing hormone (CRH) test (Baghai et al., 2002). Evidence from challenge studies indicates that depressed and remitted depressed patients show blunted neuroendocrine responses to drugs that stimulate serotonin turnover, suggesting decreased serotonin responsiveness (Bhagwagar et al., 2002a; Bhagwagar et al., 2002b; Flory et al., 1998; Riedel et al., 2002). These results indicate that blunted cortisol responses to a neuroendocrine challenge may be a vulnerability marker for depression.

Heart rate variability

Cardiovascular disease (CVD) is the leading cause of death in the United States (American Heart Association, 2006). Depression has been found to be an independent risk factor for CVD (see for a review Rugulies, 2002). Depression after a myocardial infarction also predicts mortality (Anda et al., 1993). Decreased heart rate variability (HRV) is a risk factor for CVD (Stein & Kleiger, 1999) and has also been associated with depression and may thus

underlie the increased risk of cardiovascular disease in depression (Gorman & Sloan, 2000; Grippo & Johnson, 2002; Musselman et al., 1998). HRV is a measure of autonomic regulation of the heart (Krantz & McCeney, 2002). HRV reflects the capacity of the autonomic nervous system to vary the intervals between consecutive heartbeats (Grippo & Johnson, 2002). Reductions in HRV are not exclusively related to depression (Agelink et al., 2002; Rechlin et al., 1994) but are also associated with generalized anxiety disorder (Thayer & Lane, 2000), impulse control disorders such as ADHD (Beauchaine et al., 2001), and alcoholism (Ingjaldsson et al., 2003). Negative results have also been found (Gehi et al., 2005). Serotonin dysfunction is suggested to play an etiological role in both depression and cardiac dysfunction (Grippo & Johnson, 2002), and may thus underlie the association between HRV and depression.

Considering the different vulnerability factors for depression that were discussed above and the fact that serotonin plays an important role in the pathophysiology and the treatment of depressive disorders, it would be interesting to investigate the specific role that serotonin plays in the cognitive and biological vulnerability to depression. Experimental manipulations of serotonin function may influence cognitive and/ or biological factors in individuals that are vulnerable to depression (e.g. remitted or recovered depressed patients). Since serotonin is linked to cognitive performance, the cortisol response to stress and heart rate variability, experimental changes in serotonin function may affect these processes, resembling the findings in depressed patients.

Research aims

This thesis will investigate the effects of three different serotonin manipulations (an alpha-lactalbumin enriched diet, low-dose ATD, high-dose ATD) on mood and cognitive processing in euthymic patients with a history of depressive disorder and healthy controls. The literature regarding a possible link between serotonin induced changes in mood and emotional information processing will also be discussed.

The first project that was carried out as part of the current thesis investigated the effects of an alpha-lactalbumin enriched diet, which increases serotonin activity, on mood and different aspects of neutral information processing in recovered depressed patients and healthy controls. The second project focussed on the effects of acute tryptophan depletion, which lowers serotonin function, on mood and neutral as well as emotional information processing in medicated remitted depressed patients. In addition to these two empirical studies, an overview of the literature is given on the effects of serotonin manipulations on mood and emotional information processing, to evaluate a possible link between serotonin induced changes in mood and emotional information processing. Apart from the effects of serotonin manipulations on cognitive processing, the link between serotonin activity and two different biological vulnerability factors for depression was also investigated. The first study additionally investigated the effects of alpha-lactalbumin on stress-induced cortisol response and the second study also looked at the effect of acute tryptophan depletion on heart rate variability.

Outline of this thesis

In Chapter 2, results of a study are reported in which remitted depressed patients are compared to healthy controls to investigate possible residual

cognitive impairments that persist into the euthymic phase. Chapter 3 will describe the effects of an alpha-lactalbumin enriched diet on cognitive performance in unmedicated recovered depressed patients and healthy controls. In Chapter 4 the effects of alpha-lactalbumin on mood and stress-induced cortisol response in unmedicated recovered depressed patients and healthy controls are reported. Chapter 5 describes the effects of low-dose and high-dose ATD on mood and neutral as well as emotional information processing in medicated remitted depressed patients. In Chapter 6, the effects of low-dose and high-dose tryptophan depletion on individual plasma tryptophan levels and the ratio tryptophan/LNAA will be discussed. In Chapter 7 the effects of ATD on heart rate variability in medicated remitted depressed patients are reported. A literature overview of studies investigating the effects of serotonin manipulations on emotional information processing and mood is given in Chapter 8. Also, evidence for a possible sequential link between serotonin induced changes in emotional information processing and mood is evaluated. Chapter 9 contains a summary and integration of the main findings, as well as methodological strengths and limitations, directions for future research and clinical implications of the findings reported in this thesis.