



REVIEW

Depressive disorders—is it time to endorse different pathophysiologies?

Irina A. Antonijevic*

Department of Psychiatry, University Medicine, University of Berlin, Charité, Germany

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Summary Enhanced activity of the hypothalamic-pituitary-adrenal (HPA) axis, involving elevated secretion of corticotropin-releasing hormone (CRH), is considered a key neurobiological alteration in major depression. Enhanced CRH secretion is also believed to contribute to the typical sleep alterations and the clinical presentation of major depression.

While it is acknowledged that HPA overdrive and hypernoradrenergic function is associated with melancholic depression, there is growing evidence that hypoactivity of the HPA axis and afferent noradrenergic pathways is present in patients with atypical features of depression. The clinical relevance of such a differentiation is highlighted by findings which suggest distinct responses to pharmacological treatments. Moreover, it has been reported that female patients respond better to selective serotonin re-uptake inhibitors (SSRI) than tricyclic antidepressants. Interestingly, the female predominance among patients with depression seems to be restricted to the atypical subtype.

Besides HPA axis activity, distinct alterations of the serotonergic system may also play a critical role for the melancholic and atypical phenotypes, namely a reduced restrained via 5-HT_{1A} autoreceptors in the former and primarily reduced serotonin synthesis in the latter. Moreover, there is evidence for an immune activation in patients with depression, the extent and duration of which may be distinguishable for the melancholic and the atypical subtype. In this regard, lessons can be learned from depressive symptoms in patients with autoimmune disease, associated with different alterations of the HPA axis, and in patients undergoing cytokine therapy.

In conclusion, the available data today suggest that clinically relevant differences in the underlying pathophysiology in patients with depression exist. The identification of distinct endophenotypes for major depression will not only improve our understanding of the disease, but will also contribute to more specific treatment strategies.

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1. Introduction

There is growing evidence that depressive disorders encompass a group of disorders, which differ with

* Address. Lundbeck Research USA, 170 Williams Drive, Ramsey, NJ 07446, USA. Tel.: +1 201 350 0546; fax: +1 201 818 1011.

E-mail address: irinaariane@yahoo.co.uk.

regard to hypothalamic-pituitary adrenal (HPA) axis activity, immune functions and the treatment response (Kornstein et al., 2000a; Gold and Chrousos, 2002; Murck, 2003; Murck et al., 2005). As early as 1992, Chrousos and Gold put forward the hypothesis that sustained stress system dysfunction, characterised by either hyper- or hypoactivity of the HPA axis, play a role for various pathophysiologic states, including a range of psychiatric, endocrine and inflammatory diseases (Chrousos and Gold, 1992). The HPA axis, in turn, plays a critical role for sleep regulation, which is distinctly disturbed in patients with typical symptoms of major depression (Kupfer, 1995; Steiger, 2002).

One effort to clinically define a subtype of depression with a possibly distinct pathophysiology and response to treatment is reflected by the renewed discussion about the concept of atypical depression (Quitkin et al., 1993; Posternak and Zimmerman, 2002; Parker et al., 2002; Angst et al., 2002; Benazzi, 2003; Murck, 2003). Though the debate regarding the best clinical criteria for atypical depression continues, the available data suggest that the neuroendocrine pathophysiology is different, and even opposite, to that observed in patients with melancholic depression (Chrousos and Gold, 1992; Gold and Chrousos, 2002; Murck, 2003).

Another interesting field of research focuses on the role of immune activation for depressive disorders (for review see Licinio and Wong (1999), Leonard (2001), Anisman and Merali (2002)). Evidence for an association includes data showing a high incidence of depressive symptoms in some patients with activation of the inflammatory response system. The latter includes in particular patients with cancer, infectious and autoimmune diseases (Garland and Zis, 1991; Fassbender et al., 1998; Raison and Miller, 2001; Musselman et al., 2001b; Raison and Miller, 2003; Musselman et al., 2003; Feinstein, 2004). Moreover, cytokine therapies, used for treatment of hepatitis C and cancer, have been repeatedly associated with an enhanced incidence of depressive symptoms (Bonaccorso et al., 2001; Musselman et al., 2001b; Capuron et al., 2002; Schaefer et al., 2003; Capuron et al., 2003a).

A better understanding of the differences in the underlying pathophysiology is critical for a classification of patients based on one hand on the clinical presentation and on the other hand on the (neuro-) biological profile. Ultimately, the identification of endophenotypes for depression will help to choose the most appropriate treatment for a given patient (Hasler et al., 2004). Thus, over the last years, several publications have suggested that subgroups of patients with depression may

respond more favourably to one rather than another antidepressant medication (Quitkin et al., 1993; Kornstein et al., 2000a; Stewart et al., 2002; Joyce et al., 2004; Murck et al., 2005). This strategy can, in turn, contribute to our understanding of the underlying pathophysiology of subtypes of depression. Such knowledge may be particularly useful when exploring phenotype-genotype relationships. Though most publications today distinguish primarily the melancholic and atypical subtype, it is likely that the identification of further endophenotypes will be possible in the future.

The present review summarises recent findings on differences with regard to sleep-endocrine and immunological alterations among patients with depression. Based on the model proposed by Gold and Chrousos (Gold and Chrousos, 2002), recent data on altered regulation of sleep, immune and serotonin functions are also integrated.

2. HPA axis activity in depressive disorders

Many studies have shown that a major depressive episode is characterised by typical neuroendocrine and sleep-EEG alterations. Overactivity of the HPA axis, a key neuroendocrine alteration observed in patients suffering from an acute major depressive episode, is assumed to reflect an elevation of hypothalamic corticotropin-releasing hormone (CRH) and vasopressin secretion (Gold and Chrousos, 1985; Roy et al., 1987; Nemeroff, 1988; Kupfer et al., 1990; Lauer et al., 1991; Steiger et al., 1994; Buysse et al., 1997; Holsboer, 1999; Antonijevic et al., 2000b; Steiger, 2002). Enhanced secretion of CRH is considered to play an important role for behavioral symptoms typically associated with major depression, namely enhanced anxiety, lost responsiveness to the environment, a diurnal variation with depressed mood at its worst in the morning, disturbed sleep continuity, psychomotor alterations, decreased appetite and libido as well as cognitive impairment (Gold and Chrousos, 1985, 2002; Holsboer, 1999). The effects of centrally released CRH are thought to be mediated by CRH-R1 and R2 receptors in limbic areas such as the hippocampus and the amygdala as well as afferent neurons in the locus coeruleus and the dorsal raphe (Holsboer, 1999; Roozendaal et al., 2002; Gold and Chrousos, 2002; Bale and Vale, 2003; Thomas et al., 2003). Serotonergic neurons in the dorsal raphe nucleus, as well as noradrenergic neurons in the brainstem and the locus coeruleus are important afferents for the regulation of hypothalamic CRH secretion

(Cunningham et al., 1990; Vertes, 1991; Valentino et al., 1993; Calogero, 1995; Dayas et al., 2001). Moreover, a forward circuit between hypothalamic CRH neurons and noradrenergic neurons of the locus coeruleus, which is involved in the stress response, has been described (Valentino et al., 1992, 1993). Similarly, a circuit exists between brainstem and dorsal raphe nuclei and the amygdala complex (Imai et al., 1986; Vertes, 1991; Van Bockstaele et al., 1998; Linthorst et al., 2002; Commons et al., 2003). As projections from the amygdala can stimulate the HPA axis (Weidenfeld et al., 2002), a vicious circle may sustain enhanced CRH secretion, hyperactivity of the amygdala and noradrenergic system in patients with major depression (Roy et al., 1987; Wong et al., 2000; Gold and Chrousos, 2002; Drevets, 2003).

The clinical correlate of sustained HPA overactivity, enhanced amygdala activation and hyper-noradrenergic function is depression with melancholic features (Wong et al., 2000; Gold and Chrousos, 2002). The somatic consequences of these neuroendocrine disturbances include coronary artery disease and osteoporosis (Schweiger et al., 1994; Gold and Chrousos, 1999, 2002).

A nearly complete opposite neuroendocrine disturbance, with reduced HPA activity and CRH secretion, mediated by an enhanced negative feedback by cortisol and hyponoradrenergic function, has been described initially more than 10 years ago (Chrousos and Gold, 1992). Today, various authors have substantiated the evidence for HPA hypofunction in a subgroup of depressed patients (Asnis et al., 1995; McGinn et al., 1996; Levitan et al., 2002). The associated symptom cluster, which includes hypersomnia, hyperphagia and lethargy or fatigue, is referred to as atypical depression or depression with reversed neurovegetative symptoms (Thase et al., 1991; Chrousos and Gold, 1992; Gold and Chrousos, 2002). However, the validity of this concept remains a matter of debate, which is addressed in a separate paragraph.

3. Sleep-EEG findings in depressive disorders

Typically, patients with major depression report sleep disturbances (Benca et al., 1992; Kupfer, 1995), which comprise difficulties falling asleep, remaining asleep and early morning awakening. Examinations of the sleep-EEG in acutely depressed patients showed a decrease in slow wave sleep and overall non-REM sleep duration, a shortened REM latency, and an increase in REM

density (Kupfer et al., 1990; Lauer et al., 1991; Steiger et al., 1994; Buysse et al., 1997; Antonijevic et al., 2000b). Animal and human studies support a critical involvement of central CRH secretion in these sleep alterations (Ehlers et al., 1986, 1997; Holsboer et al., 1988; Opp, 1995; Chang and Opp, 2001; Steiger, 2002). Thus, CRH disturbs sleep continuity, promotes EEG activity in the higher frequency range and reduces slow wave sleep (Ehlers et al., 1986, 1997; Holsboer et al., 1988; Opp, 1995; Chang and Opp, 2001; Steiger, 2002). Opposite effects have been noted for hypothalamic growth hormone-releasing hormone (GHRH), which improves sleep continuity, and promotes slow wave sleep and EEG activity in the lower frequency range (Steiger, 2002; Obal and Krueger, 2004). Hence, sleep-EEG alterations in patients with major depression have been attributed to a relative predominance of hypothalamic CRH over GHRH secretion (Ehlers et al., 1997; Holsboer, 1999; Steiger, 2002).

The few published studies examining the sleep-EEG specifically in patients classified as suffering from atypical depression showed that, unlike in melancholic patients, sleep continuity was not disturbed, while changes in REM sleep may be related to the presence of anxiety (Quitkin et al., 1985; Wager et al., 1990). The reported hypersomnia and fatigue in patients with atypical features could indicate that more subtle alterations of the sleep architecture occur in this subgroup.

While the first reports on sleep-EEG alterations in patients with major depression focused on REM sleep parameters, in recent years alterations of non-REM sleep have received increasing attention (Kupfer et al., 1990; Buysse et al., 1997; Armitage et al., 2001; Antonijevic et al., 2003). In particular, alterations of the pattern of delta EEG activity, which comprises the slow, high-amplitude waves, have been described (Kupfer et al., 1990; Buysse et al., 1997; Armitage et al., 2001; Antonijevic et al., 2003). Normally, delta activity is highest during the first non-REM period and declines markedly over the course of the night and with each subsequent non-REM period. Therefore, the ratio of delta sleep during the first and the second non-REM period (initially described by Kupfer and colleagues and named 'delta sleep ratio' (Kupfer et al., 1990; Kupfer, 1995)) is normally greater than 1. A shift of delta EEG activity from the first to the second non-REM period or a predominant decline in delta activity during the first non-REM period results in a reduced 'delta sleep ratio', which has been described in patients with an acute major depressive episode (Kupfer et al., 1990; Armitage et al.,

2001; Antonijevic et al., 2003; Jindal et al., 2003). A reduced 'delta sleep ratio' seen during a depressive episode has been associated with a higher risk for recurrence of depression (Kupfer et al., 1990; Kupfer, 1995). In a recent study, treatment with selective serotonin re-uptake inhibitors (SSRI) led to a normalisation of the delta sleep ratio and clinical improvement in patients with depression (Jindal et al., 2003).

We have shown that pre-menopausal women with depression showed primarily a reduced 'delta sleep ratio', but otherwise little disturbances of the sleep-EEG (Antonijevic et al., 2003). Similarly, another recent study described in adolescent female patients with depression primarily a reduction of delta sleep selectively for the first non-REM sleep period (Armitage et al., 2001). As the authors hypothesised that this finding could represent a marker for the chronicity of depression in young female patients (Armitage et al., 2001), a reduced 'delta sleep ratio' may be a useful marker to identify early on patients at high risk for recurrence and chronic course of disease.

4. Immune system alterations and depressive disorders

The first observations that patients with an acute major depression show altered immune responses date back to the late eighties (Darko et al., 1988). In particular, changes in cellular immunity have been reported in depression and have been associated with hypercortisolism (Evans et al., 1988). Today, several studies reported evidence for an inflammatory immune reaction during a major depressive episode and a reduction of pro-inflammatory cytokine secretion with clinical improvement during antidepressant drug treatment (Maes et al., 1994, 1995; Rothermundt et al., 2001; Owen et al., 2001; Musselman et al., 2001b; Penninx et al., 2003; Thomas et al., 2005).

Since some of the early studies were based on small sample sizes and did not always control for antidepressant medication, it has not been possible to clearly distinguish patients with atypical vs melancholic features by their cytokine profile (Anisman et al., 1999). However, all studies taken together suggest that an acute depressive episode is primarily characterised by an acute phase immune response (Zorrilla et al., 2001), which can further impair corticosteroid-mediated negative feedback inhibition of the HPA axis (Schobitz et al., 1994). In contrast, a chronic course of depression, that has been associated with atypical features, seems to be

associated with a persistently enhanced secretion of the pro-inflammatory cytokine interleukin (IL)-1 β (Anisman et al., 1999; Anisman and Merali, 2002). Low HPA activity in these patients may preclude a normal limitation of the immune response and thus facilitate a chronic inflammatory reaction (Elenkov and Chrousos, 2002).

On the other hand, two recent studies in elderly patients with depression showed an association of pro-inflammatory cytokine secretion, namely IL-1 β and IL-6, and acute phase immune changes, with depressed mood and depression severity (Penninx et al., 2003; Thomas et al., 2005). In line with a previous observation (Anisman et al., 1999), pro-inflammatory cytokine secretion was strongly correlated with the duration of the current episode (Thomas et al., 2005). These findings suggest that, at least in elderly patients, both severity and duration of depressive symptoms contribute to greater inflammatory cytokine secretion and hence may increase the risk for somatic consequences (Licinio and Wong, 1999).

An association between immune activation and depression is also supported by studies describing a high incidence of depressive symptoms in patients undergoing immunostimulatory therapies such as interferon alpha for hepatitis C or IL-6 and IL-2 for cancer (Bonaccorso et al., 2001; Musselman et al., 2001a,b; Capuron et al., 2003a,b). Some studies even noted an association between the extent of therapy-induced pro-inflammatory cytokine release and depressive symptoms (Bonaccorso et al., 2001; Musselman et al., 2001b). In particular elevated secretion of the pro-inflammatory cytokine IL-6 has been repeatedly associated with typical depressive symptoms in patients with various diseases (Bonaccorso et al., 2001; Musselman et al., 2001b).

Further support for a role of immune activation for depressive symptoms comes from studies showing a reduction in pro-inflammatory, but increase in anti-inflammatory cytokine secretion by various antidepressants, and in particular those promoting serotonergic transmission (Lin et al., 2000; Leonard, 2001; Maes, 2001; Kenis and Maes, 2002). As pro-inflammatory cytokines can reduce serotonin levels as well as tryptophan availability by increasing the serotonin metabolism, it is intriguing that SSRI have been shown to reduce immunotherapy-induced depression (Musselman et al., 2001a; Capuron et al., 2003a). The impairment of serotonergic neurotransmission by immune stimulation involves activation of the enzyme indoleamine-2,3-dioxygenase, resulting in a preferential production of kynurenine and quinolinic acid rather than serotonin from tryptophan (Konsman et al.,

2002). The clinical relevance of this altered metabolism is demonstrated by the inverse correlation between pro-inflammatory cytokine secretion and availability of plasma tryptophan (Maes et al., 1994; Song et al., 1998). Moreover, a greater decrease in serum tryptophan was observed in patients who developed depressive symptoms while undergoing immunostimulatory treatment with IL-2 or interferon alpha (Capuron et al., 2002).

5. On the relationship between the immune system, HPA axis activity and sleep regulation in depressive disorders

One mechanism through which pro-inflammatory cytokines, in particular IL-1 β and IL-6, could contribute to depressive symptoms is via their stimulation of the HPA axis, including hypothalamic CRH secretion (Licinio and Wong, 1999; Leonard, 2001; Elenkov and Chrousos, 2002; Capuron and Dantzer, 2003). Inflammatory cytokines, in turn, affect sleep regulation in a concentration-dependent manner: while low concentrations promote slow wave sleep and sleep continuity, high concentrations disturb sleep continuity and reduce the amount of time spent in slow wave sleep (Mullington et al., 2000; Opp and Imeri, 2001; Pollmächer et al., 2002). The latter effect involves elevated secretion of CRH (Opp, 1995). In line with these data is the observation that the IL-1 β inhibits the locus coeruleus at low concentrations, but enhances locus coeruleus activity at high concentrations (Borsody and Weiss, 2002). A reduced activity of the locus coeruleus, in turn, is a prerequisite for REM sleep and slow wave sleep (Aston-Jones et al., 2001).

Interestingly, the sleep-endocrine effects of pro-inflammatory cytokines also depend on the responsiveness of the HPA axis (Opp and Imeri, 2001): animals with a reduced HPA responsiveness to stimulation with IL-1 β showed a rapid and pronounced increase in slow wave sleep. The increase in slow wave sleep was much less pronounced and restricted to the lower dose of IL-1 β in rats with a normal HPA responsiveness. In contrast, animals with an exaggerated responsiveness showed initially a profound dose-dependent increase in waking. Though it remains to be shown that similar mechanisms operate in humans, and in particular in patients with depression, the data open up the possibility that the responsiveness of the HPA axis to an immune stimulus may influence the symptom cluster of patients with depression,

in particular the development of atypical or typical features.

Indeed, a recent study showed that patients who developed typical symptoms of depression during therapy with interferon alpha showed an exaggerated response of the HPA axis to the first injection of interferon alpha compared to those patients who did not develop depression during therapy (Capuron et al., 2003b).

Furthermore, in patients suffering from immune-mediated diseases with concurrent HPA overactivity such as multiple sclerosis (Fassbender et al., 1998; Then Bergh et al., 1999) a high prevalence of depressive symptoms has been repeatedly described (Garland and Zis, 1991; Feinstein, 2004). On the other hand, the role of HPA activity in multiple sclerosis seems complex: while enhanced HPA activity may restrain pathological immune activation (Schumann et al., 2002; Huitinga et al., 2004), prolonged overactivity of the HPA axis may contribute to depressive syndromes.

In animal models, a single administration of IL-1 β induced a long-lasting activation of the HPA axis, which was accompanied by an increased expression of hypothalamic CRH, increased co-storage of CRH and vasopressin, as well as an increased evoked noradrenaline release (Huitinga et al., 2000; Schmidt et al., 2001, 2003). Priming with a single stimulus with IL-1 β resulted in an exaggerated HPA response not only to a second immune stimulus but also to an emotional stressor (Schmidt et al., 2001, 2003). These findings open up the hypothesis that individuals who have experienced a sensitisation of the HPA axis may respond to a subsequent emotional stressor with sustained HPA axis overactivity. This, in turn, could enhance the risk to develop depression with typical features. On the other hand, individuals with a reduced responsiveness of the HPA axis, i.e. to an immune stimulus, may not mount an appropriate HPA axis activation. This situation could entail a sustained inflammatory response which is not adequately controlled by (elevated) corticosteroid concentrations and may represent a risk to develop depression with atypical features (Anisman et al., 1999; Elenkov and Chrousos, 2002).

6. On the role of gender for depressive disorders, HPA axis activity, sleep regulation and immune functions

A higher prevalence of depressive disorders in females has been reported for many years. Recently, however, two studies reported a markedly higher prevalence of depression with atypical

features in women compared to men, while no such gender bias was noted for non-atypical depression (Silverstein, 2002; Angst et al., 2002). Another elegant study provides further support for a critical influence of gender for the symptom cluster during a depressive episode. In a large group of male-female dizygotic twins females reported more fatigue and hypersomnia, and slightly more increased appetite, while males reported more insomnia and agitation (Khan et al., 2002).

A better treatment response to SSRI than tricyclic antidepressants in women, and particularly pre-menopausal women, with major depression has been reported (Kornstein et al., 2000a). Also, women may respond better to SSRI than men (Kornstein et al., 2000a; Murck et al., 2003; Joyce et al., 2004). Interestingly, some studies suggested that patients with atypical depression respond better to psychopharmacological treatment with monoamine-oxidase-inhibitors (MAOI) or SSRI than tricyclic antidepressants (Quitkin et al., 1993; Stewart et al., 1998, 2002; Joyce et al., 2004). These findings point to the possibility that among female patients with major depression a substantial proportion presents with atypical features, as has been suggested previously (Thase, 1998). Thus, atypical features may be quite typical, at least among younger female patients with depression, while later onset depression may be associated with more severe sleep-endocrine alterations and more melancholic features (Maes, 2002). Support for this assumption is provided by a study showing that particularly in elderly female patients with melancholic depression hypernoradrenergic function paralleled HPA overactivity (Wong et al., 2000). In line with the above observations we have shown recently that in female patients with depression sleep-endocrine alterations considered typical for major depression are observed primarily in post-menopausal patients (Antonijevic et al., 2003). While post-menopausal patients compared to age-matched controls showed a decline in slow wave sleep and sleep continuity, an increase in REM density as well as higher nocturnal cortisol and ACTH secretion, pre-menopausal patients compared to pre-menopausal controls showed primarily a reduced 'delta sleep ratio', but not other changes commonly noted during a major depressive episode (Antonijevic et al., 2003). Since most patients had not experienced recurrent depressive episodes, the groups examined were different with regard to the onset of depression (i.e. before or after menopause), which may also have contributed to our observation.

It has been suggested that chronicity of depression affects women more seriously, with

first symptoms occurring earlier and leading to a poorer quality of life (Kornstein et al., 2000b). This observation has also been reported by other authors, who associated a reduced 'delta sleep ratio' in female adolescent patients with a more chronic course of depression (Armitage et al., 2001). Depression with reversed neurovegetative symptoms also seems to affect younger patients and to follow a more chronic course (Angst et al., 2002; Stewart et al., 2002). A higher incidence of comorbid personality and anxiety disorders in early-onset depression could also account for the more chronic course of the depressive episode in these patients (Fava et al., 1996; Klein et al., 1999; Kornstein et al., 2000b).

Activity of the HPA axis, including hypothalamic CRH secretion, and ascending aminergic pathways seem critical for the depressive symptom cluster. It is noteworthy that gonadal steroids modulate hypothalamic CRH secretion as well as neuronal activity in afferent nuclei, namely the locus coeruleus and the brainstem (Herbison et al., 1990; Antonijevic et al., 1995; Conde et al., 1995; Dayas et al., 2000). The serotonergic system is also modulated by female gonadal steroid hormones, albeit in a complex manner, with changes in the density and function of pre- as well as postsynaptic serotonin receptors and transporters (Fink and Sumner, 1996; Lu and Bethea, 2002; Klink et al., 2002). Interestingly, women have higher somatodendritic 5-HT_{1A} receptor binding than men (Parsey et al., 2002), opening up the possibility that at least in pre-menopausal women serotonergic transmission is more restrained than in men (Stahl, 1998). In addition, male compared to female rats showed higher activity of serotonergic dorsal raphe neurons due to a greater GABA-mediated tonic inhibitory influence in the latter (Klink et al., 2002). Since oestrogen stimulates GABA-ergic transmission through stimulation of GABA-A receptor expression as well as GABA release (Herbison and Fenelon, 1995; Herbison, 1997), these data indicate that females, in particular during the pre-menopausal years, may be at a greater risk for attenuated afferent serotonergic neurotransmission. This in turn could contribute to HPA hypoactivity and an increased risk to develop atypical depression. In support of the above, it has been shown that women are more susceptible to the effects of tryptophan depletion as they showed a markedly greater reduction in serotonin synthesis, a more marked lowering of mood, and an impaired processing of fear related cues (Ellenbogen et al., 1996; Nishizawa et al., 1997; Harmer et al., 2003).

Interestingly, a recent study demonstrated that a reduced serotonin synthesis in the dorsal raphe

nucleus leads to a prolongation of slow wave sleep (Gao et al., 2002). Hence the observation that young female patients with depression showed no reduction of slow wave sleep (Reynolds et al., 1990; Antonijevic et al., 2003) could reflect reduced serotonin synthesis in the dorsal raphe nucleus.

Moreover, IL-1 β injected into the serotonergic dorsal raphe nucleus acutely inhibited serotonergic neurons and REM sleep and enhanced non-REM sleep (Manfridi et al., 2003), suggesting that a sustained elevation of IL-1 β could contribute to sleep-endocrine alterations in young female patients with (atypical) depression.

Gender is also increasingly recognised to play a critical role in the immune system: women are in general more susceptible to autoimmune diseases than men (Whitacre, 2001). In line with a biphasic dose effects of oestrogens, with a facilitation of immune responses by lower concentrations, but a suppression at higher concentrations, many studies showed that inflammatory cytokine secretion is greater from female than male immune cells (Bebo et al., 1998; Whitacre, 2001; Angele and Faist, 2002; Voskuhl, 2002; Wichmann et al., 2003).

A recent study noted that in patients with rheumatoid arthritis, an autoimmune disease associated with hypoactivity of the HPA axis (Wilder, 2002), depression is associated with high levels of anxiety (VanDyke et al., 2004). Since women constituted more than two-thirds of the depressed group, it would be interesting to examine whether these patients fulfilled the criteria for atypical depression.

In contrast, multiple sclerosis is an autoimmune disease associated with enhanced HPA activity (Fassbender et al., 1998; Then Bergh et al., 1999) and a high prevalence of depression (Garland and Zis, 1991; Feinstein, 2004). Though no formal assessment of the subtype of depression has been published so far, we have shown that female patients with multiple sclerosis are susceptible to develop sleep alterations associated with typical depression, namely a shortened REM latency, a high REM density and reduced stage 2 sleep (Antonijevic and Steiger, 2003). Moreover, we noted a pronounced reduction of the 'delta sleep ratio' upon prolonged treatment with high doses of corticosteroids in patients with multiple sclerosis and development of typical depression if the reduced 'delta sleep ratio' was sustained (Antonijevic and Steiger, 2003). Interestingly, the exact opposite sleep-EEG changes have been noted in young healthy volunteers after administration of a combined serotonin reuptake inhibitor and 5-HT_{1A} receptor agonist (Murck et al., 2001). Although

the data in multiple sclerosis patients are very preliminary, they support a broader relevance of a reduced 'delta sleep ratio' as a marker for individuals at high risk for depressive disorders, as proposed originally by Kupfer and colleagues for patients with major depression (Kupfer et al., 1990; Kupfer, 1995). Whether impaired 5-HT_{1A} receptor function plays a critical role for the reduced 'delta sleep ratio' remains to be confirmed.

Interestingly, 5-HT₂ receptors also modulate effects of IL-1 β on the slow wave sleep pattern. While blockade of 5-HT₂ receptors enhanced the acute stimulatory effects of IL-1 β on slow wave sleep, it attenuated the effect later on (Imeri et al., 1999). These data suggest that modulation of the sleep EEG by cytokines depends on the timing of the immune stimulus as well as the status of the serotonin system.

Since gender influences the serotonin system, HPA axis activity and cytokine secretion, it seems likely that an interaction between these function contributes to the behavioral symptoms, including the sleep regulation, of patients with depressive disorders.

6.1. On the role of the serotonin system for different pathophysiologies of depressive disorders

As outlined above, the level of HPA axis activity plays a critical role for the pathophysiology of major depression (Chrousos and Gold, 1992; Gold and Chrousos, 2002). While HPA overactivity is associated with hypernoradrenergic function and melancholic features of depression (Roy et al., 1987; Wong et al., 2000), reduced noradrenergic activity has been postulated in atypical depression (Asnis et al., 1995; McGinn et al., 1996). This critical role of afferent noradrenergic pathways from the locus coeruleus for HPA activity and hence the clinical presentation of depression has been acknowledged by Gold and Chrousos in their recently published scheme (Gold and Chrousos, 2002).

Similar to the ascending noradrenergic pathways, serotonergic pathways from the dorsal raphe nucleus modulate hypothalamic and limbic nuclei involved in depressive symptoms (Vertes, 1991; Calogero, 1995; Thomas et al., 2003; Commons et al., 2003). In addition, as indicated in the previous paragraphs, the serotonin system may play a critical role for the clinical features of depression. Firstly, the afferent serotonergic pathways are modulated by gonadal steroids and gender

(Fink and Sumner, 1996; Lu and Bethea, 2002; Klink et al., 2002; Parsey et al., 2002) as well as IL-1 β (Manfridi et al., 2003), secondly, the efficacy of SSRI to treat a depressive episode is influenced by gender (Kornstein et al., 2000a; Murck et al., 2003; Joyce et al., 2004) and thirdly, immune stimulation alters serotonin metabolism and availability of its precursor tryptophan (Maes et al., 1994; Capuron et al., 2002; Konsman et al., 2002).

Moreover, several of the serotonin receptors are assumed to be critically involved in the pathophysiology as well as efficacy of pharmacological treatment of depression (for review, see Cryan and Leonard (2000), Neumeister et al. (2004), Serretti et al. (2004)). In particular somatodendritic 5-HT_{1A} receptor dysfunction, including decreased binding as well as impaired receptor signalling, in the afferent neurons of the raphe nuclei has been reported in patients with major depression (Drevets et al., 1999; Hsiung et al., 2003; Rabiner et al., 2004; Bhagwagar et al., 2004). An elegant study in rodents showed that the 5-HT_{1A} receptor is critical for the treatment response to SSRI, while no such role was noted with regard to the efficacy of other antidepressants (Santarelli et al., 2003). Interestingly, a superior efficacy of tricyclic antidepressants compared to SSRI in patients with severe depression has been reported, though controversial views exist (Perry, 1996; Sonawalla and Fava, 2001; Young et al., 2004). Recently, escitalopram, the S-enantiomer of the SSRI citalopram, has been shown to have greater efficacy than the racemate, particularly in severely depressed patients (Llorca et al., 2005). This observation may be related to affinity-modulating allosteric effects at the 5-HT transporter (Chen et al., 2005), which may contribute to the observed greater inhibition of dorsal raphe neurons (Sanchez et al., 2003).

A possible explanation for a reduced efficacy of most SSRI in patients with severe (melancholic) depression is that 5-HT_{1A} receptor function may be impaired due to the marked HPA hyperactivity and elevated corticosteroid concentrations (Meerlo et al., 2001; Czyrak et al., 2002; Fairchild et al., 2003). Also, not only the overall level of corticosteroids, but a flattened rhythm with higher trough levels has been associated with disturbed 5-HT_{1A} functioning (Leitch et al., 2003). The latter observation seems particularly relevant for depressive illness, as an elevation of trough levels of cortisol, which normally occur in the early morning hours, has been shown more consistently than overall elevations of cortisol secretion (Wong et al., 2000; Antonijevic et al., 2000b). In line with the above, dysfunction of 5-HT_{1A} receptors has been seen particularly in

depressed patients with dexamethasone non-suppression (Pitchot et al., 2001).

Some authors have questioned the role of elevated corticosteroids for 5-HT_{1A} dysfunction in depression (Bhagwagar et al., 2003; Neumeister et al., 2004). However, Bhagwagar and colleagues used a single administration of corticosteroids, while the available data suggest that only a prolonged elevation in corticosteroid levels will impair or reduce 5-HT_{1A} receptors (Meerlo et al., 2001; Czyrak et al., 2002; Fairchild et al., 2003). On the other hand, reduced 5-HT_{1A} receptor binding has been proposed to be a trait rather than a state marker of depression (Bhagwagar et al., 2004). In this regard, it is interesting that a gene polymorphism in the 5-HT_{1A} promotor has been associated with depression and particularly with suicide (Lemondé et al., 2003). Since in the group of suicide completers less than half had an established psychiatric diagnosis, and among these only half met criteria for depression, the clinical implication of these data for patients with major depression remains to be confirmed.

Of clinical interest is another recent study which showed an inverse correlation between preferential 5-HT_{1A} autoreceptor occupancy and severity of depression, assessed by the HAMD score, in an admittedly small group of patients treated mostly with SSRI (Rabiner et al., 2004). These data could indicate that patients who responded to SSRI experienced an increase in 5-HT_{1A} autoreceptor binding during the treatment. Alternatively, the group of patients with lower HAMD scores (and higher preferential somatodendritic 5-HT_{1A} binding) may include patients with atypical depression, a reduced serotonin transmission but relatively unimpaired 5-HT_{1A} autoreceptor function and hence a good response to treatment with SSRI (Santarelli et al., 2003). This is in line with findings that early sleep-EEG changes during SSRI treatment in patients with depression predicted clinical outcome later on (Murck et al., 2003).

In summary, differential 5-HT_{1A} autoreceptor function may contribute to the distinct pathophysiology of patients with melancholic/typical vs atypical depression. In the former, HPA overactivity may involve impaired restraint of afferent serotonergic neurons due to dysfunctional 5-HT_{1A} autoreceptors and hence reduced efficacy of SSRI (Perry, 1996; Young et al., 2004). In contrast, in patients with atypical features, low HPA activity may entail normal 5-HT_{1A} autoreceptor function and hence good response to SSRI. Since a marked female predominance has been shown selectively for patients with atypical features (Angst et al., 2002; Matza et al., 2003), this could explain the

reported greater responsiveness of females to SSRI (Kornstein et al., 2000a; Murck et al., 2003).

Besides 5-HT_{1A} receptors, the distinct role of postsynaptic 5-HT₂ receptors for sleep-regulation opens up the possibility that 5-HT₂ receptors are also differentially affected in different groups of depressed patients. In particular, antagonism of 5-HT₂ receptors induces sleep-EEG changes opposite to those reported in typical depression, namely an increase in REM latency and time spent in slow wave sleep and a suppression of cumulative REM sleep (Tortella et al., 1989; Roza Davis et al., 1992). These observations are in line with a reported enhanced sensitivity of 5-HT₂ receptors in patients with severe melancholic depression (Rosel et al., 1999). Though no data on 5-HT₂ receptor function in patients with atypical features have been reported so far, the lack of slow wave sleep alterations in patients with atypical features (Quitkin et al., 1985) could indicate that 5-HT₂ receptor function is not impaired. Interestingly, enhanced amount of slow wave sleep in young female compared to male and elderly female patients with depression has been noted (Reynolds et al., 1990; Antonijevic et al., 2000a, 2003). These findings could indicate that in young women with depression either 5-HT₂ receptor function is selectively impaired or the attenuated serotonin secretion manifests itself in a reduced 5-HT₂ receptor activation.

7. Subtypes of depression: the debate on the concept of atypical depression

The DSM-IV allows to further specify a mood disorder according to the clinical features as catatonic, melancholic or atypical. In particular, depression with so-called atypical features, described already many years ago, has received renewed attention recently (Chrousos and Gold, 1992; Quitkin et al., 1993; Posternak and Zimmerman, 2002; Parker et al., 2002; Angst et al., 2002; Stewart et al., 2002; Matza et al., 2003; Benazzi, 2003; Murck et al., 2005).

The DSM-IV criteria for melancholic features of major depression are widely recognised and include loss of pleasure, depressed mood at its worst in the morning, early morning awakening, reduced appetite and/or substantial weight loss and psychomotor alterations. In contrast, the atypical features specifier, representing an almost opposite syndrome, continues to be a matter of debate (Thase et al., 1991; Posternak and Zimmerman, 2002; Parker et al., 2002; Stewart et al., 2002; Benazzi, 2003; Joyce et al., 2004). The current criteria listed

in the DSM-IV include mood reactivity as a mandatory criterion and at least two of the following criteria: (1) significant weight gain or increase in appetite, (2) hypersomnia, (3) leaden paralyses and (4) long-standing pattern of interpersonal rejection sensitivity.

It has been suggested that a reversal of neurovegetative symptoms, i.e. an increase in appetite and/or weight gain and hypersomnia, may be more relevant than mood reactivity for the endophenotype and the treatment response (Thase et al., 1991; Murck et al., 2005). Of note, a higher percentage of chronic disease courses in patients with atypical features without mood reactivity compared to patients with mood reactivity has been reported (Angst et al., 2002). This finding seems to be supported by data indicating that the lack of mood reactivity characterises more severe depression (Parker et al., 2002) and points to the necessity to identify and subsequently treat these patients early on. Rejection sensitivity has also been suggested to delineate a distinct subgroup of atypical depression, irrespective of neurovegetative symptoms, and a different response to pharmacological treatment (Posternak and Zimmerman, 2002; Joyce et al., 2004). Another area of ongoing discussion is the relevance of co-morbid anxiety disorders in atypical depression, which has repeatedly been shown to be very high (Quitkin et al., 1990; Posternak and Zimmerman, 2002; Parker et al., 2002). Finally, there is the suggestion that atypical features of depression are more prevalent in patients with bipolar and particularly bipolar II disorder (Benazzi, 2003). This discussion highlights the need for a further differentiation of subtypes, as even depressed patients fulfilling the DSM-IV criteria for atypical features may show differences in the underlying pathophysiology. This recognition also underscores the need for biological markers to identify relevant endophenotypes of depression, which can then be examined in prospective clinical trials.

8. Summary and conclusion

Different markers have been examined with the aim to identify subgroups of patients based on the susceptibility for depression, the risk for a recurrence, and the treatment response. The examined markers include tests of the neuroendocrine stress axis, such as the dexamethasone suppression test (Mendlewicz et al., 1984) or the more refined dexamethasone-CRH test (Modell et al., 1998; Zobel et al., 1999), and also sleep-EEG parameters

(Kupfer, 1995; Steiger, 2002). While the latter focused initially primarily on REM sleep parameters, it has been shown that non-REM sleep parameters, and more recently a reduced 'delta sleep ratio', are also of clinical relevance (Kupfer, 1995; Antonijevic et al., 2003). In addition, immunological alterations in patients with depression have been described (Licinio and Wong, 1999; Leonard, 2001; Anisman and Merali, 2002). Albeit these may prove useful, they have not yet been tested vigorously with regard to their potential to identify the subtype of depression, and to predict susceptibility for depression and risk of recurrence. In addition, distinct alterations of the serotonin system, including impaired 5-HT_{1A} receptor function and/or reduced serotonin synthesis, provide support for the existence of distinct pathophysiologicals.

So far, none of the above parameters can be considered clearly superior to the others or of more general relevance. Rather, the different parameters supplement each other and thus should be used in combination to allow a better classification of patients, based on clinical and neurobiological alterations. In this regard, the renewed discussion on the concept of the atypical features specifier is very useful, as it highlights the importance of a better clinical characterisation of patients and stimulates further studies to examine pathophysiological differences.

At present, the model by Gold and Chrousos (Gold and Chrousos, 2002) is most valuable, and allows to integrate additional data on altered serotonin and immune functions. Thus, the melancholic subtype with noradrenergic and HPA axis overdrive seems to be associated with reduced 5-HT_{1A} autoreceptor function and hence enhanced serotonergic activation of the HPA axis, as well as an acute phase immune reaction. The latter contributes to HPA axis stimulation and reduces negative feedback inhibition by corticosteroid receptors. The resulting hypercortisolism can further impair 5-HT_{1A} receptor functions, leading to a vicious circle, which may not be effectively resolved by most SSRI.

On the other hand, patients with atypical depression and low HPA activity seem to have reduced noradrenergic and serotonergic afferent stimulation, possibly due to reduced serotonin synthesis and, unlike melancholic patients, an unimpaired 5-HT_{1A} autoreceptor function. A moderate but sustained secretion of inflammatory cytokines may facilitate reduced tryptophan availability, which can further diminish serotonergic transmission. In this situation, SSRI and MAOI may be the treatment of choice. This endophenotype

seems particularly prominent among young female patients with depression.

Though this model is an important first step, it is likely that the currently proposed subtypes of depression, and particularly the atypical features specifier, will require a further refinement, i.e. with regard to the role of co-morbid anxiety. In view of the search for genetic markers of depression and response to treatment, the best possible characterisation of subgroups of depression, based on clinical as well as neurobiological parameters, is of paramount importance.

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References

- Angele, M.K., Faist, E., 2002. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit. Care* 6, 298-305.
- Angst, J., Gamma, A., Sellaro, R., Zhang, H., Merikangas, K., 2002. Toward validation of atypical depression in the community: results of the Zurich cohort study. *J. Affect. Disord.* 72, 125-138.
- Anisman, H., Merali, Z., 2002. Cytokines, stress, and depressive illness. *Brain Behav. Immun.* 16, 513-524.
- Anisman, H., Ravindran, A.V., Griffiths, J., Merali, Z., 1999. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. *Mol. Psychiatry* 4, 182-188.
- Antonijevic, I.A., Steiger, A., 2003. Depression-like changes of the sleep-EEG during high dose corticosteroid treatment in patients with multiple sclerosis. *Psychoneuroendocrinology* 28, 780-795.
- Antonijevic, I., Bicknell, R.J., Leng, G., Russell, J.A., 1995. Progesterone suppression of activation of supraoptic nucleus (SON) neurones in late pregnancy in the rat. *Adv. Exp. Med. Biol.* 395, 195-196.
- Antonijevic, I.A., Murck, H., Frieboes, R.M., Steiger, A., 2000a. Sexually dimorphic effects of GHRH on sleep-endocrine activity in patients with depression and normal controls. Part I: the sleep EEG. *Sleep Res. Online* 3, 5-13.
- Antonijevic, I.A., Murck, H., Frieboes, R.M., Steiger, A., 2000b. Sexually dimorphic effects of GHRH on sleep-endocrine activity in patients with depression and normal controls. Part II: hormone secretion. *Sleep Res. Online* 3, 15-21.
- Antonijevic, I.A., Murck, H., Frieboes, R.M., Uhr, M., Steiger, A., 2003. On the role of menopause for sleep-endocrine alterations associated with major depression. *Psychoneuroendocrinology* 28, 401-418.

- Armitage, R., Emslie, G.J., Hoffmann, R.F., Rintelmann, J., Rush, A.J., 2001. Delta sleep EEG in depressed adolescent females and healthy controls. *J. Affect. Disord.* 63, 139-148.
- Asnis, G.M., McGinn, L.K., Sanderson, W.C., 1995. Atypical depression: clinical aspects and noradrenergic function. *Am. J. Psychiatry* 152, 31-36.
- Aston-Jones, G., Chen, S., Zhu, Y., Oshinsky, M.L., 2001. A neural circuit for circadian regulation of arousal. *Nat. Neurosci.* 4, 732-738.
- Bale, T.L., Vale, W.W., 2003. Increased depression-like behaviors in corticotropin-releasing factor receptor-2-deficient mice: sexually dichotomous responses. *J. Neurosci.* 23, 5295-5301.
- Bebo, B.F.J., Zelinka-Vincent, E., Adamus, G., Amundson, D., Vandenbark, A.A., Offner, H., 1998. Gonadal hormones influence the immune response to PLP 139-151 and the clinical course of relapsing experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* 84, 122-130.
- Benazzi, F., 2003. Testing DSM-IV definition of atypical depression. *Annu. Clin. Psychiatry* 15, 9-16.
- Benca, R.M., Obermeyer, W.H., Thisted, R.A., Gillin, J.C., 1992. Sleep and psychiatric disorders. A meta-analysis. *Arch. Gen. Psychiatry* 49, 651-668.
- Bhagwagar, Z., Montgomery, A.J., Grasby, P.M., Cowen, P.J., 2003. Lack of effect of a single dose of hydrocortisone on serotonin(1A) receptors in recovered depressed patients measured by positron emission tomography with [¹¹C]WAY-100635. *Biol. Psychiatry* 54, 890-895.
- Bhagwagar, Z., Rabiner, E.A., Sargent, P.A., Grasby, P.M., Cowen, P.J., 2004. Persistent reduction in brain serotonin(1A) receptor binding in recovered depressed men measured by positron emission tomography with [¹¹C]WAY-100635. *Mol. Psychiatry* 9, 386-392.
- Bonaccorso, S., Puzella, A., Marino, V., Pasquini, M., Biondi, M., Artini, M., Almerighi, C., Levvero, M., Egyed, B., Bosmans, E., Meltzer, H.Y., Maes, M., 2001. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Res.* 105, 45-55.
- Borsody, M.K., Weiss, J.M., 2002. Peripheral endotoxin causes long-lasting changes in locus coeruleus activity via IL-1 in the brain. *Acta Neuropsychiatrica* 14, 303-321.
- Buyse, D.J., Frank, E., Lowe, K.K., Cherry, C.R., Kupfer, D.J., 1997. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. *Biol. Psychiatry* 41, 406-418.
- Calogero, A.E., 1995. Neurotransmitter regulation of the hypothalamic corticotropin-releasing hormone neuron. *Annu. NY Acad. Sci.* 771, 31-40.
- Capuron, L., Dantzer, R., 2003. Cytokines and depression: the need for a new paradigm. *Brain Behav. Immun.* 1 (17 Suppl.), S119-S124.
- Capuron, L., Ravaut, A., Neveu, P.J., Miller, A.H., Maes, M., Dantzer, R., 2002. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol. Psychiatry* 7, 468-473.
- Capuron, L., Neutrauer, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H., 2003a. Interferon-alpha-induced changes in tryptophan metabolism. Relationship to depression and paroxetine treatment. *Biol. Psychiatry* 54, 906-914.
- Capuron, L., Raison, C.L., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Miller, A.H., 2003b. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha therapy. *Am. J. Psychiatry* 160, 1342-1345.
- Chang, F.C., Opp, M.R., 2001. Corticotropin-releasing hormone (CRH) as a regulator of waking. *Neurosci. Biobehav. Rev.* 25, 445-453.
- Chen, F., Larsen, M.B., Sanchez, C., Wiborg, O., 2005. The S-enantiomer of R,S-citalopram, increases inhibitor binding to the human serotonin transporter by an allosteric mechanism. Comparison with other serotonin transporter inhibitors. *Eur. Neuropsychopharmacol.* 15, 193-198.
- Chrousos, G.P., Gold, P.W., 1992. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 267, 1244-1252.
- Commons, K.G., Connolly, K.R., Valentino, R.J., 2003. A neurochemically distinct dorsal raphe-limbic circuit with a potential role in affective disorders. *Neuropsychopharmacology* 28, 206-215.
- Conde, G.L., Bicknell, R.J., Herbison, A.E., 1995. Changing patterns of Fos expression in brainstem catecholaminergic neurons during the rat oestrous cycle. *Brain Res.* 672, 68-76.
- Cryan, J.F., Leonard, B.E., 2000. 5-HT_{1A} and beyond: the role of serotonin and its receptors in depression and the antidepressant response. *Hum. Psychopharmacol.* 15, 113-135.
- Cunningham, E.T.J., Bohn, M.C., Sawchenko, P.E., 1990. Organization of adrenergic inputs to the paraventricular and supraoptic nuclei of the hypothalamus in the rat. *J. Comp. Neurol.* 292, 651-667.
- Czyrak, A., Mackowiak, M., Chocyk, A., Fijał, K., Tokarski, K., Bijak, M., Wedzony, K., 2002. Prolonged corticosterone treatment alters the responsiveness of 5-HT_{1A} receptors to 8-OH-DPAT in rat CA1 hippocampal neurons. *Naunyn-Schmiedeberg Arch. Pharmacol.* 366, 357-367.
- Darko, D.F., Lucas, A.H., Gillin, J.C., Risch, S.C., Golshan, S., Hamburger, R.N., Silverman, M.B., Janowsky, D.S., 1988. Age, cellular immunity and the HP axis in major depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 12, 713-720.
- Dayas, C.V., Xu, Y., Buller, K.M., Day, T.A., 2000. Effects of chronic oestrogen replacement on stress-induced activation of hypothalamic-pituitary-adrenal axis control pathways. *J. Neuroendocrinol.* 12, 784-794.
- Dayas, C.V., Buller, K.M., Day, T.A., 2001. Medullary neurones regulate hypothalamic corticotropin-releasing factor cell responses to an emotional stressor. *Neuroscience* 105, 707-719.
- Drevets, W.C., 2003. Neuroimaging abnormalities in the amygdala in mood disorders. *Annu. NY Acad. Sci.* 985, 420-444.
- Drevets, W.C., Frank, E., Price, J.C., Kupfer, D.J., Holt, D., Greer, P.J., Huang, Y., Gautier, C., Mathis, C., 1999. PET imaging of serotonin 1A receptor binding in depression. *Biol. Psychiatry* 46, 1375-1387.
- Ehlers, C.L., Reed, T.K., Henriksen, S.J., 1986. Effects of corticotropin-releasing factor and growth hormone-releasing factor on sleep and activity in rats. *Neuroendocrinology* 42, 467-474.
- Ehlers, C.L., Somes, C., Seifritz, E., Rivier, J.E., 1997. CRF/NPY interactions: a potential role in sleep dysregulation in depression and anxiety. *Depress. Anxiety* 6, 1-9.
- Elenkov, I.J., Chrousos, G.P., 2002. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Annu. NY Acad. Sci.* 966, 290-303.
- Ellenbogen, M.A., Young, S.N., Dean, P., Palmour, R.M., Benkelfat, C., 1996. Mood response to acute tryptophan depletion in healthy volunteers: sex differences and temporal stability. *Neuropsychopharmacology* 15, 465-474.

- Evans, D.L., Pedersen, C.A., Folds, J.D., 1988. Major depression and immunity: preliminary evidence of decreased natural killer cell populations. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 12, 739-748.
- Fairchild, G., Leitch, M.M., Ingram, C.D., 2003. Acute and chronic effects of corticosterone on 5-HT_{1A} receptor-mediated autoinhibition in the rat dorsal raphe nucleus. *Neuropharmacology* 45, 925-934.
- Fassbender, K., Schmidt, R., Mossner, R., Kischka, U., Kuhnen, J., Schwartz, A., Hennerici, M., 1998. Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: association with cerebral inflammation. *Arch. Neurol.* 55, 66-72.
- Fava, M., Alpert, J.E., Borus, J.S., Nierenberg, A.A., Pava, J.A., Rosenbaum, J.F., 1996. Patterns of personality disorder comorbidity in early-onset versus late-onset major depression. *Am. J. Psychiatry* 153, 1308-1312.
- Feinstein, A., 2004. The neuropsychiatry of multiple sclerosis. *Can. J. Psychiatry* 49, 157-163.
- Fink, G., Sumner, B.E., 1996. Oestrogen and mental state. *Nature* 383, 306.
- Gao, J., Zhang, J.X., Xu, T.L., 2002. Modulation of serotonergic projection from dorsal raphe nucleus to basolateral amygdala on sleep-waking cycle of rats. *Brain Res.* 945, 60-70.
- Garland, E.J., Zis, A.P., 1991. Multiple sclerosis and affective disorders. *Can. J. Psychiatry* 36, 112-117.
- Gold, P.W., Chrousos, G.P., 1985. Clinical studies with corticotropin releasing factor: implications for the diagnosis and pathophysiology of depression. Cushing's disease, and adrenal insufficiency. *Psychoneuroendocrinology* 10, 401-419.
- Gold, P.W., Chrousos, G.P., 1999. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc. Assoc. Am. Physicians* 111, 22-34.
- Gold, P.W., Chrousos, G.P., 2002. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol. Psychiatry* 7, 254-275.
- Harmer, C.J., Rogers, R.D., Tunbridge, E., Cowen, P.J., Goodwin, G.M., 2003. Tryptophan depletion decreases the recognition of fear in female volunteers. *Psychopharmacology* 167, 411-417.
- Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29, 1765-1781.
- Herbison, A.E., 1997. Estrogen regulation of GABA transmission in rat preoptic area. *Brain Res. Bull.* 44, 321-326.
- Herbison, A.E., Fenelon, V.S., 1995. Estrogen regulation of GABA_A receptor subunit mRNA expression in preoptic area and bed nucleus of the stria terminalis of female rat brain. *J. Neurosci.* 15, 2328-2337.
- Herbison, A.E., Heavens, R.P., Dyer, R.G., 1990. Oestrogen modulation of excitatory A1 noradrenergic input to rat medial preoptic gamma aminobutyric acid neurones demonstrated by microdialysis. *Neuroendocrinology* 52, 161-168.
- Holsboer, F., 1999. The rationale for corticotropin-releasing hormone receptor (CRH-R) antagonists to treat depression and anxiety. *J. Psychiatr. Res.* 33, 181-214.
- Holsboer, F., von Bardeleben, U., Steiger, A., 1988. Effects of intravenous corticotropin-releasing hormone upon sleep-related growth hormone surge and sleep EEG in man. *Neuroendocrinology* 48, 32-38.
- Hsiung, S.C., Adlersberg, M., Arango, V., Mann, J.J., Tamir, H., Liu, K.P., 2003. Attenuated 5-HT_{1A} receptor signaling in brains of suicide victims: involvement of adenylyl cyclase, phosphatidylinositol 3-kinase, Akt and mitogen-activated protein kinase. *J. Neurochem.* 87, 182-194.
- Huitinga, I., Schmidt, E.D., van der Cammen, M.J., Binnekade, R., Tilders, F.J., 2000. Priming with interleukin-1 β suppresses experimental allergic encephalomyelitis in the Lewis rat. *J. Neuroendocrinol.* 12, 1186-1193.
- Huitinga, I., Erkut, Z.A., van Beurden, D., Swaab, D.F., 2004. Impaired hypothalamus-pituitary-adrenal axis activity and more severe multiple sclerosis with hypothalamic lesions. *Annu. Neurol.* 55, 37-45.
- Imai, H., Steindler, D.A., Kitai, S.T., 1986. The organization of divergent axonal projections from the midbrain raphe nuclei in the rat. *J. Comp. Neurol.* 243, 363-380.
- Imeri, L., Mancina, M., Opp, M.R., 1999. Blockade of 5-hydroxytryptamine (serotonin)-2 receptors alters interleukin-1-induced changes in rat sleep. *Neuroscience* 92, 745-749.
- Jindal, R.D., Friedman, E.S., Berman, S.R., Fasiczka, A.L., Howland, R.H., Thase, M.E., 2003. Effects of sertraline on sleep architecture in patients with depression. *J. Clin. Psychopharmacol.* 23, 540-548.
- Joyce, P.R., Mulder, R.T., McKenzie, J.M., Luty, S.E., Cloninger, C.R., 2004. Atypical depression, atypical temperament and a differential antidepressant response to fluoxetine and nortriptyline. *Depress. Anxiety* 19, 180-186.
- Kenis, G., Maes, M., 2002. Effects of antidepressants on the production of cytokines. *Int. J. Neuropsychopharmacol.* 5, 401-412.
- Khan, A.A., Gardner, C.O., Prescott, C.A., Kendler, K.S., 2002. Gender differences in the symptoms of major depression in opposite-sex dizygotic twin pairs. *Am. J. Psychiatry* 159, 1427-1429.
- Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Thase, M.E., Rush, A.J., LaVange, L., Harrison, W.M., Keller, M.B., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. *J. Affect. Disord.* 55, 149-157.
- Klink, R., Robichaud, M., Debonnel, G., 2002. Gender and gonadal status modulation of dorsal raphe nucleus serotonergic neurons. Part II. Regulatory mechanisms. *Neuropharmacology* 43, 1129-1138.
- Konsman, J.P., Parnet, P., Dantzer, R., 2002. Cytokine-induced sickness behaviour: mechanisms and implications. *Trends Neurosci.* 25, 154-159.
- Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Davis, S.M., Harrison, W.M., Keller, M.B., 2000a. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am. J. Psychiatry* 157, 1445-1452.
- Kornstein, S.G., Schatzberg, A.F., Thase, M.E., Yonkers, K.A., McCullough, J.P., Keitner, G.I., Gelenberg, A.J., Ryan, C.E., Hess, A.L., Harrison, W., Davis, S.M., Keller, M.B., 2000b. Gender differences in chronic major and double depression. *J. Affect. Disord.* 60, 1-11.
- Kupfer, D.J., 1995. Sleep research in depressive illness: clinical implications-a tasting menu. *Biol. Psychiatry* 38, 391-403.
- Kupfer, D.J., Frank, E., McEachran, A.B., Grochocinski, V.J., 1990. Delta sleep ratio. A biological correlate of early recurrence in unipolar affective disorder. *Arch. Gen. Psychiatry* 47, 1100-1105.
- Lauer, C.J., Riemann, D., Wiegand, M., Berger, M., 1991. From early to late adulthood. Changes in EEG sleep of depressed patients and healthy volunteers. *Biol. Psychiatry* 29, 979-993.
- Leitch, M.M., Ingram, C.D., Young, A.H., McQuade, R., Gartside, S.E., 2003. Flattening the corticosterone rhythm attenuates 5-HT_{1A} autoreceptor function in the rat: relevance for depression. *Neuropsychopharmacology* 28, 119-125.

- Lemondé, S., Turecki, G., Bakish, D., Du, L., Hrdina, P.D., Bown, C.D., Sequeira, A., Kushwaha, N., Morris, S.J., Basak, A., Ou, X.M., Albert, P.R., 2003. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J. Neurosci.* 23, 8788-8799.
- Leonard, B.E., 2001. The immune system, depression and the action of antidepressants. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 25, 767-780.
- Levitan, R.D., Vaccarino, F.J., Brown, G.M., Kennedy, S.H., 2002. Low-dose dexamethasone challenge in women with atypical major depression: pilot study. *J. Psychiatry Neurosci.* 27, 47-51.
- Licinio, J., Wong, M.L., 1999. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Mol. Psychiatry* 4, 317-327.
- Lin, A., Song, C., Kenis, G., Bosmans, E., De Jongh, R., Scharpe, S., Maes, M., 2000. The in vitro immunosuppressive effects of moclobemide in healthy volunteers. *J. Affect. Disord.* 58, 69-74.
- Linthorst, A.C., Penalva, R.G., Flachskamm, C., Holsboer, F., Reul, J.M., 2002. Forced swim stress activates rat hippocampal serotonergic neurotransmission involving a corticotropin-releasing hormone receptor-dependent mechanism. *Eur. J. Neurosci.* 16, 2441-2452.
- Llorca, P.-M., Azorin, J.-M., Despiegel, N., Verpillat, P., 2005. Efficacy of escitalopram in patients with severe depression: a pooled analysis. *Int. J. Clin. Pract.* 59, 268-275.
- Lu, N.Z., Bethea, C.L., 2002. Ovarian steroid regulation of 5-HT_{1A} receptor binding and G protein activation in female monkeys. *Neuropsychopharmacology* 27, 12-24.
- Maes, M., 2001. The immunoregulatory effects of antidepressants. *Hum. Psychopharmacol.* 16, 95-103.
- Maes, M., 2002. Effects of age and gender on the classification and phenomenology of unipolar depression. *Acta Neuropsychiatrica* 14, 29-35.
- Maes, M., Scharpe, S., Meltzer, H.Y., Okayli, G., Bosmans, E., D'Hondt, P., Vanden Bossche, B.V., Cosyns, P., 1994. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. *Psychiatry Res.* 54, 143-160.
- Maes, M., Meltzer, H.Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., Desnyder, R., 1995. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J. Affect. Disord.* 34, 301-309.
- Manfridi, A., Brambilla, D., Bianchi, S., Mariotti, M., Opp, M.R., Imeri, L., 2003. Interleukin-1 β enhances non-rapid eye movement sleep when microinjected into the dorsal raphe nucleus and inhibits serotonergic neurons in vitro. *Eur. J. Neurosci.* 18, 1041-1049.
- Matza, L.S., Revicki, D.A., Davidson, J.R., Stewart, J.W., 2003. Depression with atypical features in the National Comorbidity Survey: classification, description, and consequences. *Arch. Gen. Psychiatry* 60, 817-826.
- McGinn, L.K., Asnis, G.M., Robinson, E., 1996. Biological and clinical validation of atypical depression. *Psychiatry Res.* 60, 191-198.
- Meerlo, P., Horvath, K.M., Luiten, P.G., Angelucci, L., Catalani, A., Koolhaas, J.M., 2001. Increased maternal corticosterone levels in rats: effects on brain 5-HT_{1A} receptors and behavioral coping with stress in adult offspring. *Behav. Neurosci.* 115, 1111-1117.
- Mendlewicz, J., Kerkhofs, M., Hoffmann, G., Linkowski, P., 1984. Dexamethasone suppression test and REM sleep in patients with major depressive disorder. *Br. J. Psychiatry* 145, 383-388.
- Modell, S., Lauer, C.J., Schreiber, W., Huber, J., Krieg, J.C., Holsboer, F., 1998. Hormonal response pattern in the combined Dex-CRH test is stable over time in subjects at high familial risk for affective disorder. *Neuropsychopharmacology* 18, 253-262.
- Mullington, J., Korth, C., Hermann, D.M., Orth, A., Galanos, C., Holsboer, F., Pollmächer, T., 2000. Dose-dependent effects of endotoxin on human sleep. *Am. J. Physiol.* 278, R947-R955.
- Murck, H., 2003. Atypical depression spectrum disorder—neurobiology and treatment. *Acta Neuropsychiatrica* 15, 227-241.
- Murck, H., Frieboes, R.M., Antonijevic, I.A., Steiger, A., 2001. Distinct temporal pattern of the effects of the combined serotonin-reuptake inhibitor and 5-HT_{1A} agonist EMD 68843 on the sleep EEG in healthy men. *Psychopharmacology* 155, 187-192.
- Murck, H., Nickel, T., Kunzel, H., Antonijevic, I.A., Schill, J., Zobel, A., Steiger, A., Sonntag, A., Holsboer, F., 2003. State markers of depression in sleep EEG: dependency on drug and gender in patients treated with tianeptine or paroxetine. *Neuropsychopharmacology* 28, 348-358.
- Murck, H., Fava, M., Alpert, J., Nierenberg, A.A., Mischoulon, D., Otto, M.W., Zajecka, J., Mannel, M., Rosenbaum, J.F., 2005. Hypericum extract in patients with MDD and reversed vegetative signs: re-analysis from data of a double-blind, randomized trial of hypericum extract, fluoxetine, and placebo. *Int. J. Neuropsychopharmacol.* 8, 215-221.
- Musselman, D.L., Lawson, D.H., Gurnick, J.F., Manatunga, A.K., Penna, S., Goodkin, R.S., Greiner, K., Nemeroff, C.B., Miller, A.H., 2001a. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* 344, 961-966.
- Musselman, D.L., Miller, A.H., Porter, M.R., Manatunga, A., Gao, F., Penna, S., Pearce, B.D., Landry, J., Glover, S., McDaniel, J.S., Nemeroff, C.B., 2001b. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am. J. Psychiatry* 158, 1252-1257.
- Musselman, D.L., Betan, E., Larsen, H., Phillips, L.S., 2003. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol. Psychiatry* 54, 317-329.
- Nemeroff, C.B., 1988. The role of corticotropin-releasing factor in the pathogenesis of major depression. *Pharmacopsychiatry* 21, 76-82.
- Neumeister, A., Bain, E., Nugent, A.C., Carson, R.E., Bonne, O., Luckenbaugh, D.A., Eckelman, W., Herscovitch, P., Charney, D.S., Drevets, W.C., 2004. Reduced serotonin type 1A receptor binding in panic disorder. *J. Neurosci.* 24, 589-591.
- Nishizawa, S., Benkelfat, C., Young, S.N., Leyton, M., Mzengeza, S., de Montigny, C., Blier, P., Diksic, M., 1997. Differences between males and females in rates of serotonin synthesis in human brain. *Proc. Natl Acad. Sci. USA* 94, 5308-5313.
- Obal Jr., F., Krueger, J.M., 2004. GHRH and sleep. *Sleep Med. Rev.* 8, 367-377.
- Opp, M.R., 1995. Corticotropin-releasing hormone involvement in stressor-induced alterations in sleep and in the regulation of waking. *Adv. Neuroimmunol.* 5, 127-143.

- Opp, M.R., Imeri, L., 2001. Rat strains that differ in corticotropin-releasing hormone production exhibit different sleep-wake responses to interleukin 1. *Neuroendocrinology* 73, 272-284.
- Owen, B.M., Eccleston, D., Ferrier, I.N., Young, A.H., 2001. Raised levels of plasma interleukin-1beta in major and postviral depression. *Acta Psychiatr. Scand.* 103, 226-228.
- Parker, G., Roy, K., Mitchell, P., Wilhelm, K., Malhi, G., Hadzi-Pavlovic, D., 2002. Atypical depression: a reappraisal. *Am. J. Psychiatry* 159, 1470-1479.
- Parsey, R.V., Oquendo, M.A., Simpson, N.R., Ogden, R.T., Van Heertum, R., Arango, V., Mann, J.J., 2002. Effects of sex, age, and aggressive traits in man on brain serotonin 5-HT_{1A} receptor binding potential measured by PET using [C-11]WAY-100635. *Brain Res.* 954, 173-182.
- Penninx, B.W., Kritchovsky, S.B., Yaffe, K., Newman, A.B., Simonsick, E.M., Rubin, S., Ferrucci, L., Harris, T., Pahor, M., 2003. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition study. *Biol. Psychiatry* 54, 566-572.
- Perry, P.J., 1996. Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. *J. Affect. Disord.* 39, 1-6.
- Pitchot, W., Herrera, C., Anseau, M., 2001. HPA axis dysfunction in major depression: relationship to 5-HT(1A) receptor activity. *Neuropsychobiology* 44, 74-77.
- Pollmächer, T., Haack, M., Schuld, A., Reichenberg, A., Yirmiya, R., 2002. Low levels of circulating inflammatory cytokines—Do they affect human brain functions? *Brain Behav. Immun.* 16, 525-532.
- Posternak, M.A., Zimmerman, M., 2002. The prevalence of atypical features across mood, anxiety, and personality disorders. *Compr. Psychiatry* 43, 253-262.
- Quitkin, F.M., Rabkin, J.G., Stewart, J.W., McGrath, P.J., Harrison, W., Davies, M., Goetz, R., Puig-Antich, J., 1985. Sleep of atypical depressives. *J. Affect. Disord.* 8, 61-67.
- Quitkin, F.M., McGrath, P.J., Stewart, J.W., Harrison, W., Tricamo, E., Wager, S.G., Ocepke-Welikson, K., Nunes, E., Rabkin, J.G., Klein, D.F., 1990. Atypical depression, panic attacks, and response to imipramine and phenelzine. A replication. *Arch. Gen. Psychiatry* 47, 935-941.
- Quitkin, F.M., Stewart, J.W., McGrath, P.J., Tricamo, E., Rabkin, J.G., Ocepke-Welikson, K., Nunes, E., Harrison, W., Klein, D.F., 1993. Columbia atypical depression. A subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. *Br. J. Psychiatry Suppl.*, 30-34.
- Rabiner, E.A., Bhagwagar, Z., Gunn, R.N., Cowen, P.J., Grasby, P.M., 2004. Preferential 5-HT_{1A} autoreceptor occupancy by pindolol is attenuated in depressed patients: effect of treatment or an endophenotype of depression? *Neuropsychopharmacology* 29, 1688-1698.
- Raison, C.L., Miller, A.H., 2001. The neuroimmunology of stress and depression. *Semin. Clin. Neuropsychiatry* 6, 277-294.
- Raison, C.L., Miller, A.H., 2003. Depression in cancer: new developments regarding diagnosis and treatment. *Biol. Psychiatry* 54, 283-294.
- Reynolds, C.F., Kupfer, D.J., Thase, M.E., Frank, E., Jarrett, D.B., Coble, P.A., Hoch, C.C., Buysse, D.J., Simons, A.D., Houck, P.R., 1990. Sleep, gender, and depression: an analysis of gender effects on the electroencephalographic sleep of 302 depressed outpatients. *Biol. Psychiatry* 28, 673-684.
- Roosendaal, B., Brunson, K.L., Holloway, B.L., McGaugh, J.L., Baram, T.Z., 2002. Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. *Proc. Natl Acad. Sci. USA* 99, 13908-13913.
- Rosel, P., Arranz, B., Vallejo, J., Alvarez, P., Menchon, J.M., Palencia, T., Navarro, M.A., 1999. Altered [3H]imipramine and 5-HT₂ but not [3H]paroxetine binding sites in platelets from depressed patients. *J. Affect. Disord.* 52, 225-233.
- Rothermundt, M., Arolt, V., Peters, M., Gutbrodt, H., Fenker, J., Kersting, A., Kirchner, H., 2001. Inflammatory markers in major depression and melancholia. *J. Affect. Disord.* 63, 93-102.
- Roy, A., Pickar, D., Linnoila, M., Chrousos, G.P., Gold, P.W., 1987. Cerebrospinal fluid corticotropin-releasing hormone in depression: relationship to noradrenergic function. *Psychiatry Res.* 20, 229-237.
- Roza Davis, J.M., Sharpley, A.L., Solomon, R.A., Cowen, P.J., 1992. Sleep and 5-HT₂ receptor sensitivity in recovered depressed patients. *J. Affect. Disord.* 24, 177-181.
- Sanchez, C., Bergqvist, P.B., Brennum, L.T., Gupta, S., Hoggm, S., Larsen, A., Wiborg, O., 2003. Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent effects in animal models predictive of antidepressant and anxiolytic activities. *Psychopharmacology* 167, 353-362.
- Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 301, 805-809.
- Schaefer, M., Schwaiger, M., Pich, M., Lieb, K., Heinz, A., 2003. Neurotransmitter changes by interferon-alpha and therapeutic implications. *Pharmacopsychiatry* 3 (36 Suppl.), S203-S206.
- Schmidt, E.D., Schoffelemeier, A.N., De Vries, T.J., Wardeh, G., Dogterom, G., Bol, J.G., Binnekade, R., Tilders, F.J., 2001. A single administration of interleukin-1 or amphetamine induces long-lasting increases in evoked noradrenaline release in the hypothalamus and sensitization of ACTH and corticosterone responses in rats. *Eur. J. Neurosci.* 13, 1923-1930.
- Schmidt, E.D., Aguilera, G., Binnekade, R., Tilders, F.J., 2003. Single administration of interleukin-1 increased corticotropin releasing hormone and corticotropin releasing hormone-receptor mRNA in the hypothalamic paraventricular nucleus which paralleled long-lasting (weeks) sensitization to emotional stressors. *Neuroscience* 116, 275-283.
- Schobitz, B., Sutanto, W., Carey, M.P., Holsboer, F., De Kloet, E.R., 1994. Endotoxin and interleukin 1 decrease the affinity of hippocampal mineralocorticoid (type I) receptor in parallel to activation of the hypothalamic-pituitary-adrenal axis. *Neuroendocrinology* 60, 124-133.
- Schumann, E.M., Kumpfel, T., Then, B.F., Trenkwalder, C., Holsboer, F., Auer, D.P., 2002. Activity of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: correlations with gadolinium-enhancing lesions and ventricular volume. *Annu. Neurol.* 51, 763-767.
- Schweiger, U., Deuschle, M., Korner, A., Lammers, C.H., Schmider, J., Gotthardt, U., Holsboer, F., Heuser, I., 1994. Low lumbar bone mineral density in patients with major depression. *Am. J. Psychiatry* 151, 1691-1693.
- Serretti, A., Zanardi, R., Franchini, L., Artioli, P., Dotoli, D., Pirovano, A., Smeraldi, E., 2004. Pharmacogenetics of selective serotonin reuptake inhibitor response: a 6-month follow-up. *Pharmacogenetics* 14, 607-613.
- Silverstein, B., 2002. Gender differences in the prevalence of somatic versus pure depression: a replication. *Am. J. Psychiatry* 159, 1051-1052.

- Sonawalla, S.B., Fava, M., 2001. Severe depression: is there a best approach? *CNS Drugs* 15, 765-776.
- Song, C., Lin, A., Bonaccorso, S., Heide, C., Verkerk, R., Kenis, G., Bosmans, E., Scharpe, S., Whelan, A., Cosyns, P., De Jongh, R., Maes, M., 1998. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J. Affect. Disord.* 49, 211-219.
- Stahl, S.M., 1998. Mechanism of action of serotonin selective reuptake inhibitors—serotonin receptors and pathways mediate therapeutic effects and side effects. *J. Affect. Disord.* 51, 215-235.
- Steiger, A., 2002. Sleep and the hypothalamo-pituitary-adrenocortical system. *Sleep Med. Rev.* 6, 125-138.
- Steiger, A., Guldner, J., Colla-Müller, M., Friess, E., Sonntag, A., Schier, T., 1994. Growth hormone-releasing hormone (GHRH)-induced effects on sleep EEG and nocturnal secretion of growth hormone, cortisol and ACTH in patients with major depression. *J. Psychiatr. Res.* 28, 225-238.
- Stewart, J.W., Garfinkel, R., Nunes, E.V., Donovan, S., Klein, D.F., 1998. Atypical features and treatment response in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J. Clin. Psychopharmacol.* 18, 429-434.
- Stewart, J.W., McGrath, P.J., Quitkin, F.M., 2002. Do age of onset and course of illness predict different treatment outcome among DSM IV depressive disorders with atypical features? *Neuropsychopharmacology* 26, 237-245.
- Thase, M.E., 1998. Depression, sleep, and antidepressants. *J. Clin. Psychiatr.* 4 (59 Suppl.), 55-65.
- Thase, M.E., Carpenter, L., Kupfer, D.J., Frank, E., 1991. Clinical significance of reversed vegetative subtypes of recurrent major depression. *Psychopharmacol. Bull.* 27, 17-22.
- Then Bergh, F., Kümpfel, T., Trenkwalder, C., Rupprecht, R., Holsboer, F., 1999. Dysregulation of the hypothalamo-pituitary-adrenal axis is related to the clinical course of MS. *Neurology* 53, 772-777.
- Thomas, E., Pernar, L., Lucki, I., Valentino, R.J., 2003. Corticotropin-releasing factor in the dorsal raphe nucleus regulates activity of lateral septal neurons. *Brain Res.* 960, 201-208.
- Thomas, A.J., Davis, S., Morris, C., Jackson, E., Harrison, R., O'Brien, J.T., 2005. Increase in interleukin-1 β in late-life depression. *Am. J. Psychiatry* 162, 175-177.
- Tortella, F.C., Echevarria, E., Pastel, R.H., Cox, B., Blackburn, T.P., 1989. Suppressant effects of selective 5-HT₂ antagonists on rapid eye movement sleep in rats. *Brain Res.* 485, 294-300.
- Valentino, R.J., Page, M., Van Bockstaele, E., Aston-Jones, G., 1992. Corticotropin-releasing factor innervation of the locus coeruleus region: distribution of fibers and sources of input. *Neuroscience* 48, 689-705.
- Valentino, R.J., Foote, S.L., Page, M.E., 1993. The locus coeruleus as a site for integrating corticotropin-releasing factor and noradrenergic mediation of stress responses. *Ann. NY Acad. Sci.* 697, 173-188.
- Van Bockstaele, E.J., Colago, E.E.O., Valentino, R.J., 1998. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J. Neuroendocrinol.* 10, 743-757.
- VanDyke, M.M., Parker, J.C., Smarr, K.L., Hewett, J.E., Johnson, G.E., Slaughter, J.R., Walker, S.E., 2004. Anxiety in rheumatoid arthritis. *Arthritis Rheum.* 51, 408-412.
- Vertes, R.P., 1991. A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. *J. Comp. Neurol.* 313, 643-668.
- Voskuhl, R.R., 2002. Gender issues and multiple sclerosis. *Curr. Neurol. Neurosci. Rep.* 2, 277-286.
- Wager, S., Robinson, D., Goetz, R., Nunes, E., Gully, R., Quitkin, F., 1990. Cholinergic REM sleep induction in atypical depression. *Biol. Psychiatry* 27, 441-446.
- Weidenfeld, J., Newman, M.E., Itzik, A., Gur, E., Feldman, S., 2002. The amygdala regulates the pituitary-adrenocortical response and release of hypothalamic serotonin following electrical stimulation of the dorsal raphe nucleus in the rat. *Neuroendocrinology* 76, 63-69.
- Whitacre, C.C., 2001. Sex differences in autoimmune disease. *Nat. Immunol.* 2, 777-780.
- Wichmann, M.W., Muller, C., Meyer, G., Adam, M., Angele, M.K., Eisenmenger, S.J., Schildberg, F.W., 2003. Different immune responses to abdominal surgery in men and women. *Langenbecks Arch. Surg.* 387, 397-401.
- Wilder, R.L., 2002. Neuroimmunoendocrinology of the rheumatic diseases: past, present, and future. *Annu. NY Acad. Sci.* 966, 13-19.
- Wong, M.L., Kling, M.A., Munson, P.J., Listwak, S., Licinio, J., Prolo, P., Karp, B., McCutcheon, I.E., Geraciotti, T.D.J., DeBellis, M.D., Rice, K.C., Goldstein, D.S., Veldhuis, J.D., Chrousos, G.P., Oldfield, E.H., McCann, S.M., Gold, P.W., 2000. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl Acad. Sci.* 97, 325-330.
- Young, E.A., Altemus, M., Lopez, J.F., Kocsis, J.H., Schatzberg, A.F., DeBattista, C., Zubieta, J.K., 2004. HPA axis activation in major depression and response to fluoxetine: a pilot study. *Psychoneuroendocrinology* 29, 1198-1204.
- Zobel, A.W., Yassouridis, A., Frieboes, R.M., Holsboer, F., 1999. Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. *Am. J. Psychiatry* 156, 949-951.
- Zorrilla, E.P., Luborsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkle, R., Seligman, D.A., Schmidt, K., 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav. Immun.* 15, 199-226.