

Neuroimmune endocrine effects of antidepressants

Marco Antonioli

Joanna Rybka

Livia A Carvalho

Psychoimmunology Translational
Laboratory, Health Science Research
Centre, Roehampton University,
London, UK

Abstract: Antidepressant pharmacotherapy is to date the most often used treatment for depression, but the exact mechanism of action underlying its therapeutic effect is still unclear. Many theories have been put forward to account for depression, as well as antidepressant activity, but none of them is exhaustive. Neuroimmune endocrine impairment is found in depressed patients; high levels of circulating corticosteroids along with hyperactivation of the immune system, high levels of proinflammatory cytokines, low levels of melatonin in plasma and urine, and disentrainment of circadian rhythms have been demonstrated. Moreover, antidepressant treatment seems to correct or at least to interfere with these alterations. In this review, we summarize the complex neuroimmune endocrine and chronobiological alterations found in patients with depression and how these systems interact with each other. We also explain how antidepressant therapy can modify these systems, along with some possible mechanisms of action shown in animal and human models.

Keywords: antidepressant agents, biological markers, human, cytokines, neuroinflammation, psychoneuroimmunology, endophenotype

Introduction

Major depressive disorder is a widespread illness of great socioeconomic impact, and according to the World Health Organization, will be the second leading cause of disability in terms of burden disease in the future. A US epidemiological study reports depression to have a lifetime prevalence of 16.2%.¹ Possible therapeutic strategies involve social, psychological, and pharmacological treatments. Current pharmacotherapy is associated with a 55%–70% lack of responsiveness in treated subjects, being also associated with a delayed onset of action of several weeks and important side effects. Therefore, there is a need for further investigation of possible treatments for depression. Immune endocrine disturbances have been shown to play a role in the pathophysiology of depression and to be restored by effective antidepressant treatment.^{2–7} Thus, agents which correct the neuroimmune endocrine imbalance have been proposed as potential novel therapeutics for depression. In this review, we will discuss the main mechanisms that support the hypothesis that antidepressants exert their therapeutic benefit by correcting immune and endocrine disturbances.

Neuroendocrine disturbances in depressed patients Melatonin

Abnormalities in neuroendocrine regulation are widespread in depressive illness. One of the focuses of research in depressed patients has been melatonin, a naturally

Correspondence: Livia A Carvalho
Department of Life Sciences,
Holybourne Avenue, Roehampton
University, SW15 4JD, London, UK
Tel +44 208 392 3452
Email livia.carvalho@roehampton.ac.uk

occurring “lights off” hormone. Melatonin is released according to a daily rhythm, depending on the prevailing light/dark phase of the day.⁸ Although many organs are now shown to produce it, the diurnal rhythm of melatonin in the blood is exclusively driven by its secretion from the pineal gland.⁹ Temporal organization in humans presents a daily adjustment to the environmental light/dark cycle; during the night, the master circadian clock in the suprachiasmatic nuclei of the hypothalamus stimulates the pineal gland via a polysynaptic noradrenergic pathway.¹⁰ This gland produces and releases the nocturnal hormone, melatonin, which circulates throughout the body and adjusts several bodily functions according to the existence and duration of darkness. During the day, environmental light detected by the retina adjusts the central clock in the suprachiasmatic nuclei, ie, melanopsin-containing ganglion cells send stimulatory glutamatergic signals to the suprachiasmatic nuclei that modulate the expression of specific clock genes suppressing the stimulation of the pineal gland.¹¹ This modulation will lead, in turn, to a reduction of circulating melatonin.^{12,13} Suprachiasmatic nuclei neurons also receive afferent serotonergic projections from the raphe nuclei^{14,15} which exert inhibitory control over the suprachiasmatic nuclei neuronal response to light.^{16,17} Melatonin synthesis is a multistage process that happens inside pinealocytes, which are the functional cells of the pineal gland. Melatonin is synthesized from tryptophan, which is hydroxylated by tryptophan hydroxylase, then decarboxylated into serotonin, transformed into N-acetylserotonin by arylalkylamine N-acetyltransferase (AANAT), which is the reported rate-limiting melatonin synthesis enzyme, and finally transformed into melatonin by acetyl serotonin-O-methyltransferase. Norepinephrine binds β 1 adrenergic receptors from the membrane of the pinealocytes; these, through G protein adenylate

cyclase, increase cytosolic cyclic adenosine monophosphate (cAMP), which stimulates the nuclear synthesis of AANAT and increases the rate of transformation of serotonin into melatonin.¹⁸ Due to its regulation, it has been suggested that melatonin could be used as a readout of noradrenergic function after antidepressant administration.^{19,20} Moreover, to support the idea that melatonin synthesis is regulated by light and day cycles, expression of tryptophan-hydroxylase mRNA and the activity of the enzyme have been analyzed during the day; peak levels of both occur at night, which is when we can measure the highest level of circulating melatonin.²¹

Melatonin is excreted from pinealocytes into the circulatory system where it exerts a wide range of activities (Figure 1), ie, regulating circadian rhythms and sleep,²² promoting neurogenesis,²³ modulating the immune system, improving defenses and/or decreasing inflammation,^{24–27} and regulating metabolism,²⁸ especially in lipids.²⁹ It also has very strong antioxidant and oncostatic effects,^{30–32} and most of these functions are exerted through the G protein-coupled membrane receptors, MT1 and MT2.¹⁸

What happens to depressed patients? Many studies have been done so far investigating melatonin impairment in depression, and have focused mainly on circadian melatonin rhythm profiles, plasma melatonin, urinary 6-sulphatoxymelatonin (aMT6s), the main melatonin metabolite, and the expression of enzymes implicated in melatonin synthesis.

There are reports showing lower plasma melatonin levels in depressed patients compared with controls.^{33–35} There are also some hints that maximum nocturnal plasma melatonin levels are lower in patients with major unipolar or bipolar depression in the coexistence of an abnormal dexamethasone suppression test (DST) compared with controls and patients with a normal DST. The intensity of depression is negatively

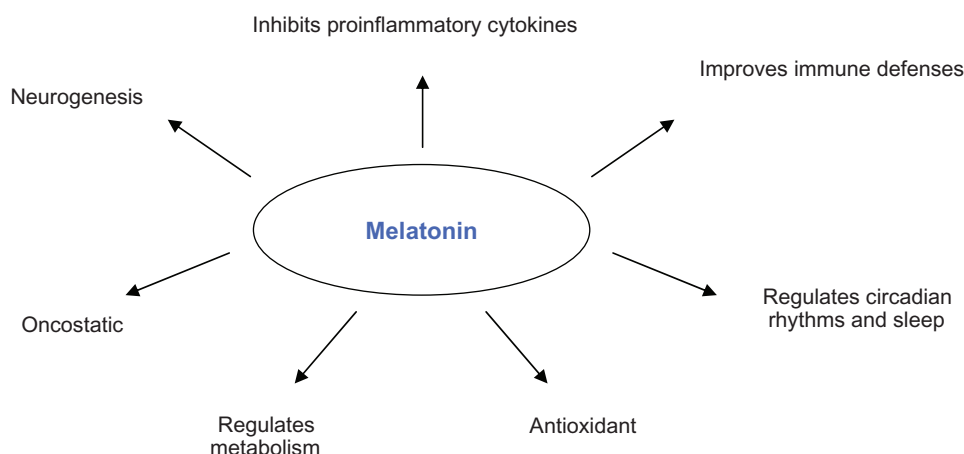


Figure 1 Schematic representation of the main effects exerted by melatonin.

correlated with maximum nocturnal plasma melatonin levels,^{34,36} as well as sensitivity of pineal β -adrenoceptors. As shown in a study of depressed patients that correlated overnight urinary melatonin before and after administration of atenolol, a β -adrenoceptor antagonist, the greater the decrease in melatonin after atenolol, the more severe the depression.³⁵ Moreover, the duration in hours that melatonin was present in the plasma correlates with depressive symptomatology.³⁷ Some studies focusing on the melancholic subtype of depression found a smaller rise in melatonin and lower serum melatonin compared with controls,^{38,39} while postpartum depression was related to higher plasma melatonin levels.³³ Furthermore, a history of depression was related to melatonin impairment,³³ and postmenopausal women showed a longer duration of aMT6s excretion if they had a family history of depression, as well as delayed offset of aMT6 excretion with current major depression and a later nocturnal peak with both current and past depression.⁴⁰ We still do not know the exact mechanism by which melatonin impairment occurs in patients with depression, but studies in animals have given us some hints, ie, administration of melatonin seemed to have antidepressant efficacy in mice, preventing changes in behavior, coat state, and an increase in cortisol levels when they were subjected to unpredictable stressors.⁴¹ Moreover, the melatonin receptor, MT1 has been investigated, and MT1 knockout mice showed an increased immobility time in the forced swim test (a depressive-like behavior) compared with wild-type mice.⁴² MT1 receptors are widespread in the human hypothalamus and in some parts of the pituitary gland, as well as in the pineal gland, and are colocalized in some corticotropin-releasing hormone neurons.⁴³ These areas are implicated in neuroendocrine modulation and in the regulation of the circadian system,⁴⁴ suggesting again that melatonin can be involved in the pathogenesis of the neuroendocrine impairment found in depressed patients. Recent research has attempted to investigate deeper into the biological mechanisms that lie behind melatonin impairment in depression. A study conducted in 2010 undertook a genetic investigation in 181 patients with recurrent depression and 149 controls. The investigators analyzed for the presence of two different single nucleotide polymorphisms, rs4446909 and rs5989681, in the promoter B region of the acetylserotonin methyltransferase (ASMT) enzyme for melatonin synthesis, and found three different genotype forms for each of these single nucleotide polymorphisms, ie, rs4446909 was present in AA, AG, and GG form, and rs5989681 instead was present in CC, GC, and GG forms. They showed that the AA type (for rs4446909)

and the GG type (for the rs5989681) led to increased expression of the enzymes compared with the other genotypes and, interestingly, that they were both associated with a decreased risk of having recurrent depression. Moreover, it was shown that depressed patients had significant decreased ATMS expression compared with the controls.⁴⁵ These studies, taken together, point even more to the involvement of melatonin in the pathogenesis of depression.

Circadian rhythms

Depressed patients have shown abnormalities in many circadian systems, including sleep/wake cycles, with generally early morning waking, changes in sleep architecture with shortened rapid eye movement latency, and the rapid eye movement-sleep phase advanced to the first third of the sleep cycle, as well as diurnal mood changes, seasonal changes, variation in the temperature nadir time, peak cortisol levels, and time of melatonin onset.^{3,46} Circadian impairments have been hypothesized to be involved in the development of seasonal affective disorder;⁴⁷ specifically phase shift theories have been proposed, and light therapy has proven its efficacy in both seasonal and nonseasonal affective disorders.⁴⁸ Understanding the basis of circadian biology is the key to explain those alterations. How does our body create and regulate circadian rhythms? Regulatory centers, such as the suprachiasmatic nucleus, contain the so-called “clock cells” with active clock genes in the nucleus. These cells, through autoregulatory transcription-(post)translational feedback loops, generate electric impulses in the form of synchronized neuronal signals toward sympathetic and parasympathetic nuclei. The latter send nerve connections to many organs, regulating adrenal corticosteroid excretion, amongst other processes. These hormones, in turn, regulate the circadian rhythm with a negative feedback by resetting the time of the clock cells.⁴⁹ Clock genes are found also in the adrenal glands, and mutations in these can alter daily corticosteroid excretion.⁵⁰ In 1985, Linkowski et al found early timing of adrenocorticotrophic hormone (ACTH) cortisol secretion, as well as higher mean plasma cortisol levels, in 18 depressed patients (eight unipolar and 10 bipolar) compared with eight controls.⁵¹ Another study compared biological variables, such as core body temperature, cortisol, norepinephrine, thyroid-stimulating hormone, and melatonin, in three groups of patients with major affective disorder, ie, 16 depressed patients, 15 depressed patients who recovered after 3 weeks of antidepressant treatment, and 16 controls. They found higher levels of cortisol and lower levels of nocturnal melatonin in depressed patients than in the controls.⁵² Moreover, they

found a negative correlation between the amplitude of circadian rhythms and Hamilton depression scores, ie, the lower the amplitude, the more severe the depression, and recovery was associated with reversal of circadian impairment. Clock genes can also be modulated by different hormones; ACTH is known to increase PER1 (period 1) mRNA in the adrenal glands, stimulating the excretion of cortisol, while melatonin itself can dampen these ACTH-correlated effects, as shown by a recent study.⁵³ This mechanism may partially explain the previously elicited alterations found in depressed patients. Since melatonin is known to be low in these patients, cortisol levels may be high because of this lack of inhibitory melatonin effect. Another characteristic of depression is the association of severity of the illness with phase angles of different circadian variables, such as dim light melatonin onset and the average midpoint of sleep,⁵⁴ dim light melatonin onset and core body temperature,⁵⁵ and dim light melatonin onset and cortisol acrophase (the 24-hour peak).⁵⁵ Other circadian abnormalities found in depressed patients were a tendency toward eveningness, a later sleep onset and midpoints, and a delayed dim light melatonin onset.⁵⁵ These findings highlight the presence of neuroendocrine abnormalities, such as circadian misalignments, in depressed patients.⁵⁶

HPA axis and glucocorticoid receptors

In addition to the melatonergic and circadian disturbances found in major depression, clinical studies have also demonstrated impairments in the hypothalamo-pituitary-adrenal (HPA) axis. Glucocorticoids are secreted by the adrenal gland through a neuroendocrine pathway, ie, the hypothalamus stimulates the pituitary gland via corticotropin-releasing hormone (CRH) which in turn stimulates the adrenal gland to release glucocorticoids via ACTH. The main function of these steroid hormones is to regulate energy metabolism,

thereby increasing gluconeogenesis, lipolysis, and protein degradation. These hormones also have a crucial anti-inflammatory action.⁵⁷ They exert many other functions, like inducing behavioral adaptations in stressful situations; when exposed to environmental, psychological, or biological stressors, our bodies produce cortisol, which causes adaptive behavior, like focused attention, alertness, and immune system suppression.⁵⁷ In addition, cortisol has been shown to regulate memory, emotional appraisal of events, neurogenesis, and neuronal survival (Figure 2).⁵⁸

Glucocorticoids exert their function through the glucocorticoid receptor (GR) and the mineralocorticoid receptor.⁵⁹ These are widespread in body tissues, but particular attention has been focused on the ones implicated in the negative feedback regulation of the HPA axis. These are found in the paraventricular nucleus of the hypothalamus, in the CRH/vasopressin neurons of the anterior pituitary, and in the hippocampus and upstream regulator of the HPA axis, as well as in other areas of the brain.^{60,61} The HPA axis is regulated also by biological stimuli, such as proinflammatory cytokines, ie, interleukin (IL)-1 and IL-6,^{62,63} and psychologically stressful situations.⁶⁴ A huge number of findings show that many depressed patients (up to 80% when severely depressed) are shown to have hyperactivation of the HPA axis, impairment comparable with a sustained stress response, in the absence of a stressor.^{65–69} High cortisol levels in the cerebrospinal fluid, plasma, and urine,⁷⁰ impairment in the negative feedback regulation of the HPA axis,^{68,71} and hyperplasia of the adrenal and pituitary glands are also found in depressed patients.^{72,73} GR-mediated negative feedback has been widely investigated using specific tests which demonstrated nonsuppression of cortisol secretion following administration of a synthetic DST; dexamethasone pretreatment also showed a lack of the inhibition of ACTH responses to CRH expected in healthy

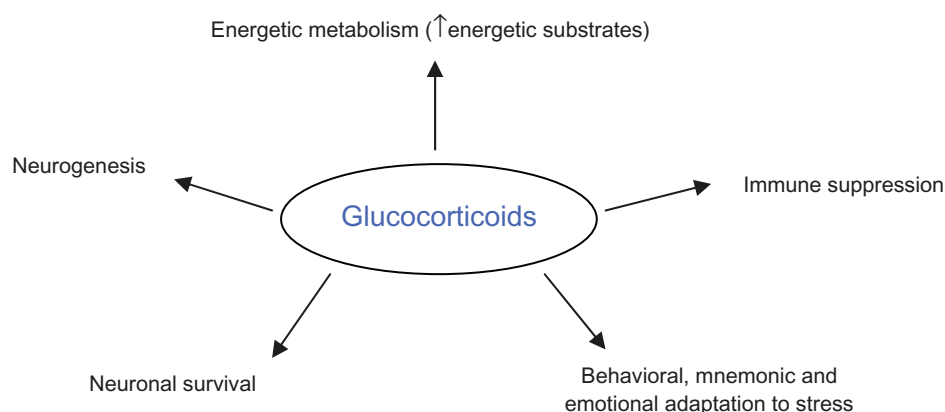


Figure 2 Schematic representation of the main effects exerted by glucocorticoids.

subjects (dexamethasone/CRH test).^{68,74} While DST and the dexamethasone/CRH test suggest impaired feedback inhibition at the level of the pituitary,⁵⁹ impaired responsiveness to hydrocortisone challenge in depressed patients may represent feedback alterations in the brain,⁷⁵ although this latter finding is inconsistent.⁷⁶ Furthermore, DST and dexamethasone/CRH tests are a biomarker of treatment success; resolution of disturbances in negative feedback in patients who are nonsuppressors before treatment is associated with efficacious antidepressant treatment, with up to 75% of nonsuppressor patients switching to suppressor status coincident with a treatment response.^{77,78}

Furthermore, another analysis of HPA reactivity to stress is the so-called “cortisol awakening response” measured in salivary cortisol samples taken after awaking. Depressed patients with current or remitted depression show a higher cortisol awakening response compared with controls, and this has been suggested to be indicative of increased biological vulnerability to depression.⁷⁹ Studies conducted so far (as reviewed elsewhere)^{80,81} have shown that the noradrenergic system exerts an inhibitory action on the HPA axis, decreasing the release of ACTH, probably through α -1 receptors. Moreover, it has been found that normal diurnal fluctuation of the activity of the adrenal cortex requires integrity of the serotonergic system, particularly referring to the suprachiasmatic nucleus, anterior hypothalamus, and limbic system. Because these two systems are impaired in depressed patients, as shown by norepinephrine and serotonin abnormalities,⁵ it is possible that these neurological alterations can contribute to the endocrine impairments we have spoken of so far. This connection between noradrenergic and serotonergic impairment and HPA axis activity suggests a possible link between monoamines and the neuroendocrine abnormalities found in depressed patients.

Pineal-HPA axis

There is evidence of reciprocal interference between melatonin and cortisol, but it is not yet known if this cross talk is directly involved in the neuroendocrine impairment found in depressed patients. Studies conducted in animals give us some clues, in that rats show hypertrophy of the adrenal and pituitary glands following pinealectomy.^{82,83} Also, under acute or chronic stress, they show a decreased adrenocortical response when treated chronically with melatonin, compared with controls. Moreover, melatonin-treated rats have an increase in HPA axis sensitivity to the glucocorticoid suppression test.⁸⁴ These findings suggest that there is a modulatory role of melatonin on HPA axis activity and a positive effect in restoring negative glucocorticoid feedback, in particular when the animal is under stress. One study of the neuroendocrine effects of agomelatine, a new antidepressant, compared with melatonin in transgenic rats with impaired GR found that melatonin increased GR mRNA expression in the dentate gyrus, compared with wild-type animals.⁸⁵ Moreover, it was found that melatonin had an inhibitory action on GR function in mouse thymocytes, in particular reducing GR receptor nuclear translocation.⁸⁶ Furthermore, rats treated with corticosterone showed a two-fold increase in nocturnal melatonin *in vivo*, and extracted pineal glands from treated rats showed a significant increase in melatonin enzyme activity compared with controls.^{87,88} A possible pathway was shown in a study⁸⁹ where isolated pineal glands from rats were cultured with three different substances, ie, ALLN, a proteasome inhibitor, an antagonist of the nuclear factor κ B (NF- κ B), or corticosterone, with or without a GR antagonist, all before stimulation with norepinephrine. As shown in Figure 3, corticosterone increased the norepinephrine-mediated elevation of melatonin and N-acetylserotonin, and this effect was inhibited

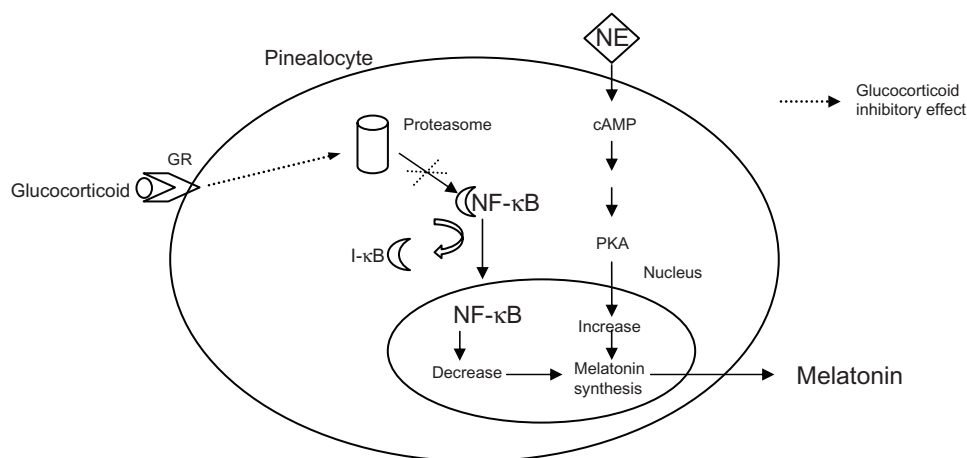


Figure 3 Schematic representation of intracellular interaction between glucocorticoid and melatonin.

Abbreviations: GR, glucocorticoid receptor; NE, norepinephrine.

by GR antagonists; the potentiating effect of corticosteroids was then mimicked by treatment with an NF- κ B antagonist as well as with ALLN. Physiologically, proteasomes are necessary for the translocation of NF- κ B into the nucleus since they degrade inhibitory factors (I- κ B) which keep NF- κ B bound to the cytosol. These results show a clear pathway by which corticosterone increases melatonin production through inhibition of nuclear translocation of NF- κ B.

Accordingly, one placebo-controlled study conducted in 12 blind human subjects analyzed the effect of a single dose of melatonin on neuroendocrine parameters of sleep and found that melatonin could alter nocturnal cortisol and ACTH levels depending on the period of sleep. In the first half, ACTH was higher than placebo and even higher in the second half, while cortisol levels were lower in the first half and increased in the second half.⁹⁰ In summary, it seems that melatonin has an inhibitory action on adrenal and pituitary volume and a positive action on GR expression in the brain, thus increasing HPA negative feedback. On the other hand, glucocorticoids have a positive modulating effect on melatonin production. The pineal gland, expressing the GR, seems to monitor glucocorticoid levels and control their excessive elevation, as happens under stress conditions. This cross talk suggests that neuroendocrine impairments may work together in the development of the whole constellation of neurobiological alterations found in depression.

Melatonin and the inflammatory system

In the past ten years, an increasing amount of evidence suggests that activation of the inflammatory system is involved in the pathogenesis of depression. Firstly, depressed patients have high levels of cytokines, with increased levels of IL-6 being the most frequently observed,^{91–95} and an elevation in IL-1- β and tumor necrosis factor alpha has also been reported.^{96–99} Furthermore, major depression is strongly associated with increased levels of acute phase proteins, including C-reactive protein.^{100,101} Inflammatory markers not only increase the risk for depression and correlate positively with severity of depressive symptoms¹⁰² but also modulate responsiveness to antidepressants.^{103,104} Secondly, clinical administration of cytokines or agents which increase production of proinflammatory cytokines can induce depressive symptoms in patients with no previous mental health issues,^{105–107} while inflammatory-induced depression can also be treated with antidepressants.¹⁰⁸ Thirdly, activation of the immune system and administration of proinflam-

matory cytokines to laboratory animals induces behavior that is similar to depression in humans.¹⁰⁹ Activation of the inflammatory system and cytokine secretion is one possible mechanism that could bring about neuroendocrine abnormalities in depression.

Cytokines are a large and diverse family of small signal molecules, best known for their immunomodulatory effect, resulting in production of other cytokines (chemotaxis) and an increase in the number of surface receptors for other molecules, activation of leukocytes, or suppression of their own effect. The most prevalent group of cytokines is composed of various subtypes of interleukins; while some stimulate immune cell proliferation and differentiation, others are predominantly inhibitory. One functional group of proinflammatory cytokines includes tumor necrosis factor alpha, IL-1, IL-6, and type I interferon- α/β . Cytokines can activate the HPA axis, causing an elevation in systemic glucocorticoid levels and inhibiting GR function at multiple levels, including GR translocation and induction of GR isoforms with a reduced capacity to bind ligand.^{110,111} IL-6 has been reported to induce a prolonged increase in plasma concentrations of ACTH and cortisol in healthy men.¹¹² A number of studies have demonstrated that treatment with proinflammatory cytokines induces a decrease in GR function, as shown by lower sensitivity to the effects of glucocorticoids on functional endpoints and decreased GR affinity for ligand. Moreover, studies performed in peripheral cells and tissues of patients with inflammatory diseases such as asthma, ulcerative colitis, acquired immunodeficiency syndrome, and rheumatoid arthritis, especially those showing resistance to the therapeutic effects of glucocorticoids, have also demonstrated reductions in GR function and affinity that are similar to those induced by cytokines.^{106,113} Indeed, major depression has also been associated with evidence of immune inflammation and increased levels of proinflammatory cytokines. It has been shown that the proinflammatory cytokine IL-1 directly blocks GR translocation and function *in vitro*,¹⁰⁶ an effect that is virtually opposite to that of antidepressants in the same experimental system.^{114,115} These experiments have shown that the effects of IL-1 are mediated by stimulating p38 mitogen-activated protein kinase signal transduction.

Apart from the HPA axis, neuroimmune endocrine interactions also involve the pineal gland, which influences the development and function of the immune system, while membrane-bound melatonin receptors are found in lymphoid glands and immune cells.^{116,117} In addition to mediating immune reactions and GR function, cytokines

have been shown to alter sleep architecture significantly.¹¹² Inflammatory agents can also regulate melatonin synthesis. It is known that tumor necrosis factor leads to inhibition of AANAT transcription and production of N-acetylserotonin and melatonin in cultured glands. Furthermore, pinealocytes express receptors for lipopolysaccharide, which can trigger the NF- κ B pathway and inhibit melatonin synthesis. Negative modulation of norepinephrine-induced melatonin production by tumor necrosis factor alpha is a transient phenomenon in the sequence of the inflammatory response, while a self-regulatory response in the pineal gland would allow restoration of the nocturnal melatonin surge.¹¹⁸ This regulatory mechanism is disrupted when very high systemic tumor necrosis factor alpha levels are present, resulting in abnormalities in the secretion of circadian melatonin, mainly related to an absence of the diurnal rhythm. Therefore, the melatonin cycle impairment reported in depression^{40,55,56,119} may occur at the onset of an inflammatory response. AANAT is considered to play a key role in the regulation of melatonin biosynthesis because changes in its activity are paralleled by alterations in melatonin levels.¹²⁰ The interaction of endogenous norepinephrine with β -adrenoceptors has been suggested to increase AANAT activity and melatonin release.¹²¹ β -adrenoceptor stimulation has been shown to increase gene expression and protein production of tumor necrosis factor alpha as well as IL-1 β and IL-6.¹²² However, the available data suggest that enhanced adrenergic tone leads to immunosuppression, primarily via alpha 2-receptor-mediated mechanisms.¹²³ Consequently, chronic β -receptor blockade reduces plasma levels of IL-6.¹²⁴ Also, stress-induced activation of NF- κ B in peripheral blood mononuclear cells appears to be dependent on norepinephrine and can be brought down by α 1-adrenoceptor blockade.¹²⁵ It has been reported that mice kept under constant light or receiving injections of β -adrenergic blockers (propranolol) to inhibit melatonin synthesis had an inability to mount a primary antibody response to sheep red blood cells, decreased cellularity in the thymus and spleen, and a depressed autologous mixed lymphocyte reaction. All of these effects were reversed by melatonin administration when given in the late afternoon.¹²⁶ β -adrenoceptor blockers, which depress melatonin secretion, exert immunosuppressive effects only when given in the evening,³⁵ when the immunoenhancing effect of melatonin is highest. Exogenous melatonin reverses beta-blocker-induced immunosuppression and enhances immune parameters.

Melatonin on the one hand promotes inflammation but on the other counteracts it. These effects can in fact be dependent on the interaction between melatonin and NF- κ B;

the hormone has been reported to inhibit NF- κ B in various animal models.^{127,128} As a matter of fact, melatonin is also able to activate NF- κ B, thus regulating the expression of adhesion molecules on circulating leukocytes.^{129,130} NF- κ B, a determinant of inflammatory responses, is constitutively expressed in the pineal gland, which possesses receptors to trigger the NF- κ B pathway.¹¹⁸ Activation of NF- κ B exaggerates the inflammatory response including the release of the proinflammatory cytokines, tumor necrosis factor alpha, IL-1, and IL-6, while inhibition of pineal NF- κ B leads to enhancement of melatonin production.¹¹⁸ In turn, melatonin inhibits translocation of NF- κ B to the nucleus¹²⁸ and inflammation mediated by NF- κ B. It has been suggested that NF- κ B inhibition can be achieved through activation of transcription factor Nrf2 which protects cells and tissues from oxidative stress by activating protective antioxidants and detoxifying enzymes. Reports that Nrf2 disruptions are associated with increased NF- κ B further support this hypothesis.^{131,132} The mechanism mentioned above further expands and integrates the concept of melatonin being a powerful antioxidant with anti-inflammatory properties.

In addition, not only cytokines but also glucocorticoids transmit signals through a common NF- κ B pathway to induce and turn off inflammatory responses, respectively,¹³³ which suggests an even more profound effect of melatonin on the inflammatory response. Melatonin has been shown to abolish several effects of exogenous corticoids inducing immune depression,¹²⁶ and is believed to work as an antiadrenocortical or antistress factor.⁸⁴ The melatonin/corticoid relationship is significant because high absolute levels of corticoids and disorganization of the normal rhythm of corticoid release are also involved in the pathogenesis of depression. In line with these findings, melatonin acts against the negative effects of stress on immune homeostasis; characteristics such as sleep duration can also entail variations in inflammatory markers. There is also evidence of elevated levels of IL-6 and C-reactive protein in short sleeping women.¹³⁴ Moreover, patients with major depression show abnormal IL-6 production across the melatonin cycle,⁹³ indicating a possible modulating effect of melatonin on the immune system. In line with this, humoral and cellular immunities are significantly influenced by melatonin,¹³⁵ through specific receptors, MT1/MT2, and high affinity nuclear receptors (RZR) found on leukocytes. Furthermore, the last can synthesize melatonin, having the enzyme necessary for its production.¹³⁶ Gender, age, the effects of maturation or activation on the immune system, and stressful conditions are all factors influencing the effects of melatonin on the immune system,¹³⁷

which from one side promotes and from the other counteracts inflammation simultaneously because of its differential proinflammatory and anti-inflammatory roles.¹³⁶ Pineal activity induces feedback of an inflammatory response, and factors secreted by activated immune cells act as messages which are understood by the pineal gland, closing the regulatory loop of the immune-pineal axis.

Another main pathway by which cytokines can induce neuroendocrine abnormalities in depression involves tryptophan metabolism. Tryptophan either leads to the synthesis of serotonin and melatonin or to the kynurenine pathway. Tryptophan via indoleamine-2,3-dioxygenase is converted into kynurenine, which in turn can take two different pathways, ie, one leading to a neuroprotective metabolite, kynurenic acid, and the other through kynurene-3-mono-oxygenase to neurotoxic metabolites (3-hydroxykynurenine and then quinolinic acid).⁶ Proinflammatory cytokines have a positive effect on kynurene-3-mono-oxygenase, shifting tryptophan metabolism towards a neurotoxic pathway.^{138–140} External or psychosocial factors as well as internal inflammatory conditions may trigger depression through an inflammatory process.¹⁴¹ Furthermore, lipopolysaccharide-treated mice show depressive-like behavior that was prevented by administration of anti-inflammatory drugs which attenuated cytokine expression induced by lipopolysaccharide or directly by a kynurene-3-mono-oxygenase antagonist. Those treatments also normalized the kynurenine/tryptophan ratio, while direct administration of kynurenine induced depressive-like behavior in healthy mice.¹⁴² These results reinforce the idea that kynurene-3-mono-oxygenase is a central enzyme in the development of depressive-like behavior induced by inflammation. All these findings taken together contribute to the idea that depression is the symptomatic manifestation of a multifactorial disease which involves, in addition to well known psychological and social factors, underlying abnormalities in the complex web of neuroendocrine pathways and possibly the intercommunications between all these systems.

Therapeutic actions of antidepressants

How do antidepressants exert their therapeutic action? Although the exact etiopathogenesis of depression is not clear, pharmacotherapy has to date targeted and modulated various sites of action believed to be impaired in this major disease, ie, monoamine levels, serotonin transporter, receptor abnormalities, neuropeptide systems, glutamatergic neurotransmission, HPA axis, and circadian rhythm misalignment.¹⁴³ In this section, we focus attention on the possible

effects of antidepressants on the main neuroendocrine abnormalities found in depression, in particular melatonin, cortisol, and immune system impairment.

Effects on melatonin

The effects of antidepressant medication on melatonin synthesis, metabolism, and circulating levels have been extensively studied. Almost every class of antidepressant has been tested, ie, tricyclic antidepressants, tetracyclic antidepressants, monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors.

Studies on isolated rat pineal glands incubated with desipramine (a tricyclic antidepressant) showed increased levels of melatonin and increased activity of N-acetyltransferase compared with controls.^{144,145} A similar effect was found with venlafaxine (a serotonin-norepinephrine reuptake inhibitor) on acute treatment.¹⁴⁶ However, melatonin levels were attenuated by subchronic treatment, possibly because of adaptive desensitization of the pinealocyte β -adrenoceptors that maintain normal pineal function after modification of overall pineal synaptic function.^{145,146} Another study showed that fluoxetine (a selective serotonin reuptake inhibitor) had a positive effect on AA-NAT gene expression in the hippocampus and striatum, indicating a possible pathway via antidepressants which modulate melatonin synthesis.¹⁴⁷ Moreover, fluvoxamine (a selective serotonin reuptake inhibitor) seems to have an inhibitory effect on hepatic cytochrome peroxidase (CYP450), which is implicated in melatonin catabolism,^{148,149} but this was not confirmed by other antidepressants, except for paroxetine, a selective serotonin reuptake inhibitor, given to supratherapeutic concentrations. Another possible target of selective serotonin reuptake inhibitors seems to be hepatic tryptophan pyrrolase (the main enzyme degrading tryptophan), that paroxetine has been shown to inhibit¹⁵⁰ which, in turn, can increase circulating tryptophan levels, leading indirectly to an increase in the pineal substrate for melatonin synthesis.

Studies in depressed patients seem to confirm the idea that antidepressants modulate melatonin (Table 1). A large number have tested desipramine and consistently found that it increases circulating melatonin levels and urinary aMT6s concentrations after treatment compared with controls after one day,²⁰ one week,^{151,152} 3 weeks,¹⁵³ and 6 weeks.²⁰ Interestingly, one study found that long-term treatment (6 weeks) led to normalization of urinary aMT6s after an initial increase in the short term. This normalization can be explained again by an adaptive mechanism on the part of β 1-adrenoceptors in

Table 1 Antidepressant effect on melatonin in depressed patients

Reference	Antidepressant	Treatment	Plasma melatonin	Urinary 6-sulphatoxymelatonin
Thompson et al ¹⁵³	Desipramine	3 weeks	↑	
Golden et al ¹⁵⁴	Tranlycypromine	3–6 weeks		↑
	Clorgyline			↑
	Desipramine			↑
Bearn et al ¹⁵¹	Desipramine	1 day		=
		1 week		↑
		2 weeks		↑
		3 weeks		↑
Kennedy and Brown ¹⁵²	Desipramine	1 week		↑
		6 weeks		=
Palazidou et al ¹⁶¹	Desipramine	After 1 day	↑	
		Six weeks	↑	
Brown ³⁸	Desipramine	5 weeks		↑
Rabe-Jabłońska and Szymanska ¹⁵⁷	Clomipramine	8 weeks	↓	
Miller et al ¹⁵⁸	Fluvoxamine	6 weeks		↑ in responders
	Imipramine	6 weeks		↓ in nonresponders
				↑ in responders
				↓ in nonresponders
Schmid et al ¹⁵⁵	Mirtazapine	Long-term (28 days)	↑	
Carvalho and Pariente ⁴	Fluoxetine	8 weeks		=
	Duloxetine			↑
				↑
				↑

the pineal gland to the constant high levels of norepinephrine in the synaptic cleft.¹⁵² Similar results were found following 3–6 weeks of treatment with a monoamine oxidase inhibitor, tranlycypromine or clorgyline, with regard to urinary aMT6s in 27 depressed patients.¹⁵⁴ These findings were confirmed also for mirtazapine (a tetracyclic antidepressant) given in the long term.¹⁵⁵ Furthermore, a recent study by Carvalho et al showed an increase in melatonin production after treatment with fluoxetine and duloxetine, a serotonin-norepinephrine reuptake inhibitor, in drug-free depressed patients compared with placebo; both groups had the same improvement in emotional state, suggesting a pharmacological effect of antidepressants on melatonin which may not be directly related to their therapeutic action.¹⁵⁶ In contrast with those findings, another study¹⁵⁷ measured plasma melatonin before and after 8 weeks of treatment with clomipramine (a tricyclic antidepressant) in 20 depressed patients compared with 14 healthy subjects. Surprisingly, they showed that depressed patients had higher levels of both diurnal and nocturnal melatonin compared with controls. Further, like previous studies, they showed that clomipramine significantly increased diurnal melatonin but controversially decreased nocturnal secretion; however, this latter finding was not significant. Finally, pineal reactivity to antidepressants seems to be a potential biomarker of patient response to treatment, as shown by a study in 24 depressed outpatients treated with either the

selective serotonin reuptake inhibitor, fluvoxamine, or the tricyclic antidepressant, imipramine, for 6 weeks. When measuring urinary aMT6s, the results divided responders into those who showed an increase in the metabolite and nonresponders who showed a decrease.¹⁵⁸

Similar results were found observing melatonin modulation by antidepressants given to healthy subjects (Table 2). Two interesting studies investigated the effect of desipramine in the short and long term and shed some light on the possible mechanisms of interaction between antidepressants and melatonin. Desipramine¹⁹ induced an initial increase in plasma melatonin during the first week of treatment, while for the other days it caused a progressive decrease until it reached normal levels again. Moreover, there was a rebound effect after treatment withdrawal. The authors suggested that desipramine caused adaptive inhibition of the presynaptic junction firing rate leading to a desensitization of presynaptic α_2 -adrenoceptors implicated in the control of the negative feedback on the presynaptic portion; when desipramine is withdrawn, there is an increased firing rate at the prejunctional synapses, which, in the presence of reduced negative feedback, leads to increased norepinephrine outflow, and thus in plasma melatonin secretion.¹⁹ A second study indicates that the effect of desipramine on melatonin is due more to increased norepinephrine availability at the synaptic junction induced by the antidepressant than to other effects on melatonin metabolism.

Table 2 Antidepressant effect on melatonin in healthy subjects

Name	Antidepressant	Treatment	Plasma melatonin	Urinary 6-sulphatoxymelatonin
Cowen et al ¹⁵⁹	Desipramine	Acute	↑	
		3 weeks	=	
Demisch et al ¹⁶⁰	Fluvoxamine	Acute (once)	↑	
Demisch et al ¹⁶⁴	Tranylcypromine	Baseline – 3 weeks	= – =	
	Pirlindole	"	= – =	
	Maprotiline	"	= – =	
	Fluvoxamine	"	↑ – ↑	
Franey et al ¹⁵⁹	Desipramine	Acute	↑	↑
Palazidou et al ¹⁶²	Mirtazapine	Acute	↑	
Palazidou et al ¹⁶¹	(+)Oxaprotiline	3 weeks	↑	
	(–)Oxaprotiline	3 weeks	=	
Skene et al ¹⁶⁵	Fluvoxamine	Acute	↑	↓
	Desipramine	Acute	=	↑
Markus et al ¹⁶³	Clomipramine	Acute		↑
		3 weeks		=

Eight male volunteers administered desipramine at 4 pm showed an increase in plasma melatonin at 9 pm, 10 pm, 11 pm, and midnight and an increase in nocturnal aMT6s at 11 pm and midnight, but no significant effect on total aMT6s in one day. Moreover, in the later hours, there was no significant increase in plasma melatonin levels, perhaps because of adaptive desensitization of pineal β -adrenoceptors to high levels of norepinephrine or because the peak capacity of the pineal gland to synthesize melatonin was reached.¹⁵⁹ Like desipramine, fluvoxamine also had a positive effect on melatonin after acute administration,¹⁶⁰ and the same results were found for both acute and chronic administration of oxaprotiline, a serotonin-norepinephrine reuptake inhibitor.¹⁶¹ A positive effect was found also for mirtazapine¹⁶² and clomipramine,¹⁶³ but the latter was associated also with a normalization of pineal activity after long-term treatment. Here the increase in melatonin also seemed to be associated with an improvement in emotional state. The monoamine oxidase inhibitors, tranylcypromine and pirlindole, the tetracyclic antidepressant maprotiline, and the serotonin S2-receptor antagonist, mianserin, were compared with fluvoxamine, each given for 3 weeks, but only the latter had an effect on melatonin.¹⁶⁴ Interestingly, total melatonin excretion was increased by desipramine, advancing onset, and by fluvoxamine, delaying offset. The acrophase was also modulated, being delayed with fluvoxamine and advanced with desipramine. Similarly opposite effects in melatonin metabolism were seen whereby increased aMT6s levels followed desipramine and decreased levels followed fluvoxamine. These studies confirm the hypothesis that the effect of desipramine is exerted mainly on melatonin synthesis, while fluvoxamine modulates its catabolism.¹⁶⁵

In summary, antidepressants appear to modulate melatonin via three main mechanisms: pineal β -adrenoceptor stimulation by elevated levels of norepinephrine in the synaptic junction, though this effect seems susceptible to adaptive desensitization of receptors; modulation of melatonin catabolism; serotonergic stimulation of the suprachiasmatic nuclei by projections from the raphe nuclei which modulate the response of the suprachiasmatic nuclei to light signals from the retinohypothalamic tract. Antidepressants also may modulate melatonin by a direct effect on expression of the enzymes involved in its synthesis, and the increase in circulating serotonin by some antidepressants like monoamine oxidase inhibitors and fluoxetine can be another mechanism.^{166,167} Fewer studies have investigated the effects of selective serotonin reuptake inhibitors on melatonin. Fluoxetine increases melatonin levels after effective antidepressant treatment.^{156,168} In contrast, paroxetine caused no alterations in melatonin in eight healthy volunteers.¹⁶⁹ Tan et al showed no significant differences with selective serotonin reuptake inhibitors, but it is noteworthy that they positively associated the amplitude of melatonin secretion and improvement in recovery from depression after fluoxetine treatment.¹⁷⁰

Effects on circadian rhythm

Can antidepressants influence biological rhythms? This issue is summarized in Table 3. Some hints come from studies in rats which tested mainly the effects of activation of the serotonergic system on the suprachiasmatic nucleus. Serotonergic agonists and selective serotonin reuptake inhibitors, like fluoxetine, seem to have both a photic (night-time phase shifts) and nonphotic influence (daytime phase shifts and night-time photic resetting attenuation). The first

Table 3 Antidepressant effects on circadian rhythm

Name	Antidepressant	Treatment	Neuroendocrine alterations
Cuesta et al ¹⁷¹	Fluoxetine	Rats	Clock gene expression modulation (Per1, Per2, Ror-beta)
Sprouse et al ¹⁷²	Fluoxetine + tryptophan	Rat slices	Phase advances in neuron firing

probably occurs through 5-HT(3) and 5-HT(2C) receptor interactions, while the second seems related to direct modulation of clock genes, possibly through 5-HT(1A) receptors, ie, downregulation of Per1 and Ror-beta expression and upregulation of Rev-erb-alfa, correlated with daytime behavioral phase advance, while night-time photic resetting attenuation is associated with altered expression of Per1, Per2, and Ror-beta.¹⁷¹ A consistent phase advance in neuronal firing was showed in rat slices after treatment with fluoxetine and tryptophan.¹⁷²

Effects on the HPA axis

Glucocorticoids exert their physiological action through GR. We know that impairment of the HPA axis is implicated in the etiology of depression, and because there is evidence that antidepressants may have an effect on these receptors, we believe that this is part of their therapeutic action (Table 4). Several studies have demonstrated that GR is upregulated by antidepressants; rats treated with desipramine or imipramine showed an increase in hippocampal and hypothalamic GR mRNA levels,¹⁷³ and in vitro antidepressant treatment for

24 hours increased GR expression, promoted GR nuclear translocation, and enhanced GR function in mouse fibroblasts.^{114,174} Similar results were found for animal neuronal cells treated with either selective serotonin reuptake inhibitors or tricyclic antidepressants.¹⁷⁵ Such treatment also showed modulation of GR function in peripheral red blood cells.¹⁷⁶ Furthermore, recent studies have shown an effect of antidepressants on circulating levels of corticosteroids. Fluoxetine effectively reduced cortisol levels when given to alcohol-treated rats.¹⁷⁷ Also, perinatal exposure to maternal selective serotonin reuptake inhibitors can induce a lower basal cortisol level in the newborn.¹⁷⁸ Long-term mirtazapine treatment decreases levels of cortisol and dehydroepiandrosterone, an androgen secreted by the adrenal gland, a decrease in which can be used to assess HPA axis function,¹⁷⁹ and there seems to be a relationship between dehydroepiandrosterone reduction and the therapeutic effect of an antidepressant.^{180,181} Also, one study found that restoring of HPA axis hyperactivity in 194 depressed patients was associated with remission, and, moreover, the integrity of negative feedback in the HPA axis, as assessed by DST, predicted the response to

Table 4 Antidepressant effects on HPA axis

Name	Antidepressant	Treatment	Neuroendocrine alterations
Peiffer et al ¹⁷³	Desipramine, imipramine	Rats	↑ hippocampal and hypothalamus GR mRNA
Pariante et al ¹¹⁴	Desipramine	In vitro mouse fibroblasts cells	↑ GR expression, promote GR nuclear translocation and enhance GR function
Pariante and Miller ⁶⁹	Dexamethasone + amitriptyline, clomipramine, paroxetine, citalopram		
Okugawa et al ¹⁷⁵	Dexamethasone + desipramine amitriptyline Desipramine, amitriptyline mianserin, paroxetine sulpiride	Rat hippocampal neurons	↑ GR binding ↑ GR mRNA
Carvalho et al ¹⁷⁶	Clomipramine, amitriptyline, sertraline, paroxetine, venlafaxine	Peripheral red blood cells of healthy subjects	↓ GR function
Hu et al ¹⁷⁷	Fluoxetine	Alcohol-treated rats	↓ cortisol levels
Oberlander et al ¹⁷⁸	Serotonin	Newborn after prenatal exposure	↓ basal cortisol level
Schule et al ¹⁸⁰	Mirtazapine	Depressed patients	↓ cortisol ↓ dehydroepiandrosterone sulfate
Paslakis et al ¹⁸¹	Mirtazapine Venlafaxine	Depressed patients	↓ dehydroepiandrosterone sulfate

Abbreviations: HPA, hypothalamo-pituitary-adrenal; GR, glucocorticoid receptor.

an antidepressant.¹⁸² In accordance with this, a recent study found that resistance to treatment was associated with an abnormal HPA axis negative feedback response, as assessed by prednisolone activation of the GR and mineralocorticoid receptor.¹⁸³ Some controversial results come from two studies^{184,185} measuring the effects of venlafaxine or sertraline on cortisol and showing no effect or even increased levels; however, these studies are limited by their small sample sizes, while previous studies refer to much bigger sample sizes, and are thus more reliable.

Effects on the immune system

There are many studies showing a direct effect of antidepressants on inflammatory cytokines. Results come from studies in cells, animals, and humans (Table 5). Two studies conducted in animal glial cells showed a decrease in proinflammatory cytokines after exposure to an antidepressant and stimulation with interferon gamma, fluvoxamine, reboxetine, and imipramine, along with decreased levels of nitric oxide¹⁸⁶ when treated with lipopolysaccharide, while amitriptyline and nortriptyline decreased levels of IL-1 and tumor necrosis factor alpha.¹⁸⁷ Another study in encephalitogenic T cell clones, splenocytes, and peritoneal macrophages from rats showed that venlafaxine induced a decrease in generation of IL-12, tumor necrosis factor alpha, and interferon gamma.¹⁸⁸ Moreover, experiments conducted in stimulated peripheral white blood cells are in accordance with these findings, ie, imipramine, mianserin, clomipramine, sertraline, and citalopram reduced proinflammatory

cytokine levels and increased anti-inflammatory cytokine levels.^{189–191} Accordingly, whole blood from healthy controls and treatment-resistant patients incubated with lipopolysaccharide and treated with antidepressants showed markedly reduced levels of proinflammatory cytokines compared with untreated blood.^{192,193} Finally, studies in depressed patients confirm the hypothesis that antidepressants have an anti-inflammatory effect. In patients with major depression, long-term treatment with selective serotonin reuptake inhibitors decreased tumor necrosis factor alpha, C-reactive protein, and leukocyte levels similar to those found in controls.^{2,98} In one study, 48 depressed patients received either bupropion, mirtazapine, citalopram, paroxetine, or venlafaxine for 6 weeks, and again there was a significant decrease in proinflammatory cytokines.¹⁹⁵ Furthermore, desipramine and fluoxetine seem to have an inhibitory effect on indoleamine-2,3-dioxygenase activity.¹⁹⁶ More details on the effects of antidepressants on the immune system have been reviewed by Janssen et al.¹⁹⁷

Agomelatine

Promising results have been reported for agomelatine, a new antidepressant with both serotonergic and melatonergic activity. Agomelatine inhibits the serotonergic system through its 5HT-2C receptor antagonist properties, and stimulates the melatonergic system via melatonin receptor agonist binding. Serotonergic blockade leads to enhancement of the frontocortical adrenergic and dopaminergic pathways responsible for its antidepressant activity, and melatonergic stimulation accounts

Table 5 Antidepressant effects on immune system

Name	Antidepressant	Type	Neuroendocrine alterations
Hashioka et al ¹⁸⁶	Fluvoxamine, reboxetine, imipramine	Murine glia cells	↓ NO levels after IFN γ stimulation
Obuchowicz et al ¹⁸⁷	Amitriptyline, nortriptyline	Rat glia cells	↓ IL1 and TNF α after LPS stimulation
Vollmar et al ¹⁸⁸	Venlafaxine	Rat encephalitogenic T cell clones, splenocytes, peritoneal macrophages	↓ IL12, TNF α , and IFN γ
Taler et al ¹⁸⁹ Xia et al ¹⁹⁰ Szuster-Ciesielska et al ¹⁹¹	Imipramine, mianserin, clomipramine, sertraline and citalopram	Human peripheral white blood cells	↓ proinflammatory cytokines ↑ anti-inflammatory cytokines
Kubera et al ¹⁹³	Imipramine, venlafaxine, fluoxetine	Healthy human whole blood	↓ IL-10
Tuglu et al ⁹⁸	Sertraline, citalopram, fluoxetine, fluvoxamine, paroxetine	Treatment resistant Depressed patients	↓ TNF α , CRP and leukocyte count
Kim et al ¹⁹⁴	Bupropion, mirtazapine, citalopram, paroxetine, venlafaxine	Depressed patients	↓ IL-6 and TGF-beta I
Sutcgil et al ¹⁹⁵	Sertraline	Depressed patients	↓ IL-12 ↑ IL-4 and TGF-beta I
Walsh and Daya ¹⁹⁶	Desipramine and fluoxetine	Rats	↓ IDO activity

Abbreviations: CRP, C-reactive protein; IDO, indoleamine-2,3-dioxygenase; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor; IFN γ , interferon gamma; LPS, lipopolysaccharide.

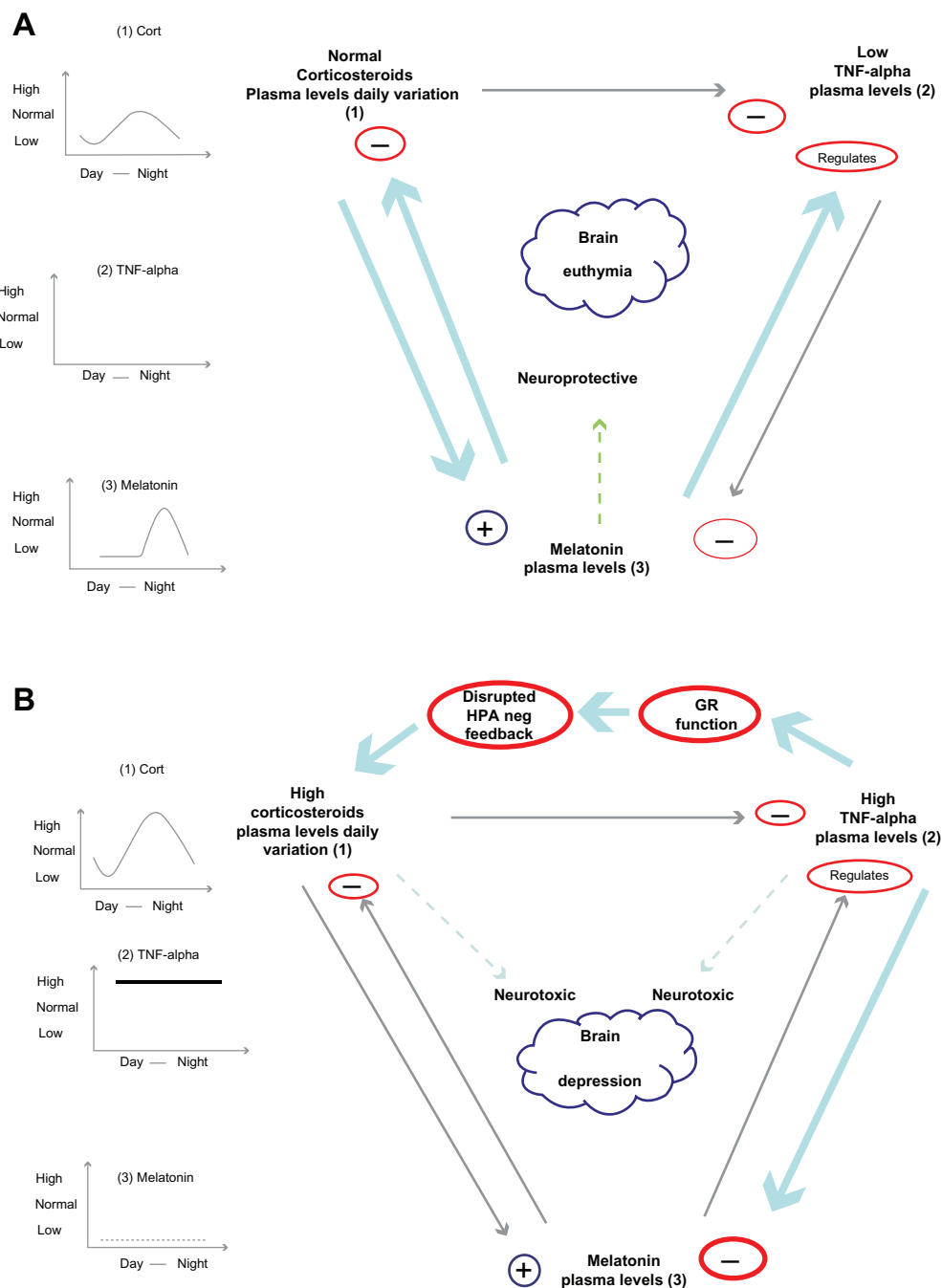


Figure 4 Reciprocal influences of the corticosteroid, melatonin and immune systems in the normal **(A)** and in chronically stressed/depressed state **(B)**. **Abbreviations:** Cort, corticosteroids; TNF, tumor necrosis factor.

for its chronobiotic re-entrainment features.^{198–200} Studies in rats,^{201,202} healthy subjects^{203,204} and depressed patients^{205–207} had interesting findings with regard to the capacity of agomelatine to re-entrain abnormal circadian rhythms. Moreover, it has a better side effect profile,²⁰⁸ in particular concerning sexual impairment in comparison with other antidepressants,²⁰⁹ and low discontinuation symptoms after withdrawal compared with the selective serotonin reuptake inhibitor, paroxetine.²¹⁰

Conclusion

Major depression is a multifactorial and complex disorder, with social, psychological, and biological components. In this review, we have focused mainly on the neuroendocrine basis of these abnormalities. It is clear that melatonin, the HPA axis, immune system, and circadian rhythms are profoundly altered in depressed patients compared with healthy subjects. Moreover, we show how all those systems are

interconnected (Figure 4). Melatonin, in addition to being a well known circadian rhythm modulator, has been shown to regulate immune system activity, having proinflammatory and anti-inflammatory actions, to downregulate the HPA axis and cortisol secretion, and to modulate excessive elevations in corticosteroids. Glucocorticoids, in addition to their established immunosuppressive action, seem to have an upregulatory effect on melatonin synthesis. Cytokines, on the other hand, have been shown to inhibit GR function, and inflammation has shown a negative effect on melatonin synthesis. These interconnections may play an important role in the pathogenesis of depression. The immune system and the HPA axis, along with elevation of corticosteroids, act as important biological defense systems under conditions of stress. It seems that prolonged and chronic activation of these mechanisms leads to neurotoxic alterations in the brain that may eventually trigger depression; also, a genetic predisposition to this is shown, ie, polymorphism in melatonin promoter enzymes. We tried to determine in the literature if antidepressants could play a role in these neuroendocrine alterations. We identified that these agents work separately on each of these interconnected systems. In fact, they have anti-inflammatory actions, stimulate melatonin synthesis, restore negative glucocorticoid feedback by upregulation of GR, and modulate circadian rhythm. It is possible then that all these modifications influence each other synergistically. Inhibition of inflammation itself may first restore melatonin levels, having the least anti-inflammatory properties, and, secondly, benefit negative feedback in the HPA axis. Restoration of GR may positively influence the anti-inflammatory action of glucocorticoids, their stimulation of melatonin secretion by the pineal gland, and perhaps their influence on negative feedback by adrenal gland clock genes. An increase in melatonin on the other hand may influence the other systems. It seems that antidepressants, in addition to increasing primary monoamine levels in the synaptic cleft, work at different neuroendocrine levels, each closely related to others. Further research will help to clarify the complex mechanisms underlying depression and the actions of antidepressants upon all the neuroendocrine systems.

Acknowledgments

LAC is funded by a Young Investigator Award from National Alliance for Research on Schizophrenia and Depression, the European College of Neuropsychopharmacology, the Partek-British Council Partnership and the Seventh Framework Programme Collaborative Project, grant agreement 22963 (Mood Inflammation). MA is funded by an ERASMUS placement

grant within the LLP/ERASMUS placement program. JR is funded by a ZPORR grant from the European Union.

Disclosure

The authors have no relevant financial interest to disclose in this work.

References

1. Kessler RC. Epidemiology of women and depression. *J Affect Disord.* 2003;74(1):5–13.
2. O'Brien SM, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol.* 2004;19(6):397–403.
3. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol.* 2008;23(7):571–585.
4. Carvalho LA, Pariante CM. In vitro modulation of the glucocorticoid receptor by antidepressants. *Stress.* 2008;11(6):411–424.
5. Lee S, Jeong J, Kwak Y, Park SK. Depression research: where are we now? *Mol Brain.* 2010;3:8.
6. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(3):722–779.
7. Anacker C, Zunszain PA, Carvalho LA, Pariante CM. The glucocorticoid receptor: pivot of depression and of antidepressant treatment? *Psychoneuroendocrinology.* 2011;36(3):415–425.
8. Axelrod J, Wurtman RJ, Snyder SH. Control of hydroxyindole O-methyltransferase activity in the rat pineal gland by environmental lighting. *J Biol Chem.* 1965;240:949–954.
9. Hardeland R. Melatonin: signaling mechanisms of a pleiotropic agent. *Biofactors.* 2009;35(2):183–192.
10. Maronde E, Stehle JH. The mammalian pineal gland: known facts, unknown facets. *Trends Endocrinol Metab.* 2007;18(4):142–149.
11. Hankins MW, Lucas RJ. The primary visual pathway in humans is regulated according to long-term light exposure through the action of a nonclassical photopigment. *Curr Biol.* 2002;12(3):191–198.
12. Brainard GC, Sliney D, Hanifin JP, et al. Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms.* 2008;23(5):379–386.
13. Jasser SA, Blask DE, Brainard GC. Light during darkness and cancer: relationships in circadian photoreception and tumor biology. *Cancer Causes Control.* 2006;17(4):515–523.
14. Deurveilher S, Semba K. Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. *Neuroscience.* 2005;130(1):165–183.
15. Leander P, Vrang N, Moller M. Neuronal projections from the mesencephalic raphe nuclear complex to the suprachiasmatic nucleus and the deep pineal gland of the golden hamster (*Mesocricetus auratus*). *J Comp Neurol.* 1998;399(1):73–93.
16. Ying SW, Rusak B. Effects of serotonergic agonists on firing rates of photically responsive cells in the hamster suprachiasmatic nucleus. *Brain Res.* 1994;651(1–2):37–46.
17. Quintero JE, McMahon DG. Serotonin modulates glutamate responses in isolated suprachiasmatic nucleus neurons. *J Neurophysiol.* 1999;82(2):533–539.
18. Reiter RJ, Tan DX, Fuentes-Broto L. Melatonin: a multitasking molecule. *Prog Brain Res.* 2010;181:127–151.
19. Cowen PJ, Green AR, Grahame-Smith DG, Braddock LE. Plasma melatonin during desmethylimipramine treatment: evidence for changes in noradrenergic transmission. *Br J Clin Pharmacol.* 1985;19(6):799–805.
20. Palazidou E, Papadopoulos A, Ratcliff H, Dawling S, Checkley SA. Noradrenaline uptake inhibition increases melatonin secretion, a measure of noradrenergic neurotransmission, in depressed patients. *Psychol Med.* 1992;22(2):309–315.

21. Sugden D. Comparison of circadian expression of tryptophan hydroxylase isoform mRNAs in the rat pineal gland using real-time PCR. *J Neurochem*. 2003;86(5):1308–1311.
22. Agez L, Laurent V, Guerrero HY, Pevet P, Masson-Pevet M, Gauer F. Endogenous melatonin provides an effective circadian message to both the suprachiasmatic nuclei and the pars tuberalis of the rat. *J Pineal Res*. 2009;46(1):95–105.
23. Sotthibundhu A, Phansuwan-Pujito P, Govitrapong P. Melatonin increases proliferation of cultured neural stem cells obtained from adult mouse subventricular zone. *J Pineal Res*. 2010;49(3):291–300.
24. Srinivasan V, Spence DW, Trakht I, Pandi-Perumal SR, Cardinali DP, Maestroni GJ. Immunomodulation by melatonin: its significance for seasonally occurring diseases. *Neuroimmunomodulation*. 2008;15(2):93–101.
25. Maldonado MD, Murillo-Cabezas F, Calvo JR, et al. Melatonin as pharmacologic support in burn patients: a proposed solution to thermal injury-related lymphocytopenia and oxidative damage. *Crit Care Med*. 2007;35(4):1177–1185.
26. Maldonado MD, Murillo-Cabezas F, Terron MP, et al. The potential of melatonin in reducing morbidity-mortality after craniocerebral trauma. *J Pineal Res*. 2007;42(1):1–11.
27. Cernysiov V, Gerasimcik N, Mauricas M, Girkontaite I. Regulation of T-cell-independent and T-cell-dependent antibody production by circadian rhythm and melatonin. *Int Immunol*. 2010;22(1):25–34.
28. Agil A, Rosado I, Ruiz R, Figueroa A, Zen N, Fernandez-Vazquez G. Melatonin improves glucose homeostasis in young Zucker diabetic fatty rats. *J Pineal Res*. July 26, 2011. [Epub ahead of print.]
29. Sanchez-Hidalgo M, Lu Z, Tan DX, Maldonado MD, Reiter RJ, Greggerman RI. Melatonin inhibits fatty acid-induced triglyceride accumulation in ROS17/2.8 cells: implications for osteoblast differentiation and osteoporosis. *Am J Physiol Regul Integr Comp Physiol*. 2007;292(6):R2208–R2215.
30. Reiter RJ, Tan DX, Leon J, Kilic U, Kilic E. When melatonin gets on your nerves: its beneficial actions in experimental models of stroke. *Exp Biol Med (Maywood)*. 2005;230(2):104–117.
31. Tan DX, Manchester LC, Terron MP, Flores LJ, Reiter RJ. One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J Pineal Res*. 2007;42(1):28–42.
32. Garcia-Navarro A, Gonzalez-Puga C, Escames G, et al. Cellular mechanisms involved in the melatonin inhibition of HT-29 human colon cancer cell proliferation in culture. *J Pineal Res*. 2007;43(2):195–205.
33. Parry BL, Meliska CJ, Sorenson DL, et al. Plasma melatonin circadian rhythm disturbances during pregnancy and postpartum in depressed women and women with personal or family histories of depression. *Am J Psychiatry*. 2008;165(12):1551–1558.
34. Beck-Friis J, Kjellman BF, Aperia B, et al. Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. *Acta Psychiatr Scand*. 1985;71(4):319–330.
35. Paparrigopoulos T. Melatonin response to atenolol administration in depression: indication of beta-adrenoceptor dysfunction in a subtype of depression. *Acta Psychiatr Scand*. 2002;106(6):440–445.
36. Beck-Friis J, Ljunggren JG, Thoren M, von RD, Kjellman BF, Wetterberg L. Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. *Psychoneuroendocrinology*. 1985;10(2):173–186.
37. Parry BL, Meliska CJ, Sorenson DL, et al. Increased melatonin and delayed offset in menopausal depression: role of years past menopause, follicle-stimulating hormone, sleep end time, and body mass index. *J Clin Endocrinol Metab*. 2008;93(1):54–60.
38. Brown R, Kocsis JH, Caroff S, et al. Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. *Am J Psychiatry*. 1985;142(7):811–816.
39. Fountoulakis KN, Karamouzis M, Iacovides A, et al. Morning and evening plasma melatonin and dexamethasone suppression test in patients with nonseasonal major depressive disorder from northern Greece (latitude 40–41.5 degrees). *Neuropsychobiology*. 2001;44(3):113–117.
40. Tuunainen A, Kripke DF, Elliott JA, et al. Depression and endogenous melatonin in postmenopausal women. *J Affect Disord*. 2002;69(1–3):149–158.
41. Detanico BC, Piatto AL, Freitas JJ, et al. Antidepressant-like effects of melatonin in the mouse chronic mild stress model. *Eur J Pharmacol*. 2009;607(1–3):121–125.
42. Weil ZM, Hotchkiss AK, Gatten ML, Piek-Dahl S, Nelson RJ. Melatonin receptor (MT1) knockout mice display depression-like behaviors and deficits in sensorimotor gating. *Brain Res Bull*. 2006;68(6):425–429.
43. Wu YH, Zhou JN, Balesar R, et al. Distribution of MT1 melatonin receptor immunoreactivity in the human hypothalamus and pituitary gland: colocalization of MT1 with vasopressin, oxytocin, and corticotropin-releasing hormone. *J Comp Neurol*. 2006;499(6):897–910.
44. Rosenwasser AM. Functional neuroanatomy of sleep and circadian rhythms. *Brain Res Rev*. 2009;61(2):281–306.
45. Galecki P, Szemraj J, Bartosz G, et al. Single-nucleotide polymorphisms and mRNA expression for melatonin synthesis rate-limiting enzyme in recurrent depressive disorder. *J Pineal Res*. 2010;48(4):311–317.
46. Boyce P, Barriball E. Circadian rhythms and depression. *Aust Fam Physician*. 2010;39(5):307–310.
47. Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder: a review. *J Psychiatry Neurosci*. 2000;25(5):469–480.
48. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162(4):656–662.
49. Okamura H. Suprachiasmatic nucleus clock time in the mammalian circadian system. *Cold Spring Harb Symp Quant Biol*. 2007;72:551–556.
50. Pilonis V, Steinlechner S, Oster H. Age and oestrus cycle-related changes in glucocorticoid excretion and wheel-running activity in female mice carrying mutations in the circadian clock genes *Per1* and *Per2*. *Physiol Behav*. 2009;96(1):57–63.
51. Linkowski P, Van Cauter E, Leclercq R, et al. ACTH, cortisol and growth hormone 24-hour profiles in major depressive illness. *Acta Psychiatr Belg*. 1985;85(5):615–623.
52. Souetre E, Salvati E, Belugou JL, et al. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res*. 1989;28(3):263–278.
53. Campino C, Valenzuela FJ, Torres-Farfan C, et al. Melatonin exerts direct inhibitory actions on ACTH responses in the human adrenal gland. *Horm Metab Res*. 2011;43(5):337–342.
54. Emens J, Lewy A, Kinzie JM, Arntz D, Rough J. Circadian misalignment in major depressive disorder. *Psychiatry Res*. 2009;168(3):259–261.
55. Hasler BP, Buysse DJ, Kupfer DJ, Germain A. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Res*. 2010;178(1):205–207.
56. Buckley TM, Schatzberg AF. A pilot study of the phase angle between cortisol and melatonin in major depression – a potential biomarker? *J Psychiatr Res*. 2010;44(2):69–74.
57. Pariante CM. Glucocorticoid receptor function in vitro in patients with major depression. *Stress*. 2004;7(4):209–219.
58. Herbert J, Goodyer IM, Grossman AB, et al. Do corticosteroids damage the brain? *J Neuroendocrinol*. 2006;18(6):393–411.
59. de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr Rev*. 1998;19(3):269–301.
60. Tasker JG, Di S, Malcher-Lopes R. Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology*. 2006;147(12):5549–5556.
61. de Kloet ER, Derijk RH, Meijer OC. Therapy insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nat Clin Pract Endocrinol Metab*. 2007;3(2):168–179.
62. Navarra P, Tsagarakis S, Faria MS, Rees LH, Besser GM, Grossman AB. Interleukins-1 and -6 stimulate the release of corticotropin-releasing hormone-41 from rat hypothalamus in vitro via the eicosanoid cyclooxygenase pathway. *Endocrinology*. 1991;128(1):37–44.

63. Karalis K, Muglia LJ, Bae D, Hilderbrand H, Majzoub JA. CRH and the immune system. *J Neuroimmunol*. 1997;72(2):131–136.
64. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. *Endocrinology*. 1993;133(6):2523–2530.
65. Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*. 2000;23(5):477–501.
66. McQuade R, Young AH. Future therapeutic targets in mood disorders: the glucocorticoid receptor. *Br J Psychiatry*. 2000;177:390–395.
67. Heuser I, Yassouridis A, Holsboer F. The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. *J Psychiatr Res*. 1994;28(4):341–356.
68. Nemeroff CB. The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry*. 1996;1(4):336–342.
69. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry*. 2001;49(5):391–404.
70. Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). *N Engl J Med*. 1988;319(6):348–353.
71. Carroll BJ, Feinberg M, Greden JF, et al. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. *Arch Gen Psychiatry*. 1981;38(1):15–22.
72. Axelsson DA, Doraiswamy PM, Boyko OB, et al. In vivo assessment of pituitary volume with magnetic resonance imaging and systematic stereology: relationship to dexamethasone suppression test results in patients. *Psychiatry Res*. 1992;44(1):63–70.
73. Rubin R, Dinan TJ, Scott LV. The neuroendocrinology of affective disorders. In: Pfaff D, Arnold AP, Etgen AM, Fahrbach SE, Moss PL, Rubin RT, editors. *Hormones, Brain and Behaviour*. New York, NY: New York Academic Press; 2001.
74. Kunugi H, Ida I, Owashi T, Kimura M, et al. Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: a multicenter study. *Neuropsychopharmacology*. 2006;31(1):212–220.
75. Young EA, Haskett RF, Murphy-Weinberg V, Watson SJ, Akil H. Loss of glucocorticoid fast feedback in depression. *Arch Gen Psychiatry*. 1991;48(8):693–699.
76. Cooney JM, Dinan TG. Preservation of hypothalamic-pituitary-adrenal axis fast-feedback responses in depression. *Acta Psychiatr Scand*. 1996;94(6):449–453.
77. Linkowski P, Mendlewicz J, Kerkhofs M, et al. 24-hour profiles of adrenocorticotropin, cortisol, and growth hormone in major depressive illness: effect of antidepressant treatment. *J Clin Endocrinol Metab*. 1987;65(1):141–152.
78. Heuser IJ, Schweiger U, Gotthardt U, et al. Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. *Am J Psychiatry*. 1996;153(1):93–99.
79. Bhagwagar Z, Hafizi S, Cowen PJ. Increase in concentration of waking salivary cortisol in recovered patients with depression. *Am J Psychiatry*. 2003;160(10):1890–1891.
80. Tuomisto J, Mannisto P. Neurotransmitter regulation of anterior pituitary hormones. *Pharmacol Rev*. 1985;37(3):249–332.
81. Plotsky PM, Cunningham ET Jr, Widmaier EP. Catecholaminergic modulation of corticotropin-releasing factor and adrenocorticotropin secretion. *Endocr Rev*. 1989;10(4):437–458.
82. Wurtman RJ, Altschule Md, Holmgren U. Effects of pinealectomy and of a bovine pineal extract in rats. *Am J Physiol*. 1959;197(1):108–110.
83. Konakchieva R, Mitev Y, Almeida OF, Patchev VK. Chronic melatonin treatment and the hypothalamo-pituitary-adrenal axis in the rat: attenuation of the secretory response to stress and effects on hypothalamic neuropeptide content and release. *Biol Cell*. 1997;89(9):587–596.
84. Konakchieva R, Mitev Y, Almeida OF, Patchev VK. Chronic melatonin treatment counteracts glucocorticoid-induced dysregulation of the hypothalamic-pituitary-adrenal axis in the rat. *Neuroendocrinology*. 1998;67(3):171–180.
85. Barden N, Shink E, Labbe M, Vacher R, Rochford J, Mocaer E. Antidepressant action of agomelatine (S20098) in a transgenic mouse model. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(6):908–916.
86. Presman DM, Hoijman E, Ceballos NR, Galigniana MD, Pecci A. Melatonin inhibits glucocorticoid receptor nuclear translocation in mouse thymocytes. *Endocrinology*. 2006;147(11):5452–5459.
87. Fernandes PA, Bothorel B, Clesse D, et al. Local corticosterone infusion enhances nocturnal pineal melatonin production in vivo. *J Neuroendocrinol*. 2009;21(2):90–97.
88. Couto-Moraes R, Palermo-Neto J, Markus RP. The immune-pineal axis: stress as a modulator of pineal gland function. *Ann N Y Acad Sci*. 2009;1153:193–202.
89. Ferreira ZS, Fernandes PA, Duma D, Assreuy J, Avellar MC, Markus RP. Corticosterone modulates noradrenaline-induced melatonin synthesis through inhibition of nuclear factor kappa B. *J Pineal Res*. 2005;38(3):182–188.
90. Fischer S, Smolnik R, Herms M, Born J, Fehm HL. Melatonin acutely improves the neuroendocrine architecture of sleep in blind individuals. *J Clin Endocrinol Metab*. 2003;88(11):5315–5320.
91. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116(3):214–217.
92. Jehn CF, Kuhnhardt D, Bartholomae A, et al. Association of IL-6, hypothalamus-pituitary-adrenal axis function, and depression in patients with cancer. *Integr Cancer Ther*. 2010;9(3):270–275.
93. Alesci S, Martinez PE, Kelkar S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab*. 2005;90(5):2522–2530.
94. Bouhuys AL, Flentge F, Oldehinkel AJ, van den Berg MD. Potential psychosocial mechanisms linking depression to immune function in elderly subjects. *Psychiatry Res*. 2004;127(3):237–245.
95. Tiemeier H, Hofman A, van Tilj HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. *Epidemiology*. 2003;14(1):103–107.
96. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000;22(4):370–379.
97. Mikova O, Yakimova R, Bosmans E, Kenis G, Maes M. Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *Eur Neuropsychopharmacol*. 2001;11(3):203–208.
98. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl)*. 2003;170(4):429–433.
99. Owen BM, Eccleston D, Ferrier IN, Young AH. Raised levels of plasma interleukin-1beta in major and postviral depression. *Acta Psychiatr Scand*. 2001;103(3):226–228.
100. Ford DE, Erlinger TP. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2004;164(9):1010–1014.
101. Danner M, Kasl SV, Abramson JL, Vaccarino V. Association between depression and elevated C-reactive protein. *Psychosom Med*. 2003;65(3):347–356.
102. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT. Increase in interleukin-1beta in late-life depression. *Am J Psychiatry*. 2005;162(1):175–177.
103. Yu YW, Chen TJ, Hong CJ, Chen HM, Tsai SJ. Association study of the interleukin-1 beta (C-511T) genetic polymorphism with major depressive disorder, associated symptomatology, and antidepressant response. *Neuropsychopharmacology*. 2003;28(6):1182–1185.

104. Jun TY, Pae CU, Hoon H, et al. Possible association between G308A tumour necrosis factor- α gene polymorphism and major depressive disorder in the Korean population. *Psychiatr Genet*. 2003;13(3):179–181.
105. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon- α . *Biol Psychiatry*. 2004;56(11):819–824.
106. Pariante CM, Pearce BD, Pisell TL, et al. The proinflammatory cytokine, interleukin-1 α , reduces glucocorticoid receptor translocation and function. *Endocrinology*. 1999;140(9):4359–4366.
107. Orru MG, Baita A, Sitzia R, et al. Interferon- α -induced psychiatric side effects in patients with chronic viral hepatitis: a prospective, observational, controlled study. *Epidemiol Psychiatr Soc*. 2005;14(3):145–153. Italian.
108. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon α . *N Engl J Med*. 2001;344(13):961–966.
109. Huang Y, Henry CJ, Dantzer R, Johnson RW, Godbout JP. Exaggerated sickness behavior and brain proinflammatory cytokine expression in aged mice in response to intracerebroventricular lipopolysaccharide. *Neurobiol Aging*. 2008;29(11):1744–1753.
110. Pace TW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain Behav Immun*. 2007;21(1):9–19.
111. Haddad JJ, Saade NE, Safieh-Garabedian B. Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic-pituitary-adrenal revolving axis. *J Neuroimmunol*. 2002;133(1–2):1–19.
112. Spath-Schwalbe E, Hansen K, Schmidt F, et al. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *J Clin Endocrinol Metab*. 1998;83(5):1573–1579.
113. Maddock C, Pariante CM. How does stress affect you? An overview of stress, immunity, depression and disease. *Epidemiol Psychiatr Soc*. 2001;10(3):153–162. Italian.
114. Pariante CM, Pearce BD, Pisell TL, Owens MJ, Miller AH. Steroid-independent translocation of the glucocorticoid receptor by the antidepressant desipramine. *Mol Pharmacol*. 1997;52(4):571–581.
115. Wang X, Wu H, Miller AH. Interleukin 1 α (IL-1 α) induced activation of p38 mitogen-activated protein kinase inhibits glucocorticoid receptor function. *Mol Psychiatry*. 2004;9(1):65–75.
116. Pierpaoli W. Neuroimmunomodulation of aging. A program in the pineal gland. *Ann NY Acad Sci*. 1998;840:491–497.
117. Skwarlo-Sonta K, Majewski P, Markowska M, Oblap R, Olszanska B. Bidirectional communication between the pineal gland and the immune system. *Can J Physiol Pharmacol*. 2003;81(4):342–349.
118. da Silveira Cruz-Machado S, Carvalho-Sousa CE, Tamura EK, et al. TLR4 and CD14 receptors expressed in rat pineal gland trigger NF κ B pathway. *J Pineal Res*. 2010;49(2):183–192.
119. Branchey L, Weinberg U, Branchey M, Linkowski P, Mendlewicz J. Simultaneous study of 24-hour patterns of melatonin and cortisol secretion in depressed patients. *Neuropsychobiology*. 1982;8(5):225–232.
120. Blomeke B, Golka K, Griefahn B, Roemer HC. Arylalkylamine N-acetyltransferase (AANAT) genotype as a personal trait in melatonin synthesis. *J Toxicol Environ Health A*. 2008;71(13–14):874–876.
121. Cardinali DP, Vacas MI, Keller Sarmiento MI, Etchegoyen GS, Pereyra EN, Chuluyan HE. Neuroendocrine integrative mechanisms in mammalian pineal gland: effects of steroid and adenohipophyseal hormones on melatonin synthesis in vitro. *J Steroid Biochem*. 1987;27(1–3):565–571.
122. Murray DR, Prabhu SD, Chandrasekar B. Chronic beta-adrenergic stimulation induces myocardial proinflammatory cytokine expression. *Circulation*. 2000;101(20):2338–2341.
123. Schauenstein K, Felsner P, Rinner I, et al. In vivo immunomodulation by peripheral adrenergic and cholinergic agonists/antagonists in rat and mouse models. *Ann NY Acad Sci*. 2000;917:618–627.
124. Mayer B, Holmer SR, Hengstenberg C, Lieb W, Pfeifer M, Schunkert H. Functional improvement in heart failure patients treated with beta-blockers is associated with a decline of cytokine levels. *Int J Cardiol*. 2005;103(2):182–186.
125. Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A*. 2003;100(4):1920–1925.
126. Maestroni GJ, Conti A, Pierpaoli W. Role of the pineal gland in immunity. Circadian synthesis and release of melatonin modulates the antibody response and antagonizes the immunosuppressive effect of corticosterone. *J Neuroimmunol*. 1986;13(1):19–30.
127. Chuang JI, Mohan N, Meltz ML, Reiter RJ. Effect of melatonin on NF- κ B DNA-binding activity in the rat spleen. *Cell Biol Int*. 1996;20(10):687–692.
128. Mohan N, Sadeghi K, Reiter RJ, Meltz ML. The neurohormone melatonin inhibits cytokine, mitogen and ionizing radiation induced NF- κ B. *Biochem Mol Biol Int*. 1995;37(6):1063–1070.
129. Cristofanon S, Uguccioni F, Cerella C, et al. Intracellular prooxidant activity of melatonin induces a survival pathway involving NF- κ B activation. *Ann NY Acad Sci*. 2009;1171:472–478.
130. Cecon E, Fernandes PA, Pinato L, Ferreira ZS, Markus RP. Daily variation of constitutively activated nuclear factor kappa B (NF κ B) in rat pineal gland. *Chronobiol Int*. 2010;27(1):52–67.
131. Jin W, Wang H, Yan W, et al. Disruption of Nrf2 enhances upregulation of nuclear factor- κ B activity, proinflammatory cytokines, and intercellular adhesion molecule-1 in the brain after traumatic brain injury. *Mediators Inflamm*. 2008;2008:725174.
132. Thimmulappa RK, Lee H, Rangasamy T, et al. Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. *J Clin Invest*. 2006;116(4):984–995.
133. Smoak KA, Cidlowski JA. Mechanisms of glucocorticoid receptor signaling during inflammation. *Mech Ageing Dev*. 2004;125(10–11):697–706.
134. Miller MA, Kandala NB, Kivimaki M, et al. Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep*. 2009;32(7):857–864.
135. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. *Endocrine*. 2005;27(2):189–200.
136. Radogna F, Diederich M, Ghibelli L. Melatonin: a pleiotropic molecule regulating inflammation. *Biochem Pharmacol*. 2010;80(12):1844–1852.
137. Skwarlo-Sonta K. Melatonin in immunity: comparative aspects. *Neuro Endocrinol Lett*. 2002;23 Suppl 1:61–66.
138. Wichers MC, Maes M. The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon- α -induced depression. *J Psychiatry Neurosci*. 2004;29(1):11–17.
139. Wichers MC, Koek GH, Robaey G, Verkerk R, Scharpe S, Maes M. IDO and interferon- α -induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Mol Psychiatry*. 2005;10(6):538–544.
140. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry*. 2007;12(11):988–1000.
141. Maes M, Yirmiya R, Norberg J, et al. The inflammatory and neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab Brain Dis*. 2009;24(1):27–53.
142. O'Connor JC, Lawson MA, Andre C, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol Psychiatry*. 2009;14(5):511–522.
143. Racagni G, Popoli M. The pharmacological properties of antidepressants. *Int Clin Psychopharmacol*. 2010;25(3):117–131.
144. Parfitt A, Klein DC. Increase caused by desmethylinipramine in the production of [3H]melatonin by isolated pineal glands. *Biochem Pharmacol*. 1977;26(9):904–905.

145. Cowen PJ, Fraser S, Grahame-Smith DG, Green AR, Stanford C. The effect of chronic antidepressant administration on beta-adrenoceptor function of the rat pineal. *Br J Pharmacol*. 1983;78(1):89–96.
146. Franklin M, Clement EM, Campling G, Cowen PJ. Effect of venlafaxine on pineal melatonin and noradrenaline in the male rat. *J Psychopharmacol*. 1998;12(4):371–374.
147. Uz T, Ahmed R, Akhisaroglu M, et al. Effect of fluoxetine and cocaine on the expression of clock genes in the mouse hippocampus and striatum. *Neuroscience*. 2005;134(4):1309–1316.
148. Pastrakuljic A, Tang BK, Roberts EA, Kalow W. Distinction of CYP1A1 and CYP1A2 activity by selective inhibition using fluvoxamine and isosafrole. *Biochem Pharmacol*. 1997;53(4):531–538.
149. Hartter S, Wang X, Weigmann H, et al. Differential effects of fluvoxamine and other antidepressants on the biotransformation of melatonin. *J Clin Psychopharmacol*. 2001;21(2):167–174.
150. Badawy AA, Morgan CJ. Effects of acute paroxetine administration on tryptophan metabolism and disposition in the rat. *Br J Pharmacol*. 1991;102(2):429–433.
151. Bearn J, Franey C, Arendt J, Checkley SA. A study of the effects of desipramine treatment alone and in combination with L-triiodothyronine on 6-sulphatoxymelatonin excretion in depressed patients. *Br J Psychiatry*. 1989;155:341–347.
152. Kennedy SH, Brown GM. Effect of chronic antidepressant treatment with adinazolam and desipramine on melatonin output. *Psychiatry Res*. 1992;43(2):177–185.
153. Thompson C, Mezey G, Corn T, et al. The effect of desipramine upon melatonin and cortisol secretion in depressed and normal subjects. *Br J Psychiatry*. 1985;147:389–393.
154. Golden RN, Markey SP, Risby ED, Rudorfer MV, Cowdry RW, Potter WZ. Antidepressants reduce whole-body norepinephrine turnover while enhancing 6-hydroxymelatonin output. *Arch Gen Psychiatry*. 1988;45(2):150–154.
155. Schmid DA, Wichniak A, Uhr M, et al. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. *Neuropsychopharmacology*. 2006;31(4):832–844.
156. Carvalho L, Gorenstein C, Moreno R, Pariante C, Markus R. Effect of antidepressants on melatonin metabolite in depressed patients. *J Psychopharmacol*. 2009;23(3):315–321.
157. Rabe-Jablonska J, Szymanska A. Diurnal profile of melatonin secretion in the acute phase of major depression and in remission. *Med Sci Monit*. 2001;7(5):946–952.
158. Miller HL, Ekstrom RD, Mason GA, Lydiard RB, Golden RN. Noradrenergic function and clinical outcome in antidepressant pharmacotherapy. *Neuropsychopharmacology*. 2001;24(6):617–623.
159. Franey C, Aldhous M, Burton S, Checkley S, Arendt J. Acute treatment with desipramine stimulates melatonin and 6-sulphatoxy melatonin production in man. *Br J Clin Pharmacol*. 1986;22(1):73–79.
160. Demisch K, Demisch L, Bochnik HJ, et al. Melatonin and cortisol increase after fluvoxamine. *Br J Clin Pharmacol*. 1986;22(5):620–622.
161. Palazidou E, Skene DJ, Arendt J, Everitt B, Checkley SA. The acute and chronic effects of (+) and (–) oxaprotiline upon melatonin secretion in normal subjects. *Psychol Med*. 1992;22(1):61–67.
162. Palazidou E, Papadopoulos A, Sitsen A, Stahl S, Checkley S. An alpha 2 adrenoceptor antagonist, Org 3770, enhances nocturnal melatonin secretion in man. *Psychopharmacology (Berl)*. 1989;97(1):115–117.
163. Markus RP, Franco DG, Carvalho LA, Gentil V, Gorenstein C. Acute increase in urinary 6-sulfatoxymelatonin after clomipramine, as a predictive measure for emotional improvement. *J Psychopharmacol*. 2010;24(6):855–860.
164. Demisch K, Demisch L, Nickelsen T, Rieth R. The influence of acute and subchronic administration of various antidepressants on early morning melatonin plasma levels in healthy subjects: increases following fluvoxamine. *J Neural Transm*. 1987;68(3–4):257–270.
165. Skene DJ, Bojkowski CJ, Arendt J. Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans. *Br J Clin Pharmacol*. 1994;37(2):181–186.
166. Celada P, Perez J, Alvarez E, Artigas F. Monoamine oxidase inhibitors phenelzine and brofaromine increase plasma serotonin and decrease 5-hydroxyindoleacetic acid in patients with major depression: relationship to clinical improvement. *J Clin Psychopharmacol*. 1992;12(5):309–315.
167. Zolkowska D, Rothman RB, Baumann MH. Amphetamine analogs increase plasma serotonin: implications for cardiac and pulmonary disease. *J Pharmacol Exp Ther*. 2006;318(2):604–610.
168. Childs PA, Rodin I, Martin NJ, et al. Effect of fluoxetine on melatonin in patients with seasonal affective disorder and matched controls. *Br J Psychiatry*. 1995;166(2):196–198.
169. Nathan PJ, Norman TR, Burrows GD. Nocturnal plasma melatonin concentrations in healthy volunteers: effect of single doses of d-fenfluramine, paroxetine, and ipsapirone. *J Pineal Res*. 1996;21(2):55–58.
170. Tan ZL, Bao AM, Zhao GQ, Liu YJ, Zhou JN. Effect of fluoxetine on circadian rhythm of melatonin in patients with major depressive disorder. *Neuro Endocrinol Lett*. 2007;28(1):28–32.
171. Cuesta M, Mendoza J, Clesse D, Pevet P, Challet E. Serotonergic activation potentiates light resetting of the main circadian clock and alters clock gene expression in a diurnal rodent. *Exp Neurol*. 2008;210(2):501–513.
172. Sprouse J, Braselton J, Reynolds L. Fluoxetine modulates the circadian biological clock via phase advances of suprachiasmatic nucleus neuronal firing. *Biol Psychiatry*. 2006;60(8):896–899.
173. Peiffer A, Veilleux S, Barden N. Antidepressant and other centrally acting drugs regulate glucocorticoid receptor messenger RNA levels in rat brain. *Psychoneuroendocrinology*. 1991;16(6):505–515.
174. Pariante CM, Makoff A, Lovestone S, et al. Antidepressants enhance glucocorticoid receptor function in vitro by modulating the membrane steroid transporters. *Br J Pharmacol*. 2001;134(6):1335–1343.
175. Okugawa G, Omori K, Suzukawa J, Fujiseki Y, Kinoshita T, Inagaki C. Long-term treatment with antidepressants increases glucocorticoid receptor binding and gene expression in cultured rat hippocampal neurones. *J Neuroendocrinol*. 1999;11(11):887–895.
176. Carvalho LA, Garner BA, Dew T, Fazakerley H, Pariante CM. Antidepressants, but not antipsychotics, modulate GR function in human whole blood: an insight into molecular mechanisms. *Eur Neuropsychopharmacol*. 2010;20(6):379–387.
177. Hu J, Xia Y, Wu Z, Liu L, Tang C. Fluoxetine might alleviate brain damage and hypercortisolemia related to chronic alcohol in rats. *J Stud Alcohol Drugs*. 2010;71(2):290–294.
178. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics*. 2008;3(2):97–106.
179. Fischli S, Jenni S, Allemann S, et al. Dehydroepiandrosterone sulfate in the assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab*. 2008;93(2):539–542.
180. Schule C, Baghai TC, Eser D, Schwarz M, Bondy B, Rupprecht R. Effects of mirtazapine on dehydroepiandrosterone-sulfate and cortisol plasma concentrations in depressed patients. *J Psychiatr Res*. 2009;43(5):538–545.
181. Paslakis G, Luppia P, Gilles M, et al. Venlafaxine and mirtazapine treatment lowers serum concentrations of dehydroepiandrosterone-sulfate in depressed patients remitting during the course of treatment. *J Psychiatr Res*. 2010;44(8):556–560.
182. Binder EB, Kunzel HE, Nickel T, et al. HPA-axis regulation at inpatient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. *Psychoneuroendocrinology*. 2009;34(1):99–109.
183. Juruena MF, Pariante CM, Papadopoulos AS, Poon L, Lightman S, Cleare AJ. Prednisolone suppression test in depression: prospective study of the role of HPA axis dysfunction in treatment resistance. *Br J Psychiatry*. 2009;194(4):342–349.

184. Hallam KT, Begg DP, Olver JS, Norman TR. An investigation of the effect of immediate and extended release venlafaxine on nocturnal melatonin and cortisol release in healthy adult volunteers. *Hum Psychopharmacol*. 2008;23(2):129–137.
185. Ahrens T, Frankhauser P, Lederbogen F, Deuschle M. Effect of single-dose sertraline on the hypothalamus-pituitary-adrenal system, autonomic nervous system, and platelet function. *J Clin Psychopharmacol*. 2007;27(6):602–606.
186. Hashioka S, Klegeris A, Monji A, et al. Antidepressants inhibit interferon-gamma-induced microglial production of IL-6 and nitric oxide. *Exp Neurol*. 2007;206(1):33–42.
187. Obuchowicz E, Kowalski J, Labuzek K, Krysiak R, Pendzich J, Herman ZS. Amitriptyline and nortriptyline inhibit interleukin-1 release by rat mixed glial and microglial cell cultures. *Int J Neuropsychopharmacol*. 2006;9(1):27–35.
188. Vollmar P, Nessler S, Kalluri SR, Hartung HP, Hemmer B. The antidepressant venlafaxine ameliorates murine experimental autoimmune encephalomyelitis by suppression of pro-inflammatory cytokines. *Int J Neuropsychopharmacol*. 2009;12(4):525–536.
189. Taler M, Gil-Ad I, Lomnitski L, et al. Immunomodulatory effect of selective serotonin reuptake inhibitors (SSRIs) on human T lymphocyte function and gene expression. *Eur Neuropsychopharmacol*. 2007;17(12):774–780.
190. Xia Z, DePierre JW, Nassberger L. Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology*. 1996;34(1):27–37.
191. Szuster-Ciesielska A, Tustanowska-Stachura A, Slotwinska M, Marmurowska-Michalowska H, Kandefer-Szerszen M. In vitro immunoregulatory effects of antidepressants in healthy volunteers. *Pol J Pharmacol*. 2003;55(3):353–362.
192. Maes M, Song C, Lin AH, et al. Negative immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology*. 1999;20(4):370–379.
193. Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J Clin Psychopharmacol*. 2001;21(2):199–206.
194. Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB. Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1044–1053.
195. Sutçigil L, Oktenli C, Musabak U, et al. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. *Clin Dev Immunol*. 2007;2007:76396.
196. Walsh HA, Daya S. Influence of the antidepressants desipramine and fluoxetine on tryptophan-2,3-dioxygenase in the presence of exogenous melatonin. *Life Sci*. 1998;62(26):2417–2423.
197. Janssen DG, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Hum Psychopharmacol*. 2010;25(3):201–215.
198. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine_{2C} receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther*. 2003;306(3):954–964.
199. de Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. *Nat Rev Drug Discov*. 2010;9(8):628–642.
200. Howland RH. Critical appraisal and update on the clinical utility of agomelatine, a melatonergic agonist, for the treatment of major depressive disease in adults. *Neuropsychiatr Dis Treat*. 2009;5:563–576.
201. Martinet L, Guardiola-Lemaitre B, Mocaer E. Entrainment of circadian rhythms by S-20098, a melatonin agonist, is dose and plasma concentration dependent. *Pharmacol Biochem Behav*. 1996;54(4):713–718.
202. Van RO, Weibel L, Olivares E, Maccari S, Mocaer E, Turek FW. Melatonin or a melatonin agonist corrects age-related changes in circadian response to environmental stimulus. *Am J Physiol Regul Integr Comp Physiol*. 2001;280(5):R1582–R1591.
203. Cajochen C, Krauchi K, Mori D, Graw P, Wirz-Justice A. Melatonin and S-20098 increase REM sleep and wake-up propensity without modifying NREM sleep homeostasis. *Am J Physiol*. 1997;272(4 Pt 2):R1189–R1196.
204. Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol*. 1997;272(4 Pt 2):R1178–R1188.
205. Llorca PM. The antidepressant agomelatine improves the quality of life of depressed patients: implications for remission. *J Psychopharmacol*. 2010;24(Suppl 2):21–26.
206. Quera-Salva MA, Lemoine P, Guilleminault C. Impact of the novel antidepressant agomelatine on disturbed sleep-wake cycles in depressed patients. *Hum Psychopharmacol*. 2010;25(3):222–229.
207. Kasper S, Hajak G, Wulff K, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J Clin Psychiatry*. 2010;71(2):109–120.
208. Olie JP, Kasper S. Efficacy of agomelatine, a MT₁/MT₂ receptor agonist with 5-HT_{2C} antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol*. 2007;10(5):661–673.
209. Serretti A, Chiesa A. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. *J Clin Psychopharmacol*. 2009;29(3):259–266.
210. Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol*. 2004;19(5):271–280.

Neuropsychiatric Disease and Treatment

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS.

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.