Neuroimmune endocrine effects of antidepressants

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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
occurring “lights off” hormone. Melatonin is released according to a daily rhythm, depending on the prevailing light/dark phase of the day. 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.

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. 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. This modulation will lead, in turn, to a reduction of circulating melatonin.

Suprachiasmatic nuclei neurons also receive afferent serotonergic projections from the raphe nuclei which exert inhibitory control over the suprachiasmatic nuclei neuronal response to light. 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 β1 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. Due to its regulation, it has been suggested that melatonin could be used as a readout of noradrenergic function after antidepressant administration. 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.

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, promoting neurogenesis, modulating the immune system, improving defenses and/or decreasing inflammation and regulating metabolism, especially in lipids. It also has very strong antioxidant and oncostatic effects and most of these functions are exerted through the G protein-coupled membrane receptors, MT1 and MT2.

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-sulphatoximelatonin (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. 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, 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. Moreover, the duration in hours that melatonin was present in the plasma correlates with depressive symptomatology. Some studies focusing on the melancholic subtype of depression found a smaller rise in melatonin and lower serum melatonin compared with controls, while postpartum depression was related to higher plasma melatonin levels.

Furthermore, a history of depression was related to melatonin impairment, 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. 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.

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. 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. These areas are implicated in neuroendocrine modulation and in the regulation of the circadian system, 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 GC, CC, and GG forms. They showed that the AA type (for rs4446909) and the GG type (for 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. 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. Circadian impairments have been hypothesized to be involved in the development of seasonal affective disorder, specifically phase shift theories have been proposed, and light therapy has proven its efficacy in both seasonal and nonseasonal affective disorders. 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. Clock genes are found also in the adrenal glands, and mutations in these can alter daily corticosteroid excretion. In 1985, Linkowski et al found early timing of adrenocorticotropic 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. 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. 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. 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, dim light melatonin onset and core body temperature, and dim light melatonin onset and cortisol acrophase (the 24-hour peak). Other circadian abnormalities found in depressed patients were a tendency toward evenness, a later sleep onset and midpoints, and a delayed dim light melatonin onset. These findings highlight the presence of neuroendocrine abnormalities, such as circadian misalignments, in depressed patients.

**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. 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. In addition, cortisol has been shown to regulate memory, emotional appraisal of events, neurogenesis, and neuronal survival (Figure 2).

Glucocorticoids exert their function through the glucocorticoid receptor (GR) and the mineralocorticoid receptor. 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. The HPA axis is regulated also by biological stimuli, such as proinflammatory cytokines, ie, interleukin (IL)-1 and IL-6, and psychologically stressful situations. 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. High cortisol levels in the cerebrospinal fluid, plasma, and urine, impairment in the negative feedback regulation of the HPA axis, and hyperplasia of the adrenal and pituitary glands are also found in depressed patients. 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.](https://www.dovepress.com/https://www.dovepress.com)
While DST and the dexamethasone/CRH test suggest impaired feedback inhibition at the level of the pituitary, impaired responsiveness to hydrocortisone challenge in depressed patients may represent feedback alterations in the brain, although this latter finding is inconsistent. 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.

Furthermore, another analysis of HPA reactivity to stress is the so-called "cortisol awakening response" measured in salivary cortisol samples taken after awakening. 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. Studies conducted so far (as reviewed elsewhere) 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, 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. 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. 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. Moreover, it was found that melatonin had an inhibitory action on GR function in mouse thymocytes, in particular reducing GR receptor nuclear translocation. 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. A possible pathway was shown in a study where isolated pineal glands from rats were cultured with three different substances, ie, ALLN, a proteasome inhibitor, an antagonist of the nuclear factor κB (NF-κB), 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.
by GR antagonists; the potentiating effect of corticosteroids was then mimicked by treatment with an NF-κB antagonist as well as with ALLN. Physiologically, proteasomes are necessary for the translocation of NF-κB into the nucleus since they degrade inhibitory factors (I-κB) which keep NF-κB bound to the cytosol. These results show a clear pathway by which corticosterone increases melatonin production through inhibition of nuclear translocation of NF-κB.

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. In summary, it seems that melatonin has an inhibitory action on adrenal and pituitary volume and a positive action on GR expression. 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, and an elevation in IL-1β and tumor necrosis factor alpha has also been reported. Moreover, major depression is strongly associated with increased levels of acute phase proteins, including C-reactive protein. Inflammatory markers not only increase the risk for depression and correlate positively with severity of depressive symptoms but also modulate responsiveness to antidepressants. 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, while inflammatory-induced depression can also be treated with antidepressants. Thirdly, activation of the immune system and administration of proinflammatory cytokines to laboratory animals induces behavior that is similar to depression in humans. 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. IL-6 has been reported to induce a prolonged increase in plasma concentrations of ACTH and cortisol in healthy men. 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. 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, an effect that is virtually opposite to that of antidepressants in the same experimental system. 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. In addition to mediating immune reactions and GR function, cytokines
have been shown to alter sleep architecture significantly.\textsuperscript{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-acetylseryotonin and melatonin in cultured glands. Furthermore, pinealocytes express receptors for lipopolysaccharide, which can trigger the NF-κB 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{120} The interaction of endogenous norepinephrine with β-adrenoceptors has been suggested to increase AANAT activity and melatonin release.\textsuperscript{121} β-adrenoceptor stimulation has been shown to increase gene expression and protein production of tumor necrosis factor alpha as well as IL-1β and IL-6.\textsuperscript{122} However, the available data suggest that enhanced adrenergic tonus leads to immunosuppression, primarily via alpha 2-receptor-mediated mechanisms.\textsuperscript{123} Consequently, chronic β-receptor blockade reduces plasma levels of IL-6.\textsuperscript{124} Also, stress-induced activation of NF-κB in peripheral blood mononuclear cells appears to be dependent on norepinephrine and can be brought down by α1-adrenoceptor blockade.\textsuperscript{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.\textsuperscript{126} β-adrenoceptor blockers, which depress melatonin secretion, exert immunosuppressive effects only when given in the evening,\textsuperscript{127} 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-κB; the hormone has been reported to inhibit NF-κB in various animal models.\textsuperscript{127,128} As a matter of fact, melatonin is also able to activate NF-κB, thus regulating the expression of adhesion molecules on circulating leukocytes.\textsuperscript{129,130} NF-κB, a determinant of inflammatory responses, is constitutively expressed in the pineal gland, which possesses receptors to trigger the NF-κB pathway.\textsuperscript{118} Activation of NF-κB 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-κB leads to enhancement of melatonin production.\textsuperscript{113} In turn, melatonin inhibits translocation of NF-κB to the nucleus\textsuperscript{128} and inflammation mediated by NF-κB. It has been suggested that NF-κB 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-κB further support this hypothesis.\textsuperscript{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-κB pathway to induce and turn off inflammatory responses, respectively,\textsuperscript{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,\textsuperscript{120} and is believed to work as an antiadrenocortical or antistress factor.\textsuperscript{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.\textsuperscript{134} Moreover, patients with major depression show abnormal IL-6 production across the melatonin cycle,\textsuperscript{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,\textsuperscript{135} through specific receptors, 71/MT2, and high affinity nuclear receptors (RZR) found on leukocytes. Furthermore, the last can synthesize melatonin, having the enzyme necessary for its production.\textsuperscript{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.\textsuperscript{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 kynurenine-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 kynurenine-3-mono-oxygenase antagonist. Those treatments also normalized the kynurenine/tryptophan ratio, while the direct administration of kynurenine induced depressive-like behavior in healthy mice.142 These results reinforce the idea that kynurenine-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 catabolism148,149 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 inhibit50 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 β1-adrenoceptors in
the pineal gland to the constant high levels of norepinephrine in the synaptic cleft. Similar results were found following 3–6 weeks of treatment with a monoamine oxidase inhibitor, tranylcypromine or clorgyline, with regard to urinary aMT6s in 27 depressed patients. These findings were confirmed also for mirtazapine (a tetracyclic antidepressant) given in the long term. 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. In contrast with those findings, another study 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.

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. Desipramine 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 a2-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. 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 1 Antidepressant effect on melatonin in depressed patients

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<td>↑</td>
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<tr>
<td>Rabe-Jablonska and Szymanska</td>
<td>Clomipramine</td>
<td>8 weeks</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Miller et al</td>
<td>Fluvoxamine, Imipramine</td>
<td>6 weeks</td>
<td>↑ in responders, ↓ in nonresponders</td>
<td>↑ in responders, ↓ in nonresponders</td>
</tr>
<tr>
<td>Schmid et al</td>
<td>Mirtazapine</td>
<td>Long-term (28 days)</td>
<td>↑</td>
<td>=</td>
</tr>
<tr>
<td>Carvalho and Pariante</td>
<td>Fluoxetine, Duloxetine</td>
<td>8 weeks</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Neuropsychiatr Dis 2012:8
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

Table 2  Antidepressant effect on melatonin in healthy subjects

<table>
<thead>
<tr>
<th>Name</th>
<th>Antidepressant</th>
<th>Treatment</th>
<th>Plasma melatonin</th>
<th>Urinary 6-sulphatoximelatonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowen et al19</td>
<td>Desipramine</td>
<td>Acute</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demisch et al160</td>
<td>Fluvoxamine</td>
<td>Acute (once)</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Demisch et al164</td>
<td>Tranylcypromine</td>
<td>Baseline – 3 weeks</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td></td>
<td>Pirlindole</td>
<td>&quot;</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td></td>
<td>Maprotiline</td>
<td>&quot;</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>&quot;</td>
<td>↑ – ↑</td>
<td></td>
</tr>
<tr>
<td>Franey et al159</td>
<td>Desipramine</td>
<td>Acute</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Palazidou et al162</td>
<td>Mirtazapine</td>
<td>Acute</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Palazidou et al164</td>
<td>(+)Oxaprotiline</td>
<td>3 weeks</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(–)Oxaprotiline</td>
<td>3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skene et al165</td>
<td>Fluvoxamine</td>
<td>Acute</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>Acute</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>Markus et al163</td>
<td>Clomipramine</td>
<td>Acute</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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. A consistent phase advance in neuronal firing was showed in rat slices after treatment with fluoxetine and tryptophan.

**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, and in vitro antidepressant treatment for 24 hours increased GR expression, promoted GR nuclear translocation, and enhanced GR function in mouse fibroblasts. Similar results were found for animal neuronal cells treated with either selective serotonin reuptake inhibitors or tricyclic antidepressants. Such treatment also showed modulation of GR function in peripheral red blood cells. 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. Also, perinatal exposure to maternal selective serotonin reuptake inhibitors can induce a lower basal cortisol level in the newborn. 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, and there seems to be a relationship between dehydroepiandrosterone reduction and the therapeutic effect of an antidepressant. Also, one study found that restoring of HPA axis hyperactivity in 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>
<thead>
<tr>
<th>Table 3 Antidepressant effects on circadian rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>Cuesta et al</td>
</tr>
<tr>
<td>Sprouse et al</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4 Antidepressant effects on HPA axis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>Peiffer et al</td>
</tr>
<tr>
<td>Pariante et al</td>
</tr>
<tr>
<td>Pariante and Miller</td>
</tr>
<tr>
<td>Okugawa et al</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Carvalho et al</td>
</tr>
<tr>
<td>Hu et al</td>
</tr>
<tr>
<td>Oberlander et al</td>
</tr>
<tr>
<td>Schule et al</td>
</tr>
<tr>
<td>Paslakis et al</td>
</tr>
</tbody>
</table>

**Abbreviations:** HPA, hypothalamo-pituitary-adrenal; GR, glucocorticoid receptor.
an antidepressant. 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. Some controversial results come from two studies 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 oxide when treated with lipopolysaccharide, while amitriptyline and nortriptyline decreased levels of IL-1 and tumor necrosis factor alpha. 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. 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. 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. 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. 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. Furthermore, desipramine and fluoxetine seem to have an inhibitory effect on indoleamine-2,3-dioxygenase activity. More details on the effects of antidepressants on the immune system have been reviewed by Janssen et al.

**Table 5 Antidepressant effects on immune system**

<table>
<thead>
<tr>
<th>Name</th>
<th>Antidepressant</th>
<th>Type</th>
<th>Neuroendocrine alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashioka et al</td>
<td>Fluvoxamine, reboxetine, imipramine</td>
<td>Murine glia cells</td>
<td>↓ NO levels after IFNγ stimulation</td>
</tr>
<tr>
<td>Obuchowicz et al</td>
<td>Amitriptyline, nortriptyline</td>
<td>Rat glia cells</td>
<td>↓ IL1 and TNFα after LPS stimulation</td>
</tr>
<tr>
<td>Vollmar et al</td>
<td>Venlafaxine</td>
<td>Rat encephalitogenic T cell clones, splenocytes, peritoneal macrophages</td>
<td>↓ IL12, TNFα, and IFNγ</td>
</tr>
<tr>
<td>Taler et al</td>
<td>Imipramine, mianserin, clomipramine, sertraline and citalopram</td>
<td>Human peripheral white blood cells</td>
<td>↓ proinflammatory cytokines</td>
</tr>
<tr>
<td>Xia et al</td>
<td>Imipramine, venlafaxine, fluoxetine</td>
<td>Healthy human whole blood</td>
<td>↑ anti-inflammatory cytokines</td>
</tr>
<tr>
<td>Kubera et al</td>
<td>Imipramine, venlafaxine, fluoxetine</td>
<td>Treatment resistant</td>
<td>↓ IL-10</td>
</tr>
<tr>
<td>Tuglu et al</td>
<td>Sertraline, citalopram, fluoxetine, fluvoxamine, paroxetine</td>
<td>Depressed patients</td>
<td>↓ TNFα, CRP and leukocyte count</td>
</tr>
<tr>
<td>Kim et al</td>
<td>Bupropion, mirtazapine, citalopram, paroxetine, venlafaxine</td>
<td>Depressed patients</td>
<td>↓ IL-6 and TGF-beta I</td>
</tr>
<tr>
<td>Sutcigil et al</td>
<td>Sertraline</td>
<td>Depressed patients</td>
<td>↓ IL-12</td>
</tr>
<tr>
<td>Walsh and Daya</td>
<td>Desipramine and fluoxetine</td>
<td>Rats</td>
<td>↑ IL-4 and TGF-beta I</td>
</tr>
</tbody>
</table>

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

**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...
for its chronobiotic re-entrainment features. Studies in rats, healthy subjects, and depressed patients had interesting findings with regard to the capacity of agomelatine to re-entrain abnormal circadian rhythms. Moreover, it has a better side effect profile, in particular concerning sexual impairment in comparison with other antidepressants, and low discontinuation symptoms after withdrawal compared with the selective serotonin reuptake inhibitor, paroxetine.

**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

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**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.
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.

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