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Review article

# Psychoneuroendocrinological links between chronic stress and depression

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**Abstract**

*Objective*: The goal of this report is to develop a comprehensive model, which integrates psychosocial and neurobiological aspects, for better understanding the link between chronic stress and mood disorders. *Method*: A selective review of the relevant bibliography was conducted. The significant data were integrated with clinical and preclinical findings, particularly focusing on the effect of the hypothalamo–pituitary–adrenal (HPA) activity on the serotonergic neurotransmission in the CNS. *Results*: The reviewed data shows that chronic application of stress responses may lead to alterations in the regulation of the HPA system, and the resulting hypercortisolism may be reflected in various psychoneuroendocrinological processes, such as the observed in the serotonergic system, which was implicated in the origin and development of depression. *Conclusions*: The analysis of the interactions between the different components of this process, suggests that normalization of the HPA system, either directly through psychopharmacologic strategies, or indirectly through psychotherapeutic approaches oriented to improve the cognitive appraisal of stressful situations, may provide us with more effective diagnostic, preventive, and therapeutic methods in the treatment of widespread anxiety and mood disorders.


*Keywords:* Depression; Psychoneuroendocrinology; Stress

## 1. Introduction

Stability in the internal environment of a living organism is the result of a complex equilibrium, which is constantly challenged by intrinsic or extrinsic forces, physical or psychological stimuli, known as *stressors*. This tendency toward stability was called *homeostasis* (Cannon, 1932), and therefore *stress* is defined as a state of threatened homeostasis, to which the organism, to preserve its internal equilibrium, reacts with an array of adaptive responses (Akil and Morano, 1995; Chrousos and Gold, 1992).

Basically, not all states of stress are necessarily noxious or negative. Mild, brief and controllable challenges, or *eustress*, could be perceived as pleasant or exciting stimuli and could be a positive input for the emotional and intellectual development, while the more intense, persistent, and uncontrollable situations of threat, or *distress*, may lead to maladaptive responses (Selye, 1976, 1978). However, in clinical and scientific contexts, the term *stress*, unless defined otherwise, refers generally to *distress*.

The link between stress and depression has long been observed, particularly at the clinical level, where chronic exposure to stressful life events has been associated with the development of depressive symptoms in certain individuals, under certain conditions. This has been shown to depend on the characteristics of stressful life events and the psychological resources of each individual to cope with them. In the following, we intend to shed light on the psychoneuroendocrinological events underlying these processes.

*Abbreviations:* ACTH, adrenocorticotropic hormone; ANS, autonomic nervous system; AP-1, activating protein 1; AR, adrenaline; BDNF, brain-derived neurotrophic factor; BNST, bed-nucleus of the stria terminalis; CNS, central nervous system; CRE, cAMP response element; CREB, cAMP response element binding protein; CRH, corticotropin-releasing hormone; DA, dopamine; DRN, dorsal raphe nucleus; GR, glucocorticoid receptors; GRE, glucocorticoid response element; HPA, hypothalamo–pituitary–adrenal; IEG, immediate-early genes; LH, lateral hypothalamus; L-HPA, limbic–hypothalamo–pituitary–adrenal; M-C, mesocortical; M-L, mesolimbic; MR, mineralocorticoid receptors; MRN, median raphe nucleus; NA, noradrenaline; NAC, nucleus accumbens; NLC, nucleus locus coeruleus; POMC, proopiomelanocortin; PVN, paraventricular nucleus; SAN, sympatho–adrenergic–noradrenergic; T-A, thalamo–amygdala; T-C-A, thalamo–cortico–amygdala; VTA, ventral tegmental area.

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## 2. Stress and adaptation

Adaptation is a dynamic process, coordinated principally by the central nervous system (CNS), which involves the processing of sensory information, integration with previous experiences, neural and neuroendocrine adjustments, and planning of behavioral responses to facilitate the functions of adaptive neural pathways that promote arousal, attention, and adequate responsiveness, while inhibiting their non-adaptive counterparts, that promote vegetative functions such as eating, sleeping, and sexual behavior (Gold et al., 1988a). This process is meant to be acute and restricted to stressful situations. Hence, the cumulative and persistent exertion of adaptive responses may lead to overreaction of the *stress system*, a situation described primarily as the *general adaptation* or *stress syndrome* (Selye, 1936, 1946). In human research, *adaptation* has primarily the connotation of adjustment to psychosocial challenges, especially those with relevant emotional implications. Moreover, psychosocial stress is widely recognized as an important trigger in the expression of various psychiatric syndromes, including major depression and anxiety disorders (Gold et al., 1988b).

The principal components of the adaptive response to stress are the sympatho–adrenergic–noradrenergic (SAN) and the limbic–hypothalamo–pituitary–adrenal (L-HPA) systems. The SAN system implies the biosynthesis and release of adrenaline (AR) and noradrenaline (NA), regulated respectively by the sympathetic division of the autonomic nervous system (ANS), and the nucleus locus coeruleus (NLC), in the CNS. The L-HPA system involves limbic structures, such as the amygdala and the hippocampus, in association with the HPA axis, and their respective interconnections (Fig. 1). The SAN and L-HPA systems also participate in their mutual positive regulation, so that activation of one of them involves the activation of the other as well (Chrousos et al., 1988). In addition, the stress system also includes other brain areas involved in important functions such as the analysis and retrieval of information, the appraisal process, the setting of emotional tone, the evaluation of coping strategies, and the implementation of appropriate adaptive responses (Chrousos and Gold, 1992).

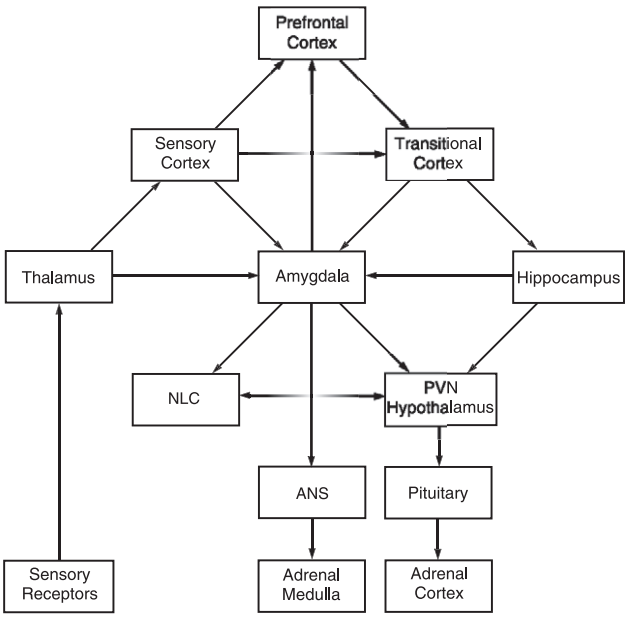


Fig. 1. Schematic representation of the neural and neuroendocrine structures involved in the adaptive response to stress. Environmental stimuli are perceived as sensory input by the sensory receptors, which convey information to their respective sensory thalamus, primary sensory cortices, and higher order sensory cortices. Basic sensory information is simultaneously transmitted to the amygdala from these structures, and from association cortices, particularly the prefrontal cortex, through transitional cortices and the hippocampus. Therefore, these limbic structures regulate the activation of both neural and neuroendocrine responses: the neural component involves the noradrenergic system, represented by the NLC, and the adrenergic system, through the lateral nucleus of the hypothalamus, which activates the SNS and the adrenal medulla. The neuroendocrine component involves the activation of the PVN of the hypothalamus, the anterior pituitary, and the adrenal cortex, with the consequent release of CRH, ACTH, and cortisol.

## 3. Stress and the limbic system

Environmental stimuli, playing as external stressors, are perceived by specific sensory receptor systems, which convey information to their respective sensory areas of the thalamus (Fig. 1). Then, sensory information concerning individual stimuli is transmitted to the amygdala through direct thalamo–amygdala (T-A) connections, or indirectly through thalamo–cortico–amygdala (T-C-A) connections. The T-A is a shorter and faster transmission pathway, but since it eludes the cortical processing, it can only provide a primary, preconscious representation of the input. This, in combination with noradrenergic stimulation from the LC, is crucial to activate the arousal, or alarm reaction, of the primary stress response. Both, T-A and T-C-A pathways convey their information to the lateral nucleus of the amygdala, which processes the information and projects to other components, including the basal, accessory basal, and central nuclei of the amygdala (Aggleton, 1992; LeDoux, 1992, 1996).

The hippocampus, unlike the amygdala, does not receive information concerning individual sensory stimuli, but more general, contextual cues. Sensory processing systems of the neocortex receive information about external stimuli and create perceptual representations of them through primary and higher order sensory cortices. These systems project to association cortices, such as the prefrontal and the parieto–temporo–occipital, and then to the transitional cortex, including the perirhinal, parahippocampal, and entorhinal areas, where the different perceptual representations are integrated. The entorhinal cortex projects these integrated representations to the hippocampus, where in turn, even more complex representations are created (Eichenbaum and

Otto, 1992; LeDoux, 1996). Then, the hippocampus, projects back through the same pathways to the neocortex, and projects forward to the amygdala and the paraventricular nucleus (PVN) of the hypothalamus, where it seems to play an inhibitory role (Herman et al., 1989; McEwen and Brinton, 1987; Smelik, 1987). Therefore, the amygdala receives more basic sensory information through T-A pathways, more elaborated information through TCA pathways, and even more complex information, concerning the general context, from the hippocampus (LeDoux, 1996). In addition, the hippocampus and related cortical areas are implicated in the processes of formation and retrieval of explicit memories, from cortical and subcortical storages. So inputs from these areas to the amygdala, playing as internal stressors, may lead to stress responses triggered by such memories (Jacobs and Nadel, 1985), even in the absence of any external event. Hence, the amygdala is essentially involved in the analysis of the emotional significance of external stressors, either as individual stimuli or as complex situations, as well as the emotional appraisal of internal stressors (LeDoux, 1992, 1996; Rogan and LeDoux, 1996). Therefore, different outputs from the central nucleus of the amygdala regulate the expression of different behavioral, autonomic, and neuroendocrine responses (Davis, 1992): projections to the lateral hypothalamus (LH) mediate the activation of the sympathetic component of the ANS (LeDoux et al., 1988), projections to the dorsal motor nucleus of the vagus are involved in the activation of the parasympathetic component of the ANS (Hopkins and Holstege, 1978), projections to the NLC and ventral tegmental area (VTA) are involved, respectively, in the activation of the noradrenergic (Wallace et al., 1989) and dopaminergic (Beckstead et al., 1979) systems, projections to the midbrain central gray mediate certain behavioral responses, and very importantly, direct projections to the PVN of the hypothalamus (Gray et al., 1989), or indirect projections by way of the bed-nucleus of the stria terminalis (BNST) mediate the activation of the characteristic neuroendocrine responses to stress (Davis, 1992; LeDoux et al., 1988).

## 4. The hypotalamo–pituitary–adrenal system

The HPA system receives and integrates various inputs indicative of stress, converging in the PVN of the hypothalamus (Chrousos and Gold, 1992; Dunn and Berridge, 1990; Swanson and Sawchenko, 1983). Neurons of the PVN synthesize corticotropin-releasing hormone (CRH), which released to the hypophyseal portal blood reaches the anterior pituitary (Dunn and Berridge, 1990; Rock et al., 1984). There, CRH regulates the transcription of the proopiomelanocortin (POMC) gene, a common precursor for the adrenocorticotropic hormone (ACTH) and related peptides, and stimulates the release of ACTH into the bloodstream (Antoni, 1986; Autelitano et al., 1990). Other peptides, such as arginine–vasopressine, are also released to reinforce the effect of CRH (Antoni, 1986). Then, ACTH stimulates the biosynthesis and release of glucocorticoids, particularly cortisol, by cells of the adrenal cortex (Axelrod and Reisine, 1984). In response to stress, glucocorticoids exert widespread metabolic effects, particularly involved in the mobilization of energetic resources, aimed at coping with the stressful situation (Munck et al., 1984). These steroid hormones bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Evans, 1988; Truss and Beato, 1993), which belong to a family of transacting factors, structurally organized in different domains (Carlsted-Duke et al., 1987). Upon cortisol binding, these receptors undergo conformational changes to facilitate their subsequent binding to DNA (Beato, 1989; Beato et al., 1989). Therefore, the hormone-receptor complex may regulate the expression of various target genes, either through activation or deactivation. In this regard, up-regulation is often achieved through the constitution of homo- or hetero-dimers which recognize and bind to discrete DNA palindromic sequences, called glucocorticoid response element (GREs), located in the promoter region of target genes (Reichel and Jacob, 1993; Scheidereit et al., 1986). The role exerted by these transcription factors is to bring together other cofactors at the promoter region, such as the *activator-recruited cofactor*, in order to constitute a preinitiation complex that may lead to transcriptional events. Down-regulation may be achieved either directly, through binding of GRs to a negative GRE, like in the negative regulation of the POMC gene (Drouin et al., 1993) and the CRH gene (Malkoski and Dorin, 1999), or indirectly, through interference of GRs with other transcription factors that otherwise may enhance gene expression, like in the case of genes that contain an activating protein 1 (AP-1) binding site in the promoter region. This is a dimmer composed of immediate-early genes (IEG) products, such as Jun and Fos (Pfahl, 1993). If a GR is activated it interacts as a monomer with the Jun–Fos dimmer, resulting in decreased AP-1 regulated transcription. These different mechanisms illustrate how the activity of the HPA system may be regulated through a variety of possibilities (Holsboer, 2000). In order to maintain glucocorticoids within physiological ranges, the HPA axis is controlled by multiple negative-feedback loops, mediated mainly by the steroids themselves (Dallman et al., 1985; Keller-Wood and Dallmam, 1984). Therefore, the endocrine system is closely regulated by the CNS through the HPA axis, and the reciprocal interplay between both systems provides a way through which thoughts and emotions may regulate hormone secretion (McEwen and Brinton, 1987). However, under chronic stress the HPA system is dysregulated, resulting in pathophysiological changes, which may develop into various types of disorders (Selye, 1950), such as anxiety disorders and major depression. In this regard, a significant association between stress and depression is now well documented (Abramson et al., 1978; Gold et al., 1988b; Holsboer, 1995; Post, 1992) where for both syndromes hypercortisolism represents one of the

most consistent biological markers (Gold et al., 1988b; Mokrani et al., 1997; Murphy, 1997; Murphy et al., 1991).

## 5. The symptaho–adrenergic–noradrenergic system

The noradrenergic system is regulated primarily by neurons of the NLC, located in the dorsal tegmentum of the brain stem. This nucleus projects diffusely, through the dorsal bundle to the cerebral cortex, and through both the dorsal and the ventral bundle to various structures, including the amygdala, the hippocampus, and the PVN of the hypothalamus (Charney et al., 1995; Valentino et al., 1993) (Fig. 2). Acute activation of this system leads to release of NA from an extensive network of neurons throughout the brain, producing an enhanced state of arousal, which is critical for adaptive responses to stress (Anisman and Zacharko, 1990; Stone, 1975). Prolonged activation leads to compensatory increases in the biosynthesis of NA and consequently, to a sustained increase in NA release (Adell et al., 1988; Roth et al., 1982) such that brain NA contents does not decline and may even increase (Abercrombie and Zigmond, 1995). In response to chronic stress, central NA activity is affected by environmental cues, such as the availability of effective coping responses. Particularly, exposure to inescapable or uncontrollable stress may lead to dysfunction of the NLC, and consequently, to depressed NA release, which was associated with *learned helplessness* situations (Robbins and Everitt, 1995). Activation of the NA system is usually accompanied by autonomic activation (Valentino et al., 1993). In association with the NLC, the LH mediate the activation of the sympathetic component of the ANS, which is closely involved in adaptive responses through the activation of sympathetic nerves and the release of AR, and considerably less NA, by the adrenal medulla. The integration of the central and peripheral components of the SAN system, is the reason for the broad spectrum of central and autonomic symptoms observed in different stress situations.

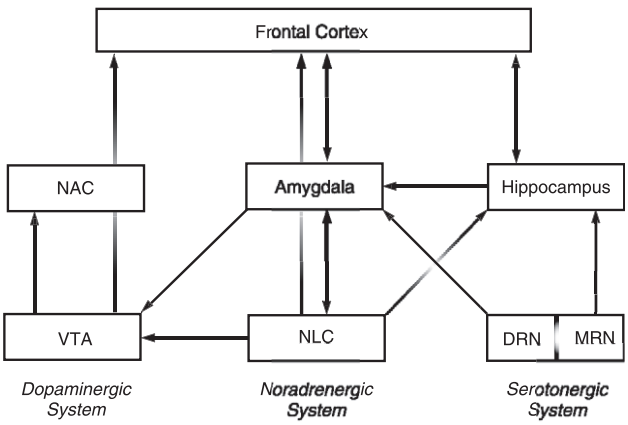


Fig. 2. Schematic representation of three neurotransmitter systems involved in the adaptive response to stress. The dopaminergic system is represented by the VTA and its projections to the NAC and the frontal cortex. The noradrenergic system is represented by projections from the NLC to the amygdala, the hippocampus, and the frontal cortex. The serotonergic system is represented by the raphe nuclei, and projections from the DRN to the amygdala, and from the MRN to the hippocampus.

## 6. The serotonergic system

Serotonin has been implicated in the stress-related regulation of the HPA axis. The serotonergic system has its cell groups mainly in the raphe nuclei, and also projects diffusely to limbic structures and neocortex (Fig. 2). The ascending serotonergic projections to the forebrain originate mainly in the superior group of the raphe nuclei, particularly in the dorsal raphe nucleus (DRN) and the median raphe nucleus (MRN) (Azmitia, 1987). The DRN–forebrain tract innervates the amygdala, the nucleus accumbens (NAC), and other forebrain structures (Azmitia and Whitaker-Azmitia, 1995; Deakin, 1991). This system would mediate the state of anticipatory anxiety, which has an adaptive function in situations of alarm. It is supposed to inform the limbic system that a stimulus or situation is associated with unpleasant experiences, and is involved in controlling emotional reactions to them (Smelik, 1987). Dysfunctional activation of the DRN-forebrain tract was associated with phobic and generalized anxiety disorders (Deakin, 1991). The MRN-forebrain tract innervates complementary structures to those innervated by the DRN, most prominently the hippocampus (Azmitia and Whitaker-Azmitia, 1995; Deakin, 1991). This system would mediate tolerance to unavoidable, persistent aversive stimuli so that acute defensive responses become attenuated with repetition (Kennett et al., 1985). It is associated with conferment of neutralizing control on negative emotional experiences by generating relaxation, satisfaction and inertia (Smelik, 1987). Dysfunction of the MRN–forebrain tract was associated with learned helplessness and subsequent depression (Deakin, 1991). In addition, serotonergic fibers from the DRN and the MRN have been shown to innervate CRH neurons in the PVN, together with serotonergic neurons located entirely in the hypothalamus There is evidence that central serotonergic systems exert a positive control on the HPA axis and the ANS, and that reciprocally, glucocorticoids and catecholamines mediate stress-induced alterations in the central serotonergic systems (Chauloff, 1993; Fuller, 1981).

## 7. The dopaminergic system

Dopamine has also been implicated in the stress-related regulation of the HPA axis, as well as in depression (Cabib and Puglisi-Allegra, 1996a,b; Zacharco and Anisman, 1991). There is evidence that central dopaminergic systems exert a positive control on the HPA axis and the SNS, and

reciprocally, glucocorticoids and catecholamines mediate stress-induced alterations. The dopaminergic system is subdivided in various subsystems, such as the mesolimbic (M-L) and mesocortical (M-C), which are involved in adaptational processes (Smelik, 1987) (Fig. 2). Both, subsystems are activated by the NLC and the ANS during stress. The M-L pathway projects from the VTA to the NAC and the septum, and is involved in the processing and reinforcement of rewarding stimuli and in motivation of behavioral responses (Iversen, 1977; Willner, 1983). This system is believed to be involved in the activation of goal-directed behavior, and its inhibition may lead to emotional indifference and lack of initiative (Smelik, 1987). This system has been shown to be highly sensitive to stress (Abercrombie et al., 1989; Cabib et al., 1988; Puglisi-Allegra and Cabib, 1990). The M-C pathway projects mainly to the frontal cortex, which is critical for cognitive functions such as judgment and planning of behavioral responses (Glowinski et al., 1977), and more specially to the prefrontal cortex, a region thought to be involved in anticipatory phenomena and focused attention (Smelik, 1987). It was suggested that stressful experiences alter dopamine (DA) metabolism and release in the M-L system (Imperato et al., 1992). Moreover, repeated exposure to stress may lead to different responsiveness to subsequent stressful experiences depending on the stressor, leading to different changes on M-L function. Exposure to a single unavoidable/uncontrollable aversive experience may lead to inhibition of DA release in the NAC as well as to impaired response to both rewarding and aversive stimuli (Cabib and Puglisi-Allegra, 1996a,b). The effects of stressful experiences on DA functioning in the M-L system, can be very different or even opposite depending on the controllability of the situation, the genetic background of the organism and its life history (Cabib and Puglisi-Allegra, 1996a,b).

## 8. Stress, appraisal and coping

It has been shown that the adaptive response to psychosocial stress is mediated predominantly by the activation of the SAN system, with the consequent release of AR and NA, and the L-HPA system, with the consecutive release of CRH, ACTH, and glucocorticoids (Akil and Morano, 1995; Chrousos and Gold, 1992). The quality of this adaptive response will be determined by the characteristics of the stressor itself, its appraisal processing, and the resulting coping strategies (Lazarus and Folkman, 1984). Accordingly, there have been described two major reaction patterns in response to distressful situations: the *active* mode of response represents a defense reaction, with effortful coping, produced in situations of perceived threat to control, and mainly characterized by the activation of the SAN system. In contrast, the *passive* mode of response is a defeat reaction, associated with situations of perceived loss of control, inability to cope, or *helplessness*, and the predominant activation of the HPA system. Therefore, chronic activation of this system, due to intensive or prolonged exposure to stress, in combination with a perceived difficulty to cope with it, or even loss of controllability, will result in an impaired negative feed-back of the HPA axis, with the persistent activation of the system, and the consequent increase of circulating cortisol (Croes et al., 1993; Henry, 1992) Hence, the normal activity of the HPA axis, characterized by wide circadian variations, with morning zeniths and evening nadirs, is altered during chronic stress (Halbreich et al., 1985) resulting in sustained increase in plasma cortisol levels (Ottenweller et al., 1989) and a blunted circadian curve, mostly due to elevation during the evening and discrete changes in the morning (Chrousos and Gold, 1998).

Adaptive responses are meant to be acute, limited by the characteristics of the stress, and therefore, an essential component of adaptation is the protection of the organism against overreaction of the system. If the organism is incapable of terminating the response at the end of stress exposure or if it is exposed to chronic, unavoidable situations of stress, then the sustained adaptive responses may lead to pathophysiological changes produced by dysregulation of the stress syndrome. These changes could be perceived as different symptoms, or combinations of them, and may lead to a wide variety of disorders, including different psychosomatic diseases, chronic anxiety disorders, and depression.

## 9. Depression, the immune system and the HPA axis

The evidence of common molecules shared among the nervous, the endocrine, and the immune system, has shed new light in the peripheral regulation of the central function, with special regard to the HPA axis as a crucial point in the genesis of depression (Gold et al., 1988a,b).

Substantial evidence supports the reciprocal regulatory role of the immune system and the HPA axis, with special focus on the CRH hypothalamic neuron, shown to be a major junction point between peripheral events and CNS responses (Makino et al., 2002; Blalock, 1984). In this regard, if glucocorticoid secretion is physiologically activated in response to an inflammatory process, with the aim to restrain tissue damage consequent to the immune reaction (Weigent and Blalock, 1987), a number of experimental data indicate that other mediators of the inflammatory/immune response, including cytokines, activate the HPA axis via the hypothalamic CRH neuron (Sapolsky et al., 2000; Bernardini et al., 1990; Woloski et al., 1985), or, in alternative, via pituitary corticotroph (Benton et al., 1987) or the adrenal cortex (Weber et al., 1997), leading to pathological responses, such as, for example, depression. In fact, is not a casualty that a number of immune disorders may be associated to depression (Maddock and Pariante, 2001).

In particular, IL-1 has been found to stimulate the HPA axis in vitro and in vivo (Sternberg et al., 1989a,b). IL-1 activates the HPA axis in animal models of hypercortisolism (Bernardini et al., 2001), suggesting how an inflammatory event in hypercortisolemic individuals may enhance the appearance of depressive symptoms (Johnson et al., 1996). Other proinflammatory cytokines, such as TNF-α, seem connected to CNS disorders and are able to stimulate CRH secretion directly (Sapolsky et al., 2000).

The cross talk between the immune and the nervous system is not mediated exclusively by cytokines. The property of the latter to activate the HPA axis via the CRH neuron is shared with lipid mediators of inflammation, such as, for example, eicosanoids (Calogero et al., 1988) and platelet-activating factor (Bernardini et al., 1989). The current hypothesis which would explain such interactions concerns the possibility that cytokines and other immune response mediators work as "sensor" molecules, deputated to transform noncognitive stimuli (i.e., an inflammatory process) into cognitive stimuli, allowing the CNS to recognize them (Gold and Chrousos, 2002), with the aim to elaborate an integrated response to the peripheral event. Therefore, molecules released during peripheral inflammatory events may influence central factors controlling homeostasis and behavior (Van West and Maes, 1999).

In turn, the CNS may react to such stimuli, for instance, by inducing hypercortisolism and subsequent immune suppression (Schleifer et al., 2002, 1999; Raison and Miller, 2001). However, if such hypercortisolemic status is pathologically prolonged, as it may occur in chronic stress and depressed individuals, subsequent immunosuppression may lead to higher incidence of infectious, tumoral, and autoimmune diseases (Birmaher et al., 1994; Maes, 1993).

If on a side immune system molecules may influence the CNS, where they have also been shown to affect neurotransmission processes (Spangelo et al., 2000; Ye et al., 2001; Karalis et al., 1991), peptides from the HPA axis, namely CRH, may, in turn, have themselves a peripheral role integrated to stress responses. This could explain how, in depressed or stressed individuals, neuropeptides could directly affect peripheral functions.

In conclusion, the role of CRH and HPA hormones appears relevant in the regulation of an array of peripheral functions in depressed individuals, who bear chronically hyperactivation of the hypothalamic CRH neuron and the HPA axis cascade.

## 10. Stress and depression

Psychosocial stress has been widely recognized as an important trigger in the expression of various clinical syndromes, particularly anxiety and mood disorders (Gold et al., 1988b; Post, 1992). Regarding depression, it constitutes a syndrome characterized by psychological symptoms, such as depressed mood and loss of interest, and certain biological alterations. In this regard, various neurotransmitter systems have been investigated concerning their physiopathology in the CNS and its possible role in the origin and development of depression, giving rise to different aminergic hypotheses. The serotonergic hypothesis of depression postulates that a deficient serotonergic neurotransmission in the CNS may account for a higher vulnerability to this disorder. Hence, the role of serotonin in the physiopathology of depression has long been investigated, giving rise and supporting this hypothesis (Chauloff, 1993; Henninger, 1995; Maes and Meltzer, 1995; Meltzer and Lowy, 1987; Owens and Nemeroff, 1994). At the molecular level, serotonergic neurotransmission is regulated by the rapid removal of serotonin from the synaptic cleft, mostly re-uptaken into the presynaptic terminals by the serotonin transporter (Amara and Kuhar, 1993; Barker and Blakely, 1995). This process exerts control on the effective concentration of the neurotransmitter at the synaptic cleft, and its availability for the interaction with both pre- and postsynaptic receptors (Barker and Blakely, 1995).

Several lines of evidence indicate that enhancement of the serotonergic neurotransmission in the CNS may account for the therapeutic effect of different antidepressants, including tricyclics and selective-serotonin-re-uptake inhibitors, therefore focusing on the serotonin transporter as their most relevant target (Hoffman et al., 1991; Kanner and Schuldiner, 1987).

The syndrome of major depression, and particularly the melancholic type, also seems to reflect alterations in the adaptive response to stress (Chrousos and Gold, 1992, 1998). In this regard, an hyperactive HPA axis, with the consequent hypercortisolism, observed in patients with major depression, represents one of the most consistent findings in biological psychiatry (Gold et al., 1988b). In general, depressive patients carry higher levels of circulating cortisol (Gold et al., 1988b; Mokrani et al., 1997; Murphy, 1997; Murphy et al., 1991). An increased level of cortisol (Carroll et al., 1976; Charles et al., 1986), as well as an increased release of CRH (Nemeroff et al., 1984; Roy et al., 1987), but normal levels of ACTH (Fang et al., 1981; Rod et al., 1986), have been also reported in these patients (Akil and Morano, 1995; Peeters and Broekkamp, 1994).

Regarding the effect of cortisol, various areas in the CNS have been shown to be affected by glucocorticoids, particularly the hippocampus, where MRs and specially a high density of GRs have been observed (McEwen et al., 1979, 1986), and have been involved in processes of neuronal excitability, neurochemistry and neuroplasticity (DeKloet et al., 1998). When normal secretion of glucocorticoids is altered, leading to increased levels of cortisol, this may result in down-regulation of hippocampal GRs (Sapolsky and McEwen, 1985). This potentially adaptive response observed in neural tissues, apparently directed to counteract an excessive concentration of glucocorticoids, may lead to alteration of the negative feed-back mechanisms, resulting

in increased levels of circulating cortisol, which may persist longer after termination of the original stimulus that gave rise to it (McEwen and Brinton, 1987; Sapolsky and McEwen, 1985), and could also result in degenerative changes in the hippocampus (Sapolsky and McEwen, 1985). Hence, the hippocampal alteration produced by prolonged and excessive cortisol levels, with the consequent impairment of the negative feed back loop at this stage, could account for the inability of the glucocorticoid to regulate its own secretion during chronic stress (Chrousos and Gold, 1998; McEwen, 1998).

These observations gave rise to the hypothesis that links the origin of depression with an alteration of the L-HPA system, particularly focusing on the down regulation of GRs at hippocampal and hypothalamic levels (Barden et al., 1995; Holsboer, 2000), with the resulting hypercortisolism. Hence, and according to this notion, antidepressants could act through improving GR function, therefore leading to normalization of the HPA axis. Another hypothesis, complementary to this one, associates the origin and development of depression with a stress-induced decrease of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus (Duman et al., 1997). The BDNF gene contains a specific response element, called cAMP response element (CRE), to which phosphorylated cAMP response element binding protein (CREB) binds and enhances transcription. Therefore, glucocorticoids could interfere indirectly this process through binding of the cortisol–GR complex to CREB, preventing its phosphorylation, and therefore blocking the expression of target genes such as BDNF. Hence, antidepressants could act either through enhancement of BDNF expression or blocking the stress-induced decrease of BDNF. Both hypotheses have been raised in order to explain the mechanism of action of antidepressants at the psycho-neuroendocrine level, particularly as modulators of the HPA axis (Holsboer, 2000).

It has been proposed that increased levels of cortisol could be involved by itself in the characteristic mood changes observed in depression (McEwen and Sapolsky, 1995; Peeters and Broekkamp, 1994). In this regard, several lines of evidence converge to support the notion of a direct correlation between increased cortisol levels and an altered serotonergic function in major depression. Therefore, another hypothesis, proposed more recently by our group (Tafet et al., 2001a), is not only complementary with those referred previously, but is also intended to link a potential alteration of the L-HPA system with the serotonergic hypothesis of depression. According to this, upon incubation with cortisol it has been observed an increased uptake of serotonin in human lymphocytes, as well as in human neuroblastoma cells. This effect was associated with the induction of synthesis of the serotonin transporter, which may then integrate into the cell membrane, thus increasing the uptake of the neurotransmitter. This was understood as a direct effect of the cortisol–GR complex, which regulates different transcriptional responses through binding to the GRE, in the promoter region of target genes (Reichel and Jacob, 1993). Hence, increased levels of cortisol, as those registered during chronic stress or major depression, could down-regulate the effective concentrations of serotonin at the synaptic cleft, therefore contributing to the development of the characteristic symptoms of depression. This hypothesis was further supported by a more recent study, where lymphocytes from hypercortisolemic patients, with chronic stress or depression, presented a similar pattern of response in their serotonin uptake upon incubation with cortisol in vitro (Tafet et al., 2001b).

It has been shown that normalization of circulating cortisol levels in depressed patients was correlated with successful clinical treatment and good prognosis (Amsterdam et al., 1982). Furthermore, hypercortisolemic depressed patients treated with antiglucocorticoid interventions, experience alleviation in their depressive symptomatology (Molkowitz et al., 1993; Murphy, 1997; Murphy et al., 1991; Reus et al., 1997). Considering the facts that the serotonin transporter in lymphocytes and neuronal tissues are identical (Faraj et al., 1994, 1997) and that hypercortisolism is not limited to the CNS but is a systemic phenomenon, the observation that blood cells from both groups of hypercortisolemic patients presented a similar pattern of response, provides further support to the association between both conditions, and suggest the possibility that depression could be understood not only as a consequence, but also as a chronic stress disorder by itself.

## 11. Conclusion

Psychosocial stress may lead to depression in certain individuals, depending on the psychobiological background (Dinan, 1994; Dolan et al., 1985; Post, 1992) and psychosocial variables, such as the attributional style (Abramson et al., 1978) and the cognitive resources, that may lead a person to appraise him or herself, his or her experience, and his or her future, in a certain, cognitively distorted, negative manner (Beck et al., 1979).

The proposed link between high cortisol levels, produced by dysregulation of the HPA axis, and the decreased serotonergic activity, is in line with both psychobiological and cognitive models of depression, and further supports the notion that specific interventions, directed at normalization of the HPA system, could represent a potential strategy to prevent the development of depression in chronically stressed subjects. This could be achieved either directly, through pharmacological approaches, such as the proposed in the anticortisol therapies (Reus et al., 1997; Sapse, 1997; Thakore and Dinan, 1995), or indirectly through psychotherapeutic strategies aimed at reinforcing the subjective feeling of controllability on potentially stressful situations (Tafet et al., submitted for publication).

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