



## Review

## Corticosteroid–serotonin interactions in the neurobiological mechanisms of stress-related disorders

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## ABSTRACT

Among psychiatric disorders, depression and generalized anxiety are probably the most common stress-related illnesses. These diseases are underlain, at least partly, by dysfunctions of neurotransmitters and neurohormones, especially within the serotonergic (5-HT) system and the hypothalamo–pituitary–adrenal (HPA) axis, which are also the targets of drugs used for their treatment. This review focuses on the nature of the interactions between central 5-HT and corticosterone systems in animal models, in particular those allowing the assessment of serotonergic function following experimental manipulation of the HPA axis. The review provides an overview of the HPA axis and the 5-HT system organization, focusing on the 5-HT<sub>1A</sub> receptors, which play a pivotal role in the 5-HT system regulation and its response to stress. Both molecular and functional aspects of 5-HT/HPA interactions are then analyzed in the frame of psychoaffective disorders. The review finally examines the hippocampal neurogenesis response to experimental paradigms of stress and antidepressant treatment, in which neurotrophic factors are considered to play key roles according to the current views on the pathophysiology of depressive disorders.

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## Contents

1. Introduction . . . . .	1175
2. Hypothalamo–pituitary–adrenal axis and corticosteroids . . . . .	1175
2.1. Hypothalamo–pituitary–adrenal axis . . . . .	1175
2.2. Corticosteroid receptors in the central nervous system . . . . .	1176
2.3. Transcriptional control by corticosteroid receptors . . . . .	1176
2.4. Membrane-associated glucocorticoid receptor . . . . .	1176
3. 5-HT system and 5-HT <sub>1A</sub> receptors . . . . .	1177
3.1. Organization and functions of the 5-HT system . . . . .	1177
3.2. Functional characteristics and regulatory properties of 5-HT <sub>1A</sub> receptors . . . . .	1177
3.3. 5-HT <sub>1A</sub> receptors and affective disorders . . . . .	1178
4. Regulation of the serotonergic system by the HPA axis . . . . .	1178
4.1. Reciprocal interactions between the 5-HT system and the HPA axis . . . . .	1178
4.2. Effects of corticosteroids on 5-HT <sub>1A</sub> receptor expression and function . . . . .	1179
4.2.1. Molecular aspects . . . . .	1179
4.2.2. Functional aspects . . . . .	1179
4.3. 5-HT <sub>2C</sub> receptor-mediation of 5-HT system – HPA axis interactions . . . . .	1179
5. Interactions between the HPA axis and the 5-HT system in relation to depressive disorders . . . . .	1180
5.1. Stress, models of depression and 5-HT system . . . . .	1180

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5.2. Neurotrophic factors beyond the HPA/5-HT interactions.....	1181
6. Conclusion.....	1182
Acknowledgements.....	1182
References.....	1182

## 1. Introduction

Stress, originally defined by Hans Selye as a “non-specific response of the body to a demand”, may also be described as any environmental change, either internal or external, that disturbs the maintenance of homeostasis (Leonard, 2005). The term “stress” can be used in two ways: either to identify events or circumstances that are perceived adversely (“stressors”) or to describe the state induced by such events or circumstances (the “stress reaction”) (Glue et al., 1993). The purpose of the stress response is to maintain homeostasis (Sapolsky, 2003), which include a series of physiological reactions such as endocrine activation (especially of the hypothalamo–pituitary–adrenal – HPA axis) and cardiovascular changes, which, *per se*, do not produce pathological changes. It is only when a prolonged and sustained stimulation exceeds the body capacity to maintain homeostasis that stress can have psychopathological sequelae. Indeed, consequences of exposure to repeated stressors are multiple. After an acute reacting phase, long-term symptomatology emerges and encompasses anxiety, irritability and a feeling of being unable to cope which may ultimately result in depression.

Depression is probably the most common stress-related disorder. However, repeated stress *per se* is not sufficient to cause depression. Interactions between a genetic predisposition and some environmental stressors are probably necessary to induce this disease (Caspi and Moffitt, 2006). In addition, not only the HPA axis, but also brain neuronal systems, including the monoaminergic systems and in particular the serotonergic (5-hydroxytryptamine, 5-HT) one, are clearly involved in stress-related disorders. Limbic brain regions, such as the hippocampus and the septum, which play a key role in mood control, are abundantly innervated by serotonergic projections and are also particularly sensitive to glucocorticoids (Moore and Halaris, 1975; Hugin-Flores et al., 2004). The HPA axis and the 5-HT system are closely cross-regulated under normal physiological conditions in mammals (Chaouloff, 1993; Lopez et al., 1998). In addition, their interactions are of particular relevance when considering pathological conditions such as depression, in which dysfunctioning actually concerns both the HPA axis and the 5-HT system (Lesch et al., 1990; Barden, 1999; Porter et al., 2004). A deficiency in brain serotonergic activity has been proposed to increase vulnerability to major depression (Asberg et al., 1986). This could notably be the case when a diminished availability of the 5-HT precursor, 5-HTP, impairments in 5-HT synthesis, release or metabolism, and/or 5-HT receptor abnormalities occur (Maes and Meltzer, 1995). On the other hand, increased tonic activity of the HPA axis has been consistently reported in major depression. This change results from a deficit in the negative feedback regulation of HPA axis as shown by the failure of glucocorticoid receptor (GR) activation to decrease plasma levels of ACTH and cortisol in the “dexamethasone suppression test” (Montgomery et al., 1988). Interestingly, lesions of 5-HT nerve terminals in animals have been found to potentiate the stress-induced rise in plasma corticosterone, in line with the hypothesis that a low 5-HT tone is, at least in part, involved in the etiology of depression, through resulting increased tonic activity of the HPA axis (Richardson, 1984).

This review aims at synthesizing recent progress in the knowledge of the neurobiological mechanisms of stress-related

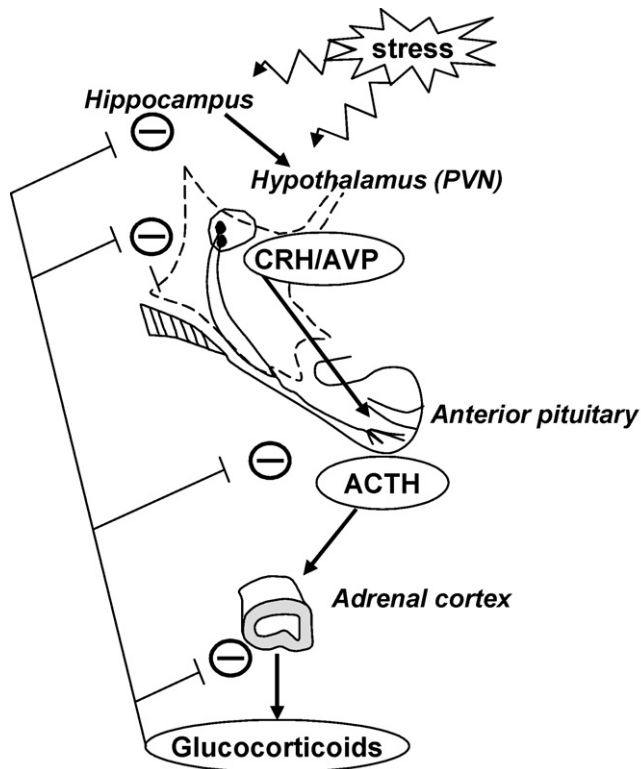
disorders, especially depression, with a particular focus on the 5-HT system and the HPA axis. Indeed, interactions between this monoamine system and the stress axis appear to be critical regarding both the onset and maintenance of a depressive episode. After a brief overview of the HPA axis and the 5-HT system, we will analyze the molecular and functional aspects of their interactions, to finally examine how alterations in these interactions can underlie, at least in part, psychoaffective disorders such as depression.

## 2. Hypothalamo–pituitary–adrenal axis and corticosteroids

### 2.1. Hypothalamo–pituitary–adrenal axis

When an organism is exposed to a stressor, several mechanisms are activated to restore homeostasis. Stress initiates processes in the central nervous system (CNS), particularly in the paraventricular nucleus (PVN) of the hypothalamus. When this brain region is stimulated by stress, it releases corticotropin-releasing hormone (CRH) and its co-secretagogue arginine–vasopressin (AVP). CRH and AVP reach the anterior pituitary gland, where they cause the release of adrenocorticotropin hormone (ACTH) into the circulation. At the level of adrenal glands, ACTH stimulates glucocorticoid-producing cortex cells, which ends with the secretion of cortisol (in human) or corticosterone (in rodents) in blood (Palkovits, 1987) (Fig. 1). These hormones, the corticosteroids, exert numerous actions at the periphery and in the CNS. At the periphery, corticosteroids are involved in energy mobilization (glycogenolysis), and exert modulatory controls on the immune system, bone and muscle growth, epithelial cell growth, erythroid cell production and the cardiovascular system (McEwen and Stellar, 1993; Tronche et al., 1998).

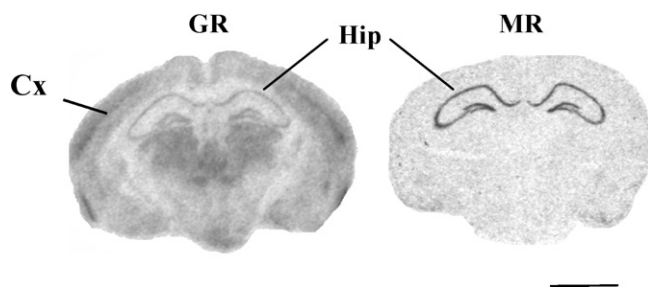
Corticosteroids act through binding onto two types of intracellular steroid receptors, the mineralocorticoid (MR) or type I, and the GR or type II, receptors (de Kloet et al., 1998; Gass et al., 2001). These receptors are abundantly expressed in the limbic brain areas where they mediate distinct and complementary actions. They have identical structure both in the periphery and in the brain (Patel et al., 1989). The MR is a high-affinity receptor which binds corticosterone at low concentration (Kd ~0.5 nM). Its affinity for corticosterone is 10-fold higher than that of GR (Kd ~5 nM). Therefore, *in vivo*, MR is almost completely occupied (90%) by basal corticosterone levels and this contributes to maintaining homeostasis. In contrast, GR is occupied at only ~10% under such basal (“resting”) conditions (Reul and de Kloet, 1986). But when the level of corticosterone rises up to its circadian maximum or during stress, GR becomes substantially occupied by the hormone ligand (de Kloet et al., 1998). Due to this differential occupation of MR and GR, a difference in function has been proposed, with a more tonic inhibitory control function for the MR and a role for the GR in the negative feedback regulation of the HPA axis during stress or at circadian peak (Bradbury et al., 1994; de Kloet et al., 1998). Indeed, under physiological conditions, HPA axis activity is mainly determined by two factors, stress (either physical or psychological) which increases its activity, and the normal circadian rhythm (de Kloet, 2000). Both factors can be dysregulated in a number of diseases and disorders.



**Fig. 1.** Glucocorticoid-mediated feedback regulation of the HPA axis. In response to stress and under the influence of hippocampal inputs, hypothalamic neurons synthesize and release corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP). In turn, the latter neurohormones stimulate the anterior pituitary gland to release adrenocorticotropin hormone (ACTH) into the circulation. ACTH reaches the adrenal glands, where it promotes cortisol/corticosterone secretion. The return to basal resting activity level is achieved through negative feedback control triggered mainly by GR activation by cortisol/corticosterone in adrenal cortex, anterior pituitary and brain structures.

## 2.2. Corticosteroid receptors in the central nervous system

Corticosterone passes easily through the blood brain barrier and reaches the various brain regions that express GR and/or MR (Fig. 2). MR is expressed mainly in limbic regions such as the hippocampus (Jacobson and Sapolsky, 1991), whereas GR has a more widespread distribution in the brain (Reul and de Kloet, 1986), with high densities not only in the hippocampus but also the PVN, the locus coeruleus and the dorsal raphe nucleus (DRN) (Harfstrand et al., 1986; Reul and de Kloet, 1986; Fuxe et al., 1987). In the latter structure, *in situ* hybridization and immunocytochemical studies have shown that both GR mRNA and protein are



**Fig. 2.** *In situ* hybridization mapping of GR and MR mRNAs in the mouse brain. Coronal sections at the level of the cerebral cortex (Cx) and hippocampus (Hip) were labeled by [<sup>35</sup>S]UTP antisense RNA probe specific to mouse GR or MR mRNA sequence. GR mRNA is widely distributed throughout brain areas whereas MR mRNA is restricted mainly to the hippocampus. Scale bar, 2 mm.

expressed exclusively by serotonergic neurons (Harfstrand et al., 1986; Fuxe et al., 1987; Morimoto et al., 1996). Thus, a potential role for circulating glucocorticoids is to regulate gene expression in DRN 5-HT neurons.

In the hippocampus, MR is present at high levels in all layers, whereas GR is found principally in the CA1 and CA2 regions; only a low density of GR is present in CA3, and the dentate gyrus expresses intermediate levels of this receptor (Reul and de Kloet, 1986; de Kloet et al., 2008). Both MR and GR are co-expressed in hippocampal pyramidal neurons. These high levels of corticosteroid receptors in the hippocampus make this structure of critical importance in the feedback control of HPA axis activity (de Kloet, 2000). Furthermore, corticosteroids within the hippocampus affect neuron survival, cell proliferation, gene expression, neuronal excitability, and also neuronal networks and signaling mechanisms underlying cognitive processes such as learning and memory (Gould and Tanapat, 1999; McEwen and Magarinos, 2001; Sapolsky, 2001; Kim and Diamond, 2002).

## 2.3. Transcriptional control by corticosteroid receptors

Corticosteroid receptors belong to the superfamily of nuclear receptors (Beato and Sanchez-Pacheco, 1996; Tasker et al., 2006). After crossing the cell membrane, corticosteroids in the cytosol bind to and activate their intracellular receptors, which then translocate into the cell nucleus. Both MR and GR comprise a ligand-binding domain in their C terminal portion, a DNA-binding domain with two zinc finger motifs and an N-terminal domain involved in transrepression (Beato and Sanchez-Pacheco, 1996). Each receptor type forms a multiprotein complex with heat shock proteins and immunophilin, a protein that binds immunosuppressive drugs (Jenkins et al., 2001). The multiprotein complex is rapidly dissociated after binding of corticosteroid onto the receptor. The activated receptor is then dimerized and acquires a high affinity for nuclear domains. Both homo- and heterodimers of MR and GR can be formed. They attach as dimers to specific DNA sequences called glucocorticoid response elements (GREs) present in promoter regions of target genes, which, in turn, affects transcription (Truss and Beato, 1993; Stockner et al., 2003). Regarding GR, both positive and negative regulations of target genes have been described. Activation of transcription occurs via well-conserved GREs, while negative regulation (transrepression) is mediated by less conserved inhibitory GREs (nGREs) (Gass et al., 2001).

Furthermore, GR monomers can either repress or activate gene transcription via protein–protein interactions with other transcription factors, such as CREB, AP-1 and Stat5, C-Jun and c-Fos, as well as NF- $\kappa$ B (Diamond et al., 1990; Yang-Yen et al., 1990).

## 2.4. Membrane-associated glucocorticoid receptor

Studies conducted by several teams and in different species have recently suggested that corticosteroid hormones could also exert rapid non-genomic effects on neuronal function, in particular in the hippocampal CA1 region and the hypothalamus, via the activation of one or more membrane-associated receptors (de Kloet et al., 2008). Indeed, the incompatibility between the rapid onset of some corticosteroid-induced effects and the (unlikely) mediation of such effects through genomic mechanisms has suggested that acute physiological and behavioral effects of glucocorticoids involve actions at molecular targets in the plasma membrane (Tasker et al., 2006). In line with this hypothesis, acute glucocorticoid application has been shown to enhance long-term potentiation of Schaffer collateral inputs to CA1 pyramidal neurons in hippocampal slices (Wiegert et al., 2006). Furthermore, Hinze and Hirschelmann (2000) demonstrated that in addition to the slow,

gene transcription-dependent actions of glucocorticoids which occur at each of the glucocorticoid feedback target sites along the HPA axis, glucocorticoids can also suppress CRH-induced ACTH secretion within minutes via a rapid, transcription-independent mechanism. Although the membrane-associated glucocorticoid receptor(s) have not yet been fully characterized, there is a growing body of data that suggest that these receptors involve G protein-dependent mechanisms (Tasker et al., 2006).

### 3. 5-HT system and 5-HT<sub>1A</sub> receptors

#### 3.1. Organization and functions of the 5-HT system

Serotonin is a neurotransmitter that exerts a wide influence over many brain functions. In the brain, it is synthesized from the essential amino acid L-tryptophan exclusively in serotonergic neurons located within the raphe nuclei. From these nuclei, 5-HT neurons project to virtually all parts of the CNS, thereby making the serotonergic network one of the most diffused neurochemical systems in the brain. In particular, the hippocampus receives a dense projection of 5-HT fibers mainly from neurons in the median raphe nucleus and is rich in various 5-HT receptor types (Jacobs and Azmitia, 1992). The widespread distribution of 5-HT fibers throughout the CNS accounts for the large variety of functions that can be controlled by 5-HT (Hamon, 1997), including food intake, sleep, memory and learning, thermoregulation, sexual behavior, cardiovascular function, locomotion, endocrine regulation, and psychoaffective tone.

During the last 20 years, numerous 5-HT receptor types have been cloned and extensively characterized (Fig. 3). To date, at least 15 distinct encoding genes have been identified, some of which giving rise to several proteins (up to 24, with discrete variations in amino acid sequence, in case of the 5-HT<sub>2C</sub> receptor encoding gene). All 5-HT receptor types, except one (the 5-HT<sub>3</sub> type), are

members of the G-protein-coupled superfamily. Their stimulation affects various enzymes (for instance adenylyl cyclase, phospholipases A and C, mitogen-activated protein-kinases or MAPKS) and cation channels (especially K<sup>+</sup> and Ca<sup>2+</sup> channels) through the activation of specific G proteins in plasma membrane (Kushwaha and Albert, 2005). Among these receptors, many of them have been proposed to be involved in stress-related disorders, but, one receptor has been shown to play a pivotal role in depressive disorders, the 5-HT<sub>1A</sub> receptor (Lanfumey and Hamon, 2004).

#### 3.2. Functional characteristics and regulatory properties of 5-HT<sub>1A</sub> receptors

The 5-HT<sub>1A</sub> receptor, expressed as postsynaptic heteroreceptor in the limbic system and as somatodendritic autoreceptor on serotonergic neurons in raphe nuclei, plays an important dual role for central 5-HT neurotransmission (Hamon, 1997). 5-HT<sub>1A</sub> receptors are coupled to various effector systems mainly via a Gi/Go type of G protein (Raymond et al., 2001). Chronic treatment with selective serotonin reuptake inhibitors (SSRIs) as well as 5-HT transporter gene disruption (5-HTT<sup>-/-</sup>) are known to induce functional desensitization of 5-HT<sub>1A</sub> autoreceptors in the DRN, but no change in postsynaptic 5-HT<sub>1A</sub> heteroreceptors in the hippocampus (Chaput et al., 1986; Le Poul et al., 2000; Mannoury la Cour et al., 2001). In the DRN, this adaptive regulation is associated with decreased 5-HT<sub>1A</sub> receptor-mediated [<sup>35</sup>S]GTP-γ-S binding, suggesting an alteration of the receptor/G-protein coupling in both SSRI-treated and 5-HTT<sup>-/-</sup> knock-out animals (Fabre et al., 2000; Hensler, 2002). Immunoaffinity chromatography coupled to Western blot experiments showed that 5-HT<sub>1A</sub> receptors interact mainly with Gα<sub>o</sub> in the hippocampus and exclusively with Gα<sub>i3</sub> in the anterior raphe area (Mannoury la Cour et al., 2006). Such a disparity in G-protein coupling could explain regional differences in adaptive regulations of brain 5-HT<sub>1A</sub> receptors.

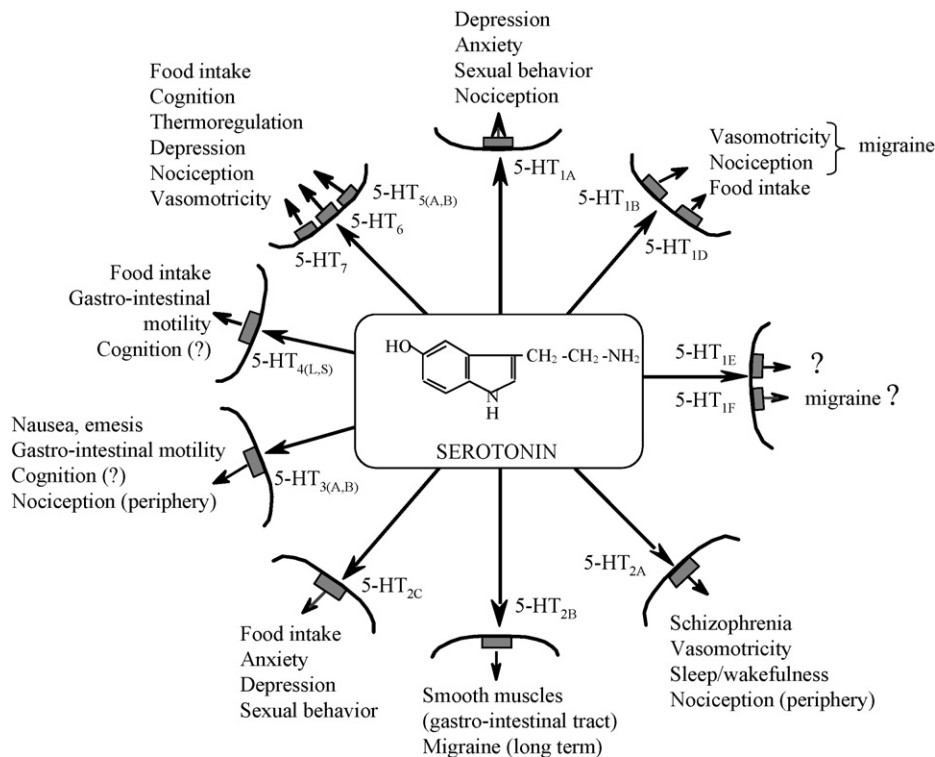


Fig. 3. Multiple 5-HT receptor-mediated functions. Schematic overview of the 5-HT receptor types and their involvement in physiological, psychoaffective and physiopathological conditions.

The level of expression of somatodendritic 5-HT<sub>1A</sub> autoreceptors determines – at least partly – the brain 5-HT tone, through parallel variations in the efficacy of 5-HT-mediated inhibitory feedback control of 5-HT neuron firing. Thus, 5-HT<sub>1A</sub> receptor knock-out mice are characterized both by an increased rate of 5-HT neuron discharge (Richer et al., 2002) and by elevated baseline dialysate levels of extracellular 5-HT in the frontal cortex and hippocampus (Parsons et al., 2001). Interestingly, this raised 5-HT tone is associated with an increased tendency of 5-HT<sub>1A</sub><sup>-/-</sup> mice to avoid novel and fearful environment and to escape stressful situation, indicating an increased anxiety and sensitivity to stress in these mutants (Parks et al., 1998; Overstreet et al., 2003).

### 3.3. 5-HT<sub>1A</sub> receptors and affective disorders

Whether 5-HT<sub>1A</sub> receptors are also involved in depressive-like disorders and their treatment is a question that has been widely addressed. Genetic studies in humans have notably explored the hypothesis that 5-HT<sub>1A</sub> receptor dysfunction might occur in severe depression and suicide. These studies focused on polymorphism(s) of the 5-HT<sub>1A</sub> receptor encoding gene, by looking for possible association between these polymorphisms and depression symptoms in suicide victims. So far, most of the studies concluded that no association exists between 5-HT<sub>1A</sub> receptor gene polymorphisms and major depression (Xie et al., 1995; Nishiguchi et al., 2002). However, Lemonde et al. (2003) reported an association of the C(-1019)G 5-HT<sub>1A</sub> promoter polymorphism with major depression and suicide. According to these authors, the increased

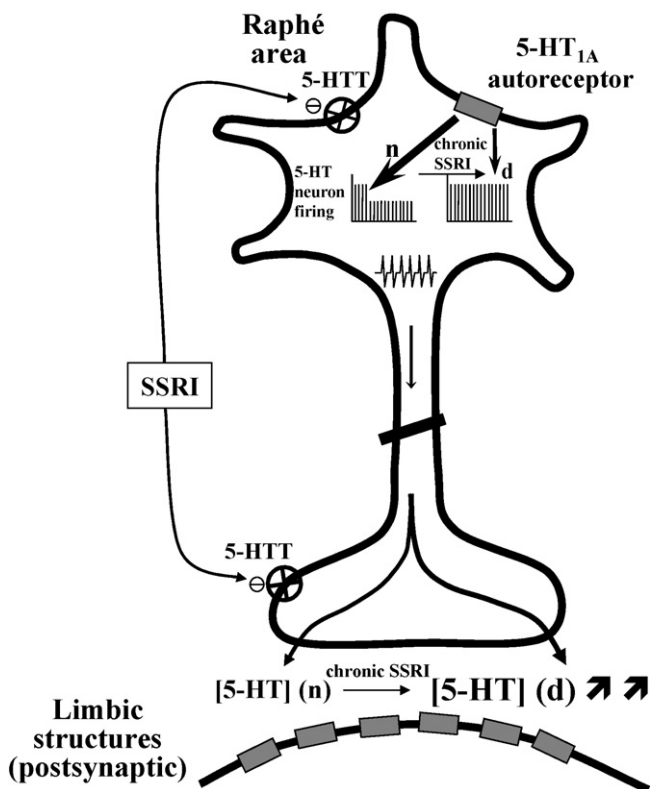
frequency of the G allele in depressed patients would lead to a decreased 5-HT tone caused by a stronger inhibitory feedback control of 5-HT neurotransmission through an elevated expression of 5-HT<sub>1A</sub> autoreceptors in raphe nuclei (Lemonde et al., 2003).

On the other hand, a large body of evidence supports the idea that 5-HT<sub>1A</sub> receptors play a pivotal role in the mechanism of action of various antidepressant drugs (Mongeau et al., 1997). In particular, through the blockade of 5-HT reuptake, SSRIs should produce an increase in brain levels of extracellular 5-HT within minutes following their administration. However, under acute treatment conditions, this expected increase at postsynaptic targets of serotonergic projections is counteracted by the negative feedback triggered by the stimulation of 5-HT<sub>1A</sub> autoreceptors at the 5-HT cell body/dendrite level in the DRN. Indeed, 5-HT<sub>1A</sub> autoreceptor stimulation leads to a reduction of terminal 5-HT release, thereby preventing the increase in extracellular 5-HT levels normally caused by reuptake blockade (Hamon, 1997). In contrast, after repeated SSRI treatment, 5-HT<sub>1A</sub> autoreceptors desensitize, which inactivates the 5-HT inhibitory feedback control and allows extracellular 5-HT concentration to raise markedly as a result of sustained 5-HT reuptake blockade in projection areas of serotonergic fibers, leading to increased activation of receptors including 5-HT<sub>1A</sub> heteroreceptors in forebrain areas (Le Poul et al., 2000) (Fig. 4). These receptors appear to play a pivotal role in the antidepressant-like effects of these drugs. In particular, experiments consisting of the selective regional rescue of 5-HT<sub>1A</sub> receptors in 5-HT<sub>1A</sub><sup>-/-</sup> knock-out mice clearly showed that postsynaptic 5-HT<sub>1A</sub> heteroreceptors are required for the anti-immobility effect of SSRI treatment in animals subjected to the tail suspension test (Overstreet et al., 2003).

## 4. Regulation of the serotonergic system by the HPA axis

### 4.1. Reciprocal interactions between the 5-HT system and the HPA axis

Marked changes in brain 5-HT turnover have been shown to occur in both rodents and humans upon activation of the HPA axis. In particular, significant increases in the synthesis and release of 5-HT have been observed in various brain areas in response to different stressful conditions such as electrical foot shocks, cold environment, immobilization sessions, or tail pinches (Pei et al., 1990; Clement et al., 1993; Inoue et al., 1994). Furthermore, salient findings showed that stress activates DRN 5-HT neuronal activity as indicated by an increase in (i) cFos expression in 5-HT neurons (Grahn et al., 1999; Greenwood et al., 2003), and (ii) 5-HT release within both the DRN (Maswood et al., 1998) and its projection areas (Bland et al., 2003; Amat et al., 2005). However, only inescapable, but not escapable, stresses apparently produce this increase in 5-HT outflow within the DRN and postsynaptic areas such as the hippocampus and the amygdala. Conversely, escapable rather than inescapable stress has been shown to increase 5-HT release specifically in the periaqueductal gray (Amat et al., 1998a,b; Maswood et al., 1998). That corticosterone plays a critical role in these effects has been substantiated by experimental procedures such as adrenalectomy (ADX) and exogenous corticosterone administration which demonstrated that the adrenal steroid hormone exerts a stimulatory influence on tryptophan hydroxylase activity and 5-HT turnover in brain (Singh et al., 1990). It is noteworthy that, contrary to the noradrenergic cells of the locus caeruleus, serotonergic neurons of the DRN do not display an increased firing rate in response to stress (although stress increases cFos expression). Accordingly, stress-induced enhancement of 5-HT output should result more from alterations in 5-HT turnover and release than from changes in DRN electrical activity (Takase et al., 2004).



**Fig. 4.** 5-HT<sub>1A</sub> autoreceptors and brain 5-HT tone – the case of SSRI-induced adaptation. Chronic SSRI-induced 5-HT<sub>1A</sub> autoreceptor desensitization (d) causes a marked reduction in the efficacy of 5-HT-mediated inhibitory feedback control of 5-HT neuron firing. Consequently, extracellular 5-HT concentrations increase markedly as a result of sustained 5-HT reuptake blockade by chronic SSRI treatment in projection areas of serotonergic fibers such as the limbic structures (hippocampus). Postsynaptic 5-HT receptors are then overstimulated. n, normal state; d, desensitization; 5-HTT, 5-HT transporter.

Reciprocally, a large body of evidence has shown that the 5-HT system exerts marked influences on the secretion of corticosteroids. In particular, administration of 5-HT receptor ligands, such as the 5-HT<sub>1A</sub> agonist ipsapirone, produces major changes (increases) in ACTH and cortisol plasma levels in both animals and humans (Wetzler et al., 1996; Klaassen et al., 2002). 5-HT<sub>1A</sub> receptors located in brain areas involved in psychogenic stress, such as the amygdala, might mediate at least part of these effects. Neuroanatomical studies also suggest an action of 5-HT through synaptic contacts between serotonergic terminals and CRH-containing cells in the PVN (Liposits et al., 1987). Indeed, immunohistochemical investigations demonstrated the presence of 5-HT<sub>1A</sub> receptors on PVN neurons, and microinjection of 8-OH-DPAT into this hypothalamic nucleus was shown to trigger ACTH secretion through local 5-HT<sub>1A</sub> receptor activation (Zhang et al., 2004; Osei-Owusu et al., 2005). In contrast, somatodendritic 5-HT<sub>1A</sub> autoreceptors are clearly not involved in the effects of 8-OH-DPAT as 5,7-dihydroxytryptamine lesions of the serotonergic neurons, which eliminate such receptors, do not prevent ACTH release evoked by this agonist (Van de Kar et al., 1998).

All these data strongly support the existence of reciprocal relationships between the 5-HT system and the HPA axis. Although several 5-HT receptor types have been shown to participate in these regulations, the most convincing data concern the 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors, as summarized in the following sections.

#### 4.2. Effects of corticosteroids on 5-HT<sub>1A</sub> receptor expression and function

##### 4.2.1. Molecular aspects

Transcription of the 5-HT<sub>1A</sub> receptor gene is negatively regulated by corticosteroids especially in the limbic system. In the rat, ADX is followed by a rapid and marked increase (within hours) of *de novo* 5-HT<sub>1A</sub> mRNA synthesis, total 5-HT<sub>1A</sub> mRNA levels, and 5-HT<sub>1A</sub> binding sites in the hippocampus and the septum (Mendelson and McEwen, 1992; Chalmers et al., 1993; Zhong and Ciaranello, 1995). In the raphe nuclei, ADX-evoked 5-HT<sub>1A</sub> autoreceptor up regulation is hardly detected (Tejani-Butt and Labow, 1994; Laaris et al., 1999). ADX-induced changes are completely reversed by treatment with low doses of corticosterone that preferentially activate MR (Mendelson and McEwen, 1992; Liao et al., 1993; Meijer and de Kloet, 1994). However, using MR- and GR-selective ligands (in the rat) and gene knockout approaches (in the mouse), Meijer and de Kloet (1995). Provided evidence that both MR (primarily) and GR are involved in a negative regulation of 5-HT<sub>1A</sub> gene expression (see also Meijer et al. (1997)).

Initial investigations of the underlying molecular mechanisms have led to the conclusion that the promoter region of the rat 5-HT<sub>1A</sub> receptor gene does not contain any GRE, but is endowed with sequence domains recognized by other known transcription factors, such as NF- $\kappa$ B (p65 subunit) and SP1 (Meijer et al., 2000; Wissink et al., 2000). Corticosteroids were shown to repress NF- $\kappa$ B-induced 5-HT<sub>1A</sub> promoter activity, mainly through GR activation which specifically inhibits the inducing effect of p65 NF- $\kappa$ B subunit. In addition, when 5-HT<sub>1A</sub> receptor gene transcription was synergistically activated by the transcription factors SP1 and p65, both GR and MR contributed to counteract this effect (Meijer et al., 2000).

More recently, Ou et al. (2001) identified a negative GRE-like sequence in the rat 5-HT<sub>1A</sub> gene promoter, at which transrepression of gene transcription was more effective with MR than GR. However, repression was the highest upon binding of MR-GR heterodimer onto this specific promoter sequence. This observation might explain why 5-HT<sub>1A</sub> receptor gene transcription is repressed by corticosterone to a greater extent in the hippocam-

pus, which expresses both MR and GR, than in the DRN, which expresses only GR (Meijer et al., 2000; Wissink et al., 2000; Ou et al., 2001). Further investigations of this specific question will be possible thanks to the recently described 5-HT<sub>1A</sub>-iCre transgenic mouse which should allow the generation of conditional mutants lacking GR specifically in 5-HT<sub>1A</sub> receptor-expressing cells (Sahly et al., 2007).

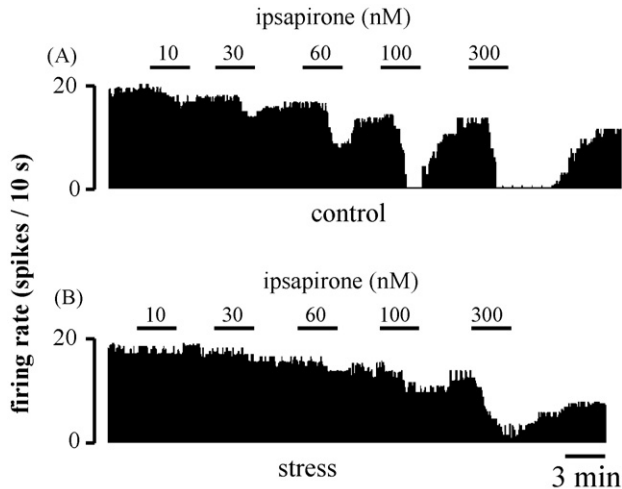
##### 4.2.2. Functional aspects

Several lines of evidence have demonstrated that 5-HT<sub>1A</sub> receptor function is under the influence of the HPA axis. In agreement with molecular biology data on the inhibitory effect of corticosteroids on 5-HT<sub>1A</sub> receptor gene transcription, chronic immobilization stress, which raises circulating levels of corticosterone, has been consistently reported to decrease hippocampal 5-HT<sub>1A</sub> receptor binding (Mendelson and McEwen, 1991). On the other hand, electrophysiological studies in ADX rats showed that selective activation of MR decreases the hyperpolarization of hippocampal CA1 pyramidal neurons in response to 5-HT<sub>1A</sub> receptor stimulation (Joels et al., 1991). Interestingly, this effect of MR activation can be reversed by the concomitant activation of GR, possibly because of some facilitation of the 5-HT<sub>1A</sub>-mediated hyperpolarizing response upon selective GR activation (Hesen and Joels, 1996). In contrast, GR activation in the DRN results in a significant decrease in the potency of 5-HT<sub>1A</sub> receptor agonists to inhibit the discharge of local serotonergic neurons, as expected of a functional desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors (Laaris et al., 1995, 1997). Similarly, moderate stress in rats and the chronic mild stress procedure in mice, which both raise serum corticosterone levels, have been shown to decrease the potency of 5-HT<sub>1A</sub> agonists to inhibit the electrical activity of serotonergic neurons in the DRN (Laaris et al., 1999; Lanfumey et al., 1999) (Fig. 5).

Electrophysiological approaches also evidenced that prolonged, but not acute, exposure to elevated corticosterone levels attenuated 5-HT<sub>1A</sub> autoreceptor function in the DRN in rats (Fairchild et al., 2003; Judge et al., 2004). Similarly, microdialysis investigations aimed at measuring 5-HT release in the rat hippocampus showed that continuous delivery of corticosterone for 14 days induced a significant decrease in the inhibitory effect of the prototypical 5-HT<sub>1A</sub> agonist, 8-OHDPAT, as expected of functional desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors (Leitch et al., 2003). Also in mice, an attenuation of 5-HT<sub>1A</sub> autoreceptor response has been observed after repeated daily injections of corticosterone. In particular, 8-OH-DPAT-induced hypothermia, that serves as an *in vivo* index of mouse somatodendritic 5-HT<sub>1A</sub> autoreceptor function, was significantly reduced after repeated administration of the glucocorticoid (Man et al., 2002).

#### 4.3. 5-HT<sub>2C</sub> receptor-mediation of 5-HT system – HPA axis interactions

As described for 5-HT<sub>1A</sub> receptor agonists (see above), administration of the 5-HT<sub>2C</sub> receptor agonist *m*-chlorophenyl-piperazine (*m*CPP) also enhances ACTH and corticosterone/cortisol plasma levels in animals and humans (Wetzler et al., 1996; Klaassen et al., 2002). Both 5-HT<sub>1A</sub> and 5-HT<sub>2C</sub> receptors are found in areas such as the amygdala and the PVN, but the latter receptors are probably the most important to mediate the stimulatory effect of 5-HT on glucocorticoid secretion during emotional stress. Indeed, while 5-HT<sub>2C</sub> receptor antagonists nearly abolish stress-induced ACTH release, the selective 5-HT<sub>1A</sub> receptor antagonist WAY-100635 is, at best, only partially effective in this respect (Groenink et al., 1996; Jorgensen et al., 1998).



**Fig. 5.** Effect of chronic mild stress on the inhibitory effect of 5-HT<sub>1A</sub> autoreceptor stimulation on the firing of DRN 5-HT neurons. Integrated firing rate histograms (in spikes per 10 s) showing the effect of the 5-HT<sub>1A</sub> receptor agonist ipsapirone on the electrical activity of a DRN 5-HT neuron in a control mouse (A) and a mouse that had been subjected to unpredictable mild stressors for 6 weeks (B). The blunted effect of ipsapirone in B reveals a stress-induced 5-HT<sub>1A</sub> autoreceptor desensitization.

In line with the aforementioned inference, a recent study using laser dissection of the PVN coupled with transcriptomic analyses indicated that the 5-HT<sub>2C</sub> receptor is the most abundant among all 5-HT receptor types expressed in this brain structure (Heisler et al., 2007). Furthermore, the enhancement of CRH secretion by the 5-HT releaser fenfluramine could be completely blocked by the 5-HT<sub>2C</sub> antagonist SB-242084, and genetic inactivation of 5-HT<sub>2C</sub> receptors abolished CRH surges induced by mCPP or the mixed 5-HT<sub>2A/2C</sub> agonist DOI (Heisler et al., 2007). The existence of functional 5-HT<sub>2C</sub> receptors on CRF-containing neurons in the PVN was further confirmed by histochemical studies of CRH mRNA and Fos-IR co-expression and by *in vitro* electrophysiological recordings in its parvocellular region (Heisler et al., 2007). All these data converge to the conclusion that 5-HT<sub>2C</sub> receptors in the PVN play a key role in the serotonergic regulation of the HPA axis. However, this conclusion does not rule out an implication of other 5-HT receptors (5-HT<sub>7</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>1B</sub>, etc.) located on cells in the vicinity of CRF-containing neurons or on serotonergic terminals in the PVN.

As we have seen for 5-HT<sub>1A</sub> receptors, convergent data support the idea that 5-HT<sub>2C</sub> receptors are also concerned by stress-induced concomitant changes in circulating levels of corticosterone and brain 5-HT tone. In particular, Holmes et al. (1995) reported that variations in basal and stress-induced corticosterone levels significantly correlated with changes in 5-HT<sub>2C</sub> mRNA expression in the hippocampus: the expression levels were higher after an acute laparotomy stress and lower after chronic arthritis stress. In addition, following inescapable stress in paradigms of depression (the learned helplessness and the forced swim test), some animal strains displayed site-specific increase in 5-HT<sub>2C</sub> pre-mRNA editing (Englander et al., 2005; Iwamoto et al., 2005). The editing process is unique to the 5-HT<sub>2C</sub> type among 5-HT receptors, and leads to a decrease in the coupling of the receptor with its signaling system downstream (McGrew et al., 2004). It is also worth noting that the 5-HT<sub>2C</sub> receptor is constitutively active (i.e. active in absence of endogenous agonist stimulation (Berg et al., 2005)) and that 5-HT depletion increases the expression of the most effective, non-edited, 5-HT<sub>2C</sub> isoform in brain (Gurevich et al., 2002). This could help conciliate the notion of a crucial role played by PVN 5-HT<sub>2C</sub> receptors in stress responses with the fact that

stress-evoked corticosterone secretion is increased rather than decreased following depletion of brain 5-HT (Harbuz et al., 1993). In contrast, long-term treatment with 5-HT<sub>2C</sub> agonists, like acute stress, increase the pool of edited 5-HT<sub>2C</sub> mRNAs that encode receptors with reduced function (Gurevich et al., 2002; Englander et al., 2005). Accordingly, the 5-HT<sub>2C</sub> mRNA editing process plays probably a key role in adapting brain 5-HT tone to HPA axis activity.

More generally, 5-HT<sub>2C</sub> receptors could be part of a negative feedback mechanism regulating the activity of monoaminergic systems during stress. Contrary to the feedback mediated by somatodendritic 5-HT<sub>1A</sub> autoreceptors, the inhibitory control by 5-HT<sub>2C</sub> receptors would be indirect. There are 5-HT<sub>2C</sub> receptors on GABAergic interneurons in both the raphe and the ventral tegmental areas (VTA) (Liu et al., 2000; Bubar and Cunningham, 2007), and activation of these receptors by specific 5-HT<sub>2C</sub> agonists decreases the firing activity of 5-HT and DA neurons via GABA-dependent mechanisms (Di Giovanni et al., 2000; Boothman et al., 2006). In a recent study (Mongeau et al., 2008), acute administration of the 5-HT<sub>2C</sub> agonist RO-60,175 was found to prevent the enhancement of 5-HT and DA turnover induced by restraint stress in the nucleus accumbens, the hippocampus, the frontal cortex and the VTA/substantia nigra region in mice. These inhibitory effects of RO-60,175 were not observed under basal conditions in absence of stress. This is consistent with a previous microdialysis study in rats which revealed an inhibitory effect of 5-HT<sub>2C</sub> receptor activation on stress-induced, but not basal, DA release in the prefrontal cortex (Pozzi et al., 2002). Because numerous antidepressant drugs have antagonist potency at 5-HT<sub>2C</sub> receptors, while other antidepressant drugs appear to desensitize 5-HT<sub>2C</sub> responses after long-term treatments, these drugs could thus limit, through one way or another, the negative feedback exerted by 5-HT<sub>2C</sub> receptors on DA and 5-HT neurotransmission during acute stress. Future studies using relevant animal models of depression have to be performed in order to assess whether the functional characteristics of 5-HT<sub>2C</sub> receptors regulating 5-HT and DA output may be altered by chronic stress.

## 5. Interactions between the HPA axis and the 5-HT system in relation to depressive disorders

### 5.1. Stress, models of depression and 5-HT system

The role of stress in psychiatric disorders is well demonstrated. In particular, epidemiological data have provided strong support to the idea that stressful life events play a role in the etiology of depression (Kendler, 1995) and anxiety (Shelton, 2004), in interaction with genetic factors (Caspi and Moffitt, 2006). Accordingly, investigations aimed at elucidating the neurobiological mechanisms underlying depression and anxiety mainly focused on animal models of “mood-related behavioral disorders” generated by exposure to chronic stress. The first model that has been developed is the chronic variable stress (CVS) model of depression by Katz et al. (1981). In this model, rats are subjected to a variety of stressors such as mild uncontrollable footshocks, cold water swim, changes in housing conditions, reversal of light and dark periods, food and water deprivation, etc., over a period of 2–3 weeks. Such a treatment results in a decrease in open field locomotor activity which can be selectively prevented by antidepressant drugs (Katz and Hersh, 1981). Years later, other chronic mild stress (CMS) paradigms have been developed and validated. In particular, Willner (2005) set up a model adapted from Katz et al. (1981) with slight differences compared to the original chronic variable stress paradigm in the selection of stressors, timing of their presentation, and the behavioral out-

comes measured. Besides reducing voluntary sucrose intake, the CMS designed by Willner (2005) has been found to antagonize place preference normally conditioned with a variety of reinforcers, such as food or amphetamine (Papp et al., 1991), and these effects can be prevented by concomitant treatment with antidepressants (Papp et al., 1991; Willner, 2005). Anhedonia, i.e. the inability to experience pleasure, is one of the core symptoms of depression in human (DSM IV), and the reduction of sucrose or saccharin consumption after chronic stress has been attributed to an anhedonic state and used as a behavioral measure of “animal depression” (Willner, 2005). In mice, a chronic “ultra” mild stress has also been proposed, in which only stressors closely related to every-day life events are applied for 3–6 weeks. This well controlled experimental condition, which involves essentially social and environmental non-continuous stressors, has been found to have consequences on decision making that could be attributed to a higher level of distractibility in the stressed mice (Pardon et al., 2000). When applied to a transgenic model of vulnerability to depression – the GR-impaired mice – the chronic “ultra” mild stress paradigm induced coping capacity dysfunctions, thereby highlighting a critical role for interactions between genetic and environmental factors in influencing susceptibility to mood disorders (Lanfumey et al., 2000; Froger et al., 2004). In this paradigm, the succession of unpredictable series of stressors, none of which being either necessary or sufficient to affect behavior on its own, chronically increases glucocorticoid production which, in turn, affects the 5-HT system, with notably a desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors in the DRN (Lanfumey et al., 1999). It is worth noting that both antidepressant treatment and chronic “ultra” mild stress desensitized DRN 5-HT<sub>1A</sub> autoreceptors, without modifying hippocampal 5-HT<sub>1A</sub> heteroreceptors (Laaris et al., 1999). Conversely, co-activation of both GR and MR, as it could occur during intense stress, decreased the sensitivity of the latter postsynaptic 5-HT heteroreceptors, leading to a decreased hippocampal 5-HT neurotransmission (Joels et al., 1991). Therefore, a mild stress might exert a facilitatory influence while intense stress might be deleterious on 5-HT neurotransmission.

### 5.2. Neurotrophic factors beyond the HPA/5-HT interactions

Among the various brain areas involved, the hippocampus seems to play a particular role in the control of 5-HT system – HPA axis interactions. This limbic structure is a key region for learning and memory processes, regulation of the HPA axis, anxiety and mood disorders in general. Neurons in the hippocampal formation are indeed especially sensitive to the deleterious effects of stress. Brain imaging studies in humans have evidenced that stress and depression cause reductions of the hippocampal volume (Sheline et al., 1996), probably because of atrophy in dendritic arborizations and loss of neurons in this structure such as those observed by Stockmeier et al. (2004) in the post-mortem hippocampus of patients who died with major depressive disorders. The fact that these morphometric alterations are most often attenuated or even reversed by antidepressant drugs further suggests that they are related to depression. Indeed, convergent data obtained in several animal species showed that stress and glucocorticoids exert a drastic negative effect on neurogenesis, leading to a rapid and prolonged decrease in the rate of cell proliferation in the adult hippocampus (see Warner-Schmidt and Duman, 2006). Repeated social interaction stress in subordinate tree shrews, intermittent social defeat for 10 successive days in mice as well as restraint stress repeated daily for 21 days in rats were all found to cause a significant depletion of dentate gyrus precursor cells (McKittrick et al., 2000; Czeh et al., 2001; Pham et al., 2003). Recently, relevant studies aimed at elucidating the complex relationships that might

exist between circulating levels of corticosterone and cell proliferation. Distinct stressful experiences, which all activate the HPA axis, were thus shown to differentially affect hippocampal cell proliferation (see Paizanis et al., 2007). Furthermore, some kind of an “incubation period” (implicating unknown intermediate factors) appeared to be necessary to observe the deleterious effects of stress on hippocampal cell proliferation (Fornal et al., 2007).

Both stress and glucocorticoids are known to reduce the brain levels of neurotrophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (Duman and Monteggia, 2006). BDNF is a major neurotrophic factor, which is required for the survival, differentiation and normal functioning of neurons in the brain. In rodents, a down-regulation of both BDNF mRNA and protein was found in several brain regions following stress (Smith et al., 1995; Gronli et al., 2006). BDNF, through its tyrosine kinase TrkB receptor, can initiate a variety of intracellular signaling cascades including the MEK (mitogen activated protein (MAP) kinase kinase) – ERK (extra-cellular signal-regulated protein kinase) pathway causing the phosphorylation of the transcriptional regulator calcium/cyclic-AMP responsive-element binding protein CREB. Like BDNF, activation of CREB within the dentate gyrus is down-regulated following stress (Alfonso et al., 2006; Gronli et al., 2006). Accordingly, reductions in both BDNF and CREB levels have been reported in the cerebral cortex of depressed patients and post mortem studies showed that the expression of BDNF was significantly less in depressed patients than in normal controls, but higher in patients receiving antidepressant at the time of death (Karege et al., 2002). In rodents, it has also been found that different classes of antidepressants increase the expression of BDNF in the hippocampus, in contrast to non-antidepressant psychotropic drugs, such as opiates, antipsychotics and psychostimulants which are ineffective, thereby demonstrating the pharmacological specificity of this effect (Duman and Monteggia, 2006). All antidepressants, regardless of their primary mechanism of action, share the ability to rapidly activate TrkB signaling and induce a long-lasting increase in BDNF production.

Recently, the role of chromatin remodeling in stress and antidepressant treatment has been emphasized with regard to resulting consequences on BDNF production and action (Tsankova et al., 2006). It has notably been observed that social defeat stress in mice produced long-lasting methylation of histone-3 subunits around the BDNF gene promoter region and that such increased methylation correlated with a suppression of BDNF gene transcription. Furthermore, chronic antidepressant treatment counteracted the reduction in BDNF mRNA and induced the acetylation of the same histone subunit. This suggests that chronic stress can exert a long-lasting repressive state and that antidepressant treatment restored the level of BDNF mRNA expression otherwise suppressed by stress. Interestingly, an antidepressant treatment that induced histone acetylation in mice previously exposed to social stress was without effect in non-stressed controls (Tsankova et al., 2006). The possibility therefore exists that increased BDNF signaling is required for the induction of the behavioral response to antidepressant drugs specifically in experimental-stressed animals (Castren et al., 2007). Indeed, BDNF signaling on its own appears to be sufficient for antidepressant-like effects, as direct infusion of BDNF into midbrain or hippocampal areas induces behavioral responses that are similar to those produced by antidepressants (Duman and Monteggia, 2006). However, in addition to BDNF, other neurotrophic factors seem to play a role in mood disorders and the action of antidepressant drugs (Duman and Monteggia, 2006). In particular, alterations in the levels of fibroblast growth factors (FGF) and their receptors have been detected in the brain of patients with major depressive



disorder, and FGFs expression can be modulated by antidepressant drugs. Similarly, brain concentrations of insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) were reported to be increased by chronic treatments with these drugs (Castren et al., 2007). These data strongly suggest that many different factors with neurotrophic properties are involved in antidepressant therapy. Whether neuroplastic changes in response to such factors are important for mood regulation and adaptive behavioral responses to stress is an important question that will need to be further addressed in the future.

## 6. Conclusion

It has long been proposed that the 5-HT system plays an important role in the regulation of autonomic and endocrine responses to stressful stimuli (Lowry, 2002). Conversely, sustained increase in glucocorticoid secretion in response to repeated stress can have numerous long-term effects on serotonergic neurotransmission. Of particular interest is the negative regulation of 5-HT<sub>1A</sub> mRNA expression by the co-activation of MR and GR receptors. A decreased hyperpolarization of hippocampal pyramidal neurons in response to 5-HT<sub>1A</sub> heteroreceptor stimulation and a marked desensitization of somatodendritic 5-HT<sub>1A</sub> autoreceptors are clear-cut functional consequences of these stress-mediated changes in 5-HT<sub>1A</sub> receptor expression. Other serotonergic receptors, notably the 5-HT<sub>2C</sub> receptor, also appear to be regulated by stress through alterations in specific mRNA expression and/or pre-mRNA editing.

The contributions of the HPA axis and the 5-HT system to the respective negative/positive control of granule cell proliferation within the dentate gyrus of the hippocampus are probably of key importance among neurobiological mechanisms associated with depression. Antidepressant therapies that increase serotonergic neurotransmission act, at least in part, by promoting dentate gyrus neurogenesis. Accordingly, deficiency in hippocampal neurogenesis is probably involved in the etiology of the disease, and possibly of other affective disorders associated with hyperactivity of the HPA stress axis. Indeed, alterations of neurogenesis and/or neuroplasticity induced by stress could result in abnormal brain functioning that underlies symptoms of depression. As emphasized in this review article, stress and antidepressants exert opposite effects on the expression of specific neurotrophic factors, notably BDNF, and on the anatomic-functional features of the hippocampus (Dranovsky and Hen, 2006). Within the frame of this “neurogenesis hypothesis”, BDNF and other neurotrophic factors are possibly key targets for the treatment of disorders such as major depression (Castren, 2005). How other brain structures in the limbic system also contribute to the physiopathology of mood disorders is much less known to date, and is therefore still a question to be addressed.

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