The Interacting Neuroendocrine Network in Stress-Inducing Mood Disorders

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Abstract: Extensive research studies showed the existing interaction between different systems of the body that maintain the stability of homeostatic processes and which allow species to adapt to its environment in response to stressors. Adaptive responses to stressors activates adaptive-mechanisms, that result in the synthesis and release of several brain neurotransmitters, peptide hormones, proinflammatory cytokines and adrenal steroids from neural, neuroendocrine and immune cells which prepared the organism to alert its systems to adopt the proper behavioral responses against stressful events. Neurotransmitters, peptide hormones and cytokines act through the HPA axis forming a regulatory loop that maintains homeostasis in response to different stressors. One route to understand the interactions between brain transmitters, neurosecretory peptide-hormones, adrenal steroids and immune-borne cytokines, including neurotrophic factors is when body`s systems and chemical communication between cells appear to be disrupted during stressful events as occurs in mood-related disorders and depression. Thus, this review will described the functional interactions between HPA axis activity and the projecting neural pathways (DRN-5HT neurons; LC-NA neurons) and brain neurotransmitters (NE, 5-HT, DA, GLU) that impinge on forebrain-limbic structures (hypothalamus, hippocampus, mPFCx) that drive the release of the CRH and CRH-dependent secretion of ACTH from anterior hypophysis and cortisol from adrenal glands, under stressful conditions. Moreover, interactions between immune-borne cytokines and HPA axis activity, and glucocorticoid receptors have been shown to be extremely important to understand the pathophysiological mechanisms that operate in mood-related disorders and MDD, including the stress-inducing altered changes in brain morphology, neuronal atrophy and neurogenesis in brain areas involved in learning processing and memory functions.

Keywords: Stress, HPA axis, peptide hormones, neuropeptides, excitatory and inhibitory neurotransmitters, brain receptors, cytokines, glucocorticoids, neurotrophic factors, nitric oxide, signaling pathways, neurogenesis, hippocampus, anxiety, depression.

1. INTRODUCTION

Over the last two decades, different studies reported about the physiological interactions between neuroendocrine and immune systems [1,2]. Neurotransmitters, hormones and cytokines act through the Hypothalamus-Pituitary-Adrenal (HPA) axis forming a regulatory loop that maintains homeostasis in response to processive and systemic stressors [3]. Years of extensive research showed that stressful challenges induce adaptive responses, in order to promote and maintain stability or homeostasis of functional systems of the body [4-6]. Adaptive responses to stressful challenges activates a wide range of neurobiological mechanisms, that result in the synthesis and release of several brain neurotransmitters, hormone-peptides (e.g., CRH, ACTH, β-endorphin, cytokines) and adrenal steroids (e.g., cortisol), neuroendocrine and immune cells, and which are required to alert the body´s systems, which allows organisms to adopt proper behavioral responses (e.g., defense) against aggressive stimuli and/or any sort of stressors [4-6].

One route to understand the interactions between brain transmitters, neurosecretory hormone-peptides, adrenal steroids and immune-borne cytokines is when functional systems in the body, the chemical balance in tissues and cells become disrupted leading to altered changes in molecular responses upon repeated stressful events, as occurs in mood-related disorders, such as, anxiety, and depression [5,6].

During development, several systems of the body become vulnerable to stress that are influenced by different experiences in early life [6]. Animal models expose to an unpredictable stress have an increase emotional response associated with an increase activity of the HPA axis, as well as increase reactivity of the autonomous nervous system (ANS) that may endure throughout the life span of animals [7]. In this context, several experiments have confirmed that rats with increase HPA reactivity show an early decrement of hippocampal-associated cognitive functions, as well as a high propensity to self administer drugs of abuse of abuse [6,8-10].

Behavioral studies using animal models of restraint stress and/or psychosocial stress have shown that stress-inducing

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effects in the brain lead to adaptive responses of the hypothalamo-pituitary–adrenal (HPA) axis, whose stimulation enhances the increase cell-secretion of glucocorticoids into the blood stream. This functional imbalance of this neuroendocrine system has been shown to promote long-lasting changes in neuron morphology (e.g., neuronal atrophy in hippocampal regions) associated with altered changes in cognitive functions, (e.g., impairment of hippocampal-dependent learning) [5,6]. Conversely, mild stress induced by brief periods of daily separation of postnatal rats from their mothers (e.g., postnatal handling) counteracts the prenatal stress effects, reducing the increase emotional responses associated with both HPA axis and autonomous nervous system (ANS) functional hyperactivities [11]. For instance, it has been observed that neonatal handling of rats induces a lower HPA reactivity and a slower rate of aging of cognitive functions associated with a reduced loss of hippocampal function [12,13]. In addition, different studies have shown that maternal care and early life manipulation of "puppets" generate important effects on cortisol and dopamine responses to stressful events across life span [14,15]. These results posit that once the emotional-dependent reactivity of the adrenocortical system are established by stressful events in early life, the subsequent activity of the HPA axis in adult life is set up and ultimately will contribute to the rate of brain and body aging [6]. In humans, few studies have shown the correlation with HPA axis activity, cortisol levels in plasma, and vulnerability to stressful challenges [16-19].

Due to the wide and complex information of interacting neural systems and neuroendocrine mediators occurring in stress and stress-inducing behavioral disorders; this review will focused only on the intervening physiopathological mechanisms and adaptive responses that impinge on the HPA axis and neurotransmission systems that become affected during chronic stress (see Fig. **1A**). Thus, this review will discuss the interaction of monoaminergic systems, which comprise the serotoninergic, noradrenergic and glutamatergic neurotransmission systems in the brain, including specific peptide transmission systems, such as *galanin* peptide system, which have recently been shown to be associated to the neuroadaptive responses to stressors and which play a crucial role in pathophysiological cascade of several mood-related behavioral disorders, such as, anxiety and depression. Furthermore, structural and functional changes in several limbic regions have been shown to correlate with the adaptive responses to chronic stressors that occur at some level during the development of mood-related disorders in affected human subjects. For instance, imaging and postmortem studies of brains of depressed individuals revealed extensive damaged resulting from stressful events in life. Moreover, morphological studies have shown a significant reduction of hippocampal and cortical volumes, as a result of neuronal atrophy and cell loss that occur upon exposure to repeated stressors in life.

In line with aforementioned data, clinical studies have shown that the increase serum levels of cortisol in MDD subjects exert important neurotoxic effects in forebrain-limbic areas (e.g., hippocampus, amygdala and NAc) [20,21]; producing morphometric changes in neurons and glia cells, whose cell atrophy and cell loss are highly linked the to the shrinkage of these brain structures [22-25].

Moreover, molecular studies have shown that that activation of the intracellular signaling pathway (e.g., cAMP-PKA/PKC) and associated transcription factors (e.g., c-Fos, CREB) upon stimulation of NMDA receptor are significantly decreased during chronic stress and depressive disorders. Moreover, similar decreases have been found in the expression and activity of the brain derived-neurotrophic factor (BDNF) and its cognate trkB-membrane receptor in cortical and hippocampal regions of the rat brain.

However, pharmacological studies showed that the expression and function of the molecules involved in the NMDA-receptor signaling pathway are significantly upregulated upon antidepressant treatment [22,26-28]. These set of evidences indicate that major depression courses with significant altered changes in morphology and stereology of neurons cells and brain tissue; whereas treatment with antidepressants may significantly overcome the cell atrophy and the reduced volumes measured in limbic structures of subjects with MDD [23,24,29,30] (see sections below).

In this context, several studies have started to highlight the importance of excitatory amino acids and their specific target receptors to the antidepressant activity in brain cells, where antidepressant compounds appear to upregulate the receptor-signaling pathway function and working molecules; inducing thus, the neuroadaptive changes and plastic events that take place during long-term exposure of clinically-effective antidepressants [31].

2. HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS

The hypothalamic-pituitary-adrenal axis (HPA axis) consist of a negative feedback regulatory loop where brain structures, neuroendocrine glands and the immune system interact through a highly regulated chemical communication between cells that ultimately defined one of the crucial *neuroendocrine network system* in mammalian species, including primates and humans [32] (see Figs. **1A-B**). This neuroendocrine axis receives several neural inputs from forebrain structures, such as the hippocampus, amygdala, bed nucleus of the stria terminalis (BNST) and paraventricular nucleus (PVN). Exposure to a physical or emotional stressor leads to the activation of the HPA axis, resulting in an increased secretion of corticotropin-releasing-hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus, where CRH acting on specific G-protein coupled receptors on corticotrophs, in the anterior pituitary gland, leads to the release of ACTH into systemic circulation [32]. CRH is a 41 amino acid peptide that has been shown to be widely distributed in several regions of the CNS of mammals, and represents one the major neuropeptide transmission system, that regulates stress responses in the brain of mammals [33]. Neuroanatomical and pharmacological studies have shed important clues about the neural control of CRH-synthesis and secretion from PVN-parvocellular neurons within the hypothalamus. These studies showed that CRH is highly controlled by several neural inputs ascending from brainstem (e.g., the LC-NA neural pathway) or the glutamate neural input that descend from cortical regions (e.g., mPFCx) including the strongest neural input provided by GABAergic neurons [34,35]. Quite interesting to note, is that immunohistochemical studies showed that most CRH-synthesizing cells display

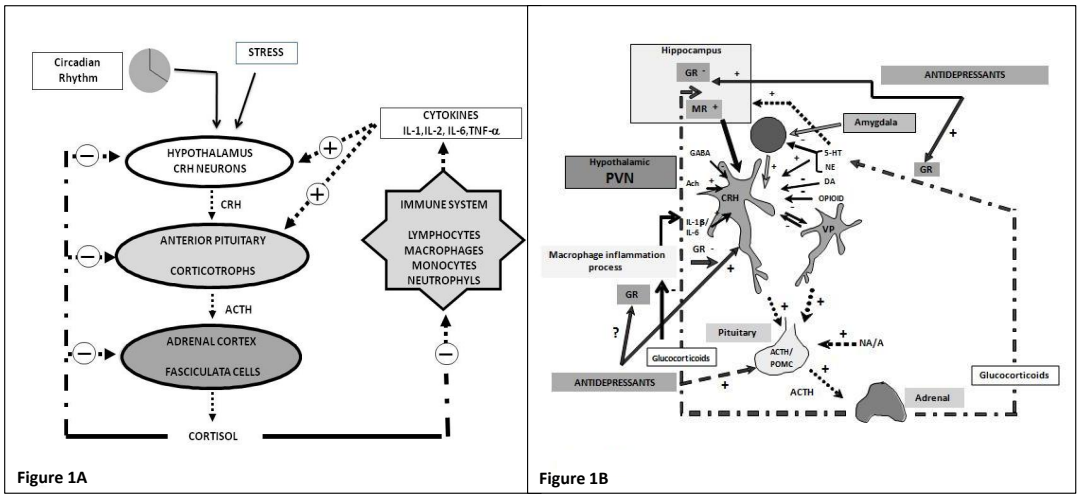

Fig. (1). Schematic representation of the the neuroendocrine network and mediators regulating the neurendocrine-immune axis (A) *The Hypothalamic-Pituitary-Adrenal-Immune axis.* This panel depicts the regulation of the HPA axis by both stress stimulus and circadian rhythm. As shown, under physiological conditions and cortisol (glucocorticoids) released into the bloodstream; from zona fasciculate in adrenals of mammals; exert a negative feedback loop after binding its intracellular receptor (GR) localized on corticotrophs in the anterior pituitary and PVN/CRH-secretory cells localized in the anterior hypothalamus. Moreover, unders stressful stimuli, high levels of cortisol in plasma will inhibit immune cell function attenuating the release of cytokines (IL-1, IL-2, IL-6, TNF-α) from macrophages. However, cytokines released from immune cells will stimulate positively the hypothesis and hypothalamic brain regiona, enhacing the release of peptide hormones involved in stress-inducing mood-related disordes (e.g., anxiety and depression; see text for more details) (text and figure adapted from [32,336,337] and subject to modifications for the present review). (**B**) *Regulation of HPA axis by neural and non-neural systems.* This panel illustrates the HPA axis regulation by several stimulatory (+) and inhibitory (-) neural inputsthat arise from distinct neuroanatomical regions of the brain and which impinge directly or indirectly into the HPA system. As shown HPA axis regulation by several neural inputs involved sites at which corticosteroids modulate HPA axis activity. Moreover, antidepressants may influence the HPA axis activity, *via* stimulatory action on either the glucocorticoid receptor (GR) or the mineralocorticoid receptor (MR) or both. Different interleukines (IL) regulate positively the corticotropin-releasing hormone (CRH) production from the hypothalamic paraventricular nucleus (PVN). As shown, both the vasopressin synthesizing-cells (VP) and the CRH synthesizing cells (PVN) are reciprocally regulated by inhibitory stimuli (-). As depicted in the illustration, several peptide and non-peptide neurotransmision systems have an important influence in the cell-activity and release of CRH from PVN neurons. Such neural transmission systems include: the endogenous opioid system (OPIOID); the cholinergic system (Ach); GABAergic sysem (GABA); the serotonin, norepinephine and dopamine neural systems (5-HT, NE, DA) including adrenal and/or circulating epinephine (E) (see text for more details) (text and figure adapted from [338] and subject to modifications for the present review).

high densities of $GABA_A$ receptor subtype [34,36,37]. In addition, different studies revealed clear evidences that increased serum levels of cortiocosterone play an important regulatory role on the GABAergic input that synapse PVN/CRH-secretory cells. For instance, it has been shown that local application of *bicuculline* ($GABA_A$ receptor antagonist) close to the PVN produces an increase expression of CRH, AVP, and c-FOS at the parvocellular subregion of the PVN, enhancing an increase release of CRH and ACTH from hypothalamic and pituitary cells, respectively, which ultimately leads to the increased levels corticosterone in serum [34,35] (see Figs. **1A-B**). As shown in both figures, **o**nce ACTH is released into the blood and binds its cognate peptide receptor on steroid-synthesizing cells in adrenals; ACTH stimulates the release of corticoids from cortical layers; where cortisol in humans, or corticosterone, in inferior mammals, represent the major stress-hormone regulating the HPA axis activity, by forming the main regulatory negative feedback loop on this axis [32].

Most of the circulating cortisol/corticosterone in blood is bound to globulin fraction in plasma and thereby detected as the corticosteroid-binding globulin, whereas the unbound "free" circulating cortisol is able to bind their specific intracellular receptors in target cells [32]. Pharmacological and molecular studies have shown that cortisol display different binding affinities for corticosteroid receptors (CR) localized inside the cytoplasm. The first one, defined as the *type I- mineralocorticoid receptor* displays a high binding affinity for cortisol and bounds completely cortisol before the *type II- glucocorticoid receptor* binds the adrenal steroid [38,39] (see sections below).

Synthetic corticosteroids, such as prednisone and dexamethasone (DEX) display also medium-to-low binding affinities to the type-II GR [39]. These receptors play a crucial role in driving the negative feedback loop for released adrenal corticoids. In this context, two different negative feedback loops have been characterized for glucorticoids impinging at the HPA axis [32].

The first one; comprise a high-regulated *negative feedback loop,* controlled directly by blood hormone concentration of cortisol. The second feedback loop, termed as *fast feedback,* is not dependent on the plasma concentration of the steroid (cortisol), but on the changing levels of steroids and the saturation rate of GRs expressed in hypothalamic and hippocampal cells, respectively [32,40-42] (see Fig. **1B**).

Clinical evaluation of the function of the HPA axis, during depression and other neuroendocrine illnesses (e.g.,

Cushing´s disease) has been widely used in clinics and hospitals based on the "neuroendocrine challenge tests". This test assess the functional cell responses of cortisol, ACTH, CRH/CRF in subjects under study [32]. For instance, the dexamethasone suppression test (DST) is one of the most common and easiest neuroendocrinological tests used in clinics and hospitals. In this test, subject s are exposed to a challenging dose of dexamethasone (DEX)in the evening and cortisol levels from blood samples are quantified next morning. In healthy subjects, a normal inhibition response on cortisol release would be expected as a result of the negative feedback loop induced by DEX. Conversely, the finding of a "non-suppression DST test" would indicate that cortisol levels did not decrease below control levels after DEX administration, suggesting the presence of high levels of cortisol in plasma [32]. An altered test using the combined DEX/CRH challenge test, has been recently developed and used to assess the functioning of HPA axis through the stimulation by CRH, and inhibited through DEX administration [43].

3. GLUCOCORTICOID RECEPTORS AND NEURAL TRANSMISSION SYSTEMS

As explained above, stressful events enhance the cell release of CRH from PVN of the hypothalamus into the *hypothalamic-hypophyseal portal system*. At the anterior pituitary lobe, CRH induces the release of ACTH and related peptide hormones (e.g., β-endorphin) after binding to its CRH-cognate receptor on corticotrope cells, which induces the release of glucocorticoids (cortisol or corticosterone) from the adrenal cortex, that negatively feedback on the HPA axis and PVN neurons [35] (see Fig. **1B**). Corticosteroids impinges on several regions of the brain, where they bind two intracellular receptors that are highly expressed in forebrain limbic structures (e.g., hippocampus, amygdala). As described above, the *mineralocorticoid receptor (MR)* displays a high binding affinity for cortisol and aldosterone; whereas the glucocorticoid receptor (GR) exhibits a nearly ten-fold-lower affinity for cortisol, but displays a high binding capacity for synthetic glucocorticoids, such as DEX [38,44,45]. This latter receptor is highly enriched at the PVN of the hypothalamus; the main neural site where corticoids mediate their stress-inhibitory feedback responses; besides of the CA1 region and dentate gyrus of the hippocampus. Pharmacological and molecular studies showed that principal neurons at the CA1 hippocampal field express low to-high levels of corticosteroid receptors (MR, CR); whose relative occupation by steroid ligands influences the neuronal activity and function of these hippocampal cells [38] (see Fig. **1B**).

At the physiological level, both GRs and MRs act as transcriptional regulators on specific segments of the DNA template, localized upstream to the promoter gene region. Molecular studies showed that both receptors act as transcription factors that bind to specific *DNA response elements*, either as homodimers or as monomers. GRs may interact with several transcription factors (e.g., CREB) or other RNA promoters forming different multimeric complexes in the nucleus of active cells [46,47]. However, under stress conditions, glucocorticoid receptors (GR) may become fully occupied in the presence of high-levels of plasma corticosteroids, as opposed to mineralocorticoid receptors (MR) [38], leading to the abnormal dysfunction of the HPA axis as well as to the altered activity of different neurotransmission systems involved in stress-associated behaviors and mood-related disorders, as shown in animals and humans, respectively [38].

Several studies have shown clear evidences that chronic stress induces an up-regulation of PVN neurons–secreting AVP and CRH, due to the decrease susceptibility to respond to the negative feedback inhibition induced by plasma corticoids when binding their cognate GRs [48]. Interesting enough, is that this apparent GR resistance at the HPA axis, seems to be amplified by factors, such as, small variations in the GR gene-polymorphisms, differential expression of co-activators or co-repressors that bind specific DNA regulatory elements [49,50]. Moreover, several studies have shown that the increase response of CRH secretion during chronic-stress may be related to a disinhibitory activity of neural inputs (e.g., noradrenergic, glutamatergic and GABAergic inputs) impinging on PVN/CRH-producing cells; that enhance the expression of facilitatory mechanisms that leads to an overall increase of CRH release [35].

Under physiological conditions (e.g., acute stress), it has been shown that increased circulating steroid hormones impinging on the hippocampus, do not disrupt the normal activity of neurotransmission systems [21,51]. However, under pathological situations that lead to chronic hyperactivity of the HPA axis and increased levels of corticosteroids, profoundly affect different transmission systems (e.g., 5-HT, NE, GABA) that influence several hippocampal functions [21,35,51] (see Fig. **1B**).

Interestingly, pharmacological studies showed that deregulation of HPA axis during chronic stress appear to be related to a decreased activity of the GABA neuronal inhibitory on CRH-secreting neurons, probably due in part, to a significant reduction of GABA neurons synapsing parvocellular/CRH neurons at the PVN [35]. Since CRH-producing neurons receive many other neural afferents besides of GABAergic inputs that overall drive the cell excitability of PVN-secreting neurons; it is quite difficult to derive conclusions which of the major hypothalamic neural inputs become highly susceptible to repeated stressors, until all known inputs are fully examined [35]. Nonetheless, at the functional level, distinct works have clearly demonstrated that a reduced GABAergic input in animals exposed to chronic stress, produces a gradual disinhibition of parvocellular/CRH-cell activity enhancing an abnormal HPA axis hyperactivity and high levels of corticoids in plasma, that overall lead to the expression of pathological behaviors and altered brain functions in the tested subjects [35].

Interesting results on animal model of chronic stress that display a functional deregulation HPA axis activity and increase concentration of plasma corticosteroids, have shown an attenuated responsiveness of the serotonin transmission system impinging on both hippocampus and hypothalamus [52]. These studies showed that 5-HT neurons exert an important regulatory control on the HPA-axis activity [53,54] whereas, stressed animals exhibit attenuated responses of the 5-HT transmission system, due to a functional impairment of the postsynaptic 5-HT_{1A}-receptor signaling pathway [35].

These data led to the hypothesis that the deregulation the HPA axis activity associated with an increased levels of cor-

ticosterone in plasma, appear to play a significant role on the altered 5-HT responses at the receptor level in several areas of the brain [52]. Although this process may represent one the major risk factors by which chronic stress may precipitate MDD in susceptible individuals; several authors argue that its quite difficult and adventure to decide which neurobiological events may be involved in the precipitation of depression symptomology in humans [35].

Different studies focused on the glutamate-transmission system in the hippocampus, showed that this excitatory system is significantly affected during chronic stress. However, it is still unclear whether the enhanced glutamatergic responses observed during stress (and which appear to be mediated through the activation of the glutamate/NMDA-receptor signaling system) depend on the increase corticosterone levels and GR activity, leading to an increased transcription of NMDA and AMPA receptors in chronically stressed animals. Nonetheless of the unclear data about the implications of the glutamate transmission system during stress, the increased glutamate activity in the hippocampus appear play a crucial role in the atrophy of apical dendrites of CA3 pyramidal cells and decreased dendritic arborization of cells in animals exposed to stressful environments [35] (see Fig. **2**). Nonetheless of the altered changes described for several monoamine systems in the brain induced by chronic stressful conditions; the most relevant issue linking stress-to-depression may be the gradual normalization of the HPA-axis hyperactivity produced under antidepressant treatment, enhancing thus, the re-establishment of the GABAergic inhibitory activity on PVN/CRH-secreting cells, associated with the restitution of the attenuated serotoninergic activity in affected limbic areas, such as the hippocampal and cortical tissues. Quite important to note, is that further functional and molecular studies are needed to upgrade our understanding on the driving mechanisms that lead to the neuroadaptive changes that occur during chronic stress in animals and/or in stress-inducing mood-related disorders in humans [35].

4. CRH SECRETION AND DEPRESSIVE DISORDERS

Clinical studies showed that depressed individuals display an abnormal deregulation of the negative feedback loop of the HPA axis. An analysis of more than 150 studies [55] showed that patients with anxiety disorders and depression expressed high levels of cortisol in plasma, displaying a positive DST non-suppression test [32,56,57]. These studies proposed that the high concentration of plasma cortisol found in patients with affective disorders might be involved in the etiology of MDD when compared to patients exhibiting Cushing´s disease [32,58,59]. Moreover, previous studies showed that high levels of CRH may be found in the cerebrospinal fluid (CSF) of MDD patients [32,60-64].

Preclinical studies showed that CRH administration into mice or rats induces anxiety disorders and depression-like symptoms, similar to those exhibited in MDD. For instance, CRH-inducing altered behaviors include, reduced eating, decreased sexual behavior, disrupted sleep pattern, altered locomotor activity and abnormal response to novel stimuli [33,65]. In addition, similar studies showed that CRH inducing depression-like symptoms in primates are associated with a decreased environmental exploration, increased huddling and prolonged lying-down behavior [66]. In humans, MDD patients express a blunted ACTH response to CRH administration, which might be corrected by lowering cortisol levels with metyrapone [67]. This attenuated response of ACTH induced by CRH, has been suggested to be related to a down-regulation of specific pituitary CRH receptors, induced by the high concentration of CRH detected in depressed individuals associate high levels of circulating cortisol [65,68-71]. This blunted ACTH response to CRH has been shown to return to normal basal state level after depressive symptoms resolve [32,72] (see Figs. **1A-B**).

Thus, it appears that a common denominator found in patients exhibiting depression is related to the functional deregulation of the HPA axis induce by CRH hypersecretion [32]. This neuroendocrine dysfunction has been shown to produce structural changes in secreting-hormone tissue, as shown for the enlarged pituitary gland and increased volume size of adrenal glands, as reported in a single MDD case-study [73-76]. Although elevated CRH concentrations has been found in other mental disorders (e.g., schizophrenia, dementia and mania) [61,63]; some authors proposed that the increased CRH levels in MDD patients, represents merely a "state associated to the mood-disorder disease" rather than a "trait marker" for depression, due that CRH levels tend to normalize after treatment [77]; albeit that this endocrine abnormality has been used as a clinical parameter for predicting the depression relapse, associated to particular changes in neural and non-neuronal tissues [32].

Clinical studies have shown that individuals with sustained high levels of cortisol, exhibit deficits on memory tasks (that measure explicit memory and selective attention) as compared to control healthy subjects whose cortisol levels were found within the baseline control range [16]. fMRI findings demonstrated that individuals with high-levels of cortisol displaying an abnormal HPA axis activity; have a 14% less hippocampal volume associated with an impairment of cognitive functions as compared to age-matched controls, who did not express sustain increased levels of cortisol in plasma [17].

Preclinical studies and imaging studies in humans showed clearly that stressful challenges (e.g., psychosocial stress) induce progressive adaptive responses in the body; leading to long-lasting changes and functional deregulation of important limbic and cortical structures, such as the hippocampus and cortical tissues. Both neural structures impinged by the HPA axis hyperactivity, increased circulating glucocorticoids and immune-secreting cytokines, have been shown to produce altered changes in higher-cognitive functions, such as decreased learning and memory processing, attention deficit, besides of poor cognitive task-performance. These altered levels of chemical mediators have been shown to mediate morphological and functional changes occurring in cell-layers of the hippocampus, such as dendritic remodeling in CA3 pyramidal neurons and suppression neurogenesis of granule cells at the dentate gyrus, as mentioned before [6,78,79] (see Fig. **2** and sections below).

5. GLUCOCORTICOIDS IMPINGING MONOAMINERGIC NEURAL SYSTEMS

Several studies have shown the deregulation of the HPA axis is associated to neuropsychiatric illnesses. For instance, clinical studies showed that posttraumatic stress disorders

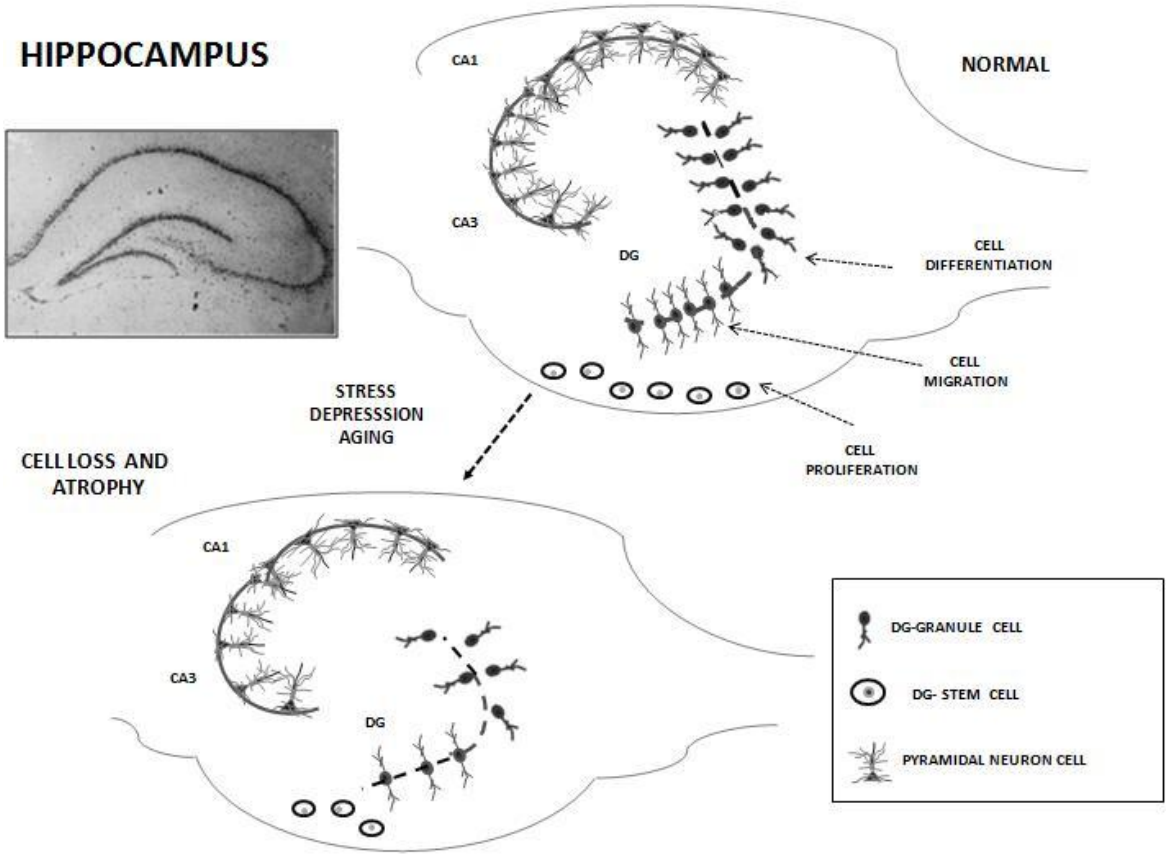

Fig. (2). Stress-induced altered changes in morphology and function in the hippocampus.- Under physiological conditions different factors regulate adult cell proliferation and neurogenesis in the adult hippocampus, such as age, strain, gender, hormones, environment, exercise and learning. Acute and chronic stress produces a dramatic decrease in both cell proliferation and neurogenesis of dentate gyrus (DG) granular cells. Cumulative effects of stress on cell proliferation, neurogenesis and survival produce changes in dendritic remodeling of CA3 pyramidal cells, a process that has been implicated in the pathology of chronic depressive disorder. Stressors produce a significant reduction in the hippocampus cell proliferation in the adult rat.) See text for precise details; text and figure adapted from [308-311, 317, 318]. Figure adapted from: www.stahlonline.cambridge.org and subject to modifications for the present review).

and fibromyalgia disease displayed a hypoactivity of this neuroendocrine system [80,81]; whereas major depression (MDD) and Alzheimer disease exhibit a hyperactivity of this system [82-84]. Although HPA hyperactivity is not an exclusive sign of depression disease, clinical observations have shown that high-risk patients exhibiting MDD, display an HPA axis hyperactivity prior to the clinical manifestations of depressive symptomology, that usually normalizes to control values with antidepressant treatment [84,85]. These studies showed that the degree of normalization of this neurosecretory system correlates negatively with relapse of disease, despite of the long-term antidepressant medication given to patients [35,84] (see Fig. **1B**).

Thus, over the past decades, it has been shown that stress-inducing mood-related disorders exhibit a significant deregulation of the HPA axis that concomitantly results to be associated with an abnormal dysfunction of the serotonin transmission system in the brain (see above). Although the mechanisms that leads to the neurochemical imbalance of several monoamine transmission systems are poorly understood, several reports have proposed the link between genetic and environmental factors by which susceptible individuals become sick [86,87]. In this context, different studies showed that mood-related disorders are associated with a functional hyperactivity of the HPA axis and a concomitant hypoactivity of the serotoninergic tone [88].

As mentioned above, HPA axis activity is highly-regulated by a negative feedback mechanism driven through the secretion of corticoids and stimulation of GRs expressed in forebrain limbic areas (e.g., cerebral cortex, hippocampus and hypothalamus) [89-92]. Behavioral studies using animal models of anxiety and depression showed that chronic stress paradigms leads to a down-regulation of GRs in both hippocampus and hypothalamus, producing an long-lasting hyperactivity of the HPA axis and a failure of the system to respond to the negative feedback loop on target cells, mediated by secreted glucocorticoids [93-96].

Functional studies in humans demonstrated that activation of GR in the brain by acute administration of exogenous glucocorticoids (e.g., dexamethasone) triggers the negative feedback mechanism on the HPA axis, inducing an inhibitory response on ACTH and cortisol secretion; which under normal circumstances, CRH induces the secretion of these

hormones in healthy subjects, as compared to depressed patients [56].

Pharmacological and molecular studies revealed that GR expression in the brain appear to be regulated under the activity of the serotonin tone [97,98]; showing that the reduced expression and function of GRs in cells contribute to the increased HPA axis activity during depression [84,99,100]. Such evidences have been supported with animal studies that showed that mice exposed to chronic mild stress (CMS) conditions displayed long-term behavioral changes associated with a abnormal dysfunction of the serotonin transmission system [52,101]. These changes were functionally reverted by long-term treatment with antidepressants [102,103].

Furthermore, transgenic animal models displaying a dysfunctional GR activity (GR-i mice) [mice bearing a transgene encoding glucocorticoid receptor (GR) antisense RNA] have been used for searching the neurobiological mechanisms that link both genetic and environmental factors in stress-inducing affective disorders in humans [84,104].

Molecular studies showed that transgenic GR-i mice express very low levels of GR-mRNA in serotoninergic neurons innervating several limbic structures (e.g., hippocampus, neocortex), in addition of DRN/5-HT neurons, as compared to the increased levels of GR mRNA detected in WT animals exposed to a four- week period to CMS paradigms or the control GR-mRNA levels in non-stressed animals [105,106].

These molecular changes detected in GR-i mice were associated with a reduced HPA axis response to glucocorticoids and a significant reduction of cytosolic fraction (cytoplasm)-GR binding sites [quantified using standard binding assays and [^{3}H]-corticosterone as the radiolabeled ligand] detected in both hippocampal and cortical neural cells [104]. These results paralleled the unchanged serum levels of corticosterone in GR-i mice compared to the increased steroid concentration (≥ 75%) in stressed WT mice. Such increased level in glucorticoids in WT mice was normalized to control levels after dexamethasone administration (2.0 μg/100 g; i.p) [104].

These results demonstrate not only that glucocorticoids activate the feedback loop of the HPA axis upon exposure of animals to acute stressful conditions [104]; but rather, the impairment of GR activity in target cells leads to the abnormal adaptive responses of the HPA axis and dysfunction of the serotoninergic transmission system during stress.

Thus, stress-inducing altered changes in the neuroendocrine and monoamine transmission systems may ultimately lead to the expression of aberrant behaviors and functions, as shown for the altered performance of learning and memory tasks in animals. All these neurobiological events and altered receptor responses may underlie the neuroendocrine imbalance occurring under chronic stressful events, such as depression disorder in humans [104].

6. SEROTONIN TRANSMISSION SYSTEM

The serotonin transmission system has been shown to mediate a vast number of physiological and behavioral responses in mammals (e.g., appetitive, emotional, motor, cognitive and autonomic) which depend on the functional serotoninergic tone of the CNS regulated by the firing activity of its serotoninergic cell bodies (somata) which are clustered along the midline of the brainstem within the median (MRN) and dorsal raphe nuclei (DRN) in the brainstem. Both midbrain and pontine regions cluster two groups of 5-HT neurons; namely, the median raphe neurons (MRN) and dorsal raphe neurons (DRN) that project to almost every forebrain structure in the brain of mammals (i.e., suprachiasmatic nucleus (SCN) and striatum](data not shown).

The serotoninergic tone appears to be regulated mostly during arousal period, *via* the activity of where serotoninergic neurons display a slow an regular firing activity (1-5 spikes/sec) which declines as the animal enters to slow-wave sleep (SWS), becoming totally silent during REM sleep as demonstrated from raphe/5-HT neurons recorded in anesthetized rats [107-110]. Moreover, electrophysiological studies showed that the firing activity of raphe/5-HT neurons appears to be regulated by the suprachiasmatic nucleus (SCN) (circadian clock) and tonically activated by locomotor activity during arousal [110-112]. These electrophysiological studies showed supporting evidences that median raphe/5-HT neurons projecting to the SCN modulate the photic activation of locomotor activity [113]; where 5-HT may act as inhibitory transmitter activating postsynaptic 5-HT receptors (e.g., 5-HT_{1A} or 5-HT_{2A} receptor subtypes). Pharmacological studies showed that lesion of the raphe-5-HT projecting pathway results in a complete disruption of locomotor rhythms associated with a loss of the diurnal rhythm of corticosterone secretion [110].

Serotonin projecting pathways impinges on a large population of neurons in forebrain structures, where 5-HT plays a crucial role in the modulation of varied bioactivities in the CNS of mammals. Based on electrophysiological and pharmacological data, it has been demonstrated that 5-HT neurons are tightly regulated by distinct neural inputs and neurotransmitters, which include; the descending prefrontal cortex (PFCx)-excitatory neural pathway containing glutamate; the adjacent noradrenergic (NA) neural input arising from locus coeruleus (LC) at the brainstem; the local dorsal/medium raphe GABAergic input; in addition of wide distribution of central peptide modulators (e.g., GAL, CRH, CCK) that appear to regulate the activity of both excitatory and inhibitory neurotransmitters that impinge on raphe/5-HT neurons and/or terminal fields of innervated areas or nuclei from ascending 5-HT projecting pathways [114,115].

In this context, pharmacological and electrophysiological studies *in vitro* and *in vivo*, shed clear evidences that both NE and GABA tonically regulate the extracellular concentration of 5-HT by inhibiting the neuronal release of 5-HT [114]. Conversely, PFCx-glutamate neural pathway (mediated by activation of either NMDA and/or AMPA receptor subtypes) has been shown to enhance the neuronal release of 5-HT at the midbrain raphe nuclei; suggesting that extracellular concentration of 5-HT in these nuclei, appears to be tightly regulated by the activity of both inhibitory and excitatory neural pathways, in addition to the intrinsic neuronal mechanisms driven mainly, through the activity of somatodendritic 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors [114]. These receptors belong to a large family of cloned G-protein

coupled receptors (GPCRs) in the brain and classified as a subfamily of somatodendritic 5-HT autoreceptors [116,117] that mediate different cell responses, *via* activation the Gi/Go transduction system and cAMP intracellular signaling pathway, which in turns leads to activation of specific transcription factors (e.g.,CREB, c-fos) which activate the expression of specific genes implicated in regulating cell functions and neuronal plasticity [115] (see Fig. **3**).

Serotonin transmission system may be altered by different kinds of drugs that elicit abnormal behaviors. Drugs impinging of serotonin receptors have been widely used to treat depression, anxiety disorders and schizophrenia [110]. At the hypothalamus, 5-HT has been found to participate with several other neurotransmitters, in the regulation of pituitary secretion of ACTH, prolactin (PRL) and growth hormone. Neuroanatomical studies have demonstrated direct synaptic connections between serotoninergic terminals and CRH-containing neurons at the paraventricular nucleus (PVN) of the hypothalamus, which support the direct effect of 5-HT on ACTH secretion on the anterior pituitary. Drugs enhancing serotonin effects (e.g., 5-HT agonists) *via* activation of 5-HT_{1A}, 5-HT_2, 5-HT_3, and 5-HT_4 receptors on target cells [53] (see Figs. **1B** and **5**), have been shown to enhance an increased neuronal release of CRH into the portal blood, where the increased peptide concentration leads to the increased synthesis of proopiomelanocortin peptide precursor (POMC), enzyme-processing of POMC derived peptides; leading to an increase cell-secretion of ACTH from anterior pituitary lobe; in addition to the release of other peptide hormones from the intermediate lobe (e.g., β-endorphin, α-MSH), and subsequently, to the secretion of corticosterone or cortisol from adrenal gland [110].

Drugs that increase brain serotonin function include serotonin reuptake inhibitors (SSRI), ligand agonists and antagonists binding 5-HT receptor subtypes, including the 5-HT precursor, L-tryptophan [110]. For instance, IV administration of L-tryptophan has been reported to increase plasma concentration of prolactin and growth hormone in rodents, but not ACTH or cortisol. Similar observations were obtained with fenfluramine administration. However, in humans, administration of agonists that display a high-binding affinity profile for 5-HT_{1A} and 5-HT_2 receptors, have been shown to increase plasma concentrations of ACTH, cortisol and prolactin. Thus, these sort of 5-HT receptor agonists have been routinely used to assess the functional activity of the serotonin system in patients exhibiting psychiatric disorders [110].

7. 5-HT_{1A} RECEPTOR LINKED TO STRESS-INDUCING ANXIETY DISORDERS

During the past three decades more than 14 serotonin receptor subtypes have been identified and cloned from the CNS of mammals, showing their functional relevance in mediating pathophysiological activities and behavioral responses in mood-related disorders (e.g., anxiety and depression) that appear to be linked to the deregulation of HPA

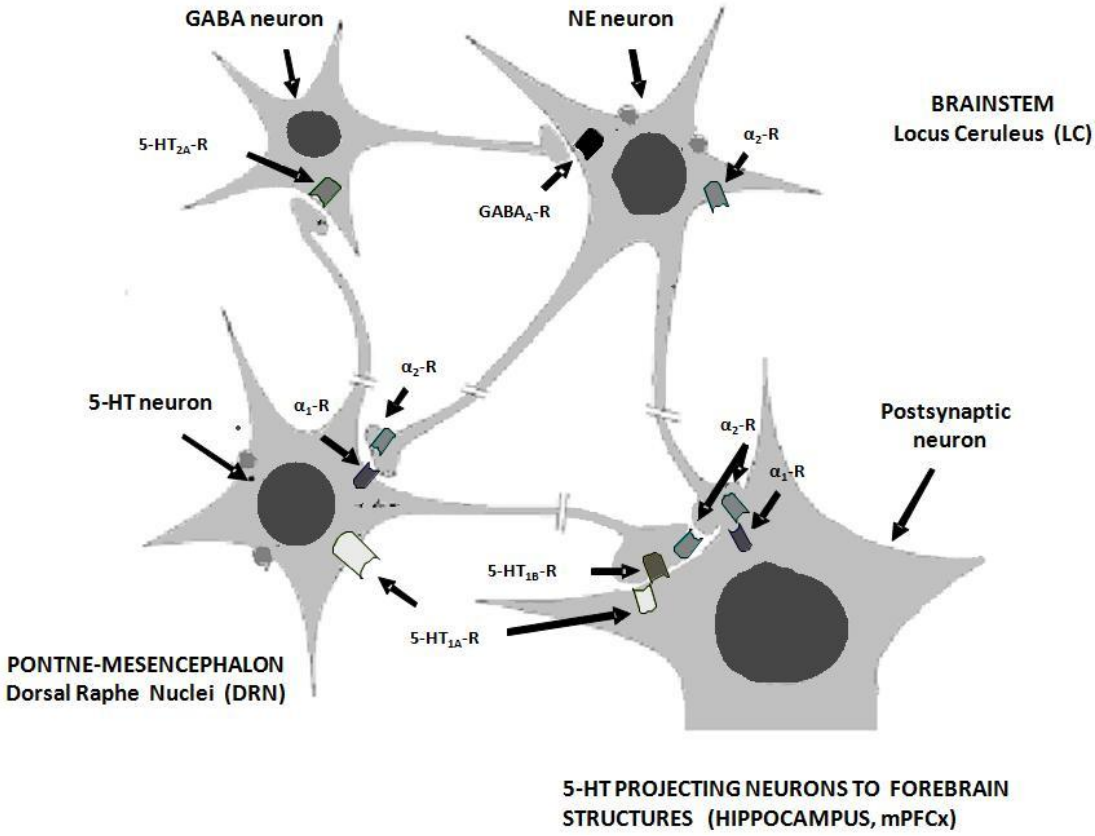

Fig. (3). Interaction between 5-HT and NE projecting neural pathways. Interaction between 5-HT and NE projecting neural pathways to forebrain limbic structures, such as the hippocampus and mPFCx, where they make synaptic connection with pyramidal cells. (see text for specific details) (text and figure adapted from [126] and subject to modifications for the present review).

axis and to the altered changes in hippocampal structure and function induced by stress (see sections below). Extensive studies describing the specific role of serotonin receptors in stress-inducing behavioral disorders (e.g., anxiety, hyperactivity) have been obtained from knockout mice lacking a specific 5-HT receptor subtype [118-121]. For instance, generation of knockout mice lacking the 5-HT_{1A} receptor have been widely used as genetic model to explore the genetic and molecular bases of anxiety disorders. Such mutant mice displayed anxiety-like phenotype behaviors, showing an intense fear reaction, besides other behavioral abnormalities, associated with stress-inducing HPA axis hyperactivity and a down-regulation of GRs in target cells [118,121]. Similar studies, using mutant mice lacking different subset of 5-HT receptors (e.g., 5-HT_3, 5-HT_6, 5-HT_7 receptor subtypes) revealed that these receptors could play important roles in the development of mood-related disorders, associated to the stress-inducing decreased of cognitive functions (e.g., learning and memory task performance). Moreover, mutant mice lacking 5-HT_{1A} and 5-$HT_{1B/1D}$ receptors have been highly linked to the generation of depressive symptomology and altered behaviors observed in MDD in humans [119,120].

Quite interesting to note is that dentate gyrus-granule cells as well as CA1and CA3 hippocampal cells express a high density of postsynaptic 5-HT_{1A} receptors, which appear to mediate adaptive responses to aversive stressful stimuli. Activation of this receptor subtype by 5-HT in CA1/CA3 hippocampal fields led to the expression of different kind of learning behaviors; whereas dysfunction of this 5-HT receptor (e.g., hippocampal decreased of 5-HT_{1A} receptor levels) was associated to the expression of stress-inducing depressive behaviors in animals and to the pathogenesis of MDD, as well [120]. Dysfunction of this 5-HT receptor subtype has been shown to parallelly run with the HPA axis hyperactivity induced by stressful events; in addition to the down-regulation of the type-I GR in target cells [119] (see Fig. **1B**).

In same line, both 5-HT_{2A} and the 5-HT_3 receptor subtypes (ligand-gated ion channel-receptor) have been found to be highly expressed in apical dendrites of CA1/CA3 pyramidal cells, glial cells and GABAergic interneurons in the hippocampus [115,122-124] and which appear to be implicated in the altered activity of distinct neurotransmission systems during depressive illness [125] or decreased in MDD subjects [6] or mediate cell loss and hippocampal atrophy during stress-inducing HPA axis hyperactivity and increased glucocorticoid responses in mood-related disorders [23,24] (see Fig. **2**).

8. SEROTONINERGIC (5-HT) AND NORADRENERGIC (NA) INTERACTIONS

For decades it has been shown that NE system plays a crucial role in the etiology of depression, besides the mechanisms of actions of several antidepressants [126]. Several electrophysiological and pharmacological studies have shown the existing interactions between 5-HT and NE neurons, including their projections to forebrain structures [127]. From this studies, it has been shown that 5-HT neurons project to NE cell bodies, localized within the locus coeruleus, where they produced an important inhibitory effect *via* the activation of presynaptic 5-HT_{1A} autoreceptors and postsynaptic 5-HT_{2A} receptors. Antidepressant treatment with SSRIs may be counterproductive due that may enhance an increased activation of the inhibitory 5-HT input to LC-NE neurons (see Fig. **3**). Moreover, based on the concept that LC-NE neural activity tonically influence the activity DRN/5-HTneurons and LC-NE projecting neural pathway are impinge and/or influence by distinct antidepressants; any inhibitory activity induced on NE neurons will cause an indirect inhibition of the brain 5-HT transmission system [126,128]. In line with aforementioned neural mechanism, several works demonstrated that chronic administration of SSRI causes an important inhibition of the LC-NE firing rate activity which enhances a significant reduction of presynaptic release of NE. These studies showed that the time course taken for SSRIs to induce their inhibitory responses on NE neurons parallels the time-period by which 5-HT_{1A} receptors become desensitized [126-128].

Moreover comparison between Mirtazapine (a specific α2-adrenoceptor antagonist) and SSRIs in the onset of action of antidepressant therapy, several works demonstrated the faster onset of Mirtazapine activity, when compared to SSRIs [129,130]. This drug has been useful in evaluating the interaction of 5-HT and NE systems based on the following observations that demonstrated that Mirtazapine inhibits the activity of α2-adrenoceptors located on the cell bodies of NE neurons, including α2-adrenoceptors localized in 5-HT nerve terminals impinging LC-NE neurons and terminal fields in forebrain-limbic structures; in addition of those α2-adrenoceptors expressed in LC-NA projecting fibers to the midbrain raphe nuclei [131,132] (see Fig. **3**). Thus, mirtazapine acting on its specific cognate adrenoceptor has been shown to produce an increase firing rate activity of LC-NE neurons which resulted to be attenuated by stimulation of α2-adrenoceptors with the potent agonist clonidine. Conversely, the induced-cell firing inhibition of NE neurons by clonidine was reversed with mirtazapine [126,131,132]. Furthermore, the increased cell firing rate induced by mirtazapine produced a significant increase of NE release from presynaptic terminals; enhancing an increment on the extracellular NE content throughout the brain [126,131,132].

As shown in Fig. (**3**), NE axon fibers project to the raphe nuclei, inducing an excitatory effect on 5-HT neurons, *via* activation of postsynaptic α1-adrenoceptors. Based on this neuroanatomical configuration, several authors made used α1-adrenoceptor antagonists (e.g., prazocin) to attenuate the DRN/5-HT neurons firing activity [132]. In this context, these results showed that tonic stimulation of 5-HT neurons are functionally dependent on the activation of α1-adrenoceptors localized in 5-HT cell bodies, suggesting that 5-HT neurons are functionally dependent on the cell activity and NE release from LC-NE neurons [126,132,133]. These results demonstrated that Mirtazapine acting on α2-heteroreceptors will enhance an increase firing rate of DRN/5-HT neurons [131-133].

In line with aforementioned description of 5-HT and NE interaction at brainstem nuclei and in forebrain limbic areas, several studies demonstrated that the application of the 5-HT_{1A} receptor antagonist (e.g., WAY 100635) reversed the inhibitory firing rate activity mediated by 5-HT on hippocampal neurons. However, it has been shown that under physiological conditions in anesthetized rats,

hippocampal-pyramidal neurons are not tonically inhibited by 5-HT, so that at this neuroanatomical level, 5-HT_{1A} receptor antagonist do not appear to display any pharmacological effect (e.g., increasing the neuronal-firing rate activity). However, application of the 5-HT_{1A} receptor antagonist, WAY 100635, produced a dramatic increase on the firing rate activity of hippocampal neurons in animals exposed to a continuous three-week treatment period (21 days) with paroxetine or mirtazapine. These results suggested that 5-HT neurotransmission system appear is enhanced by chronic antidepressant treatment [133,134]; despite of the positive short-term effects reported after acute administration of mirtazapine (e.g., 2 days) producing a potent inhibition on the firing activity of hippocampal neurons after administration of the 5-HT_{1A} receptor antagonist, WAY 100635 [135] (see Fig. **3**).

Overall these studies, suggest that mirtazapine have a faster therapeutic action compared to SSRIs, and the chronic effects display by either mirtazapine and/or paroxetine, are basically due to the additive effects on the enhancement of 5-HT transmission activity, as shown in human studies [126,135]. Moreover, it seems quite clear, that antidepressants displaying dual activity; enhancing both 5-HT and NE transmission systems, respectively; may be highly useful in clinics, due to the rapid onset of action and effective therapeuticly activity compared to antidepressants that impinge only on a single neurotransmission system [126].

9. NORADRENERGIC TRANSMISSION SYSTEM

Over the past 40 years clinicians and researchers observed the close relationship that exists between depression-like behaviors in animals and humans and changes in the NA transmission system [136]. Although these studies showed the direct implication of the noradrenergic transmission system (NA) in stress-inducing altered behaviors and depression; its direct link between the noradrenergic activity and stress-inducing depression-like behaviors has not been clearly demonstrated [137]; albeit that previous studies demonstrated the association between norepinephrine (NE) depletion in locus coeruleus (LC) neurons and the expression of behavioral changes observed in rats challenged to repeated stressful stimuli [138-140] (see Figs. **3** and **4**).

Cell bodies of catecholaminergic neurons are present in the brainstem, midbrain, hypothalamus, olfatory bulb and retina. Both noradrenergic and dopaminergic cell bodies (designated as A1 to A16) are segregated in different regions of the brain from the medulla to rostral areas in the brain 9data not shown). NE-containing cell bodies are found in the pons and medulla, as opposed to dopamine cell bodies. At the pontine area, NE-containing cells in the locus coeruleus (LC) sends long fiber projections to the hypothalamus, thalamus, limbic regions and cortex [141]. Some hypothesis offered last decade explained that the major noradrenergic (NA) transmission system in the brain, provides the neural input that influences and/or exacerbate stress- and mood-related behaviors in animals and humans (e.g., depression); by altering the dopamine neural activity at ventral tegmental area (VTA) through the release of NE and Galanin (GAL) from LC neurons (see sections below) [137] (see Figs. **4A-B**).

In humans repeated stressful events have been shown to precede depressive illness, whereas animals challenged to uncontrollable stressful stimuli (e.g., electric shocks) have been shown to induce behavioral changes that parallel somehow depression disorder [137,142]. Features of depressive-like symptomology exhibited in animals, include; decreased motor activity, decreased grooming, decreased food-intake and water consumption. These stress-inducing effects cause a dramatic weight loss associated to a significant reduction of competitive behaviors [137]. Moreover, animals displaying depressive behaviors exhibit sleep disturbances as occur in depressive illness. Humans with MDD commonly display periods of "early morning awakenings" associated to poor cognitive memory, poor learning task-performance associated with increased errors in discrimination-tasks, besides of decreased responses when tested for "reward brain stimulation" [137]. Thus, animal models of depression resemble several features of clinical depression, such as, etiology, symptoms, behavior including responsiveness to treatment [137,143]. Although several years of research failed to demonstrate the important influence of the brain NE system in depressive disorder [137]; it has been shown that changes in this cathecholaminergic projecting pathway influences directly locomotor activity responses, exploratory behavior and sleep [144-146] without leading to the expression of depressive symptomology and associated behaviors [137].

Furthermore, animal studies led authors to propose that NE depletion from LC-NA neurons in animals may lead to the expression of depressive-like behaviors, suggesting that humans displaying depressive symptoms and behaviors may result from a substantial decreased of transmitter from its synthesizing cells [137]. Under physiological conditions, NE stimulates the α2-adrenoreceptor on LC neurons; whereas in stress-inducing depressive behaviors these adrenoreceptors appeared to be functionally inhibited or blocked. Electrophysiological studies (using single-unit recordings of LC activity) showed an increase cell-firing activity and increased response (hyper-responsivity) of LC-NA neurons to excitatory stimulation in rats displaying stress-inducing depressive behaviors [147]. Moreover, same studies reported that the degree of expression of depressive-like behaviors correlated to the degree cell hyper-responsivity [147]. However, experiments related to the *in vivo* manipulation of rat LC-NA neurons-α2-adrenoreceptos, showed that receptor stimulation produced an important reduction of cell excitability associated to a decrement of NE release from NA cells [147] (see Figs. **4A-B**).

Based on aforementioned data, it appears that controversial results have been found concerning LC-NA neuronal activity and NE release linked to depressive-like state behaviors [137]. In this context, several authors proposed that dopamine (DA) system and DA release could play a crucial role on depression, based on that DA has been shown to exert a significant influence on behavioral responses (e.g., DA affects motor activity in forebrain limbic structures) [148-150] including the neural processing of reward stimuli (e.g., hedonic value of reward stimuli) [151,152]. Thus, decreased motor function and reduced hedonic for reward stimuli; two major symptoms of depression appear to be driven by brain DA. Moreover, several authors proposed that the interaction between NE and

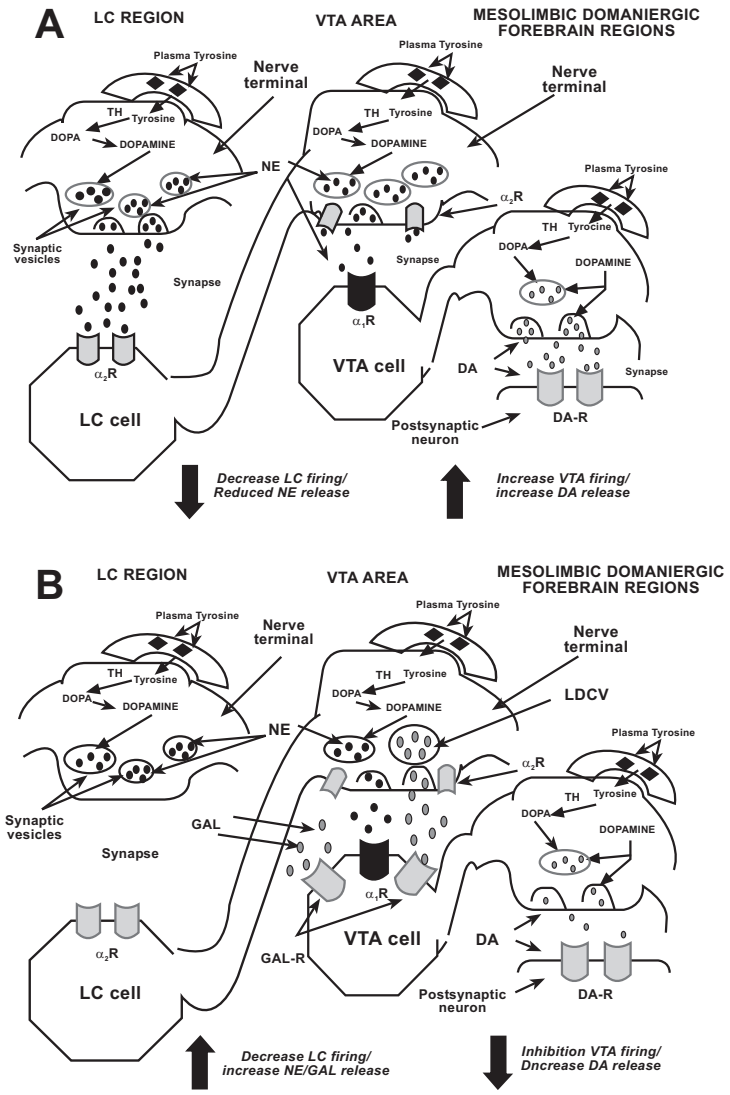

Fig. (4). Neural events linking norepineprine (NE) and dopamine (DA) transmission systems in stress-induced behavioral depression: A proposed hypothesis. (**A**) Under non-stress conditions the neural activity between these neurotransmission systems display a regular baseline-functioning pattern, showing a normal inhibition of LC neuronal firing rate produced *via* NE stimulation of α2-adrenoreceptors on LC cell bodies which leads to a less depolarization activity and release of NE from nerve terminals onto α1-adrenoreceptors, localized in the soma of dopamine neurons in the VTA. Stimulation of postsynaptic α1-adrenoreceptors induces the DA release in the mesolimbic forebrain regions. (**B**) During stress conditions, the stress-induced behavioral hypothesis of depression leads to a series of neural events, intiating with the large-scale-NE depletion from presynaptic terminals of LC neurons, which reduces the stimulation of inhibitory α2-adrenoreceptors localized on LC cells, leading to the functional blockade of these receptor subtypes. The low stimulation of these autoreceptors produces a marked increased in the firing rate of LC neurons (burst firing) leading to the release of GAL peptide in he VTA, which in turn, inhibits the VTA-DA neurons and therefore, to a significant decrease of DA in the forebrain (text and figure adapted from [137] and subject to modifications for the present review).

DA system appear to be crucially important during depression, based on the findings describing an altered LC-neuronal activity, increased NE depletion, reduced DA release in forebrain structures, and decrease postsynaptic DA receptor stimulation, would be expected to enhance depressive symptoms in humans and/or depressive-like state behaviors in animals, as described above [137] (see Figs. **4A-B**).

10. DOPAMINE TRANSMISSION SYSTEM

Since the early 70´s, pharmacological studies demonstrated that activity LC-NA neurons and NE release stimulated dopamine (DA) transmission system at the ventral tegmental area (VTA); showing that NE induced a potent increased on dopamine cell firing activity [153,154]**.** Since then, electrophysiological studies, using single-pulse LC stimulation paradigms, demonstrated the existing link between NE and DA-containing neurons; showing that the evoked-release of NE from axon terminals was able to potentiate the firing rate of local VTA-DA neurons; which was abolished by the α1-adrenoreceptor antagonist, Prazocin [155-157] (see Fig. **4A**). Although, these observations demonstrated the influence of LC-neuronal activity on DA-cell bodies at the VTA, *via* stimulation of somatodendritic

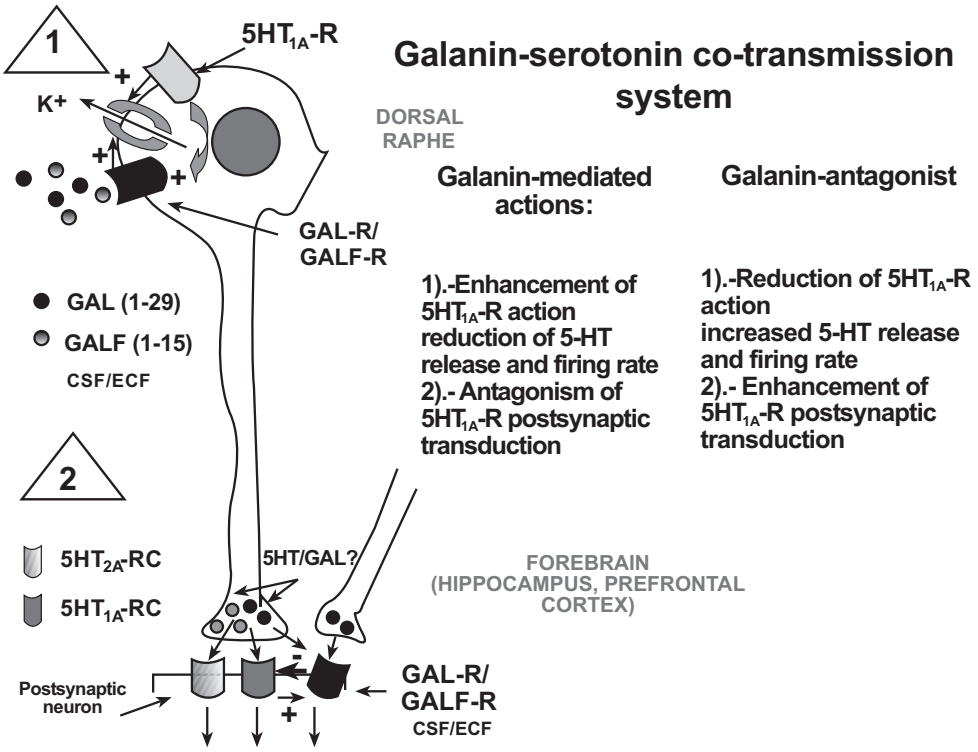

Fig. (5). Synergisitc actions between GAL and NH_2-terminal GAL fragment at both pre and postsynaptic level of serotoninergic ascending pathways to forebrain limbic areas. As shown in the illustration, GAL(1-29) or GAL fragments (1-15, 1-16) reduce the 5-HT_{1A} mediated transmission system by acting either at the soma of the 5-HT neuron in the dorsal raphe nucleus, reducing 5-HT firing rate, 5-HT release and 5-HT metabolism at presynaptic terminals in forebrain structures (e.g., hippocampus, prefrontal cortex). Moreover, GAL release from presynaptic terminals may reduce the membrane-transduction signals of the postsynaptic 5-HT1A- receptors *via* the interaction between GAL/GAL fragment/5-HT1A- receptors. The antagonistic actions of GAL-R (GAL receptor) and GALF-R (GAL fragment receptor) on 5-HT neurotransmission system may represent novel forms of employing peptide molecules as new types of antidepressant drugs (see text for details) (text and figure adapted from [161] and subject to modifications for the present review).

α1-adrenoreceptor on DA neurons; no data explaining the controversial issue between the increase levels of NE detected during depression has been clearly elucidated. An apriori hypothesis, based on aforementioned observations should state that the "stimulatory effect of VTA-DA neurons by NE are expected to induce important excitatory effects on forebrain limbic structures mediated by increased levels of DA, reverting the observed depressive symptomology, as opposed to the results showing the presence of a decrease activity of VTA-DA cells in animals exhibiting depressive-like behaviors or depression symptomology in humans [137]. In context with this hypothesis, different studies showed that repeated, but not single electrical stimulation of LC-NA neurons produce a marked suppression. DA cell activity, opposite to the previously detected electrophysiological potentiation of VTA-DA cell activity, using single-pulse LC stimulation protocols [158]. These studies led authors to posit that the induced-heightened burst firing activity of LC neurons result in a potent inhibitory VTA-DA cell activity, that convey to a reduced DA release in forebrain limbic-structures, leading to depressive-like behavioral responses in animals (e.g., reduced locomotor activity, attenuated responsiveness to rewarding stimuli) [137,147,158].

Although this hypothesis formulated could well link the LC-NE neuronal activity to stress-inducing depressive behaviors; no explanations were offered on the inhibition of DA cell firing induced by LC activity, when opposite results showed also that NE at the VTA, potentiated DA cell activity, *via* α1-adrenoceptor [137]. Under such circumsances, other explanations were offered, suggesting that a different non-catecholamine dependent mechanism was responsible for the inhibition of VTA/DA neurons, *via* the release of galanin (GAL) from LC-NA neurons [137,158] (see Figs. **4A-B** and sections below).

11. INTERACTION BETWEEN PEPTIDERGIC AND MONOAMINE TRANSMISSION SYSTEM: GALANIN (GAL) PEPTIDE INTERACTING WITH 5-HT PROJECTING NEURAL SYSTEM

In the late 80's several works shed evidences that the neuropeptide Galanin (GAL_{1-29}) interacts with serotoninergic neurons in the CNS at both presynaptic and postsynaptic level [159-161]. These studies suggested that DRN/5-HT neurons [162-164] which project to forebrain-limbic areas synthesize and express medium-to-high levels of GAL peptide, as compared to the low-expressing peptide-IR in cholinergic forebrain neurons or high-expressing peptide–IR in noradrenergic brainstem neurons [161] (see further below). However, the low synthetic rate of GAL in DRN/5-HTneurons has been supported by IHC studies that showed that GAL does not co-localize with 5-HT in presynaptic terminals projecting to forebrain structures [165,166]. In same

line, ultrastructural studies using electron microscope revealed that DRN/5-HT appear to be surrounded by nerve endings expressing Galanin immunoreactivity (GAL-IR). Thus, these studies revealed that GAL appear to co-localized with dendrites of DRN/5-HTneurons [161,166] where axo-dendritic contacts could established between axon terminals containing GAL-IR and serotoninergic dendrites [166] (see Fig. **5**). These findings support the idea that GAL neurons (nerve endings) innervate 5-HT neurons, establishing a neural input into the dorsal raphe nuclei [161,166]. Moreover, supporting previous observations; electrophysiological studies showed that GAL administration enhances (via activation of the GAL-R_1 receptor) a prolonged cell-hyperpolarization activity on DRN/5-HTneurons. This effect was proposed to be mediated through an interaction between GAL-R_1 receptor and activation of the somatodendritic 5-HT_{1A} receptor subtype localized on target neurons [161,166] (see Fig. **5**). Initial studies focused in exploring the interaction between the GAL peptide and 5-HT neurons, demonstrated that ICV injection of GAL_{1-29} (porcine) produced a significant reduction of serotonin metabolism in midbrain-raphe neurons (somatodendritic level) that project to forebrain limbic structures (e.g., ventral limbic area of the hippocampus, frontoparietal cortex) [159,161]. Moreover, immunohistochemical studies showed that GAL-IR was widely distributed in many different small to medium size nerve cell bodies and dendrites, including some pyramidal cells on both dorsal and ventral hippocampus, in addition of the dentate gyrus and striatal neurons localized at ventricular areas of the striatum [167,168]. Further IHC studies revealed that GAL immunostaining appears is localized in GABAergic neurons that express somatostatin (SMT-IR) and the NPY peptide (NPY-IR) together with GAD (GAD-IR) [167](data not shown). Radioligand binding studies showed that whereas dorsal hippocampus express high density of 5-HT_{1A} receptor-binding sites and low to moderate densities of GAL receptors (using the ^{125}I-porcine-GAL_{1-15} as radioligand to estimate the amount of binding sites) [169], forebrain structures (e.g., mPFCx, VLCx, hypothalamus, striatum)express low amounts of ^{125}I- GAL_{1-15} high binding affinity sites [161,169-172].

Quite interesting to note, is that such binding studies demonstrated a substantial overlap between the distribution of high affinity binding sites of GAL_{1-15} and ^{3}H-8-0H-DPAT in the dendritic layers of the stratum radiatum of both CA1 and CA2 hippocampal fields, in addition of detection of same overlapping between GAL-R_1 and 5-HT neurons at the molecular layer of the dentate gyrus [161,172]. Moreover, these studies revealed that high affinity GAL_{1-15} binding sites do not overlap with low affinity GAL_{1-29} binding sites in the dorsal hippocampus [161,173]. Overall, these data proposed that neurons at dorsal hippocampus appear to express a different subtype of GAL_{1-29} receptor (GAL_{1-15} fragment receptor) that display a high binding avidity for the H_2N-terminal GAL_{1-15} peptide fragment [161,173] (see Fig. **5**).

12. INTERACTION BETWEEN PEPTIDERGIC AND MONOAMINE TRANSMISSION SYSTEM: GALANIN (GAL) PEPTIDE INTERACTING WITH NOREPINEPHRINE (NE) PROJECTING NEURAL SYSTEM

IHC studies showed that Galanin (GAL) is not only expressed in serotoninergic-neural pathways that project to forebrain limbic structures (e.g., hippocampus) but also a high specific immunolabeling has been found in LC-NA neurons [174-176] projecting to VTA-DA neurons in the rat brain [175]. Complementary electrophysiological studies, demonstrated that electrical stimulation of LC-neurons produced and evoked-release of GAL from presynaptic NA-terminals [137,177,178] which appear to bind specific membrane-binding sites (postsynaptic GAL-Rs) on VTA-DA neurons, as shown *in vitro* labeling studies (using ^{125}I-GAL as radioligand tracer) [169,172].

Furthermore, related studies showed that GAL, acting on its postsynaptic receptor (GAL-R) induced a potent hyperpolarization effect on DA neurons [179-183]. These results led authors to proposed the hypothesis that LC-NA neurons exposed to high-burst firing activity leads to an increase synaptic release f GAL peptide, whose binding to its postsynaptic cognate receptor, induces an important reduction on cell-excitability of DA neurons [137] (see Fig. **4B**).

Further experiments performed to support the aforementioned hypothesis (that describes the GAL effect, producing a potent firing activity inhibition of VTA-DA neurons) include the chemically-induced neurotoxic lesion of both NE ventral and dorsal bundles (VB, DB), respectively, using the neurotoxic agent, 6-OHDA (4 μg/μl) injected directly into the rat neural tissue [137]. These experiments showed that complete destruction of the NE-DB bundle induced a complete loss of GAL-IR in LC-NA projecting axons to forebrain limbic structures (e.g., VTA, mPFCx, hippocampus, hypothalamus) compared to the strong localization of peptide immunoreactivity on LC-NA neurons and projecting axon terminals in control animals [137]. These studies provide evidences that both DB and VB lesions produced an significant reduction of GAL content in VTA-DA neurons (50-60%); suggesting that much of the GAL-IR expressed in LC-NA projecting pathway to forebrain structures, are not completely dependent on the brain NE system [137].

Thus, from the neuroanatomical point of view, these studies support that most if not all of the GAL peptide released into the VTA region originates from LC-NA neurons [137]. Pharmacological studies showed that bilateral microinjections of GAL into the VTA or into the hypothalamic areas, respectively, in normal freely-moving animals; GAL peptide completely abolished the animal´s exploratory behavior during the first 10 min after peptide injection, as compared to animals exposed to GAL injection into the lateral ventricle. These data suggested that GAL modulates motor activity at different areas of the rat CNS [137]. Similar studies showed that inbred rats exposed to forced-swim test trials (animal model of depression) displayed higher-than normal struggling activity, as compared to control animals injected with vehicle solution (ACSF, artificial cerebral spine fluid) [137,184]. However, GAL injected into the VTA (0.3 ng) showed a dose-dependent (0.003-0.03 μg) reduction of struggling behavior in inbreds exposed to forced-swim test trials, as compared to controls [137]; besides of the increased floating behavior response detected when exposed to the Porsolt immobility behavior paradigm.

The peptide-induced attenuated struggling responses were completely attenuated to control, ACSF-treated animals, with the GAL antagonist, g*alantide* (GTD, 0.3 μg) [137]. Overall, these results led to the hypothesis that GAL release from LC-NA neurons into VTA region, modulates at very low doses, stress-related behavioral responses (e.g., reduced motor activity) in animals exposed to uncontrolled stressful conditions; a situation that parallels depression behavior in humans [137].

13. INTERACTION BETWEEN GALANIN, NOREPINEPHRINE AND DOPAMINE NEURAL SYSTEMS

As described above, it appears that the interaction between both LC-NA and VTA-DA transmission systems plays a crucial role during depression [137]. A working hypothesis of depression based the functional interaction between both NA and DA systems proposes that under severe stress (uncontrollable stressor) NE depletion from LC-NA neurons resulting from a functional inhibition of α2-adrenoreceptors, may lead to a significant increase of the burst firing activity of NA neurons, in addition to the increase release of GAL into the VTA region. GAL binding its postsynaptic peptide receptor (GAL-R) will exert a potent hyperpolarization effect on VTA-DA neurons, dampening the excitatory effect induced by NE of DA cells, *via* activation of α1-adrenoreceptors, resulting in an overall inhibition of the cell firing activity [137] (see Figs. **4A-B**).

Although this final effect on the reduced cell-firing activity, may lead to a substantial decreased of DA release in forebrain limbic structures (e.g., NAc, mPFCx) conveying to the development of stress-associated depressive behaviors in animals and humans (e.g., decreased motor activity, anhedonia), as proposed [137]; in an attempt to link the DA transmission system and depression; neurochemical studies using microdialysis techniques in animals exposed to acute stressful stimuli demonstrated that the ratios of DA metabolites (e.g., DOPAC/DA and HVA/DA ratios) were highly increased in limbic structures that receive important DA inputs (e.g., NAc, mPFCx) [185-187]. However, animals exposed to uncontrollable stressful paradigms or behavioral models of depression (e.g., forced swimming, prolonged immobilization and/or continuous restraint stress) showed a significant decrement of DA activity and DA turnover [188-190]. Similar findings on the reduced DA release from presynatic DA terminals in the NAc and mPFCx were shown animals exposed uncontrollable foot shock [191,192] (see Fig. **4B**).

Thus, it appears that exposure to acute stimuli versus uncontrollable stressful challenges produced opposite effects of DA system. Behavioral experiments were performed to solve this issue, using different animal models of stress. For instance, inbred animals exposed to a three hour-session of repeated uncontrollable tail-shock stimulation were compared to animals exposed to controlled mild-stressor for 30 min (limited number of grid shocks) and these ones, compared to control animals (home cage animals) receiving no stressful stimuli, respectively.

These studies shed interesting results showing that inbred animals exposed to uncontrollable stressful stimuli displayed significant lower DOPAC/DA ratios in the NAc, suggesting that chronic stress produces a important decreased DA turnover and a significant reduction DA release from VTA-DA neurons and neural pathways targeting their specific limbic structures, in animals models of depression [137].

14. REMARKS OF LC-NA AND VTA-DA ACTIVITY ON DEPRESSIVE DISEASE

As mentioned above, LC-NA neurons appear to be highly active during depression, as shown for the increased expression of LC-tyrosine hydroxylase (TH) in individuals committing suicide [193]. Moreover, LC activity has been found to be increased for a considerable period prior to death, due that this enzyme is inducible by the high-firing rate activity of NA neurons [137]. As LC-NA neurons express low concentrations of *somatodendritic-α2-heteroreceptors*, they display a reduced neuronal inhibitory activity (see Fig. **3**). This situation led authors to propose that one major critical pathogenic factor in human depression is the LC-NA cell hyperactivity produced, as a consequence of the hypostimulation of somatodendritic-α2-heteroreceptors [137].

Based on the aforementioned hypothesis (which describes the influence of LC-NA neurons on VTA-DA projecting neural pathway during depression), it has been shown that antidepressants (SNRI) which inhibit the reuptake of NE on LC-NA neurons, promotes an increase concentration of NE in active synapses, leading to a indirect stimulation of somatodendritic α2-adrenoreceptors (see Fig. **3**); that eventually will produce significant inhibitory responses of LC neurons associated to an important decreased of NE and GAL secretion and reduced peptide activity on VTA-DA neurons [137]. This pharmacological-induced responses on LC neurons may be responsible for the decreased synaptic concentration of monoamine transmitters upon long-term administration of antidepressants for treating chronic depression [137]. Supporting evidences of these cellular effects, is the finding of the reduced concentration of TH in rat LC-NA neurons upon exposure to antidepressants [194]. Quite important to be taken into consideration, is the impact of the reduced GAL secretion from LC-NA neurons and reduced activity of this peptide on VTA-DA projecting neural pathway. This reduced activity of NE and GAL on DA neurons has been proposed as the responsible biological mechanism involved in the pathogenesis of depressive illness and depression relapse, that results from an overall reduced LC-NA activity, particularly upon long-term administration of antidepressants [137] (see Figs. **4A-B**).

15. GLUTAMATE TRANSMISSION SYSTEM

Glutamate, is the major excitatory amino acid found in the brain and proposed to act as neurotransmitter from the earliest 60`s. Anatomical and neurochemical studies showed that ≈ 30% of neurons in the forebrain synthesize and release excitatory amino acids (glutamate or aspartate) among other neurotransmission systems, including in neurons distributed in subcortical and caudal regions of the CNS [31]. High density of glutamate-reactive neurons has been detected in the cortex, either as, interneurons or as projecting pyramidal neurons located at layers IV-V (as the primary neurotransmitter). In subcortical areas, glutamate-containing neurons are found at the hippocampus, striatum, thalamic nuclei and cerebellum [25,195]. Glutamate transmission system coupled to its cognate NMDA receptor have been

shown over years to drive the cellular mechanisms responsible for inducing long-term potentiation (LTP) or long-term depression, a electrophysiological model of memory that underlies the basis of learning and memory processing in the mammalian brain [196]. The implication of the glutamate transmission system in mood-related disorders (e.g., anxiety and depression) were shown decades ago, where early reports documented that depressed subjects showed an altered glutamate metabolism [197,198], which appear to correlate with recent reports showing an increase NMDA-receptor sensitivity glutamate in platelets from subjects exhibiting MDD [199]. In line with aforementioned observations; *in vitro* studies showed that antidepressants modulate the neuronal release and reuptake of glutamate [200-203]; supporting early data that showed the high binding avidity of tricyclic antidepressants (e.g., dextromethorphan) for NMDA receptors, blocking the binding of ligand agonists for their cognate glutamate receptors [204,205].

Moreover, extensive pharmacological and behavioral studies demonstrated that functional antagonists of the NMDA receptor displayed antidepressant-like properties in rats exposed to chronic stress paradigms (e.g., forced swim, tail suspension test), including olfactory bulbectomy [206-213]. These studies showed that NMDA receptor antagonists, which bind the glutamate- receptor at distinct domains of the multimeric protein [e.g., the glutamate binding site; the glycine binding site; the polyamine bivalent-cation binding site (Zn^{2+}) and/or the ionophore ligand recognition site, such as, ketamine] display similar efficacy as tricyclic antidepressants, when administered into rats or mice [31,214-219]; and disrupt the LTP activity in forebrain areas shown to express a high levels of somatodendritic glutamate-NMDA receptor on postsynaptic neurons [31,220,221].

In addition, pharmacological studies showed that administration of NMDA antagonists, in a similar fashion to antidepressants, induced a significant reduction of β-adrenoceptors [222,223] and 5-HT_2 receptors in several regions of the rat brain [210]. These effects have been proposed to be induced through a rapid-down regulation of receptors in targeted neurons [219]. Thus, these results provided strong evidence that antagonists binding NMDA receptors display important antidepressant properties [31].

Parallel studies showed that antidepressant drugs produce a time and dose-dependent changes in the binding properties of radioligand to NMDA receptors [206,208,222,224-233]. These functional changes in the binding properties of ligands to NMDA-R, has been proposed to be mediated through a BDNF-dependent mechanism, whereby drugs induced specific changes in the functional expression of the subset of protein subunits that structure the multimeric NMDA-R in sensitive neurons [232,234,235]. Thus, these studies revealed that the altered behavioral responses induced by stressful paradigms (e.g., chronic mild stress , forced swim test) that display a high sensitivity when responding to the action of antidepressants, have been shown to be extremely linked to changes in the binding properties of radioligands to NMDA receptors [31,229,236]; demonstrating that NMDA-R antagonists behave relatively similar to several antidepressants used in clinics [31].

i. Metabotropic Glutamate Receptors

As outlined above, several years of research demonstrated that most neurotransmitter systems are affected in the pathophysiology of depression and thereby, modified with the current antidepressant treatment [237,238]: In general, these drugs comprise synthetic compounds that inhibits the neuronal reuptake or the metabolism of biogenic amines that influence the activity of monoaminergic systems (e.g.,5-HT, NE, DA) [239]. Several studies revealed that treatment with imipramine or application of electroconvulsive shock induces an increase an immunoreactive expression of group I-metabotropic glutamate receptor (mGluR1 and mGluR5) in both, CA1 and CA3 hippocampal fields of the rat brain [230,231,240,241].

ii. AMPA Receptors

It has been shown over the past decades that activation AMPA receptor (AMPA-R) increases the expression of the brain-neurotrophic factor (BNDF) both *in vitro* and *in vivo* [242-244]; and converging evidences shed important clues on role of BDNF, mediating the actions of several antidepressant drugs [245]. For instance, it has been shown that the synthetic AMPA receptor potentiator, LY390998, exhibits antidepressant-like properties, similar to imipramine in animals exposed to chronic stress paradigms [246]. Molecular studies showed that this AMPA-R potentiator produced a robust increase of BDNF-mRNA levels in primary culture neurons [247], suggesting that these receptors could display much of therapeutica benefits linked to antidepressant treatment during depression [31]. Supporting this hypothesis, it has been shown that chronic administration of antidepressants (e.g., fluoxetine) increases both, the expression of AMPA receptors (e.g., the Glu 2/3 subunit) in rat hippocampus [248] and the trafficking of protein subunits from intracellular pools to synaptic sites [248]. Similar studies based on long-term antidepressant treatment in rats, demonstrated an increase phosphorylation of serine amino acids (Ser_{831} and Ser_{845}) encoded along the primary amino acid sequence of the GluR1 subunit of the AMPA protein receptor in several regions of the rat brain (e.g., cortex, hippocampus, striatum) [249]. These results led authors to propose that AMPA receptors together with glutamate-NMDA receptors may mediate many of the clinical responses induced by antidepressants during treatment of depression. Thus, it appears that glutamate receptors might represent one the most crucial protein targets, by which antidepressant drugs induce their therapeutic responses; enhancing the functional restoration of several neuronal and non-neuronal bioactivities that resulted to be deregulated during depression [31].

iii. Nitric Oxide and Intracellular Signaling Pathways

Activation of glutamate receptors subtypes on postsynaptic neurons (e.g., AMPA, NMDA, mGLuR1 and/or mGluR5) has been shown to promote a fast increase of intracellular calcium levels $[Ca^{2+}]i$. This induced-increase of calcium concentration stimulates the $[Ca^{2+}]$-dependent calmodulin-kinase complex, which in turns leads to the synthesis of *nitric oxide (NO) by NO synthase (NOS)*; a highly regulated cytoplasmic enzyme [250]. This enzyme has the capability of converting L-Arginine to L-citrulline and then forming nitric oxide (NO) (data not shown). The

intracellular release of NO from synthesizing neurons, leads to the stimulation of a specific NO-sensitive-guanylyl cyclase which enhances the conversion of GTP to cGMP and subsequently to the target-stimulation of a phosphodiesterase II enzyme and protein kinase G (PKG). In this context, NO has been postulated to serve as a transynaptic signal modulator that affects the cell-to-cell communication (as a paracrine mediator) in distinct neural systems [31]. For instance, *in vivo* experiments have shown that NO exerts an inhibitory influence of DA release in the striatum [251] and *in vivo* perfusion of NOS inhibitors (e.g., 7NI, LNNA) produces opposite effects, increasing DA release from neurons. Similar responses have been shown for NOS-dependent release of NE [252].

Furthermore, behavioral and cellular studies showed that the increase levels of biogenic amines released from synthesizing cells in animals exposed to stressful paradigms, resulted from the activation NMDA-R and receptor activation of [Ca^{2+}]-dependent calmodulin-protein kinase enzyme pathway, leading to an increase of NO synthase (NOS) activity and increase NO release from cells [31,253]. Quite recently, different reports using animals exposed to the stress-sensitive model of depression (FST) showed that the [Ca^{2+}]-CaM-NOS-guanylyl cyclase-signaling pathway, play an important role in the behavioral sensitive responses and neurochemical effects induced long-term administration of antidepressant drugs [31,254,255]. In support to these findings, several studies have shown that fluoxetine increases the expression of inducible NOS in several regions of the rat forebrain [256]. Conversely, rats exposed to uncontrollable stress paradigms or chronic mild stress, showed a rapid and selective increase of NOS (e.g., NADPH-diaphorase) in the PVN of the hypothalamus; that resulted to be antagonized through the antidepressant treatment [31,257].

Thus, these results led to the proposition that both NOS and NO, play an important role in stress-inducing altered behaviors in animals and in depressive symptomology in humans, with considerable implications in the neuroadaptive responses induced by antidepressant therapy.

16. CYTOKINES INVOLVED IN STRESS-INDUCED ALTERED BEHAVIORS AN MOOD-RELATED DISORDERS

Cytokines represent a group of proteins released from immune (e.g., CD4+ Th1/Th2 cells); non-neuronal cells in the periphery and hypothalamic neurosecretory cells (e.g., PVN, SON), that overall regulate pleiotrophic functions mostly involved in growth, differentiation and activation of immune function [258]. These proteins grouped according to its functional responses, as *proinflammatory and/or anti-inflammatory mediators* (although several cytokines do not fit specifically into either category) have been shown to respond to a varied range of cellular stresses, including infection, inflammation and carcinogen-induced injury [258]. Cytokines produced by *CD4+ Th1 cells* comprised a group of *proinflammatory interleukins* (ILs) (e.g., IL-1α, IL-1β, IL-2, IL-12p35, IL-12p40, IL-15) and non-IL proteins (e.g., TNF-α and IFN-γ); whereas *Th2 cells* synthesize and secrete specific kind of ILs (e.g., IL-4, IL-8, IL-10, and IL-5) that mediate *anti-inflammatory responses* in the body [258]. Cytokines normally function to stimulate a host response aimed at controlling cellular stress and minimizing cellular damage, acting sometimes in a synergistic manner. The failure to resolve an injury can provoke excessive immune cell infiltration and lead to persistent cytokine production. Therefore, the host response to stress provokes changes in cytokine expression, which can impact several stages of cancer formation and progression [258].

Different studies showed that pro-inflammatory cytokines IL-1α/ IL-1β, IL-6, and TNF-α appear to mediate or elicit sickness behaviors (e.g., fatigue and soporific effects) and symptoms of anxiety/depression that may be attenuated by chronic antidepressant treatment [259]. Moreover, severe depressive illness has been shown to involved immune activation, increased cytokine production and increased serum levels of pro-inflammatory cytokines. Supporting evidences of stress-inducing depressive-disorders, several works demonstrated that ICV administration of proinflammatory cytokines (e.g., IL-2; IFN) produced depressive-like symptoms in animals that were attenuated by antidepressant treatment [260,261] (see Fig. **1A**).

17. HPA AXIS AND CYTOKINE STRESS-INDUCING ALTERED BEHAVIORS AND MOOD-RELATED DISORDERS

During the last decade preclinical and clinical studies revealed the crucial role of different chemical mediators and cellular interactions between the HPA axis and the immune system [262-265]. These studies showed that immune stimulation leads to an overt stimulation of the HPA axis, manifested by an increased ACTH secretion from AP cells; increased synthesis and secretion of glucocorticoids from adrenals, that under physiological circumstances prevent propagation of stress response and restrain the production of proinflammatory mediators [265]. Moreover, recent studies showed that the proinflammatory cytokine, IL-6 plays a crucial role on the HPA axis, where its levels appear dramatically increased upon physical, psychological, and inflammatory stress [266-268] (see Figs. **1A**-**B**).

In same line, different studies revealed that stressful challenges (e.g., inflammation) lead to the activation of IL-6 receptor in neurosecretory cells at the PVN of the hypothalamus; in addition that IL-6 injection into rodents induces both ACTH and glucocorticoid secretion from synthesizing cells**.** These findings led authors to support some previous hypothesis that mentions that — IL-6 promotes the stimulation of the HPA axis through a CRH-dependent mechanism — [269-274]. Similar studies showed that IL-6 regulates HPA axis activity through a CRH-independent mechanism upon activation of the immune system by stressful conditions [269]. In same context, human studies demonstrated that prolonged administration of IL-6 yields to an adrenal enlargement [275,276] probably mediated through a direct stimulation of IL-6 receptors on adrenal cortex as shown from adrenals of mice. Recent studies showed that IL-6 receptors expressed in cortical cells appear to induce an adrenal-dependent steroidogenesis and glucocorticoid secretion in rodents [269]. Furthermore, recent immunocytochemical studies revealed that IL-6 is localized in folliculo-stellate cells at the anterior pituitary

(AP) in different mammalian species (e.g., swine) [273,277,278], findings that correlate its functional paracrine activity between cells [279,280]. This, IL-6 paracrine activity has been confirmed through an endotoxin (stress)-stimulation the immune system assay; that lead to an important increased of IL-6 mRNA expression and IL-6 secretion from secretory cells localized at intermediate lobe (IL) of the hypophysis. These data posited that IL-6 secretion from active cells regulates the activity of ACTH on adjacent cells [281] (see Figs. **1A**-**B**).

In a similar context, different studies shed crucial information about the regulation of IL-6 secretion from AP cells. These studies showed that IL-1 and the specific intracellular messenger (e.g., lysophosphatidylcholine) stimulate the AP pituitary-cell secretion of IL-6 [282,283]. Other factors found to interact with IL-6 , stimulating IL-6 production from rat AP cells, include PACAP and CGRP peptides [273,284]. These data led authors to propose that IL-6 possibly mediates the action of CGRP on C*orticotrophs*, based on previous results that demonstrated the CGRP-dependent increase of ACTH secretion from AP cells [285]. Like IL-6, IL-11 has also been found to play a crucial modulatory activity within the pituitary regulatory system [286], showing that exogenous administration of IL-11 leads to an increase secretion ACTH, concomitantly with an increase levels of POMC mRNA in AtT20 cells. Moreover, recent studies using RT-PCR technology reported the *in vitro* expression of detectable levels of IL-11 receptor mRNA in AtT20 cells, besides of its detection in human and murine normal pituitary glands [273].

Molecular studies showed that IL-6 secretion from cytokine-producing cells follows a highly–regulated mechanism, which operates upon IL-6 binding and activation to its specific (IL-6) surface-receptor coupled to a signal transducer protein; the glycoprotein, *gp130*. IL-6 stimulation of gp 130 leads to the activation of the specific JAK/STAT signaling pathway which inhibits the cellular route implicated in the synthesis of IL-1 and TNF-α, leading to a significant reduction of circulatory proinflammatory cytokines in plasma. Conversely, activation of the same JAK/STAT signaling pathway leads to an exacerbated released of IL-6 from cytokine-producing cells, conveying to the high levels of this proinflammatory cytokine in plasma. These molecular mechanisms linking cytokine–mediated activation of signaling pathways and cellular regulation of the biosynthesis and release of proinflammatory cytokines have been postulated to underlie, the high levels of circulating IL-6 in FM patients [287,288]; in addition of the cytokine (IL-6)-induced deregulation of pain neurotransmitters (e.g., SP) and its cognate receptor, the neurokinin-1 receptor (NK1R) [288,289].

Quite interesting to note, is that cytokines [known to activate both neural and humoral communication pathways upon stressful events (e.g., infection)] have been shown to induce the secretion of similar proinflammatory cytokines from glial cells in discrete regions of the rodent`s brain [290,291]. Thus, these results support several evidences describing the crucial role of cytokines mediating stress-inducing adaptive behavioral responses in both animals and humans [292].

Functional studies provide interesting data showing that proinflammatory cytokine receptors (e.g., IL-1; IL-6 and TNF-α) are highly concentrated in brain areas involved in learning and memory processing, (e.g., hippocampus and mPFCx) [293-296], where proinflammatory cytokines have been reported to inhibit long-term potentiation (LTP) [297-299] producing deficits in hippocampal-dependent cognitive tasks [300]**.** Behavioral studies using normal (WT/IL-$6^{+/+}$) versus transgenic mutant mice deficient in IL-6 (IL-$6^{-/-}$) showed that IL-6 mediated the stress-induced altered cognitive disturbances in spatial working memory in WT/IL-$6^{+/+}$ after LPS administration, as compared to mutant IL-$6^{-/-}$ mice who displayed a dramatic resistant to the LPS-induced deficits in spatial working memory [301].

Overall, these studies support that cytokines , acting *via* paracrine and/or autocrine modes of cell-to cell communication, produce their cell responses, after activating their cognate receptors expressed in either neuroendocrine cells (e.g., corticotrophs) by which they regulate the HPA axis activity; or in brain cells (e.g., neurons and glial cells) where they yield deficits in both learning and memory tasks-performance, after binding their cytokine receptors in targeted cells in limbic structures(e.g., hippocampus) of the rat or human brain [300-302].

18. STRESS AND HIPPOCAMPAL NEUROGENESIS

Several factors have been shown to regulate adult cell proliferation and neurogenesis in the adult hippocampus, such as age, strain, gender, hormones, environment, exercise and learning [303]. As extensively described, acute and chronic stress produces a dramatic decrease in both cell proliferation and neurogenesis [304] (see Fig. **2**). Animals exposed to either acute or chronic physical stress paradigms, including psychosocial stress, have been shown to enhance a reduction of such events. For instance, using labeling procedures with specific cell markers for cell proliferation (e.g., 3[H]-thymidine, BrdU), it has been shown that acute exposure to a predator odor reduces the cell proliferation in the dentate gyrus (DG) of the hippocampus [305,306]. Following same line of experiments, several works demonstrated that animals exposed to an acute stressful paradigm (e.g., inescapable shock) produces short-term decrements of Brdu-labeled cells in the hippocampus, as detected after 7 days [307]. However, other works have clearly shown that exposure to chronic stress paradigms (e.g., restraint stress) for longer periods of time produces a dramatic and noticeable down-regulation in cell proliferation and neurogenesis, as shown to occur after 21 days [79].

Extensive studies performed over the past decades, have concluded that both acute and chronic stress induce important effects on cell proliferation, survival and neurogenesis. Although, is quite important to emphasize that despite of the extensive studies describing the effects different sort of stressors impinging cell proliferation and plasticity events in the brain, more studies are needed in order to clarify how acute versus chronic stressors induces the asymmetric differentiation of labeled-hippocampal cells into different mature cell-phenotypes[304]. Although chronic stressors represent a more real-world environment than acute stressor paradigms, both sort of stressors have been used to detect same context of a neurobiological event(e.g.,

neurogenesis); however, timing and sort of stressor represent two linked conditions that the brain requires to signal the routes and sort of neurobiological mechanisms that modulate cell proliferation and neurogenesis in the nerve tissue of representative species [304].

One hypothesis formulated for the detected changes in neurogenesis, is that the cumulative effects of stress on cell proliferation, neurogenesis and survival produce changes in dendritic remodeling, a process that has been implicated in the pathology of chronic depressive disorder [304]. Stressors, such as prenatal stress have been shown to produce a significant reduction in the hippocampal cell proliferation in the adult rat [308,309]; where female rats were shown to be more sensitive to the altered changes on cell proliferation and remodeling of dendritic spine density during exposure to chronic stress [310,311]. Is quite interesting that the incidence of depression occurs more frequent in females than in males, and several studies have demonstrated that estrogen hormones play a crucial role as a metabolic factor regulating cell proliferation [312]. Thus, from these and several other studies, it appears that functional differences in stress and cell proliferation responses exist between males and females. Therefore caution should be taken when extrapolating data from male experiments to female rats (note that most of the experiments using stress-related paradigms have been performed and reported in male species) [304] (see Fig. **2**).

Extensive studies have delineated the dramatic effects that stress induced onto the granule cell layer at the DG of the hippocampus, besides of the altered changes induced on CA3 pyramidal neurons. These effects have been linked to the exacerbated secretion of glucocorticoids (GCs) from adrenals, such as corticosterone (CORT) besides of the increased synthesis and neuronal release of excitatory amino acids [21,313] (see Figs. **1A-B)**. In this context, preclinical studies have shown that intravenous administration of CORT produces a significant decrease in hippocampal cell proliferation that was prevented by NMDA ligand antagonists (e.g., MK-801) [314]. Furthermore, same experiments revealed that induced reduction of cell proliferation by CORT is prevented by administration of male steroid hormone, dehydroepiandrosterone (DHEA) or through adrenalectomy [306].

It is quite clear that cortisol or corticosterone released during stress produce a pronounce effect on cell proliferation of DG-granule cells, by impinging on the regulatory and signaling pathways involved in the differentiation of hippocampal stem cells. However, interesting works reported that similar effects induced by corticoids on the reduction of hippocampal-cell proliferation can be observed even in the absence of increased serum levels of glucocorticoids [307]. These results imply it that several mediator other than corticosterone may be recruited during stressful events, enhancing the morphological changes observed on hippocampal neurons, reorganization of hippocampal tissue (e.g., reduced volumes) and reduced cell proliferation and neurogenesis [304] (see Figs. **1B** and **2**).

Although stress-inducing effects on hippocampal cell proliferation and remodeling of apical dendrites of CA1-CA3 pyramidal neurons within the hippocampus; these neurobiological events are not exclusively responsible for depressive symptomology occurring in humans, and thereby for the etiology and concurring physiopathology of depression disease.

Stress and depression comprise a large complex picture of neural mechanisms, where insult impinged on cell proliferation is just a single aspect of a long "track" that leads to the multifaceted range of symptoms display in depressed individuals [315]. Moreover, the individual response to stressful challenges or stressful events in life, associated with the subject genetic background will predispose individuals to develop some sort of affective disorder. However, these conditions will somehow determine the role of the stress in the induced –altered changes in both cell proliferation, neurogenesis and neuronal atrophy and morphology [304]. Despite of the extensive literature describing the stress-effects impinging on cell proliferation and neurogenesis in the rat and human brain; the link between the pathophysiology of MDD and stress responses on cell proliferation and neurogenesis are still unclear [304].

19. NEUROTROPHIC FACTORS (BDNF) AND DEPRESSION

Several studies have shown remarkable evidences that antidepressants may exert their behavioral and neurogenic activities through the increase synthesis and release of neurotrophic factors, such as BDNF and insulin-like growth factors (IGF-1), respectively [316]. For instance, different studies demonstrated that ICV administration of BDNF produced a significant increase in hippocampal neurogenesis, while ICV administration of IGF-1 increases both cell proliferation and neurogenesis in same brain tissue. These neurotrophic factors have been shown to induce a marked increase of cell differentiation of stem cells to neurons [317,318]. Moreover, antidepressant treatment has been shown to increase BDNF immunoreactivity (BDNF-ir) in limbic areas of the rat brain [319], besides of the detected increases of BDNF protein and mRNA levels in cells. This neuronal increase of BDNF induced by antidepressants, has been shown to revert the stress-inducing response effect on the down-regulation of BDNF [27]. Recent reports have shown evidences that the activity of antidepressants on BDN-gene expression is a time dependent effect, displaying a biphasic mode during gene transcription [320]. Quite interesting to note, is that intrahippocampal or ICV administration of BDNF produces antidepressants effects in different animal models of depression [319,321]. For instance, transgenic mutant mice exhibiting reduced levels of BDNF, showed a significant deficit in the activation of BDNF-trkB receptor signaling pathway, besides of a high resistant to the antidepressant effects after exposing mutant mice to different depression paradigms (e.g., forced swim test) [322]. Furthermore, several studies demonstrated that exercise (in similar context to antidepressant compounds) appear to influence the neuronal activity of BDNF, by increasing both DG-granule cell proliferation and neurogenesis in the hippocampus [316,323-325] (see Figs. **2**).

Pharmacological studies based on the activity of antidepressant activity, showed recently that administration of citalopram (10 mg/kg/day) and/or reboxetine (40 mg/kg/day) into animals, exposed simultaneously to physical

exercise (e.g., wheel running), a significant 5-HT and NA-dependent increase of BDNF mRNA expression in different areas of rat hippocampus was observed following a 14 day treatment period. These studies showed that although reboxetine treatment led to a rapid enhancement in BDNF transcription over 2 days; antidepressant treatment plus exercise produced a significant increase of BDNF expression that endured for as long as 2 weeks. Similar results were observed with citalopram, showing that short-term treatment with the antidepressant produced a significant increase of BDNF mRNA levels in the CA2 hippocampal region; whereas combined treatment (drug plus exercise) induced a long-term expression of BDNF in several hippocampal fields including the DG area, detected for as long as 2 weeks. These results demonstrated that reboxetine (an SNRI) in combination with exercise induced a more rapid and sustained increases of BDNF mRNA levels; whereas, citalopram (SSRI) appeared to require a longer treatment period to induce similar and significant increases of BDNF expression in hippocampal neurons [326]. These effects have been shown to be mediated through activation of β-adrenergic receptors when considering SNRIS effecting NE-transmission system and/or mediated through the activation of either 5-HT_{1A} and 5-HT_{2C} receptor subtypes with regard to SSRIs impinging the 5-HT transmission system [327].

Molecular studies have shown that binding of trkB-receptor by BDNF, results in the activation of the cAMP/protein kinase signal transduction pathway that leads to activation, *via* phosphorylation of the transcription factor-CREB (cAMP response element binding protein) which upon binding specific DNA segments (CRE) appear to regulate and promote the transcription of specific genes implicated in morphological and behavioral responses of antidepressants [30,304].

These studies clearly demonstrate that the TrkB-receptor activation by BDNF and the receptor-signaling pathway is crucial and required for antidepressant effects, showing that the antidepressant-induced up-regulation of BDNF may represent a common mechanism of antidepressant activity [322]. Moreover, the cAMP-CREB pathway that results to be up-regulated by chronic antidepressant medication seems to represent the molecular mechanism by which BDNF positively influences the neuronal survival and plasticity events [328]. Nonetheless, recent studies have shown that mutant mice displaying a deficit in CREB protein are able to display normal behavioral responses to antidepressants [329], suggesting that alternative independent signaling pathways, does exist besides CREB that regulate some of the pharmacological effects of antidepressants [304].

Thus, it seems clear that antidepressant activity on neural plasticity is mediated *via* neurotrophic-mediated changes in neurogenesis and behavior [304]. However, recent studies have shown that glucocorticoid receptors result to be up-regulated by long-term antidepressant treatment. These results implicates that that other chemical mediators, besides of BDNF, appear to mediate the antidepressants inducing effects, intervening in the therapeutic effects of antidepressant compounds [304].

Finally, few studies have shown that antidepressant actions might be modulated *via* glial cells, in addition to neurons. These studies showed that a small percentage of hippocampal BrdU-positive cells differentiate into glial cells from stem cells. Thus, it appears that antidepressant treatment increases the number immature cells that eventually will differentiate into glia cells. Although, drug treatment produces a net increase of mature glia cells, their amount is much smaller than the number of differentiated neurons [330]. Previous studies showed that glia cells synthesize and express a specific Ca^{2+}-binding protein, S100β-protein, which plays a significant role in both structural and regulatory functions [331]. This calcium-binding protein has been shown recently to participate in the expression of LTP, as well as, in several learning and memory processing mechanisms, which led authors to suggest that this glial protein, may be relevant in mediating synaptic plasticity events in the brain [332].

In context with aforementioned data, few studies have argued about the possibility that glial cells, could mediate, *via* activation of the S100β protein, the antidepressant-dependent responses seen on neurogenesis. This hypothesis is based on the experimental facts that demonstrated that long-term treatment with fluoxetine increases S100βprotein in the rat hippocampus [333], suggesting that astrocytes may display an active role directing neurogenesis [334] (see Fig. **2**). Interesting enough, is results from postmortem studies that showed that neurons and glial cells are significantly reduced in individuals suffering from chronic depression [23,24,304,335]. Despite of this results, several experiments are needed to delineate how glial cells participates and/or regulates hippocampal cell proliferation and neurogenesis induced by antidepressants [304].

CONCLUSIONS

Neuroendocrine network is a complex interacting chemical based-communication between cells, which regulates the homeostasis between distinct functional systems of the body. Decades of investigation have shown that this network is completely disrupted upon repeated stressors or stressful challenges in mammals, making mammalian species, including humans unable to adapt correctly to their contextual environments. Several issues outlined above that explain the interacting mechanism between neural, neuroendocrine and immune systems, where all appear to be implicated, although still unclear, in the pathogenesis and establishment of stress-inducing mood-related disorders, which include depressive illness in humans.

Although hypothetical mechanisms have been outlined from distinct pharmacological, molecular and behavioral studies; the enormous achievement in methodological strategies and technical approaches, together with the widely used recombinant DNA technology and cloning procedures led researchers to explore and search more deeply into the adaptive neurobiological mechanisms and behaviors that are responsible for the pathogenesis of stress-inducing mood-related behaviors and depressive symptomology in humans.

As depicted in this review, we disclose different topics about the neuronal, neuroendocrine and immune-related mechanisms known to drive the whole complexity of stress-inducing altered behaviors in animals, associated to the deregulation and dysfunction of distinct brain transmission systems, including several interacting neuroendocrine

systems (e.g., the HPA axis). Both CNS and neuroendocrine tissues have been shown to be highly-regulated by steroid hormones (e.g., glucocorticoids, cortisol), monoaminergic neurotransmitters (NA, 5-HT, GLU, DA), bioactive peptide modulators (CRH, β-endorphin, galanin, among many others); in addition to proinflammatory cytokines released from immune and non-immune cells; all of which exert crucial roles regulating the normal functioning of this neuroendocrine network in species, and which convey to the development of the adaptive responses to wide-range of stressors. Under normal conditions, the homeostatic balance of this neuroendocrine network enable organisms to adapt correctly to their environments. However, under abnormal or pathological situations (e.g., exposure to repeated stressors or stressful events) stressful events may convey organisms to express abnormal adaptive behavioral responses (as seen in the laboratory using animal models of chronic stress) or in the case of humans, which may lead to the development of mood-related disorders (MDD, anxiety). Past decades led us to explore novel pharmacological treatments to ameliorate depressive symptomology and whose mechanisms of actions are still under study and some of them, have been outlined above.

Despite of the extensive scientific work highlighting the significant interactions between neuroendocrine, brain transmission and immune systems, respectively; all which appear to participate in the stress-inducing neuroadaptive changes and abnormal behaviors in animals and/or depressive disorders in humans; there is still a large gap in the exploration of both cellular and molecular mechanisms by which a specific stressor promotes the whole repertoire of chemical and physiological changes of this neuroendocrine network, whose unbalance may lead to depression disease, one of the major psychiatric disorders that affect humans worldwide.

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ABBREVIATIONS

5-HT = 5-Hydroxytryptamine

ACSF = Artificial Cerebral Spine Fluid

ACTH = Adrenocorticotropic Hormone

AMPA = α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate

ANS = Autonomous Nervous System

AP = Anterior Pituitary

AVP = Arginine Vasopressin

BDNF = Brain Derived-Neurotrophic Factor

BNST = Bed Nucleus of the Stria Terminalis

BrdU = Bromodeoxyuridine

CA = Cornu Ammonis

cAMP = Cyclic Adenosine Monophosphate

CCK = Cholecystokinin

cGMP = Cyclic Guanosine Monophosphate

CGRP = Calcitonin Gene Related Peptide

CMS = Chronic Mild Stress

CNS = Central Nervous System

CORT = Corticosterone

CR = Corticosteroid Receptors

CREB = cAMP Response Element Binding

CRF = Corticotropin-Releasing-Factor

CRH = Corticotropin-Releasing-Hormone

CSF = Cerebrospinal Fluid

DA = Dopamine

DB = Dorsal Bundle

DEX = Dexamethasone

DHEA = Dehydroepiandrosterone

DNA = Deoxyribonucleic Acid

DOPAC = 3,4-Dihydroxyphenylacetic Acid

DRN = Dorsal Raphe Nuclei

DST = Dexamethasone Suppression Test

FM = Fibromyalgia

fMRI = Functional Magnetic Resonance Imaging

FST = Forced Swim Test

GABA = Gamma-aminobutyric Acid

GAD = Glutamic Acid Decarboxylase

GAL = Galanin

GAL-IR = Galanin Immunoreactivity

GCs = Glucocorticoids

GPCRs = G-Protein Coupled Receptors

GTD = Galantide

GTP = Guanosine-5'-triphosphate

HPA = Hypothalamus-Pituitary-Adrenal

HVA = Homovanillic Acid

ICV = Intracerebroventricular

IGF = Insulin-like Growth Factor

IHC = Immunohistochemical

Ils = Interleukins

IFN = Interferon

IV = Intravenous

JAK = Janus kinase

LC = Locus Coeruleus

LPS = Lipopolysaccharides

LTP = Long-Term Potentiation

MDD = Major Depressive Disorder

MR = Mineralocorticoid Receptor

MRN = Median Raphe Nuclei

mPFCx = medial Prefrontal Cortex

mRNA = Messenger Ribonucleic Acid

NA = Noradrenergic

NAC = Nucleus Accumbens

NADP = Nicotinamide Adenine Dinucleotide Phosphate

NE = Norepinephrine

NK1R = Neurokinin 1 Receptor

NMDA = N-Methyl-D-Aspartic Acid

NO = Nitric Oxide

NOS = NO Synthase

NPY = Neuropeptide Y

PACAP = Pituitary Adenylate Cyclase Activating Peptide

PFCx = Prefrontal Cortex

PKA = Protein kinase A

PKC = Protein kinase C

PKG = Protein Kinase G

POMC = Pro-opiomelanocortin

PRL = Prolactin

PVN = Paraventricular Nucleus

REM = Rapid Eye Movement

RNA = Ribonucleic Acid

RT-PCR = Reverse Transcription Polymerase Chain Reaction

SCN = Suprachiasmatic Nucleus

SMT = Somatostatin

SMT-IR = Somatostatin-Immunoreactive

SON = Supraoptic Nucleus

SSRI = Selective Serotonin Reuptake Inhibitors

STAT = Signal Transducers and Activator of Transcription

SWS = Slow-Wave Sleep

TH = Tyrosine Hydroxylase

TNF = Tumor Necrosis Factor

VB = Ventral Bundle

VLCx = Visual Cortex

VTA = Ventral Tegmental Area

WT = Wild-Type

α-MSH = Alpha-Melanocyte Stimulating Hormone

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