REVIEW

Molecular mechanism of noradrenaline during the stress-induced major depressive disorder

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Abstract

Chronic stress-induced depression is a common hallmark of many psychiatric disorders with high morbidity rate. Stress-induced dysregulation of noradrenergic system has been implicated in the pathogenesis of depression. Lack of monoamine in the brain has been believed to be the main causative factor behind pathophysiology of major depressive disorder (MDD) and several antidepressants functions by increasing the monoamine level at the synapses in the brain. However, it is undetermined whether the noradrenergic receptor stimulation is critical for the therapeutic effect of antidepressant. Contrary to noradrenergic receptor stimulation, it has been suggested that the desensitization of β-adrenoceptor is involved in the therapeutic effect of antidepressant. In addition, enhanced noradrenaline (NA) release is central response to stress and thought to be a risk factor for the development of MDD. Moreover, fast acting antidepressant suppresses the hyperactivation of noradrenergic neurons in locus coeruleus (LC). However, it is unclear how they alter the firing activity of LC neurons. These inconsistent reports about antidepressant effect of NA-reuptake inhibitors (NRIs) and enhanced release of NA as a stress response complicate our understanding about the pathophysiology of MDD. In this review, we will discuss the role of NA in pathophysiology of stress and the mechanism of therapeutic effect of NA in MDD. We will also discuss the possible contributions of each subtype of noradrenergic receptors on LC neurons, hypothalamic-pituitary-adrenal axis (HPA-axis) and brain derived neurotrophic factor-induced hippocampal neurogenesis during stress and therapeutic effect of NRIs in MDD.

Key Words: *major depression; stress; noradrenaline; noradrenaline-reuptake inhibitors; serotonin receptors; hypothalamic-pituitary-adrenal axis; locus coeruleus; selective serotonin reuptake inhibitors; serotonin noradrenaline-reuptake inhibitors*

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Introduction

Depression and stress touch every corner of our life and it colors the way how we see the world and its surroundings, which is influenced by our activity, environment and social status. Major depressive disorder (MDD) is a major psychiatric illness that adversely affects families, personal relationships, work or school life, sleeping, eating habits, and general health and current prediction indicates that by 2030 MDD will be the leading cause of disease burden globally (Ustun et al., 2004; World Health Organization, 2017). The course of MDD is complicated because of relapses, chronicity and poor treatment response. In the early 60's, it was proposed that the dysregulation of central noradrenergic system and associated "monoamine hypothesis of depression" play a major role in pathogenesis of MDD (Schildkraut, 1965). Indeed, higher affinity for the noradrenaline (NA) transporter inhibitors, nortriptyline (Georgotas et al., 1987; Borson et al., 1992; Katon et al., 1993; Sullivan et al., 1993; Reynolds et al., 1999), desipramine (Dubé et al., 2010; Pangallo et al., 2011), atomoxetine (Ustun et al., 2004; Kratochvil et al., 2005), and reboxetine (Ferguson et al., 2002; Ferguson et al., 2003; Montgomery et al., 2003; Hajos et al., 2004; Chuluunkhuu et al., 2008) are used as an antidepressant, indicating that the increase in NA in brain is effective in MDD treatment. However, effect of currently available antidepressant drugs including selective serotonin reuptake inhibitors (SSRIs) as well as NA reuptake inhibitors (NRIs) required few weeks of long term repeated treatment (Wong and Licinio, 2001; Frazer and Benmansour, 2002; Nelson et al., 2004). Interestingly, when the antidepressant reached to the clinically effective stage after the chronic administrations, the insensitivity of the NA-related adenylate cyclase activity in brain were observed with a down-regulation of the β-adrenoceptor subpopulation (Sulser, 1987). On the other hand, stress, which is one of the risk factors for the development of MDD, enhances the activity of locus coeruleus (LC) neurons and releases NA throughout the brain in response to stress. In addition, LC activation contributes to the activation of hypothalamic-pituitary-adrenal (HPA) axis which plays a central role in the etiology of stress-induced MDD (Pacak et al., 1995; Itoi and Sugimoto, 2010; George et al., 2013). NA is also increased by neuroinflammation which is one of the risk factor for development of MDD (Weiss et al., 1989; McEwen et al., 1997; Aguilera, 2011; Wang et al., 2011). This contradiction against the role of NA between therapeutic effect and stress response complicates our understanding and the etiology of MDD. Therefore, it is critical to review and discuss about the effect of acute and chronic stress on LC neurons and role of antidepressant involving the NA and noradrenergic receptors. In this review, we discuss the role of NA during stress including neuroinflammation and provide a new insight into the noradrenergic paradox and its implications in stress, anxiety, neuroinflammation and depression.

Role of NA in Stress and MDD

Repeated stress exposure cumulatively increases the risk of developing MDD (Weber et al., 2013; Vinkers et al., 2014). Particularly in young patients, impact of negative psychological stress and neuroticism significantly predicts MDD (Weber et al., 2013). Several animal studies demonstrated that stress is associated with the upregulation of released NA (Tanaka et al., 2000). Fear memory consolidation requires the increase in NA release (Krugers et al., 2011), indicating that the repeated emotional stress response involve the facilitation of NA release in brain and it causes, in part, the anxiety and the associated MDD. Indeed, higher responsivity of LC neurons is observed in stressed animals which exhibit the depressive-like behavior (Weiss and Simson, 1988; Pavcovich and Ramirez, 1991; Kreiner et al., 2011). This higher LC neuronal activity is thought to be due to lower density of Gαi protein-coupled inhibitory α_2-adrenoceptors in the region of LC in stress-induced animals (Landau et al., 2015). It has also been demonstrated that the α_2-adrenoceptors in the LC region were functionally blocked in the stress-induced depressive like state of animals and the intra-clonidine, a α_2-adrenoceptors agonist, infusion into LC area decrease the firing rate of LC neurons and reverse the depressive like state of animals (Weiss and Simson, 1988). These results indicate the two possibilities that either stress causes the lower α_2-receptor activation at the presynaptic terminal which projects to the LC neurons in the depressive like state of animals result in lower NA release level or lower postsynaptic α_2-receptor activation of the LC neurons increase the firing rate of LC neurons in itself in stress-induced depressive-like behavior. Additionally, it has been noted that significantly higher expression levels of N-methyl-D-aspartic acid (NMDA) receptor subunit genes in LC noradrenergic neurons are present in patients with major depression (Chandley et al., 2014). Taken together, the higher activity of LC neurons play a major role in stress induced depression and may be very important and critical for understanding the biological basis of stress induced depression and its etiology.

Contributions of Corticotropin Releasing Factor and Locus Coeruleus Neurons in Stress-Induced MDD

Chronic stress elicits the activation of the LC noradrenergic neurons, medullary A1 and A2 nuclei in the ventrolateral medulla (VLM) and nucleus tractus solitarius (NTS) (Itoi and Sugimoto, 2010; Kravets et al., 2015). VLM and NTS noradrenergic neurons are shown to regulate the activity of neurons containing the corticotropin releasing factor (CRF) in central nucleus of the amygdala (CeA) (Pencea et al., 2001; Kravets et al., 2015). In addition, CRF neurons in CeA also regulate the LC neuronal activity (Curtis et al., 2002). Recent study demonstrated that stress-induced acute anxiogenesis and aversive response during the place avoidance cause the hyperactivity of LC noradrenergic neurons that is driven by CRF input from the CeA to produce anxiogenesis (McCall et al., 2015). Interestingly, stress-induced acute anxiogenesis is regulated by β-adrenoceptor, whereas the aversive effects required α_1-adrenoceptor activity, following the LC neuronal activations by CRF from the CeA (McCall et al., 2015). LC neurons project throughout the brain and hyperactivity of LC neurons is thought to contribute the stress-associated depression (Sara, 2009). Paraventricular nucleus (PVN) of hypothalamus is one of the target regions of LC neuronal innervations and produce stress response (Itoi and Sugimoto, 2010). Following the NA release facilitation as the stress response, noradrenergic receptor is stimulated in the PVN which aggravates the stress through activation of the HPA axis (Itoi and Sugimoto, 2010). The innervation of the noradrenergic neurons from the LC is suggested to be important for the stress-related HPA axis activation (Pacak et al., 1995; George et al., 2013) which is mainly mediated by the CRF containing neurons in the PVN, one of main sources of CRF in the brain (Pacak et al., 1993; Itoi and Sugimoto, 2010). It has been reported that the hyperactivation of HPA-axis is observed in the patients with MDD (Pariante, 2003; Swaab et al., 2005). Blood cortisol level is shown to increase in MDD (de Kloet et al., 2007). In human, cortisol is produced by the adrenal gland in the adrenal cortex and regulated by stress-related HPA axis activation (Dedovic et al., 2009). The corticotropin-releasing hormone (CRH) from the hypothalamus is secreted by the adrenocorticotropic hormone (ACTH), which is secreted in the anterior pituitary glands. This ACTH is translocated into the vascular system and is carried to the adrenal cortex. ACTH triggers the synthesis of cortisol, glucocorticoids, and mineralocorticoids (Aguilera, 2011) (**Figure 1**). In mice, corticosterone is a main glucocorticoid, involved in regulation of stress responses through activation of PVN in the hypothalamus (Ginsberg et al., 2003; Touma et al., 2008). Chronic exposure of mice to corticosterone exhibits a depressive-like symptom that includes the behavioral despair, lower motivation and anhedonia (Gourley et al., 2008; Zhao et al., 2008; Zhou et al., 2011). The central noradrenergic system is considered to play an important role in emotion and has also been implicated in affective disorders after the sustained central responses to the chronic stress, such as fear and anxiety (Itoi and Sugimoto, 2010).

NA and Cytokine Hypothesis of Depression

Apart from the monoamine hypothesis of depression, cytokine hypothesis of depression has been proposed in the early 90's (Aguilera, 2011). Chronic psychological stress is associated with the production of various hormones, neuropeptides (McEwen et al., 1997; Wang et al., 2011) as well as activation of the immune system in the brain (Weiss et al., 1989). It has been suggested that glucocorticoid hormone and cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α are associated with major depression in humans (Curtis et al., 2002; Sara, 2009; Kravets et al., 2015) and animals (Leonard and Song, 2002; You et al., 2011). Meta-data analyses have revealed that peripheral blood elevations in IL-1β, IL-6 and TNF-α are reliable biomarkers for depression (Zorrilla et al., 2001; Dowlati et al., 2010) though some aspects of it are still debatable. Indeed,

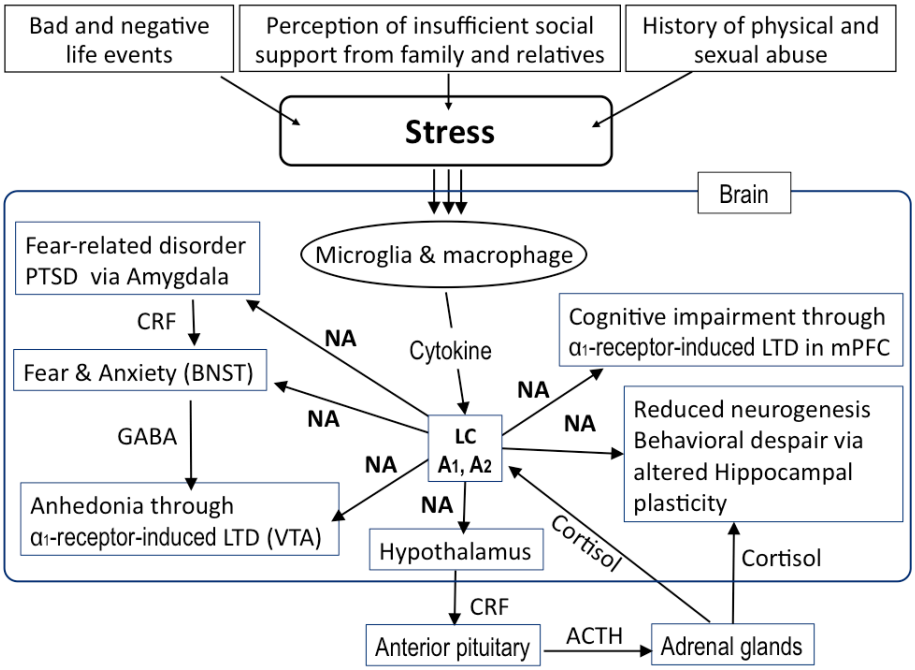

Figure 1 Flow chart of contribution of negative life related stress-induced noradrenaline release from locus coeruleus on the psychiatric symptom.

A diagram representing the central role of stress-increased noradrenaline (NA) from locus coeruleus (LC) in brain. Various factors such as bad and negative life event, a perception of insufficient social support from family and relatives, or physical and sexual abuse, *etc*., elicit the stress responses in human brain. Stress may first activate the microglia and the macrophage in brain which produces the cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α. These cytokines act on various regions in brain. LC is central target of cytokine-induced activation and increases the NA secretion which acts at various regions *via* α_1 and β-adrenergic receptors. LC neurons are activated to release NA following the increase in cytokines. Secreted NA stimulates the secretion of corticotrophin-releasing factor (CRF) from the hypothalamus, which induces adrenocorticotropic hormone (ACTH) release from the anterior pituitary and subsequent cortisol synthesis in the adrenal glands. This cortisol is thought to act on the hippocampus, and mediate decrease in the brain derived neurotrophic factor (BDNF) expression which is linked to the impairing the neurogenesis in dentate gyrus (DG) of hippocampus. Cortisol also stimulates the LC neurons and facilitates the NA release. NA also acts on the basolateral nucleus of the amygdala which is the core of fear-related disorder and posttraumatic stress disorder (PTSD). Activated amygdala CRF neurons stimulate the LC neurons. Stress-induced cytokine production, particularly, IL-1β also decreased the BDNF expression and reduced neurogenesis in hippocampus. BNST: Bed nucleus of the stria terminalis; GABA: gamma-aminobutyric acid; LTD: long-term depression; VTA: ventral tegmental area; mPFC: medial prefrontal cortex.

either subcutaneous or intramuscular administration of interferon (IFN)-α can cause the depressive-like symptom in humans (Raison et al., 2005) and intraperitoneal (i.p.) administration of IL-1β or TNF-α causes depressive-like behaviors in animals (Bluthe et al., 1994). The administration of lipopolysaccharides (LPS), a bacteria-derived endotoxins, has been widely used for investigating the mechanisms of depression because LPS causes the production of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α as well as depressive-like behaviors (Turrin et al., 2001; Frenois et al., 2007; Teeling et al., 2010; Bay-Richter et al., 2011). LPS or IL-1 also facilitate NA release in brain (Linthorst et al., 1996; MohanKumar et al., 1999; Feleder et al., 2007; Sekio and Seki, 2015) in addition with producing the cytokines (**Figure 1**). Previously, we demonstrated that the systemic administration of LPS robustly increases NA release in the ventral tegmental area (VTA) and prefrontal cortex, but not in the nucleus accumbens (NAc) (Sekio and Seki, 2015). The primary source of NA in the medial prefrontal cortex and VTA includes afferents from the LC, while the primary source of NA, with afferents to the NAc, is the A2 region of the nucleus of the solitary tract (Delfs et al., 1998; Lu et al., 2012). These findings suggested that the LPS activate the adrenergic neurons in LC. Indeed, a systemic administration of LPS increases the c-fos expression level in the noradrenergic neuron of LC region, PVN (Dunn et al., 1999) and A1 cell group of caudal VLM of mice a few hours after the injection (Sagar et al., 1995; Kurosawa et al., 2016). Intracerebroventricular (i.c.v.) pretreatment of α_1-adrenoceptor antagonist prevent the LPS-induced depressive-like behavior, such as both behavioral despair and anhedonic response (Sekio and Seki, 2015). Moreover, both behavioral despair and anhedonic response were observed when the phenylephrine, an α_1-adrenoceptor agonist such as alfuzosin and doxazosin are co-administered with mouse recombinant leptin *via* i.c.v. (Kurosawa et al., 2016). Leptin is a cytokine that has anti-inflammatory actions in the presence of lipopolysaccharide (LPS) and in mice it was found that LPS potently activated the HPA axis, as shown by significantly increased corticosterone, and increased plasma IL-1β levels (Basharat et al., 2014). LPS causes the long-lasting increased activity of LC activity *via* IL-1 in the brain (Borsody and Weiss, 2002).

Effect of Cytokines on NA Release in HPA Axis During Stress

IL-1-induced activation of HPA axis has been implicated to relate to the increase in NA secretion (Dunn et al., 1999). Injection of IL-1α in mice increases the NA release in hypothalamus (Kaur et al., 1998) and the anti-depression-like phenotypes of IL-1 receptor antagonist (IL-1Ra) knockout mice were reversed by administration of adrenergic receptor antagonists against α_1, α_2 and β subtypes (Wakabayashi et al., 2011). IL-1β treatment was previously reported to increase tyrosine hydroxylase (TH) mRNA levels in the A6 region (Sirivelu et al., 2012), and it was hypothesized that the IL-1β-induced upregulation of TH mRNA causes a sustained increase in NA levels in the PVN during the course of IL-1β-induced stress axis activation (Sirivelu et al., 2012). In contrast to the effect of cytokines on central noradrenergic systems, NA has been suggested to mediate the IL-1 production *via* β-adrenergic receptors in brain during acute stressor exposure (Johnson et al., 2008). Stress increased IL-1 production in the amygdala and i.c.v. administration of isoproterenol, a β-adrenergic receptor agonist, augmented IL-1 production in the hypothalamus of stressed animals (Porterfield et al., 2012). LC promotes HPA axis responses to acute stress (Ziegler et al., 1999). Such increased NA by stress-induced cytokines, particularly IL-1β activate the HPA axis which is consequence of adrenocortical secretion of corticosterone in rodents (Smagin et al., 1996; Ishizuka et al., 1997; Merali et al., 1997; Wieczorek and Dunn, 2006). Chronic exposure of corticosterone in brain induces depressive-like behavior (Zhao et al., 2009; van Donkelaar et al., 2014), whereas the glucocorticoid receptor antagonist mifepristone (RU-486) prevents the cold stress-induced depressive-like behaviors (Eshkevari et al., 2015). Therefore, the stress related cytokines-induced increase in the NA may be partly contributed in the development of depression though activating the HPA axis. Nevertheless, more work is necessary to better understand the effects of cytokines on the NA system in relation to cytokine-induced depression.

Impairment of Locus Coeruleus Neuronal Activity Following the Chronic Stress

Although it is well established that the increase in NA release in the brain is the acute response to the stress, NA has been suggested to regulate the cognition, motivation and social interactions (Terbeck et al., 2016). It has been demonstrated that the neuronal degenerations in the LC are caused by chronic stress (Nakamura et al., 1989, 1991; Nakamura, 1991). LC neurons dynamically alter their terminal morphology in rats exposed to one or two weeks of the stress (Nakamura et al., 1989). Axonal retraction or degeneration of central noradrenergic neurons may also be involved in the pathophysiology of MDD (Nakamura et al., 1989). When animals receive prolonged severe stress, LC neurons in some groups of the animals causes axonal retraction or degeneration in the cerebral cortex (Nakamura, 1991). These results imply that the cumulative stress responses or activation of noradrenergic neurons during long-term stress environments results in the impairment of noradrenergic neurons and exhibit the depressive-like behavior. Recently, it has been also reported that the HPA-axis independent depressive-like behavior is observed after the long-term (6 weeks) light deprivation in rats which is accompany with the apparent apoptosis of LC noradrenergic neurons with a significant decrease in the number of cortical noradrenergic synaptic boutons (Gonzalez and Aston-Jones, 2008). Light deprivation did not affect body weight gain or adrenal weight and no changes in plasma adrenocorticotropic hormone or corticosterone after the exposure of the light deprivation for 6 weeks (Gonzalez and Aston-Jones, 2008). Since chronic light deprivation-induced depressive behavior is not accompanied with the central stress responses, neurobiological and neurochemical alterations during depression may be similar with the reserpine-induced depression (Bein, 1978). Deletion of NA transporter leads to higher concentration of NA (Wang et al., 1999) and more resistant to the stress-induced depressive-like changes in behavior compared to wild type mice (Haenisch et al., 2009). Therefore, it is reasonable to believe that such degenerative noradrenergic neurons in the patients with MDD and drugs effects of antidepressants on central noradrenergic neurotransmission contribute to therapeutic actions may require the NRIs. Evidence came from the animal study showing that the lesions to the noradrenergic LC interfere with the antidepressant effects of the desipramine in animals (Danysz et al., 1985). LC in humans and rats possesses high number of binding sites for the proteins to which antidepressant compound bind, that is, NA transporter and serotonin transporters suggesting that the LC is a target for antidepressants NRIs (Richards et al., 1992; Klimek et al., 1997).

Role of Noradrenergic Receptor Subtypes Following a Chronic Treatment with Antidepressants

The mechanisms of action of antidepressant are not very well understood during depressive mood in LC neurons. While SSRIs is popular and focused on serotoninergic pathways in MDD, skepticism about their effectiveness due to patients either fail to respond or incomplete response, and prolong occurrence of residual symptoms prompt researchers and clinicians to think about the role of NA, dopamine and other systems in MDD (Nierenberg and DeCecco, 2001). Three significant issues are still contentious related to NA and mechanism by which antidepressant treatment of MDD work are i) why there is delay in onset of action of monoamine reuptake inhibitors? ii) what is the significance of stress-induced activation of the LC noradrenergic system during antidepressant treatment? and iii) what is the mechanism of action between brain NA and 5-hydroxytryptamine systems and its significance for antidepressant? Evidence gain from animal and human studies indicate that the dopamine and NA systems play crucial roles in the therapeutic effects of antidepressants (Nutt, 2006; Kasper

and Hamon, 2009). Moreover, dual-acting antidepressants, such as serotonin NA reuptake inhibitors (SNRIs) and dopamine NA reuptake inhibitors are clinician's choice because of their broad range pharmacological intervention. Since the multi-system acting monoaminergic pathways drugs have direct effects on more than one system, it is the preferred choice of antidepressants therapies for reducing residual symptoms and remission (Nemeroff et al., 2002; Smith et al., 2002). It has been suggested that the chronic administration of tricyclic antidepressants-induced down regulation of α_2-adrenoceptor results in the facilitation of NA release (Cottingham et al., 2015). Indeed this could be the possible reason that the tricyclic antidepressants have a therapeutic lag time extending a week to a month by reaching their therapeutic effect. In contrast, β_1-adrenoceptor is downregulated by chronic treatment of NRIs (Holoubek et al., 2004). It had been suggested that the down-regulation of β-adrenoceptor sensitivity is associated with the effect of antidepressant (Crews et al., 1981; Sulser, 1987) which is supported by the works of several groups showing that the SSRIs also down-regulates β-adrenoceptors in rat brain following chronic exposure to fluoxetine examined by autoradiographic techniques (Wamsley et al., 1987). Moreover, desipramine-induced elevated concentration of extracellular NA downregulates the β-adrenoceptors (Seo et al., 1999). Earlier studies demonstrated that intravenous injection of phencyclidine (PCP) (Raja and Guyenet, 1980) or MK-801 (Murase et al., 1992) also decreases the firing rate of LC neurons through inhibiting the α_2-adrenoceptors without affecting the serotonergic neurons (Raja and Guyenet, 1980). In addition, the NMDA receptor subunit gene is highly expressed in LC in the patients with MDD (Chandley et al., 2014), indicating that the higher NMDA receptor density in LC disrupts the glutamatergic-noradrenergic interaction and impaired in patients with MDD. Interestingly, earlier study have already demonstrated that the down regulation of cortical β_1-adrenoceptors was induced by chronic treatment with functional NMDA antagonists, which has similar effect like classical NRI antidepressants (Paul et al., 1992) (See also below). Hyperactivity of NMDA receptor causes the neuronal death or impair the neuronal function due to the Ca^{2+} overload into the neurons (Hardingham and Bading, 2003) and there is high possibility that this property of NMDA receptor hyperactivity-induced neuronal death might be related to the chronic stress-induced neuronal degeneration in the LC (Nakamura et al., 1989, 1991; Nakamura, 1991) and this pathophysiology may be considered to be one of antidepressant effect (Paul et al., 1992). Earlier study suggested that the chronic electroshock caused upregulation of α_1-adrenoceptors in the frontal cortex but not in the hippocampus while chronic desipramine administration did not alter the α_1-adrenoceptors density or mRNA expression level of α_1-adrenoceptors in the cerebral cortex (Kreiner et al., 2011). Therefore, reviewing the different role of adrenergic receptor subtypes during antidepressant treatment is important for understanding the relationship between NA and MDD.

Contribution of Antidepressant-Induced Increase in NA and Associated Adult Hippocampal Neurogenesis

Stress causes the remodeling of neural architecture including the dendritic shrinkage and the spine loss in hippocampus (McEwen et al., 2015), and major depression is associated with hippocampal atrophy within the central nervous system (Sapolsky, 2001; McEwen et al., 2015; Aizenstein et al., 2016). Numerous studies have suggested that chronic antidepressant treatment increases neurogenesis in adult rat hippocampus (Malberg et al., 2000) and MDD patients (Johnson et al., 2008, 2012). Increased cell proliferation and neuronal number are thought to be a mechanism of antidepressant which can reverse the stress-induced shrinkage of hippocampal volume and neuronal loss in hippocampus (Malberg et al., 2000; Johnson et al., 2008; Porterfield et al., 2012). Recent studies demonstrated that NA activated the neurogenic precursors and stem cells *via* β_3-adrenergic receptors (Jhaveri et al., 2010). The facilitation of NA release by the α_2-adrenoceptor antagonist dexefaroxan enhances hippocampal neurogenesis by increasing the survival and differentiation of new granule cells in dentate gyrus (DG) (Rizk et al., 2006). In addition, increase in the NA at the synapses by reboxetine or tranylcypromine, a monoamine oxidase inhibitor; increase the neurogenesis in the adult rats (Malberg et al., 2000). Therefore, there is possibility that antidepressant-induced increase in the neurogenesis in hippocampus is mediated by β_3-adrenergic receptor.

The contribution of antidepressants to the noradrenergic receptor activation and the expression of brain derived neurotrophic factor (BDNF)

Over past 20 years, the BDNF related neurogenesis has been suggested as effect of antidepressant action, because the BDNF has been shown to promote the differentiation and survival of neurons during development and in adult brain (Memberg and Hall, 1995). Upregulation of BDNF in hippocampus by antidepressant is associated with antidepressant reverse action against the stress-induce morphological changes and reduced neuronal proliferations in hippocampus (Nibuya et al., 1995; Chen et al., 2001). On the other hand, IL-1β has been suggested to downregulate BDNF expression in hippocampus and suppresses the induction of long-term potentiation (LTP) (Tong et al., 2012; Prieto et al., 2015). Indeed, reduced level of BDNF in hippocampus is observed after the repeated stress than single stress (Tamburella et al., 2010) (for details see **Figure 2**). Consistent with these findings, rapid antidepressant action by antidepressant also increases the BDNF expression and hippocampal neurogenesis (Yang et al., 2015; Sun et al., 2016). The cyclic adenosine mono-phosphate (cAMP) signaling cascade is an upstream of BDNF gene, which is transcriptional target of cAMP response element binding (CREB) protein *via* protein kinase A (PKA) (**Figure 2**). In addition, increase in the

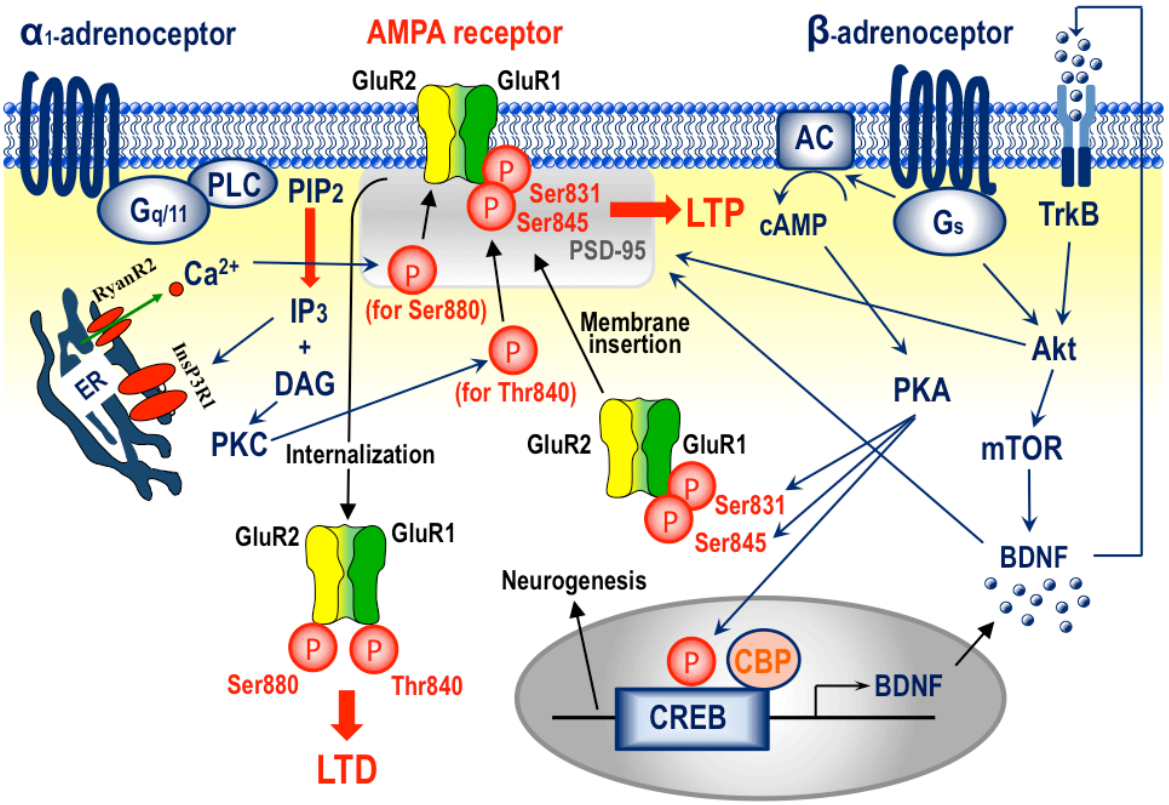

Figure 2 Role of adrenergic receptor on AMPA receptor trafficking-induced synaptic plasticity.
A schema showing the hypothesis of antidepressant-induced activation of α_2-adrenoceptor stimulation following the noradrenaline (NA)-reuptake inhibitors (NRIs)-blocked NA transporter at the presynaptic side. Enhanced released of NA stimulated the β_3-adrenoceptor which promotes the induction of brain derived neurotrophic factor (BDNF) expression and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking signaling. β_3-adrenoceptor is coupled with Gs protein which activates the adenylyl cyclase (AC) on the plasma membrane. AC activation produces the cyclic AMP (cAMP) which regulates the protein kinase A (PKA). PKA phosphorylates the cAMP response element-binding protein (CREB) which regulates the transcription of the BDNF. Gs protein coupled receptor activates another signal transduction mechanisms, such as phosphoinositide-3 kinase (PI3K) pathway which phosphorylates the Akt. Activated Akt phosphorylates the mammalian target of rapamycin (mTOR) which leads the translation of BDNF. A BDNF is capable of increasing the mRNA expression of glutamate receptor (GluR)1 and GluR2 subunit of AMPA receptor through interacting with the TrkB, a receptor of BDNF and promote the synaptic localization of GluR1 *via* transportation of postsynaptic density (PSD)-95 protein from the soma to the dendritic regions to anchor the GluR1 at the synaptic membrane in a PI3K-AKT-dependent process. This process also plays a role in maintaining the long-term potentiation (LTP) which is thought to be an effect of antidepressants in hippocampus. ER: Endoplasmic reticulum.

expression of BDNF is implicated in the effect of antidepressant (Lee and Kim, 2008; Yoshimura et al., 2009; Cattaneo et al., 2013). It has been also reported that new generation antidepressant candidate increases the BDNF through activation of mammalian target of rapamycin (mTOR) which is related theα-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking (Caldeira et al., 2007; Wang et al., 2012) and induction of LTP in hippocampus (Liu et al., 2012; Zhou et al., 2014). In addition, β-adrenoceptor stimulation induces the cAMP response and the pretreatment of β_3-adrenoceptor agonist; amibegron (SR58611A) prevents the restraint stress-induced increase in immobility time during forced swimming test and the down-regulation of BDNF mRNA in hippocampus (Consoli et al., 2007; Tamburella et al., 2010). The cAMP signaling could be accelerated by the Gαs-protein coupled β_3-adrenoceptor stimulation and activate the PKA which activate the CREB phosphorylation (Sala et al., 2000) (**Figure 2**). These findings support the hypothesis that the presence of NA at the synapses in hippocampus is important for antidepressant action at least for mediating the cAMP/PKA/CREB/BDNF (for details see **Figure 2**) pathways which might regulate the AMPA receptor trafficking (**Figure 2**). Considering that antidepressants down regulates only β_1-adrenoceptor in a month later (Kitada et al., 1986; Hosoda and Duman, 1993) and antidepressant action increases the BDNF expression and hippocampal neurogenesis (Yang et al., 2015; Sun et al., 2016) which may be mediated by β_3-adrenoceptor activation; specific β_3-adrenoceptor activation seems to be important for antidepressant effects. However, three weeks of SSRI treatment, for example, escitalopram administration reduces the transcript levels of BDNF mRNA in the hippocampus, although one week of escitalopram administration increases BDNF mRNA (Alboni et al., 2010). These contradictory results, warrant further research to know precise locations and the timing of BDNF action for increasing the hippocampal neurogenesis.

Table 1 Changes in receptor activity by stress

Receptor	Stressor or modification	Changes	Works	Target area	Effects	Reference
α_1 Adrenergic receptors	LPS	Activation	Downregulation of AMPA receptors	Prefrontal cortex and ventral tegmenntal area	Depression	Sekio and Seki (2015)
	Chronic electroshock caused	Upregulation	Not stated	Frontal cortex cerebral cortex	Not stated	Kreiner et al. (2011)
	Immobilized stress	Activation	LC neuronal activations	CRF from the CeA	Aversion	McCall et al. (2015)
α_2 Adrenergic receptors	Flinders Sensitive Line	Decreased	Disinhibition of NA release	LC neuronal area	Depression	Landau et al. (2015)
	Uncontrollable electrical shock	Decreased	Disinhibition of NA release	LC neuronal area	Depression	Weiss and Simson (1988)
β Adrenergic receptors	Immobilized stress	Activation	LC neuronal activations	CRF from the CeA	Anxiety	McCall et al. (2015)
	i.c.v. administration of isoproterenol	Activation	IL-1beta production in amygdale	Hypothalamus	Not stated	Porterfield et al. (2012)
	Escherichia coli	Activation	IL-1beta production	Brainstem	Not stated	Johnson et al. (2008)

LPS: Lipopolysaccharides; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LC: locus coeruleus; CRF: corticotrophin-releasing factor; CeA: central nucleus of the amygdala; NA: noradrenaline; IL: interleukin.

Table 2 Changes in receptor activity by antidepressants

Receptor	Antidepressant	Changes	Works	Target area	Effects	References
α Adrenergic receptors	Citalopram	No change	N/A	Frontal cortex cerebral cortex	Not stated	Kreiner et al. (2011)
α_2 Adrenergic receptors	Tricyclic antidepressants	Down regulation	LC neuronal activations and increase NA release	LC neuronal area	Improve depression	Cottingham et al., (2015)
	PCP or MK-801	Inhibit	Decreases the firing rate of LC neurons	LC neuronal area	Not stated	Raja and Guyenet, (1980)
β Adrenergic receptors	Tricyclic antidepressants	Down regulation	N/A	Hippocampus	Improve depression	Holoubek et al. (2004)
	SNRI	Down regulation	N/A	Hippocampus	Improve depression	Sulser (1987)
	Desipramine and phenoxybenzamine	Down regulation	N/A	Cortex	Improve depression	Crews et al. (1981)
	SSRIs	Down regulation	N/A	Serotonergic system	Improve depression	Wamsley et al., (1987)
	Desipramine	Down regulation	N/A	..	Improve depression	Seo et al. (1999)
	1-aminocyclopropane-carboxylic acid (ACPC) and MK-801	Down regulation	N/A	Cortex	Improve depression	Paul et al. (1992)
β_1 Adrenergic receptors	Desipramine	Down regulation	N/A	i.c.v. administration	Improve depression	Kitada et al. (1986)
	Imipramine	7–14 days increasing and 18–21 days decreasing levels of beta 1AR mRNA	N/A	Frontal cortex	Not stated	Hosoda and Duman (1993)
NMDA receptor	Ketamine	Up regulation	Inhibiton of LC neuronal	LC neuronal area	Improve depression	Chandley et al. (2014)

N/A: Not applicable; LC: locus coeruleus; NA: noradrenaline; SSRIs: selective serotonin reuptake inhibitors; i.c.v.: intracerebroventricular; NMDA: N-methyl-D-aspartic acid.

Conclusion

Activation of LC and release of NA for exciting neurons throughout the brain has been recognized as part of the response to stress-induced depression. Chronic stress induces activation of LC and HPA excitatory system which is finally involved in the development of depressive symptoms (**Figure 1**). We have demonstrated that blockade of central α_1-receptors have prevented the LPS induced depressive-like behavior (Sekio and Seki, 2015). There is strong and growing evidence that the stress causes the upregulation/stimulation of α_1-adrenoceptor in the prefrontal cortex (Kreiner et al., 2011; Sekio and Seki, 2015). Chronic treatment of NRI-induced sustained increase in NA causes the downregulation of β_1-adrenoceptor in the hippocampus (Paul et al., 1992). The intra-clonidine (α_2-adrenoceptors agonist), infusion into LC area could acutely reverse the depressive like state in stress-induced animals which shows the higher activity

of LC neurons due to the lower postsynaptic inhibitory α_2-receptors (Weiss and Simson, 1988). However, chronic stress causes the dysfunction of LC neurons, which is the target of MDD treatment (Frodl et al., 2012). Therefore, the downregulation of α_2-adrenoceptor-induced disinhibition of NA release, following the chronic treatment of classical antidepressants is currently most reliable mechanism of classical antidepressants (**Figure 2**). In addition, NRI-mediated increase of NA concentration in the synaptic cleft may enhance BDNF expression in the dentate gyrus (DG) of hippocampus *via* β_3-adrenoceptor stimulation (**Figure 2**). This idea is supported by the fact that intra-hippocampal infusion of BDNF exerts an antidepressant effect in rats which exhibited depression-like symptoms after repeated inescapable foot shock (Shirayama et al., 2002). β_3-adrenoceptor-induced neurogenesis in the DG (Jhaveri et al., 2010) and the prevention of stress-induced decrease in the BDNF expression suppresses the induction of LTP *via* β_3-adrenoceptor in the hippocampus may be one of the targets of NRI for MDD (Tamburella et al., 2010). Taken together, combination stress-induced transient activation of α_1-adrenoceptors and activation of HPA axis which are due to the stress caused the higher activation of LC neurons might be the risk for development of MDD (**Table 1**), while the down regulation of both α_2-adrenoceptor in LC area, β_1-adrenoceptor in the hippocampus, and the β_3-adrenoceptor-induced neurogenesis in the DG following the chronic treatment of antidepressant might be involved in the antidepressant effects (**Table 2** and **Figure 2**). However, more work is required to clearly understand how chronic stress leads to dysfunction of LC neurons following the activation as an acute response. Further work is needed to elucidate mechanisms of chronic stress-induced dysfunction of LC neuron along with better understanding of role of each subtype of noradrenergic receptor during stress for preventing the development of stress-induced major depression. Taken together, we think that facilitation of brain noradrenergic neurotransmission may represent a more fundamental means to achieve maximal response in stress induced MDD than hitherto understood.

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References

Aguilera G (2011) HPA axis responsiveness to stress: implications for healthy aging. Exp Gerontol 46:90-95.
Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, Jellinger KA, Kruglov LS, Meshandin IA, Mijajlovic MD, Niklewski G, Pospos S, Raju K, Richter K, Steffens DC, Taylor WD, Tene O (2016) Vascular depression consensus report - a critical update. BMC Med 14:161.
Alboni S, Benatti C, Capone G, Corsini D, Caggia F, Tascedda F, Mendlewicz J, Brunello N (2010) Time-dependent effects of escitalopram on brain derived neurotrophic factor (BDNF) and neuroplasticity related targets in the central nervous system of rats. Eur J Pharmacol 643:180-187.
Basharat S, Parker JA, Murphy KG, Bloom SR, Buckingham JC, John CD (2014) Leptin fails to blunt the lipopolysaccharide-induced activation of the hypothalamic-pituitary-adrenal axis in rats. J Endocrinol 221:229-234.
Bay-Richter C, Janelidze S, Hallberg L, Brundin L (2011) Changes in behaviour and cytokine expression upon a peripheral immune challenge. Behav Brain Res 222:193-199.
Bein HJ (1978) Prejudices in pharmacology and pharmacotherapy: reserpine as a model for experimental research in depression. Pharmakopsychiatr Neuropsychopharmakol 11:289-293.
Bluthe RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, Dantzer R (1994) Synergy between tumor necrosis factor alpha and interleukin-1 in the induction of sickness behavior in mice. Psychoneuroendocrinology 19:197-207.
Borsody MK, Weiss JM (2002) Peripheral endotoxin causes long-lasting changes in locus coeruleus activity via IL-1 in the brain. Acta Neuropsychiatr 14:303-321.
Borson S, McDonald GJ, Gayle T, Deffebach M, Lakshminarayan S, VanTuinen C (1992) Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. Psychosomatics 33:190-201.
Caldeira MV, Melo CV, Pereira DB, Carvalho R, Correia SS, Backos DS, Carvalho AL, Esteban JA, Duarte CB (2007) Brain-derived neurotrophic factor regulates the expression and synaptic delivery of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. J Biol Chem 282:12619-12628.
Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM (2013) Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology 38:377-385.
Chandley MJ, Szebeni A, Szebeni K, Crawford JD, Stockmeier CA, Turecki G, Kostrzewa RM, Ordway GA (2014) Elevated gene expression of glutamate receptors in noradrenergic neurons from the locus coeruleus in major depression. Int J Neuropsychopharmacol 17:1569-1578.
Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50:260-265.
Chuluunkhuu G, Nakahara N, Yanagisawa S, Kamae I (2008) The efficacy of reboxetine as an antidepressant, a meta-analysis of both continuous (mean HAM-D score) and dichotomous (response rate) outcomes. Kobe J Med Sci 54:E147-158.
Consoli D, Leggio GM, Mazzola C, Micale V, Drago F (2007) Behavioral effects of the beta3 adrenoceptor agonist SR58611A: is it the putative prototype of a new class of antidepressant/anxiolytic drugs? Eur J Pharmacol 573:139-147.
Cottingham C, Ferryman CJ, Wang Q (2015) α2 adrenergic receptor trafficking as a therapeutic target in antidepressant drug action. Prog Mol Biol Transl Sci 132:207-225.
Crews FT, Paul SM, Goodwin FK (1981) Acceleration of beta-receptor desensitization in combined administration of antidepressants and

phenoxybenzamine. Nature 290:787-789.
Curtis AL, Bello NT, Connolly KR, Valentino RJ (2002) Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. J Neuroendocrinol 14:667-682.
Danysz W, Kostowski W, Hauptmann M (1985) Evidence for the locus coeruleus involvement in desipramine action in animal models of depression. Pol J Pharmacol Pharm 37:855-864.
de Kloet ER, Derijk RH, Meijer OC (2007) Therapy Insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? Nat Clin Pract Endocrinol Metab 3:168-179.
Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC (2009) The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. NeuroImage 47:864-871.
Delfs JM, Zhu Y, Druhan JP, Aston-Jones GS (1998) Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res 806:127-140.
Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67:446-457.
Dubé S, Dellva MA, Jones M, Kielbasa W, Padich R, Saha A, Rao P (2010) A study of the effects of LY2216684, a selective norepinephrine reuptake inhibitor, in the treatment of major depression. J Psychiatr Res 44:356-363.
Dunn AJ, Wang J, Ando T (1999) Effects of cytokines on cerebral neurotransmission. Comparison with the effects of stress. Adv Exp Med Biol 461:117-127.
Eshkevari L, Mulroney SE, Egan R, Lao L (2015) Effects of acupuncture, RU-486 on the hypothalamic-pituitary-adrenal axis in chronically stressed adult male rats. Endocrinology 156:3649-3660.
Feleder C, Perlik V, Blatteis CM (2007) Preoptic norepinephrine mediates the febrile response of guinea pigs to lipopolysaccharide. Am J Physiol Regul Integr Comp Physiol 293:R1135-1143.
Ferguson JM, Mendels J, Schwart GE (2002) Effects of reboxetine on Hamilton depression rating scale factors from randomized, placebo-controlled trials in major depression. Int Clin Psychopharmacol 17:45-51.
Ferguson JM, Wesnes KA, Schwartz GE (2003) Reboxetine versus paroxetine versus placebo: effects on cognitive functioning in depressed patients. Int Clin Psychopharmacol 18:9-14.
Frazer A, Benmansour S (2002) Delayed pharmacological effects of antidepressants. Mol Psychiatry 7 Suppl 1:S23-S28.
Frenois F, Moreau M, O'Connor J, Lawson M, Micon C, Lestage J, Kelley KW, Dantzer R, Castanon N (2007) Lipopolysaccharide induces delayed FosB/DeltaFosB immunostaining within the mouse extended amygdala, hippocampus and hypothalamus, that parallel the expression of depressive-like behavior. Psychoneuroendocrinology 32:516-531.
Frodl T, Carballedo A, Hughes MM, Saleh K, Fagan A, Skokauskas N, McLoughlin DM, Meaney J, O'Keane V, Connor TJ (2012) Reduced expression of glucocorticoid-inducible genes GILZ and SGK-1: high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. Transl Psychiatry 2:e88.
George SA, Knox D, Curtis AL, Aldridge JW, Valentino RJ, Liberzon I (2013) Altered locus coeruleus-norepinephrine function following single prolonged stress. Eur J Neurosci 37:901-909.
Georgotas A, McCue RE, Friedman E, Cooper TB (1987) Response of depressive symptoms to nortriptyline, phenelzine and placebo. Br J Psychiatry 151:102-106.
Ginsberg AB, Campeau S, Day HE, Spencer RL (2003) Acute glucocorticoid pretreatment suppresses stress-induced hypothalamic-pituitary-adrenal axis hormone secretion and expression of corticotropin-releasing hormone hnRNA but does not affect c-fos mRNA or fos protein expression in the paraventricular nucleus of the hypothalamus. J Neuroendocrinol 15:1075-1083.
Gonzalez MM, Aston-Jones G (2008) Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. Proc Natl Acad Sci U S A 105:4898-4903.
Gourley SL, Wu FJ, Kiraly DD, Ploski JE, Kedves AT, Duman RS, Taylor JR (2008) Regionally specific regulation of ERK MAP kinase in a model of antidepressant-sensitive chronic depression. Biol Psychiatry 63:353-359.
Haenisch B, Bilkei-Gorzo A, Caron MG, Bonisch H (2009) Knockout of the norepinephrine transporter and pharmacologically diverse antidepressants prevent behavioral and brain neurotrophin alterations in two chronic stress models of depression. J Neurochem 111:403-416.
Hajos M, Fleishaker JC, Filipiak-Reisner JK, Brown MT, Wong EH (2004) The selective norepinephrine reuptake inhibitor antidepressant reboxetine: pharmacological and clinical profile. CNS Drug Rev 10:23-44.
Hardingham GE, Bading H (2003) The Yin and Yang of NMDA receptor signalling. Trends Neurosci 26:81-89.
Holoubek G, Noldner M, Treiber K, Muller WE (2004) Effect of chronic antidepressant treatment on beta-receptor coupled signal transduction cascade. Which effect matters most? Pharmacopsychiatry 37 Suppl 2:S113-119.
Hosoda K, Duman RS (1993) Regulation of beta 1-adrenergic receptor mRNA and ligand binding by antidepressant treatments and norepinephrine depletion in rat frontal cortex. J Neurochem 60:1335-1343.
Ishizuka Y, Ishida Y, Kunitake T, Kato K, Hanamori T, Mitsuyama Y, Kannan H (1997) Effects of area postrema lesion and abdominal vagotomy on interleukin-1 beta-induced norepinephrine release in the hypothalamic paraventricular nucleus region in the rat. Neurosci Lett 223:57-60.
Itoi K, Sugimoto N (2010) The brainstem noradrenergic systems in stress, anxiety and depression. J Neuroendocrinol 22:355-361.
Jhaveri DJ, Mackay EW, Hamlin AS, Marathe SV, Nandam LS, Vaidya VA, Bartlett PF (2010) Norepinephrine directly activates adult hippocampal precursors via beta3-adrenergic receptors. J Neurosci 30:2795-2806.
Johnson JD, Cortez V, Kennedy SL, Foley TE, Hanson H 3rd, Fleshner M (2008) Role of central beta-adrenergic receptors in regulating proinflammatory cytokine responses to a peripheral bacterial challenge. Brain Behav Immun 22:1078-1086.
Kasper S, Hamon M (2009) Beyond the monoaminergic hypothesis: agomelatine, a new antidepressant with an innovative mechanism of action. World J Biol Psychiatry 10:117-126.
Katon W, Sullivan M, Russo J, Dobie R, Sakai C (1993) Depressive symptoms and measures of disability: a prospective study. J Affect Disord 27:245-254.
Kaur D, Cruess DF, Potter WZ (1998) Effect of IL-1alpha on the release of norepinephrine in rat hypothalamus. J Neuroimmunol 90:122-127.
Kitada Y, Miyauchi T, Kosasa T, Satoh S (1986) The significance of beta-adrenoceptor down regulation in the desipramine action in the forced swimming test. Naunyn Schmiedebergs Arch Pharmacol 333:31-35.
Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA (1997) Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 17:8451-8458.
Kratochvil CJ, Newcorn JH, Arnold LE, Duesenberg D, Emslie GJ, Quintana H, Sarkis EH, Wagner KD, Gao H, Michelson D, Biederman J (2005) Atomoxetine alone or combined with fluoxetine for treating ADHD with comorbid depressive or anxiety symptoms. J Am Acad Child Adolesc Psychiatry 44:915-924.
Kravets JL, Reyes BA, Unterwald EM, Van Bockstaele EJ (2015) Direct targeting of peptidergic amygdalar neurons by noradrenergic afferents: linking stress-integrative circuitry. Brain Struct Funct 220:541-558.
Kreiner G, Zelek-Molik A, Kowalska M, Bielawski A, Antkiewicz-Michaluk L, Nalepa I (2011) Effects of the noradrenergic neurotoxin DSP-4 on the expression of alpha1-adrenoceptor subtypes after antidepressant treatment. Pharmacol Rep 63:1349-1358.
Krugers HJ, Zhou M, Joels M, Kindt M (2011) Regulation of excitatory synapses and fearful memories by stress hormones. Front Behav Neurosci 5:62.
Kurosawa N, Shimizu K, Seki K (2016) The development of depression-like behavior is consolidated by IL-6-induced activation of locus coeruleus neurons and IL-1beta-induced elevated leptin levels in mice. Psychopharmacology (Berl) 233:1725-1737.
Landau AM, Phan JA, Iversen P, Lillethorup TP, Simonsen M, Wegener G, Jakobsen S, Doudet DJ (2015) Decreased in vivo α2 adrenoceptor binding in the Flinders Sensitive Line rat model of depres-

sion. Neuropharmacology 91:97-102.
Lee HY, Kim YK (2008) Plasma brain-derived neurotrophic factor as a peripheral marker for the action mechanism of antidepressants. Neuropsychobiology 57:194-199.
Leonard BE, Song C (2002) Changes in the immune system in rodent models of depression. Int J Neuropsychopharmacol 5:345-356.
Linthorst AC, Flachskamm C, Holsboer F, Reul JM (1996) Activation of serotonergic and noradrenergic neurotransmission in the rat hippocampus after peripheral administration of bacterial endotoxin: involvement of the cyclo-oxygenase pathway. Neuroscience 72:989-997.
Liu RJ, Lee FS, Li XY, Bambico F, Duman RS, Aghajanian GK (2012) Brain-derived neurotrophic factor Val66Met allele impairs basal and ketamine-stimulated synaptogenesis in prefrontal cortex. Biol Psychiatry 71:996-1005.
Lu Y, Simpson KL, Weaver KJ, Lin RC (2012) Differential distribution patterns from medial prefrontal cortex and dorsal raphe to the locus coeruleus in rats. Anat Rec (Hoboken) 295:1192-1201.
Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104-9110.
McCall JG, Al-Hasani R, Siuda ER, Hong DY, Norris AJ, Ford CP, Bruchas MR (2015) CRH engagement of the locus coeruleus noradrenergic system mediates stress-induced anxiety. Neuron 87:605-620.
McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C (2015) Mechanisms of stress in the brain. Nat Neurosci 18:1353-1363.
McEwen BS, Biron CA, Brunson KW, Bulloch K, Chambers WH, Dhabhar FS, Goldfarb RH, Kitson RP, Miller AH, Spencer RL, Weiss JM (1997) The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. Brain Res Brain Res Rev 23:79-133.
Memberg SP, Hall AK (1995) Proliferation, differentiation, and survival of rat sensory neuron precursors in vitro require specific trophic factors. Mol Cell Neurosci 6:323-335.
Merali Z, Lacosta S, Anisman H (1997) Effects of interleukin-1beta and mild stress on alterations of norepinephrine, dopamine and serotonin neurotransmission: a regional microdialysis study. Brain Res 761:225-235.
MohanKumar SM, MohanKumar PS, Quadri SK (1999) Lipopolysaccharide-induced changes in monoamines in specific areas of the brain: blockade by interleukin-1 receptor antagonist. Brain Res 824:232-237.
Montgomery S, Ferguson JM, Schwartz GE (2003) The antidepressant efficacy of reboxetine in patients with severe depression. J Clin Psychopharmacol 23:45-50.
Murase S, Nisell M, Grenhoff J, Svensson TH (1992) Decreased sensory responsiveness of noradrenergic neurons in the rat locus coeruleus following phencyclidine or dizocilpine (MK-801): role of NMDA antagonism. Psychopharmacology (Berl) 109:271-276.
Nakamura S (1991) Axonal sprouting of noradrenergic locus coeruleus neurons following repeated stress and antidepressant treatment. Prog Brain Res 88:587-598.
Nakamura S, Sakaguchi T, Aoki F (1989) Electrophysiological evidence for terminal sprouting of locus coeruleus neurons following repeated mild stress. Neurosci Lett 100:147-152.
Nakamura S, Kitayama I, Murase S (1991) Electrophysiological evidence for axonal degeneration of locus coeruleus neurons following long-term forced running stress. Brain Res Bull 26:759-763.
Nelson JC, Mazure CM, Jatlow PI, Bowers MB Jr, Price LH (2004) Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry 55:296-300.
Nemeroff CB, Schatzberg AF, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV (2002) Duloxetine for the treatment of major depressive disorder. Psychopharmacol Bull 36:106-132.
Nibuya M, Morinobu S, Duman RS (1995) Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 15:7539-7547.
Nierenberg AA, DeCecco LM (2001) Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. J Clin Psychiatry 62 Suppl 16:5-9.
Nutt DJ (2006) The role of dopamine and norepinephrine in depression and antidepressant treatment. J Clin Psychiatry 67 Suppl 6:3-8.
Pacak K, Palkovits M, Kvetnansky R, Kopin IJ, Goldstein DS (1993) Stress-induced norepinephrine release in the paraventricular nucleus of rats with brainstem hemisections: a microdialysis study. Neuroendocrinology 58:196-201.
Pacak K, Palkovits M, Kvetnansky R, Yadid G, Kopin IJ, Goldstein DS (1995) Effects of various stressors on in vivo norepinephrine release in the hypothalamic paraventricular nucleus and on the pituitary-adrenocortical axis. Ann N Y Acad Sci 771:115-130.
Pangallo B, Dellva MA, D'Souza DN, Essink B, Russell J, Goldberger C (2011) A randomized, double-blind study comparing LY2216684 and placebo in the treatment of major depressive disorder. J Psychiatr Res 45:748-755.
Pariante CM (2003) Depression, stress and the adrenal axis. J Neuroendocrinol 15:811-812.
Paul IA, Trullas R, Skolnick P, Nowak G (1992) Down-regulation of cortical beta-adrenoceptors by chronic treatment with functional NMDA antagonists. Psychopharmacology (Berl) 106:285-287.
Pavcovich LA, Ramirez OA (1991) Time course effects of uncontrollable stress in locus coeruleus neuronal activity. Brain Res Bull 26:17-21.
Pencea V, Bingaman KD, Freedman LJ, Luskin MB (2001) Neurogenesis in the subventricular zone and rostral migratory stream of the neonatal and adult primate forebrain. Exp Neurol 172:1-16.
Porterfield VM, Gabella KM, Simmons MA, Johnson JD (2012) Repeated stressor exposure regionally enhances beta-adrenergic receptor-mediated brain IL-1β production. Brain Behav Immun 26:1249-1255.
Prieto GA, Snigdha S, Baglietto-Vargas D, Smith ED, Berchtold NC, Tong L, Ajami D, LaFerla FM, Rebek J, Jr., Cotman CW (2015) Synapse-specific IL-1 receptor subunit reconfiguration augments vulnerability to IL-1beta in the aged hippocampus. Proc Natl Acad Sci U S A 112:E5078-E5087.
Raison CL, Demetrashvili M, Capuron L, Miller AH (2005) Neuropsychiatric adverse effects of interferon-alpha: recognition and management. CNS Drugs 19:105-123.
Raja SN, Guyenet PG (1980) Effects of phencyclidine on the spontaneous activity of monoaminergic neurons. Eur J Pharmacol 63:229-233.
Reynolds CF, 3rd, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ (1999) Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 281:39-45.
Richards JG, Saura J, Ulrich J, Da Prada M (1992) Molecular neuroanatomy of monoamine oxidases in human brainstem. Psychopharmacology (Berl) 106 Suppl:S21-S23.
Rizk P, Salazar J, Raisman-Vozari R, Marien M, Ruberg M, Colpaert F, Debeir T (2006) The alpha2-adrenoceptor antagonist dexefaroxan enhances hippocampal neurogenesis by increasing the survival and differentiation of new granule cells. Neuropsychopharmacology 31:1146-1157.
Sagar SM, Price KJ, Kasting NW, Sharp FR (1995) Anatomic patterns of Fos immunostaining in rat brain following systemic endotoxin administration. Brain Res Bull 36:381-392.
Sala C, Rudolph-Correia S, Sheng M (2000) Developmentally regulated NMDA receptor-dependent dephosphorylation of cAMP response element-binding protein (CREB) in hippocampal neurons. J Neurosci 20:3529-3536.
Sapolsky RM (2001) Depression, antidepressants, and the shrinking hippocampus. Proc Natl Acad Sci U S A 98:12320-12322.
Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10:211-223.
Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122:509-522.
Sekio M, Seki K (2015) Lipopolysaccharide-induced depressive-like behavior is associated with alpha(1)-adrenoceptor dependent down-regulation of the membrane GluR1 subunit in the mouse medial prefrontal cortex and ventral tegmental area. Int J Neuropsychopharmacol 18:pyu005.
Seo DO, Shin CY, Lee CJ, Dailey JW, Reith ME, Jobe PC, Ko KH (1999) Effect of alterations in extracellular norepinephrine on adrenoceptors: a microdialysis study in freely moving rats. Eur J Pharmacol

365:39-46.
Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS (2002) Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 22:3251-3261.
Sirivelu MP, MohanKumar PS, MohanKumar SM (2012) Differential effects of systemic interleukin-1beta on gene expression in brainstem noradrenergic nuclei. Life Sci 90:77-81.
Smagin GN, Swiergiel AH, Dunn AJ (1996) Peripheral administration of interleukin-1 increases extracellular concentrations of norepinephrine in rat hypothalamus: comparison with plasma corticosterone. Psychoneuroendocrinology 21:83-93.
Smith D, Dempster C, Glanville J, Freemantle N, Anderson I (2002) Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 180:396-404.
Sullivan M, Katon W, Russo J, Dobie R, Sakai C (1993) A randomized trial of nortriptyline for severe chronic tinnitus. Effects on depression, disability, and tinnitus symptoms. Arch Intern Med 153:2251-2259.
Sulser F (1987) Serotonin-norepinephrine receptor interactions in the brain: implications for the pharmacology and pathophysiology of affective disorders. J Clin Psychiatry 48 Suppl:12-18.
Sun HL, Zhou ZQ, Zhang GF, Yang C, Wang XM, Shen JC, Hashimoto K, Yang JJ (2016) Role of hippocampal p11 in the sustained antidepressant effect of ketamine in the chronic unpredictable mild stress model. Transl Psychiatry 6:e741.
Swaab DF, Bao AM, Lucassen PJ (2005) The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev 4:141-194.
Tamburella A, Micale V, Leggio GM, Drago F (2010) The beta3 adrenoceptor agonist, amibegron (SR58611A) counteracts stress-induced behavioral and neurochemical changes. Eur Neuropsychopharmacol 20:704-713.
Tanaka M, Yoshida M, Emoto H, Ishii H (2000) Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. Eur J Pharmacol 405:397-406.
Teeling JL, Cunningham C, Newman TA, Perry VH (2010) The effect of non-steroidal anti-inflammatory agents on behavioural changes and cytokine production following systemic inflammation: Implications for a role of COX-1. Brain Behav Immun 24:409-419.
Terbeck S, Savulescu J, Chesterman LP, Cowen PJ (2016) Noradrenaline effects on social behaviour, intergroup relations, and moral decisions. Neurosci Biobehav Rev 66:54-60.
Tong L, Prieto GA, Kramar EA, Smith ED, Cribbs DH, Lynch G, Cotman CW (2012) Brain-derived neurotrophic factor-dependent synaptic plasticity is suppressed by interleukin-1beta via p38 mitogen-activated protein kinase. J Neurosci 32:17714-17724.
Touma C, Bunck M, Glasl L, Nussbaumer M, Palme R, Stein H, Wolferstatter M, Zeh R, Zimbelmann M, Holsboer F, Landgraf R (2008) Mice selected for high versus low stress reactivity: a new animal model for affective disorders. Psychoneuroendocrinology 33:839-862.
Turrin NP, Gayle D, Ilyin SE, Flynn MC, Langhans W, Schwartz GJ, Plata-Salaman CR (2001) Pro-inflammatory and anti-inflammatory cytokine mRNA induction in the periphery and brain following intraperitoneal administration of bacterial lipopolysaccharide. Brain Res Bull 54:443-453.
Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ (2004) Global burden of depressive disorders in the year 2000. Br J Psychiatry 184:386-392.
van Donkelaar EL, Vaessen KR, Pawluski JL, Sierksma AS, Blokland A, Canete R, Steinbusch HW (2014) Long-term corticosterone exposure decreases insulin sensitivity and induces depressive-like behaviour in the C57BL/6NCrl mouse. PLoS One 9:e106960.
Vinkers CH, Joels M, Milaneschi Y, Kahn RS, Penninx BW, Boks MP (2014) Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. Depress Anxiety 31:737-745.
Wakabayashi C, Kiyama Y, Kunugi H, Manabe T, Iwakura Y (2011) Age-dependent regulation of depression-like behaviors through modulation of adrenergic receptor α_1A subtype expression revealed by the analysis of interleukin-1 receptor antagonist knockout mice. Neuroscience 192:475-484.
Wamsley JK, Byerley WF, McCabe RT, McConnell EJ, Dawson TM, Grosser BI (1987) Receptor alterations associated with serotonergic agents: an autoradiographic analysis. J Clin Psychiatry 48 Suppl:19-25.
Wang D, Lin W, Pan Y, Kuang X, Qi X, Sun H (2011) Chronic blockade of glucocorticoid receptors by RU486 enhances lipopolysaccharide-induced depressive-like behaviour and cytokine production in rats. Brain Behav Immun 25:706-714.
Wang G, Gilbert J, Man HY (2012) AMPA receptor trafficking in homeostatic synaptic plasticity: functional molecules and signaling cascades. Neural Plast 2012:825364.
Wang YM, Xu F, Gainetdinov RR, Caron MG (1999) Genetic approaches to studying norepinephrine function: knockout of the mouse norepinephrine transporter gene. Biol Psychiatry 46:1124-1130.
Weber K, Giannakopoulos P, Herrmann FR, Bartolomei J, Digiorgio S, Ortiz Chicherio N, Delaloye C, Ghisletta P, Lecerf T, De Ribaupierre A, Canuto A (2013) Stressful life events and neuroticism as predictors of late-life versus early-life depression. Psychogeriatrics 13:221-228.
Weiss JM, Simson PE (1988) Neurochemical and electrophysiological events underlying stress-induced depression in an animal model. Adv Exp Med Biol 245:425-440.
Weiss JM, Sundar SK, Becker KJ, Cierpial MA (1989) Behavioral and neural influences on cellular immune responses: effects of stress and interleukin-1. J Clin Psychiatry 50 Suppl:43-53; discussion 54-55.
World Health Organization (2017) Depression and other common mental disorders: global health estimates.
Wieczorek M, Dunn AJ (2006) Effect of subdiaphragmatic vagotomy on the noradrenergic and HPA axis activation induced by intraperitoneal interleukin-1 administration in rats. Brain Res 1101:73-84.
Wong ML, Licinio J (2001) Research and treatment approaches to depression. Nat Rev Neurosci 2:343-351.
Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, Hashimoto K (2015) R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry 5:e632.
Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J (2009) Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. Prog Neuropsychopharmacol Biol Psychiatry 33:722-726.
You Z, Luo C, Zhang W, Chen Y, He J, Zhao Q, Zuo R, Wu Y (2011) Pro- and anti-inflammatory cytokines expression in rat's brain and spleen exposed to chronic mild stress: involvement in depression. Behav Brain Res 225:135-141.
Zhao Y, Xie W, Dai J, Wang Z, Huang Y (2009) The varying effects of short-term and long-term corticosterone injections on depression-like behavior in mice. Brain Res 1261:82-90.
Zhao Z, Baros AM, Zhang HT, Lapiz MD, Bondi CO, Morilak DA, O'Donnell JM (2008) Norepinephrine transporter regulation mediates the long-term behavioral effects of the antidepressant desipramine. Neuropsychopharmacology 33:3190-3200.
Zhou QG, Zhu LJ, Chen C, Wu HY, Luo CX, Chang L, Zhu DY (2011) Hippocampal neuronal nitric oxide synthase mediates the stress-related depressive behaviors of glucocorticoids by downregulating glucocorticoid receptor. J Neurosci 31:7579-7590.
Zhou W, Wang N, Yang C, Li XM, Zhou ZQ, Yang JJ (2014) Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur Psychiatry 29:419-423.
Ziegler DR, Cass WA, Herman JP (1999) Excitatory influence of the locus coeruleus in hypothalamic-pituitary-adrenocortical axis responses to stress. J Neuroendocrinol 11:361-369.
Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K (2001) The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun 15:199-226.