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

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; Hajes et al., 2004; Chu, Lukehkhin 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; Ito 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; Aguillera, 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 responsibility 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 Gai protein-coupled inhibitory α2-adrenoceptors in the region of LC in stress-induced animals (Landau et al., 2015). It has also been demonstrated that the α2-adrenoceptors in the LC region were functionally blocked in the stress-induced depressive like state of animals and the intra-clonidine, a α2-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 α2-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 α2-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 α2-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 (Pack 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 (Pack 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 adrenocorticotropin 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 (Aguiera, 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 (Aguiera, 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,
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 endotoxin, 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 (Linthurst 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 α1-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 α1-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 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 α1, α2, 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 isoproteanol, 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 (Smaign et al., 1996; Ishizuka et al., 1997; Meraki 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 adrenocorticotrophic 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 reserpin-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 α1-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, β1-adrenoceptor is downregulated by chronic treatment of NRIs (Holoubek et al., 2004). It had been suggested that the down-regulation of β1-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 α1-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 expressed in LC in the patients with MDD (Chandley et al., 2014).

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 β1-adrenergic receptors (Jhaveri et al., 2010). The facilitation of NA release by the α1-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 β1-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 (Nihaya 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
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 to the AMPA receptor trafficking (Caldeira et al., 2007; Wang et al., 2012) and induction of LTD in hippocampus (Liu et al., 2012; Zhou et al., 2014). In addition, β-adrenoceptor stimulation induces the cAMP response and the pretreatment of β3-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; Tamberella et al., 2010). The cAMP signaling could be accelerated by the Gαs-protein coupled β3-adrenoceptor stimulation and activate the PKA which activate the CREB phosphorylation (Sala et al., 2000) (Figure 2). These findings support the hypothesis that presence of NA at the synapses in hippocampus is important for antidepressant action at least for mediating the cAMP/PKA/CREB/BDNF pathways which regulate the AMPA receptor trafficking (Figure 2). Considering that antidepressants down regulates only β1-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 β3-adrenoceptor activation; specific β3-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.
Depression

Seki and Seki (2015)

Downregulation of CRF from the CeA

Changes

Johnson et al. (2008)

LC neuronal activations

Not stated

Cottingham et al., (2014)

Aversion

Paul et al. (1992)

Targets area

Kreiner et al. (2011)

Depression

McCall et al. (2015)

Improve depression

Kreiner et al. (2011). Chronic treatment of NRI-induced sustained increase in NA causes the downregulation of β2-adrenoceptor in the hippocampus (Paul et al., 1992). The intra-clonidine (α2-adrenoceptors agonist), infusion into LC area could acutely reverse the depressive like state in stress-induced animals which shows the higher activity behavior (Sekio and Seki, 2015). There is strong and growing evidence that the stress causes the upregulation/stimulation of α2-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 β2-adrenoceptor in the hippocampus (Paul et al., 1992). The intra-clonidine (α2-adrenoceptors agonist), infusion into LC area could acutely reverse the depressive like state in stress-induced animals which shows the higher activity

Table 1 Changes in receptor activity by stress

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Stressor or modification</th>
<th>Changes</th>
<th>Works</th>
<th>Target area</th>
<th>Effects</th>
<th>Reference</th>
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<td>α2 Adrenergic receptors</td>
<td>LPS</td>
<td>Activation</td>
<td>Downregulation of AMPA receptors</td>
<td>Prefrontal cortex and ventral tegmental area</td>
<td>Depression</td>
<td>Sekio and Seki (2015)</td>
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<td>Upregulation</td>
<td>Not stated</td>
<td>Frontal cortex</td>
<td>Not stated</td>
<td>Kreiner et al. (2011)</td>
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<td></td>
<td>Immobilized stress</td>
<td>Activation</td>
<td>LC neuronal activations</td>
<td>CRF from the CeA</td>
<td>Depression</td>
<td>McCall et al. (2015)</td>
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<td></td>
<td>Flinders Sensitive Line</td>
<td>Decreased</td>
<td>Disinhibition of NA release</td>
<td>LC neuronal area</td>
<td>Aversion</td>
<td>Landau et al. (2015)</td>
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<tr>
<td></td>
<td>Uncontrollable electrical shock</td>
<td>Decreased</td>
<td>Disinhibition of NA release</td>
<td>LC neuronal area</td>
<td>Depression</td>
<td>Weiss and Simson (1988)</td>
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<tr>
<td>β Adrenergic receptors</td>
<td>i.c.v. administration of isoproterenol Escherichia coli</td>
<td>Activation</td>
<td>LC neuronal activations</td>
<td>CRF from the CeA</td>
<td>Hypothalamus</td>
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<td>Chronic electroshock</td>
<td>Activation</td>
<td>IL-1beta production</td>
<td>Brainstem</td>
<td>Not stated</td>
<td>Johnson et al. (2008)</td>
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</table>

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

<table>
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<th>Changes</th>
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<th>Target area</th>
<th>Effects</th>
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<td>Down regulation</td>
<td>LC neuronal activations and increase NA release</td>
<td>LC neuronal area</td>
<td>Improve depression</td>
<td>Cottingham et al., (2015)</td>
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<td>Decreases the firing rate of LC neurons</td>
<td>LC neuronal area</td>
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<td>Raja and Guyenet, (1980)</td>
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<td>Down regulation</td>
<td>N/A</td>
<td>Hippocampus</td>
<td>Improve depression</td>
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<td>Hippocampus</td>
<td>Improve depression</td>
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<td>Serotonergic system</td>
<td>Improve depression</td>
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<td>Improve depression</td>
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<td>i.c.v. administration</td>
<td>Not stated</td>
<td>Kitada et al. (1986)</td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>Up regulation</td>
<td>Inhibit of LC neuronal</td>
<td>Frontal cortex</td>
<td>Improve depression</td>
<td>Chandy et al. (2014)</td>
</tr>
</tbody>
</table>

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 α2-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 α2-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 β2-adrenoceptor in the hippocampus (Paul et al., 1992). The intra-clonidine (α2-adrenoceptors agonist), infusion into LC area could acutely reverse the depressive like state in stress-induced animals which shows the higher activity

Figure 1

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of LC neurons due to the lower postsynaptic inhibitory α2-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 α2-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 β3-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). β3-adrenoceptor-induced neurogenesis in the DG (Jhaiveri et al., 2010) and the prevention of stress-induced decrease in the BDNF expression suppresses the induction of LTP via β3-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 α1-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 α1-adrenoceptor in LC area, β3-adrenoceptor in the hippocampus, and the β3-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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