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Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression

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Abstract

Uncontrollable stress, a major precipitant of depression in humans and in animal paradigms, impairs hippocampal neurogenesis, which is necessary for the behavioral effects of antidepressants in models of depression that require chronic treatment. However, the mechanisms underlying these anti-neurogenic and behavioral effects of stress have not been elucidated. Proinflammatory cytokines are thought to be contributing factors to stress and have been implicated in stress-related mood disorders such as major depression. In particular, IL-1β has been proposed to be a key mediator in a variety of behavioral actions of stress. Notably, the administration of a IL-1 receptor antagonist (IL-1Ra) blocks the stress-like effects of IL-1β in both cellular and behavioral models. This review highlights the increasing interest in the relationship between IL-1β, neurogenesis, stress and depression, and discusses the potential of IL-1Ra or other cytokine antagonists as new candidates for the treatment of depression.

Keywords

Antidepressant; depression; IL-1Ra; IL-1β; neurogenesis; stress

Introduction

Major epidemiology studies indicate that 16.2% of the US population experience depressive symptoms during their lifetime [1], and that the prevalence of depression is increasing worldwide [2]. In addition, depression produces an estimated socioeconomic cost of greater than US $83.1 billion annually in the US alone; this high cost has made depression a major focus of therapeutic research for more than 50 years [3]. However, despite research efforts, it has been difficult to identify the underlying pathophysiology of depression. Although most available classes of antidepressant medications rapidly increase synaptic levels of monoamines (notably serotonin and norepinephrine) within hours of initial treatment, a therapeutic response to these agents normally occurs after several weeks of daily treatment [4,5]; however, some exceptions have been observed with SSRIs [6].

The hippocampus is one of the key limbic brain regions implicated in depression pathophysiology [7], and is influenced by various pharmacological, behavioral and environmental factors [7,8]. For example, stressful experiences, a major contributing factor to depression in humans, impair hippocampal neurogenesis, which could contribute to the reduced size and function of the hippocampus in patients with depression [8–10]. In

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contrast, antidepressant medications increase the proliferation and survival of newborn neurons in the hippocampus [11], block the anti-neurogenic effects of stress [10,12], and reduce or reverse hippocampal atrophy in patients with depression [9,10]. The regulation of neurogenesis is important, as recent studies have demonstrated that the behavioral effects of antidepressants require increased numbers of newborn hippocampal neurons [11,13].

Interestingly, proinflammatory cytokines such as IL-1β, IL-6 and TNFα can also influence hippocampal neurogenesis [14–16], and the secretion or production of these cytokines increases in stressed individuals and patients with depression [17–19]. In addition, antidepressant medication can normalize the elevated levels of IL-1β, IL-6 and TNFα in patients with depression [17,18,20–24]. Increasing evidence also exists suggesting that the risk of depressive disorders is increased in patients undergoing cytokine or interferon therapy for the treatment of cancer and viral infection [25]. These studies suggest that cytokines or interferons significantly contribute to the depressive effects of stress, as well as the precipitation and maintenance of depression. In this review, the role of IL-1β in the cellular and behavioral actions of stress is discussed and evidence supporting the potential development and use of IL-1β antagonists for the treatment of depression and stress-related mood disorders is presented. These studies contribute to research conducted over two decades supporting the hypothesis that IL-1β, as well as other cytokines, is involved in the pathophysiology and potentially the treatment of depression [18,25,26].

IL-1β: A key mediator of stress responses

In the healthy brain, IL-1β is expressed mainly in the hypothalamus, but is also expressed in the hippocampus, cerebral cortex and thalamus [27]. The cellular sources of IL-1β are reported to be microglia, astrocytes and neurons [27]. IL-1β exerts a wide range of effects through its interaction with the IL-1β receptor, IL-1RI (80 kDa) [27–29], which is localized in several areas of the rodent brain, with the highest expression in hippocampal neurons [30–32]. When IL-1β binds to IL-1RI, the complex associates with an accessory protein (IL-1RacP), and cytoplasmic portions of the IL-1RI/IL-1RacP complex cooperate with other molecules such as MyD88 (myeloid differentiation primary response gene 88) [27–29]. The IL-1RI complex then activates signaling pathways, including NFκB, p42/44 MAPK, p38 MAPK and JNK to exert biological effects such as host defense responses [27]. The IL-1β antagonist IL-1Ra binds primarily to IL-1RI, but does not trigger a biological response because IL-1RacP does not form a complex with IL-1Ra/IL-1RI [27–29] (Figure 1).

The IL-1β/IL-1RI system has been reported to have a role in stress responses and in the pathophysiology of depression. Levels of IL-1β both in the peripheral blood circulation and in the CSF have been demonstrated to be increased in patients exposed to stress and in patients with depression [18,19,22–24]. Notably, the elevation of plasma IL-1β in patients with depression is correlated with the severity, duration and age of onset of depressive symptoms [22,23]. However, there are limitations to the correlation between immune activation and depression, with only one study in a small cohort (n = 13) demonstrating a clear association between elevated IL-1β in the CSF and depression [24], and highly variable results in other immunity measures in patients with depression, such as leukocytosis, increased CD4/CD8 ratios, reduced T- and NK-cell cytotoxicity, and reduced lymphoproliferative response [33]. Preclinical studies have demonstrated that stress increases IL-1β in the CNS in several brain regions, including the hypothalamus and hippocampus [27,34,35], and that central administration of IL-1β produces several stress-like effects, including activation of the hypothalamic-pituitary-adrenal (HPA) axis [36–38], inhibition of hippocampal long-term potentiation [39], downregulation of brain-derived neurotrophic factor (BDNF) [40], and impairment of hippocampal-dependent memory [38]. In contrast, IL-1Ra prevents these stress-like effects [38,40,41] and blocks the despair

caused by inescapable shock [42]. In addition, depressive-like symptoms produced by the administration of LPS in rodent models can be reversed by the chronic administration of some antidepressants such as fluoxetine (SSRI), tianeptine (atypical), imipramine (tricyclic), and desipramine (tricyclic), but not of paroxetine (SSRI) and venlafaxine (SNRI) [43–46]; LPS is a potent activator of the inflammatory response that can increase IL-1β levels in the hippocampus, and thus these observed effects suggest that antidepressants may have an effect on IL-1β.

IL-1β and hippocampal neurogenesis

Studies have demonstrated that hippocampal neurogenesis is impaired by treatment with LPS, irradiation and IFNα [14,47], all of which can increase IL-1β protein levels in the hippocampus [34,47,48]. This finding suggests that IL-1β could underlie the decrease in neurogenesis observed in these various experimental conditions. Some studies have provided direct evidence in support of this hypothesis [16,49]. Using a combination of pharmacological and mutant mouse approaches, it has been demonstrated that IL-1β plays an important role in the inhibitory effects of stress on hippocampal neurogenesis [16]. Specifically, it was demonstrated that the blockade of IL-1RI, either by infusions of IL-1Ra or in IL-1RI null mutant mice, completely blocks the decrease in neurogenesis caused by acute or repeated stress [16]. Studies published by Yirmiya and colleagues have confirmed these findings [49].

IL-1β is also a potent stimulator of the HPA axis [36,37,50], which causes the elevation of adrenal-glucocorticoids, a major mediator of stress and a negative regulator of hippocampal neurogenesis [8,51]. In addition, the study by Yirmiya and colleagues has suggested that IL-1β mediates the anti-neurogenic effects of chronic unpredictable stress (CUS) through the activation of the HPA axis [49] (Figure 2). However, it is also likely that IL-1β directly influences hippocampal progenitors. Using both *in vivo* and *in vitro* studies, it has been demonstrated that IL-1RI is localized to neural progenitor cells in the hippocampus of healthy animals *in vivo* and in isolated cultures of adult hippocampal progenitor cells *in vitro*, and that IL-1β signaling through IL-1RI decreases the proliferation of progenitor cells [16] (Figure 2).

The inhibitory effects of LPS on hippocampal cell proliferation could also occur via the release of IL-1β from activated microglia [52]. Interestingly, microglia can be activated by stress [53,54]. It is also possible that other proinflammatory cytokines, including IL-6 and TNFα, both of which are released from activated microglia, contribute to the suppression of hippocampal progenitor cell proliferation [14,15], although IL-1β is necessary and sufficient for the anti-proliferative effects of stress [16].

IL-1β inhibition of proliferation could result from either a loss of progenitor cells due to cell death, arrest of the cell cycle, or both. There is evidence that IL-1β induces the death of human fetal brain cells and rat oligodendrocyte progenitor cells only when combined with other cytokines such as TNFα or IFNs [55,56]. Cytotoxicity can occur at low concentrations of cytokines as a result of a resistance to growth factors (eg, TNFα-induced resistance to insulin-like growth factor-I) [57]. However, an analysis of DNA degradation (eg, TUNEL [terminal deoxynucleotidyl transferase mediated X-dUTP nick end labeling] staining) demonstrated that IL-1β and/or acute stress does not result in hippocampal cell death *in vivo* or *in vitro* [16]; these results are consistent with those from previous studies [56,58], although there is one study that suggests that severe stress increases apoptosis [59]. Thus, the anti-neurogenic actions of IL-1β are likely to occur via cell cycle arrest, not via cell death. This hypothesis is consistent with results of *in vitro* studies demonstrating that levels of certain cell cycle proteins such as cyclin D1 are decreased by IL-1β [16].

IL-1β and depressive-like behaviors

IL-1β has a key role in depressive-like behaviors, as well as in the cellular actions of stress. Peripheral and central IL-1β administration induces sickness behaviors, including anorexia, weight loss, anhedonia, fatigue, impaired social interaction and memory dysfunction, which are also symptoms observed in patients with depression [16,27,38,50]. In contrast, the inhibition of IL-1β signaling blocks the sickness-related behaviors in animals [16,27,38,50,60] (Table 1).

Studies have been conducted using the CUS model, which has a high degree of face, predictive and construct validity, as a behavioral model of depression [61,62]. The behavioral outcome in the CUS model is a reduction in sucrose preference or consumption, which models a core symptom of depression, the inability to experience pleasure (anhedonia) [16,61,62]. This deficit is reversed by chronic, but not acute, antidepressant administration, and is consistent with the time course for the therapeutic actions of antidepressants [5,62]. In a study of the effects of the blockade of IL-1RI, either using infusions of IL-1Ra or in IL-1RI deletion mutants, the anhedonia (decreased sucrose preference) that is caused by CUS was blocked [16]; similar results have been reported in another study [49].

All currently prescribed antidepressant treatments increase hippocampal neurogenesis [5,11–13]. This observation has stimulated studies to determine the functional consequences of neurogenesis; these studies have demonstrated a requirement for the induction of new cells in some behavioral models [11,13]; however, there are also studies reporting a dissociation between depressive-like behaviors and neurogenesis [63–65]. One study suggests that the actions of antidepressant treatment in an anhedonia model involve the remodeling of dendrites and synaptic contacts rather than neurogenesis in the hippocampus [65]. In addition, IL-1Ra administration (100 μg icv) prior to exposure to shock blocks behavioral despair 1 day after inescapable shock in the learned helplessness paradigm (LH) in rats [42]. This finding suggests that IL-1β also acts via some neural process (eg, synaptic function or number) that is not dependent on the more long-term process of neurogenesis (ie, proliferation and maturation of new neurons, which requires several weeks) (Figure 2).

Another example of the rapid action of antidepressants in animal models is the decreased immobility observed in the forced swim test (FST) after a single dose of imipramine (30 mg/kg ip) [66]. Although the FST has been a useful screening model for antidepressants, the rapid response rate observed in these studies leads to questions about the clinical relevance of this model given that a therapeutic response normally requires chronic antidepressant administration [4,5,67]. Previous studies have demonstrated that IL-1β infusion or LPS increases immobility in the FST [68,69], which is likely to be due to a general reduction in locomotor activity, another potential limitation of this paradigm [69]. This possibility is supported by studies of IL-1RI null mice, which would be expected to have an antidepressant behavioral profile similar to that observed in the CUS model, and opposite to the effects of IL-1β. However, the IL-1RI null mice exhibit no change in immobility in the FST or in general locomotor activity [74], suggesting that IL-1β/IL-1RI activation is not involved in the immobility in the FST. The discrepancy between the LH test and FST data might result from the different underlying neurobiology of these two behavioral paradigms, although further studies of IL-1RI null mice in the LH paradigm are necessary to directly test this hypothesis [70].

The novelty-suppressed feeding test (NSF), in which stressed mice have an increased latency to feed in novel cages, has some validity as a model of anhedonia, although it is a better model of anxiety [71]. Santarelli and colleagues demonstrated that hippocampal

neurogenesis is required for the behavioral actions of antidepressants in the NSF [11]. It has also been demonstrated that IL-1Ra infusion during CUS has a tendency to decrease the latency to feed in the novel cage, an effect similar to that observed with chronic antidepressant treatment [Koo JW, Duman RS: unpublished data]. This effect during CUS may result from an increase in hippocampal neurogenesis, and could also indicate an anxiolytic and/or anti-anhedonoic effect of IL-1Ra in the CUS paradigm. Moreover, the results suggest that the IL-1β signaling system is involved in a broad range of depressive symptoms and provide further evidence that pharmacological inhibition of this system may represent an alternative strategy for the clinical management of depression.

The hypothesis that the inhibition of IL-1β produces anxiolytic effects is supported by preclinical studies of additional anxiety models (Table 1). IL-1β infusions (100, 300 and 1000 ng ip) produced anxiogenic actions in mice in the elevated plus maze and open field tests [72]. However, the interpretation of these studies is compromised because IL-1β decreases locomotor activity, which could result in a nonspecific effect (ie, reduced locomotion would decrease movement in the open arm of the elevated plus maze and in the open field). To address this problem, the blockade of IL-1RI by either the administration of IL-1Ra or in IL-1R null mutant has been investigated. IL-1Ra overexpression produces an anxiolytic response in the elevated plus maze [73], and similar effects have been observed in IL-1RI null mutant mice [74]. In addition, IL-1RI null mice display an anxiolytic phenotype in the open field and light-dark paradigm, again without a difference in locomotor activity [74]. Taken together, these studies indicate that the blockade of IL-1β produces anxiolytic, as well as antidepressant, actions in multiple behavioral paradigms.

Limitations of IL-1β blockade for the treatment of mood disorders

Although the evidence discussed thus far supports the hypothesis that the blockade of IL-1β is a viable therapeutic target for the treatment of depression, as well as anxiety, there are several potential limitations. As a multifunctional cytokine, IL-1β affects almost every cell type in the brain, as well as peripheral tissues [28]. Therefore, the site(s) of IL-1β action need to be further elucidated before it is possible to develop safe and effective therapeutic interventions. Interestingly, the central administration of IL-1Ra blocks sickness behaviors (eg, impaired social exploration and food-motivated behavior) induced by peripheral, as well as central, IL-1β administration [75,76]; this finding suggests that peripheral IL-1β acts on IL-1RI in the brain [75]. In addition, some evidence suggests that peripheral IL-1β induces brain IL-1β production or release [77], which in turn can activate the stress responses in the brain [77]. Immunostaining studies of rat brains have demonstrated that IL-1RI is localized in neurons throughout the ventral tegmental area and substantia nigra, as well as the hypothalamus and the major subregions of the hippocampus, including the dentate gyrus granule cell layer and the CA1, CA2, and CA3/4 pyramidal cell layers [78], suggesting a potential role for these brain areas in the actions of IL-1β. Future studies are required to determine if these and other brain regions, including the mesolimbic dopamine system [79], contribute to the depressive actions of stress and IL-1β. In addition, the blockade of IL-1β actions in the periphery could also have antidepressant activity, which could expedite the use of antagonists that do not enter the brain (eg, IL-1Ra); this possibility also requires further testing.

Another interesting, yet potentially problematic, issue is the possibility that low levels of IL-1β are required for certain critical functions in the brain. For example, although substantial evidence indicates that IL-1β decreases learning and memory, some recent studies suggest that under certain circumstances, IL-1β may be important for the normal physiological regulation of memory process in the hippocampus [38,50,80]. Goshen and colleagues demonstrated that a low dose (1 ng icv) of IL-1β in the brain improves

hippocampal-dependent memory (eg, contextual fear conditioning), whereas either a relatively high dose (10 ng icv) of IL-1β or the blockade of IL-1β signaling (100 μg of IL-1Ra, icv) impairs memory [80]. It would be interesting to investigate whether this pattern of impairment (ie, when there is no IL-1β signaling or when there are high levels of IL-1β, but not when there are low levels of IL-1β) is applicable to neurogenesis-independent or -dependent depressive-like behaviors [81].

IL-1β is also implicated in various diseases, including multiple sclerosis, rheumatoid arthritis, and Parkinson's, Alzheimer's and cardiovascular diseases [26,27]. Treatments for these disorders could also include IL-1β inhibition. For example, anakinra, which is an IL-1Ra preparation that is currently being used to protect against rheumatoid arthritis, is often associated with an improvement in mood or a feeling of well being in patients with rheumatoid arthritis [82]; however, the long-term use of anakinra is often required due to the slow-onset of improvement in rheumatoid arthritis symptoms [82]. In addition, injection site reactions and a risk of serious infections are also possible side effects [26,82]. Faster acting medications via central administration with fewer side effects are needed to fully utilize IL-1β inhibition as a target for the treatment of these disorders.

Another key issue to be addressed is the relationship between IL-1β and corticosterone. This cytokine could act in part via activation of the HPA axis and elevation of corticosterone under stressful conditions [36,37,50]. One study has reported that the anti-neurogenic and anhedonic effects of IL-1β in the CUS model occur through activation of the HPA axis [49]. However, it has been demonstrated that neural progenitor cells express IL-1RI and that the proliferation of cultured progenitor cells is reduced by IL-1β in the absence of corticosterone, indicating a direct effect of IL-1β [16]. In addition, in preliminary studies, decreased hippocampal cell proliferation in response to corticosterone administration is partially blocked by IL-1Ra [Koo JW, Duman RS: unpublished data]. These data suggest that corticosterone acts in part via an IL-1β-mediated mechanism. Further analysis of corticosterone actions in response to stress in IL-1RI or IL-1β-null mice are required to fully address this issue.

Given these limitations of IL-1β, it is worthwhile to consider alternative therapeutic targets in the IL-1β signaling pathway. For example, the blockade of IL-1β converting enzyme (ICE), which cleaves the IL-1β precursor into the biologically active form [27], reduces the symptoms of anorexia, a sickness behavior [60]. Another possibility is to target downstream intracellular signaling cascades that underlie the anti-neurogenic effects of IL-1β, with particular interest in the NFκB pathway. Additional mechanisms for regulating the synthesis, processing, release and activity of IL-1β may also be identified and could represent novel targets for drug development.

Conclusion

It is generally accepted that uncontrollable stress is a major contributing factor in the etiology of depression [67,83]. Stress-induced reduction of hippocampal neurogenesis has received attention based on the hypothesis that the therapeutic effects of antidepressants involve a reversal of hippocampal impairment [12,13]. For effective clinical management of depression, it is important to elucidate the neural substrates and molecular mechanisms that underlie the effects of stress. Over two decades, the idea that depression could be treated with antagonists to proinflammatory cytokines such as IL-1β has been suggested and espoused in many studies [17,18,20–26,33]. Taken together with these studies, the evidence discussed in this review provides support for targeting the IL-1β system for the treatment of depression and other stress-related illnesses [26] (Figure 1). Further characterization of the relationship between IL-1β/IL-1RI signaling and the HPA axis, the possible interactions

with other cytokines, and additional brain areas governing the anhedonic and anxiogenic actions of IL-1β will further elucidate the pathophysiology of depression and contribute to the development of novel antidepressant medications.

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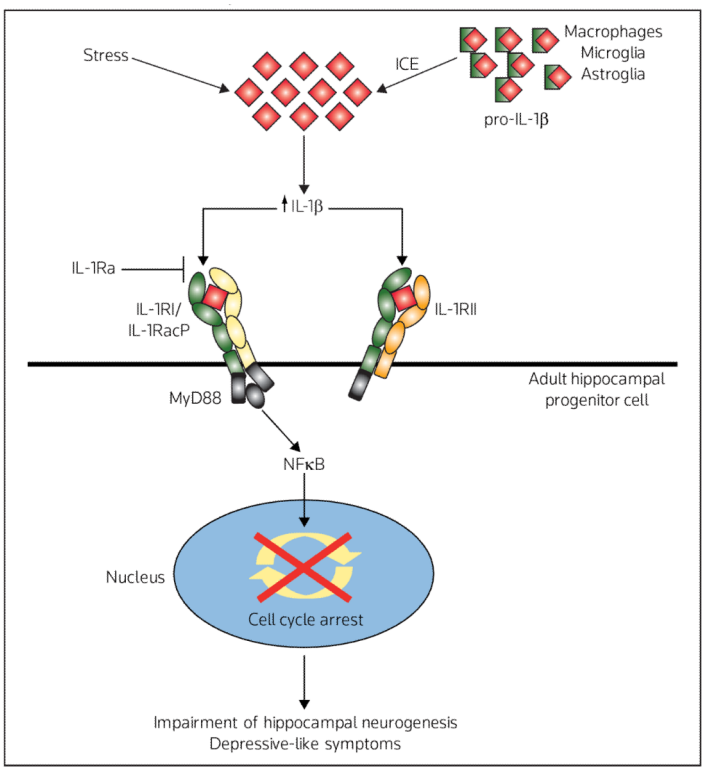

Figure 1. Model for the cellular actions of stress on IL-1β processing and signaling

The mature form of IL-1β is processed from its precursor, pro-IL-1β, by IL-1β converting enzyme (ICE). Binding of IL-1β to the IL-1RI induces the formation of a complex with the IL-1R accessory protein (IL-1RacP). The cytoplasmic portions of the IL-1RI/IL-1RacP complex interact with other molecules such as MyD88 (myeloid differentiation primary response gene 88), which then activates NFκB signaling pathways. The peptide antagonist IL-1Ra binds primarily to IL-1RI, but does not exert a biological response because IL-1Ra/IL-1RI does not form a complex with IL-1RacP. A second truncated receptor IL-1RII can bind IL-1β, but does not lead to the activation of NFκB, and can thereby block signaling by scavenging IL-1β. Recent studies have demonstrated that IL-1β signaling underlies the anti-neurogenic and anhedonic effects of stress and that these effects are blocked by IL-1Ra or in IL-1RI deletion mutants.

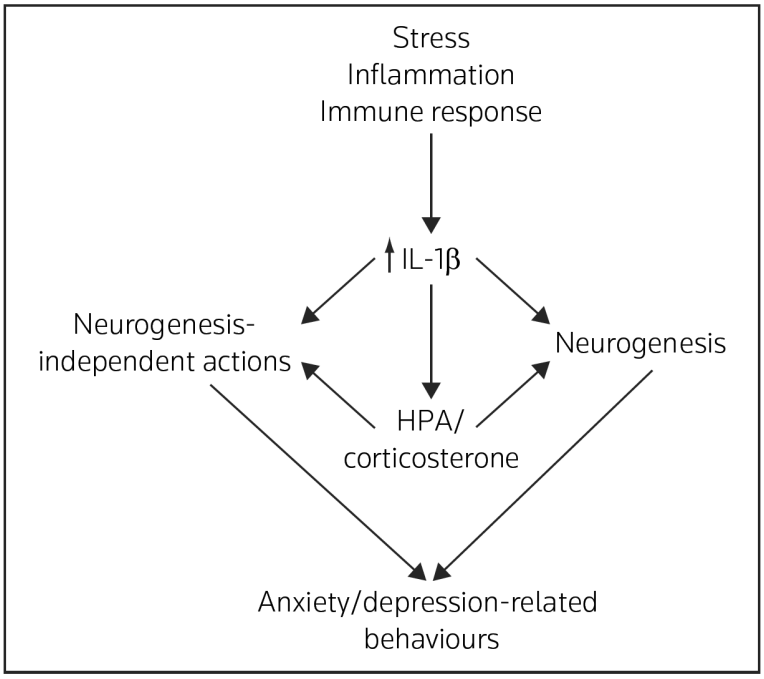

Figure 2. Model for IL-1β regulation of neurogenesis in the adult hippocampus

Neural progenitor cells in the subgranular zone (SGZ) give rise to newborn neurons that integrate into the granule cell layer (GCL). Stress decreases the proliferation of newborn neurons via increased release of IL-1β. Neural progenitor cells express the major IL-1β receptor, IL-1RI, suggesting that the effects of IL-1β occur through direct actions on cell cycling of progenitors. However, there is also evidence that the anti-neurogenic actions of IL-1β occur via activation of the hypothalamic-pituitary-adrenal (**HPA**) axis and elevation of corticosterone. In addition to the regulation of neurogenesis, the effects of IL-1β and HPA-corticosterone are mediated by neurogenesis-independent mechanisms (eg, synaptic plasticity and alterations of synapse/spine number) in the hippocampus and other brain regions.

Table 1

Role of IL-β in the regulation of neurogenesis and behavior

Endpoint	Intervention			References
	Administration of IL-1β	**Administration of IL-1Ra (inhibitor)**	**IL-1RI null mice**	
Neurogenesis	Decreased	Acute stress and CUS blocked	Acute stress and CUS blocked	[16,38]
Anhedonia				
Sucrose preference	Anhedonia observed	CUS and anhedonia blocked	CUS and anhedonia blocked	[16,38]
Despair				
Learned helplessness test	–	Antidepressant effects	–	[42]
Forced swim test	Depressive effects	–	No effect	[69,74]
Anxiety				
Novelty suppressed feeding test	Anxiogenic effects	Anxiolytic/antidepressant effects	Anxiolytic/antidepressant effects	[74]
Elevated plus maze	Anxiogenic effects	Anxiolytic effects	Anxiolytic effects	[72–74]
Open field test	Anxiogenic effects	–	Anxiolytic effects	[72,74]
Light/dark test	–	–	Anxiolytic effects	[74]
Locomotor activity	Decreased	No effect	No effect	[16,72,74]

CUS chronic unpredictable stress