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Review

Interleukin-1 (IL-1): A central regulator of stress responses

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ABSTRACT

Ample evidence demonstrates that the pro-inflammatory cytokine interleukin-1 (IL-1), produced following exposure to immunological and psychological challenges, plays an important role in the neuroendocrine and behavioral stress responses. Specifically, production of brain IL-1 is an important link in stress-induced activation of the hypothalamus-pituitary-adrenal axis and secretion of glucocorticoids, which mediate the effects of stress on memory functioning and neural plasticity, exerting beneficial effects at low levels and detrimental effects at high levels. Furthermore, IL-1 signaling and the resultant glucocorticoid secretion mediate the development of depressive symptoms associated with exposure to acute and chronic stressors, at least partly via suppression of hippocampal neurogenesis. These findings indicate that whereas under some physiological conditions low levels of IL-1 promote the adaptive stress responses necessary for efficient coping, under severe and chronic stress conditions blockade of IL-1 signaling can be used as a preventive and therapeutic procedure for alleviating stress-associated neuropathology and psychopathology.

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1. Introduction

Stress refers to the challenge, adversity, hardship, and affliction that organisms encounter in life, which jeopardize their physical and psychological well being. Stress is elicited by "stressors"—dangerous or harmful stimuli or events that take place either in the external or the internal environment, resulting in a multitude of physiological, behavioral, emotional, and cognitive alterations, termed "stress responses." To promote coping and reduce the impact of the stressor, these responses are usually highly organized and tightly regulated. Thus, in contrast with the previous notion that the function of stress responses is to restore the stability of the internal environment (homeostasis), it is now argued that stressors elicit well-organized responses with their own homeostasis, which promote adaptive coping. It should be noted, however, that under some conditions, e.g., when the stress is severe or chronic, the organization and regulation of stress responses may be disrupted and pathology ensues. Given the central role of stress in normal human experience as well as in psychopathology, much scientific effort has been concentrated on identifying and characterizing the anatomical, cellular, and molecular pathways underlying stress responses. Over the last two decades it became evident that multiple bi-directional communication pathways connect the brain, the endocrine, and the immune systems, which may be relevant to stress responses. From an initial focus on the impact of stress on immune functions and vulnerability to various disease conditions, more recent research turned to focus on the involvement of immune cells and molecules in stress responses. Interestingly, immune-like processes were found to underlie not only the responses to immune challenges but also to physiological and psychological stressors that are not associated with infection or injury. In particular, it became evident that pro-inflammatory cytokines, which are produced predominantly by activated cells of the innate immune system such as monocytes, macrophages, and brain microglia, play an important role in the neuroendocrine and behavioral responses to various stressors.

In the present review, we focus on the role of one pro-inflammatory cytokine, interleukin-1 (IL-1), in mediating immunological and psychological stress responses. Although other inflammatory cytokines, such as IL-6 and TNFα, are also associated with the responsiveness to stress, IL-1 was the first cytokine to be associated with modulation of neuroendocrine systems, particularly the hypothalamic pituitary-adrenal axis (HPA) [26,27,224], and the hypothalamic-pituitary-gonadal axis [215] in the 1980s, and IL-1 has remained the most studied inflammatory cytokine in this area to date. The studies reviewed below elucidate the role of IL-1 in stress-induced modulation of HPA axis activation, behavioral processes, and neural plasticity, indicating that this cytokine is a critical mediator of adaptive stress responses as well as stress-associated neuropathology and psychopathology.

Abbreviation: Brain IL-1, mediates stress responses.

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To elucidate the role of IL-1 in stress responses, it is important to understand the complex regulation of IL-1 signaling. A detailed presentation of this regulation is beyond the scope of the present review; therefore, only selected pertinent issues will be presented here. IL-1 is produced by many types of cells, including immune cells in the periphery as well as glia and neurons within the brain [74]. IL-1 signaling is mediated by a complex system, which includes various ligands and receptors: The cytokines IL-1α and IL-1β activate signaling, whereas IL-1 receptor antagonist (IL-1ra) serves to block the effects of IL-1 by binding to the same receptor without triggering signaling. Many types of IL-1 receptors have been identified [153]. In particular, the IL-1 receptor type I (IL-1rI) appears to mediate all of the known biological functions of IL-1, but in order to transmit a signal into the cell it has to form a complex with the IL-1 receptor accessory protein (IL-1rAcP). On the other hand, IL-1 receptor type II is a decoy receptor, which antagonizes IL-1 signaling [74,239]. IL-1 signaling is mediated by multiple pathways, including mitogen-activated protein kinase (MAPK) and NFκB cascades, translocation of transcription factors into the nucleus, and transcription of immediate-early genes like *c-jun* and *c-fos* [172].

IL-1 gene expression and protein production are elevated during various disease states, in which IL-1 orchestrates the inflammatory response to various immune stimuli. For example, it increases antibody production, induces the synthesis of other cytokines (e.g., IL-6), and augments the development of T cell clones [74]. In addition to its influence on inflammatory processes, IL-1 mediates the "sickness behavior syndrome," a collection of neurobehavioral and neurophysiological symptoms that accompanies immune activation and inflammatory conditions [63,112,134,147,263,284]. Recently, cytokines were implicated in the regulation of neurobehavioral processes not only during immune activation but in healthy animals as well [263]. Most studies in this area rely on genetic mouse strains lacking normal cytokine signaling. For example, we used several mouse strains with genetic impairments in IL-1 signaling to demonstrate a regulatory role for IL-1 in basal pain sensitivity, morphine-induced analgesia, the development of tolerance following repeated morphine administration, normal memory consolidation, and neural plasticity processes [8,101, 233,275,276].

In order to induce these neurobehavioral and neurophysiological effects, IL-1 directly influences the brain, as suggested by the presence of its receptors in various brain structures [58,153], and the fact that administration of IL-1ra into the brain blocks most of the effects of peripheral IL-1 administration [74,218]. The source of IL-1 can be either local synthesis by glia cells and neurons, or passage of peripherally-produced IL-1 into the brain [74,162]. Because IL-1α, IL-1β, and IL-1ra are large proteins, passage through the blood–brain barrier (BBB) can be accomplished either passively in circumventricular organs, in which the BBB is weak, or via active transport in other areas [12,266]. Alternatively, IL-1 can induce the synthesis and secretion of smaller mediators that can easily cross the BBB, such as prostaglandins [266]. In addition, peripheral IL-1 can influence the brain via the activation of vagal afferent fibers. Indeed, vagotomy blocks many centrally-mediated effects of peripheral immune activation [93,266], and attenuates the behavioral effects of peripherally administered IL-1 [32].

2. Brain IL-1 regulates stress-induced HPA axis activation

2.1. IL-1 activated the HPA axis—introduction and mechanisms

In addition to its role in immune regulation, IL-1 plays a major role in the modulation of neuroendocrine systems during illness, particularly the HPA axis [218]. IL-1 is expressed throughout the components of the HPA axis [30,259], and influences all of its levels. IL-1 induces the secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus [26,224], which then induces the secretion of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH, in turn, stimulates the secretion of glucocorticoids from the adrenal cortex. IL-1 does not affect only the primary stage of the axis activation, but also directly induces ACTH secretion from the pituitary [27] via IL-1 type I receptors in this region [30,259]. It also stimulates the secretion of glucocorticoids (GCs) from the adrenal, although no known IL-1 receptors were found in this gland [30,259].

Several lines of evidence indicate that IL-1-induced activation of the HPA axis is at least partly mediated by changes in hypothalamic noradrenergic neurotransmission. Following peripheral IL-1β administration, extra-cellular norepinephrine (NE) concentrations in the hypothalamus increase in a pattern similar to that of plasma CS [241]. Indeed, IL-1β increases the expression of the cellular activation marker *c-fos* in CRH-producing cells in the hypothalamic paraventricular nucleus (PVN) via ascending catecholaminergic projections from the medulla [83]. Consistently, administration of 6-hydroxydopamine (6-OHDA) into the PVN, which selectively depletes catecholaminergic terminals, reduces IL-1-induced CRH cell activation in the PVN [40], and also reduces IL-1-induced increase in plasma CS concentrations [49]. Intra-PVN administration of the axonally transported catecholamine immunotoxin antiDBH-saporin also abolishes IL-1-induced elevation in CRH mRNA in the PVN [227]. The catecholaminergic input to the PVN arrives from both the nucleus tractus solitarius (NTS) and the ventrolateral medulla (VLM) catecholamine cells, as both VLM and NTS lesions reduce the responses of PVN CRH cells to peripheral IL-1 [40]. Similarly, bilateral 6-OHDA deletion of the ventral noradrenergic ascending bundle, the neural pathway linking the brain stem and the PVN, also reduce ACTH and corticosterone elevation in response to IL-1 [49,201]. HPA axis activation by peripheral IL-1 may be mediated by vagal afferent fibers, as vagotomy blocks an IL-1β-induced increase in serum ACTH and corticosterone [88,126]. Furthermore, afferent electrical stimulation of the vagus nerve increases IL-1β levels within the hypothalamus and the hippocampus, and elevates plasma levels of ACTH and corticosterone [118].

In addition to its effects on CRH, IL-1 influences the levels and activity of another important activator of the HPA axis—the neuropeptide vasopressin. This neuropeptide is co-localized in many CRH-producing neurons in the PVN, and it strongly potentiates the ACTH releasing effect of CRH [270]. Peripheral administration of IL-1β increases vasopressin content in the PVN [264] and induces a long-lasting increase of vasopressin stores in CRH terminals, resulting in hyper-responsiveness of the HPA axis to subsequent stimuli [229]. Central infusion of IL-1 also increases blood vasopressin levels [146]. Thus, IL-1-induced increases in vasopressin levels can play an important role in HPA axis activation, especially during chronic immune stimulation.

2.2. The role of brain IL-1 in the HPA axis activation induced by immunological challenges

A role for IL-1 in illness-associated HPA activation has been documented in many clinical and experimental settings. As this topic was extensively reviewed in the past [256,259], we will describe only a few exemplary results. Immune challenges, such as local inflammation, viral or bacterial infection, and endotoxin exposure, were found to induce the production and secretion of brain IL-1, followed by activation of all components of the HPA axis [30,259]. For example, increased IL-1, ACTH, and CS levels in the serum were observed following antigen inoculation [29] or injection with the bacterial endotoxin lipopolysaccharide (LPS) [21]. In humans, we also demonstrated a marked increase in cortisol

levels following LPS administration in healthy volunteers [213]. In addition, we as well as others have used several experimental models of intracerebral immune activation to examine IL-1-mediated neuroendocrine responses. For example, intracerebroventricular (ICV) injection of either herpes simplex virus type 1 (HSV-1) or gp120, the surface protein of the human immunodeficiency virus (HIV), resulted in increased brain IL-1β gene expression [13,23] and activity [251], as well as augmented ACTH and corticosterone (CS) secretion [14,24,251]. Similarly, ICV inoculation with *mycoplasma fermentans* also caused an increase in IL-1β gene expression in various brain areas (e.g., cortex, hippocampus, amygdala and pons), concomitantly with increased ACTH and CS secretion [283].

The critical role of IL-1 in illness-induced HPA axis activation is clearly demonstrated by studies on the effects of IL-1 blockade, using IL-1ra. For example, when HSV-1 was injected ICV together with IL-1ra, the increase in ACTH and CS was blocked [24]. Peripheral administration of IL-1ra also blocked ACTH and CS secretion following Newcastle disease virus infection [80]. Additionally, IL-1ra diminished GCs secretion following a surgical procedure [70]. However, IL-1 is not the sole inducer of the HPA axis during immune activation, as there are conditions (such as inoculation with *mycoplasma fermentans* or LPS) in which blockade of IL-1 is not sufficient for the obstruction of HPA axis activation [79,283].

The role of IL-1 in immunological stress was further demonstrated by the finding of a shorter duration of HPA axis activation in IL-1α/β deficient mice [117]. These mice demonstrate a normal increase in corticosterone levels 2 h following peripheral turpentine injection (a model of local inflammation), but their level returns to baseline 8 h after the injection, whereas their WT controls still continue to evidence high corticosterone levels [117]. The same pattern of impaired HPA axis activation is found in IL-1β deficient but not in IL-1α or IL-1ra deficient mice, suggesting that IL-1β is the primary molecule responsible for inflammation-induced HPA axis activation [117].

The interaction between IL-1 and the HPA axis is bi-directional. On the one hand, IL-1 activates the HPA axis, as detailed above, and on the other hand GCs suppress the production of IL-1. This suppression is achieved via multiple mechanisms: First, by decreasing IL-1 mRNA levels, both by inhibiting its transcription and by destabilizing it [4,148]. Second, by blockade of post-transcriptional IL-1 synthesis via cAMP [139]. Third, by inhibition of the release of IL-1β into the extra-cellular fluid [135]. This suppressive effect can be demonstrated by measuring the effect of GCs removal. For example, we found that IL-1 gene expression in astrocyte cultures can be detected only when cortisol is removed from the culture medium [23]. On the other hand, when an animal is exposed to a stressor (e.g., footshock) immediately following an LPS injection, the stress-induced increase in GCs secretion diminishes the LPS-induced increase in IL-1α and IL-1β in the pituitary, hypothalamus, and hippocampus [107].

Brain IL-1 is also involved in the feedback regulation of the HPA axis. This regulation is considered to involve inhibitory actions of GCs via GC receptors. Several studies (e.g., [129] suggest that the primary target for GC feedback inhibition is not only hypothalamic CRH neurons, but also other hypothalamic and extrahypothalamic (e.g., hippocampus, pituitary) systems that regulate CRH expression and release [121,129]. The action of the feedback system is exemplified by the marked increase in ACTH levels following removal of endogenous GCs by adrenalectomy (ADX) [61]. In addition to this ACTH hyper-secretion, ADX is also associated with enhanced expression of IL-1 gene in the hypothalamus, pituitary, and brain stem, as well as increased production of IL-1 protein in the pituitary [23,106]. These findings suggest that GCs may have a tonic inhibitory effect on brain IL-1. Recently, we demonstrated that following removal of this inhibitory effect by ADX, ACTH levels were markedly elevated in WT controls, but did not increase in IL-1rKO mice or mice that overexpress IL-1ra within their nervous system (IL-1raTG) [103]. Even prenatal IL-1 blockade resulted in a significant attenuation of ACTH hyper-secretion [103]. These findings suggest that the removal of a direct inhibitory signal exerted by GCs is not sufficient for ADX-associated ACTH hyper-secretion. Rather, this hyper-secretion is critically dependent on an excitatory signal, provided by the elevated levels of IL-1, which is a potent HPA axis activator [30,259], and may be also involved in the GC negative feedback mechanism by altering the levels of brain GC receptors in the hippocampus [177,268]. Furthermore, during fetal development, IL-1 may have a role in the maturation of brain systems that regulate the HPA axis.

2.3. The role of brain IL-1 in psychological stress-induced HPA axis activation

The production, secretion, and influence of IL-1 have been traditionally considered in the context of illness-associated immune activation. However, over the last decade it became evident that IL-1 also participates in neuromodulation under conditions that do not involve the immune system [8,263,285]. An important support for this view comes from studies demonstrating that psychological stressors activate the IL-1 system, and that endogenous IL-1 activates the HPA axis not only during sickness, but also in response to various psychological stressors. Interestingly, the physiological and behavioral outcomes of both immune activation and exposure to other stressors are very similar, including sympathetic and HPA axis activation, fever and a variety of sickness behavior-like symptoms, such as increased sleep, and reduced exploratory, social, and sexual behavior [125,162,240]. Furthermore, physical and psychological stressors can even activate components of the peripheral immune system, such as elevation in acute-phase proteins like haptoglobin or α-acid glycoprotein, macrophage priming, increase in white blood cell count, and elevation in circulating cytokines [67,89,149,183,288]. These behavioral and physiological effects of stress may be mediated by central IL-1, as suggested by the finding that they are blocked by ICV administration of α-MSH [178], which antagonizes the effects of IL-1 [152].

In animal models, IL-1β (and IL-1ra) gene expression is increased following restraint stress in several brain regions (hypothalamus, hippocampus, brain stem, frontal cortex, and cerebellum), as well as in the adrenal gland, and this increase is maintained for up to 8 h [179,252]. IL-1β gene expression is also increased in the hypothalamus and hippocampus following inescapable shock [192]. An increase in IL-1 protein levels was observed following inescapable shock and repeated immobilization in various brain regions [144,189,190]. In the brain regions that are part of the HPA axis (hypothalamus and pituitary), the increase in IL-1 protein levels is immediate, whereas in other brain regions, such as the NTS and the hippocampus, the increase in IL-1 levels is observed only 24 h following stress termination [190]. In line with the inhibitory effect of the HPA axis on IL-1, the increase in IL-1 protein levels in the hypothalamus, hippocampus, cerebellum, and NTS following inescapable shock is more distinct in adrenalectomized rats [189,190]. Specifically, the level of IL-1 in the hypothalamus immediately following shock administration is almost 3 times higher in ADX rats compared to sham operated rats [190]. In addition, ADX can unmask undetectable increases in IL-1 following stress, e.g., in ADX rats the levels of IL-1 in the hippocampus were significantly increased 2 h following exposure to stress, whereas in sham operated rats no IL-1 increase was evident at this time point [190].

Milder stressors can also activate the IL-1 system when they are administered chronically. Cold stress was found to elevate IL-1β gene expression in several brain areas (medial pre-optic area, med-

ian eminence, ventromedial hypothalamus, but not cortex and hippocampus) only after it was administered for at least one week [253]. Five weeks of chronic mild stress (CMS) induces IL-1 secretion in both the brain and the periphery [100,110], and four weeks of social isolation results in elevated hippocampal IL-1 levels [25]. Shorter isolation (1–3 h) following fear-conditioning also resulted in increased hippocampal IL-1 levels [210]. On the other hand, other research groups showed no effect of chronic naturalistic stress (predator exposure) or CMS on IL-1 levels [184,202], and chronic social stress was even found to cause a reduction in hippocampal IL-1β gene expression [19].

The pattern of the brain IL-1 system activation may be at least somewhat stressor-specific, as social isolation increased IL-1β protein in the hippocampus and cerebral cortex, but not in the pituitary or the hypothalamus [25,210], whereas CMS increased IL-1 levels in the hypothalamus and hippocampus, but not in the pituitary [100,110]. In most studies, the effects of stress on IL-1 production were examined only within the brain, but one study reported that chronic restraint for 7 days induced a 5-fold increase in IL-1β in the serum [174], and another study demonstrated a similar result following CMS [110].

In contrast with the activation of the IL-1 system following immunological stimulation, the immediate trigger for IL-1 signaling in physical and psychological stress is less clear. Some evidence indicates that secretion of catecholamines, the first neurochemical response to stress, plays an important role. Two research groups have shown that the β-adrenergic blocker propranolol inhibits the increase in IL-1 protein levels following footshock in the hypothalamus and hippocampus [31,124]; likewise, ablation of noradrenergic projections from the locus coeruleus prevented stress-induced elevation in hippocampal IL-1β [124]. Furthermore, the noradrenergic reuptake inhibitor desipramine facilitated stress-induced hypothalamic IL-1 secretion [31]. These findings are in line with several studies showing that systemic NE, which can interact with various immune cells via stimulation of β2 adrenergic receptors [187], elevates peripheral IL-1 gene expression and secretion [38,289], and that systemic administration of the β-adrenergic agonist isoproterenol is sufficient to elevate IL-1 secretion in the serum, as well as in the hypothalamus, pituitary, and hippocampus [124]. Thus, the stress-induced stimulation of NE secretion within the brain, acting via β-adrenergic receptors, can trigger a rapid *de novo* production and/or secretion of pre-stored IL-1.

Stress-induced alterations in acetylcholine levels can also participate in the regulation of IL-1 production. Exposure to various stressors produces a pronounced, but transient activation of central cholinergic pathways [247], which is immediately followed by compensatory elevation of acetylcholinesterase (AChE) levels and activity [128,176], resulting in a rapid hydrolysis of ACh and a consistent suppression of cholinergic neurotransmission. In light of the findings that cholinergic stimulation is anti-inflammatory, both in the periphery [257] and the brain [203], we have suggested that stress-induced AChE activation reduces ACh levels, which in turn activates brain IL-1 production [51,247]. Interestingly, IL-1 can enhance neuronal AChE activity [151], and therefore a vicious cycle can be initiated, in which stress-induced elevation in AChE activity and IL-1 production results in further enhancement of AChE activity, reduction of ACh levels and further production of additional IL-1.

Another trigger for psychological stress-induced IL-1 production may be related to the activation of the brain-gut axis, which can result in degranulation of mast cells in the intestinal mucosa [46,86] and the release of a wide range of inflammatory mediators [84,114]. These mediators can affect gastrointestinal physiology, in general and the permeability of the intestinal epithelium, in particular [211,223]. Stress-induced intestinal hyperpermeability may allow lumen-derived food antigens and bacterial by-products, such as LPS, to reach the submucosal immune system, producing local and/or systemic inflammation, with elevated levels of plasma pro-inflammatory cytokines [86], which can, in turn, increase the levels of brain IL-1, as specified above.

The immediate cellular source of psychological stress-induced brain IL-1 may be activated microglia, as stress increases the hippocampal expression of the microglia activation marker MHC II [90], and minocycline, a selective microglial inhibitor, blocks stress-induced hypothalamic IL-1 secretion [31]. Furthermore, repeated stress exposure induces microglia proliferation, mediated by corticosterone-induced activation of the *N*-methyl-D-aspartate (NMDA) receptor within the CNS, and exogenous corticosterone administration to non-stressed mice also results in NMDA-dependent microglia proliferation [144,186].

The role of stress-induced IL-1 in mediating the activation of the HPA axis has been studied by both pharmacological and genetic approaches. Shintani et al. [237] demonstrated that the biological activity of IL-1 in the hypothalamus was increased following restraint stress [237]. Furthermore, blockade of IL-1 signaling by administration of IL-1ra into the anterior hypothalamus diminished the increase in ACTH secretion following restraint stress when it was applied 60 or 5 min before the beginning of restraint, but not 5 or 30 min afterwards [237]. These findings suggest a rapid release of pre-synthesized IL-1, because IL-1 protein synthesis cannot be completed within 5 min.

We further demonstrated the role of IL-1 in mediating stress responses by examining mice with IL-1 receptor type I deficiency (IL-1rKO) [103], which were previously reported to have a defective response to both IL-1α and IL-1β [145]. IL-1rKO mice displayed impaired HPA axis responses following mild psychological and metabolic stressors. Specifically, when exposed to either auditory stress, or a low dose of 2-deoxyglucose, which induces metabolic stress by causing cytoglucopenia, the WT controls displayed a significant increase in corticosterone secretion, whereas corticosterone levels in IL-1rKO mice remained unchanged [103]. However, following exposure to severe stressors, these mice demonstrated a normal HPA axis activation, i.e., when exposed to either 60 min of restraint stress or a high dose of 2-deoxyglucose, IL-1rKO mice demonstrated a significant increase in corticosterone secretion, similar to that of their WT controls. These findings suggest that IL-1 signaling via its type I receptor is important for HPA axis activation following mild stress. The response to stronger stressful stimuli probably involves other mediators, which may compensate for the absence of IL-1 signaling. One of these mediators may be the cytokine tumor necrosis factor-α (TNF-α), which often works in synergism with IL-1 [74,283]. It should be noted that the finding that mild stress-induced CS secretion in IL-1rKO mice is blunted during a single time point (which coincides with maximal activation in normal animals) [237,269], cannot exclude the possibility that the strain differences are due to changes in the kinetics, rather than the amplitude, of the HPA axis activation.

IL-1 is also involved in stress responses in humans. In one study, academic oral presentation was found to elicit higher levels of serum IL-1β, as well as cortisol, compared with the control level of the participants [115]. Five-minutes videotaped speech also elevated mitogen-stimulated production of IL-1β from macrophages during the stressor, and through 60 min afterwards [1]. Stressful cognitive tasks also increased IL-1β gene expression in mononuclear cells [39]. We recently demonstrated that the psychological stress-associated with surgery (i.e., in patients waiting to enter the operating room, before the beginning of any medical intervention) induces a significant increase in serum IL-1β levels [232]. In another study, undergoing two major academic examinations resulted in significantly elevated IL-1β levels in the crevicular fluid (which is mainly produced during times of inflammatory processes of the gingiva and contains immunologic defense mechanisms) [68]. Further-

more, the levels of IL-1β in the crevicular fluid remained high up to 21 days after the last examination in sites of poor oral hygiene [69]. A recent meta-analysis reported robust effects for increased levels of circulating IL-1β following acute psychological stress [249].

Elevated serum IL-1β levels have been reported in patients with combat-related posttraumatic stress disorder (PTSD), and these levels are correlated with the duration of PTSD symptoms, but not with the severity of PTSD [248]. A recent study [258] replicated the finding of high serum IL-1β levels in patients suffering from PTSD, induced by different traumatic experiences (e.g., sexual or physical abuse, life threatening events, etc.). In these patients, a reduction in the psychological symptoms following treatment was accompanied by a decrease in IL-1β levels [258].

Because IL-1ra is known to increase concomitantly with IL-1 [74,252], several studies examined IL-1ra modulation by psychological stress. Academic examinations differentially elevated the levels of IL-1ra in the subjects that responded to this stressor, but not in those who were not psychologically affected [159]. In the subjects who did not develop an anxious response to the examinations, but not in those who did, the levels of IL-10, an anti-inflammatory cytokine that blocks the activity of IL-1, were increased [159]. Undergoing the color-word interference and mirror tracing tests also induced increased IL-1ra secretion [250], and the Trier Social Stress Test (comprising of a public speaking task in a mock job interview and a mental arithmetic task) resulted in a delayed increase plasma IL-1ra, 90 min after stress [216].

To sum up, immunological and psychological stressors increase brain IL-1, which, in turn, induces the secretion of CRH from the PVN and ACTH from the pituitary. Following exposure to immunological stressors, peripheral IL-1 can directly influence brain stem nuclei, such as the NTS, the VLM, and the locus coeruleous (LC), as well as the hypothalamus via penetration to adjacent circumventricular organs. Concomitantly, IL-1 in the periphery can activate vagal afferents, which innervate and activate the NTS and VLM. These nuclei project to the hypothalamus, in which the secretion of NE induces further elevation of IL-1 levels, possibly by microglial activation. Psychological stressors can also activate the NTS and VLM, either by intrinsic brain circuits or via vagal feedback from physiological systems that are stimulated by the sympathetic nervous system. Similarly to their role in immunological stress, the NTS and VLM then elevate hypothalamic IL-1 levels, stimulating the CRH neurons (Fig. 1).

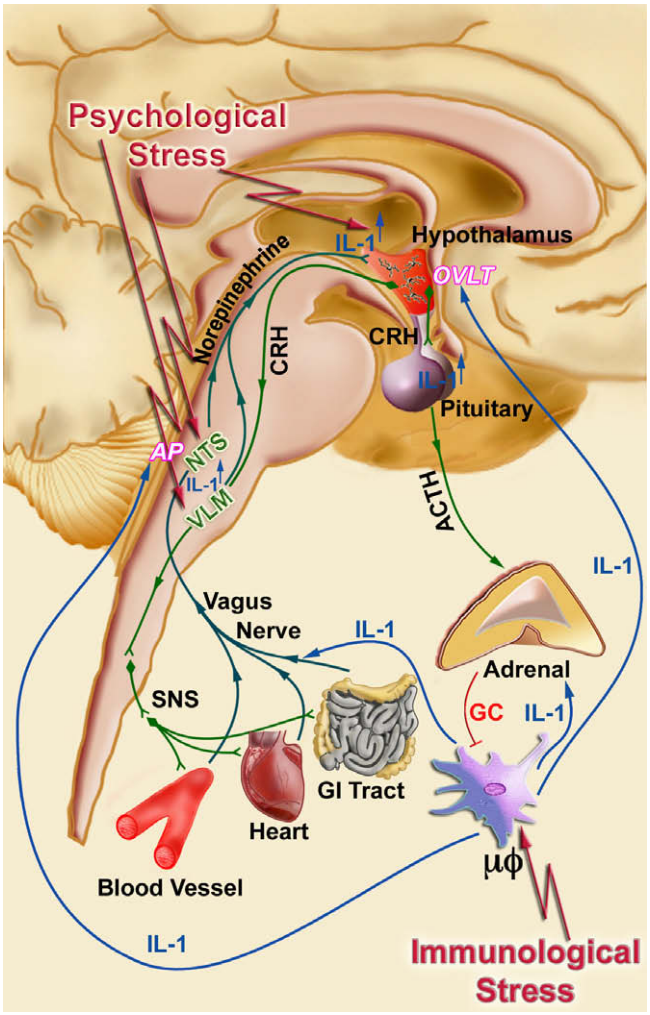

Fig. 1. IL-1 mediates stress-induced activation of the HPA axis. Immunological and psychological stressors increase the levels of IL-1 in various brain areas, including several brain stem nuclei, the hypothalamus and the hippocampus. In turn, IL-1 induces the secretion of CRH from the hypothalamic paraventricular nucleus (PVN), ACTH from the pituitary and glucocorticoids from the adrenal. Following immunological stressors, peripheral IL-1 can directly influence brain stem nuclei, such as the nucleus tractus solitarius (NTS) and ventrolateral medulla (VLM) as well as the hypothalamus via penetration to adjacent circumventricular organs, (the area postrema (AP) and the organum vasculosum of the lamina terminalis (OVLT), respectively). Concomitantly, IL-1 in the periphery can activate vagal afferents, which innervate and activate the NTS and VLM. These nuclei project to the hypothalamus, in which the secretion of NE induces further elevation of IL-1 levels, possibly by microglial activation. Psychological stressors can also activate the NTS and VLM, either by intrinsic brain circuits or via vagal feedback from physiological systems (e.g., the cardiovascular system) that are stimulated by the sympathetic nervous system. Similarly to their role in immunological stress, the NTS and VLM then elevate hypothalamic IL-1 levels, stimulating the CRH neurons.

3. Brain IL-1 regulates stress-induced alterations in behavior and neural plasticity

Many recent studies showed that IL-1 is involved in the neurobehavioral alterations that accompany both immunological and non-immunological stressors. Furthermore, the interactions between stress, IL-1, and the activation of the HPA axis were found to be relevant to several stress-induced behavioral alterations. The following section presents the involvement of stress-induced IL-1 in sickness behavior, cognitive functioning, and depressive behavior, as well as the neural plasticity and neurogenesis processes that underlie some of these behavioral changes.

3.1. The role of brain IL-1 in stress-induced alterations in sickness behavior and pain perception

As mentioned above, in addition to its involvement in inflammatory processes per-se, IL-1 mediates a collection of neurobehavioral and neurophysiological symptoms, which are termed together the "sickness behavior syndrome" [63,134,147,284]. It is fairly accepted that this syndrome is adaptive, at least under certain circumstances, helping the organism recuperate from the disease [63,112,134]. The symptoms comprising the sickness behavior syndrome include: anorexia, body weight loss, impaired cognitive function, altered sleep patterns (characterized by an increase in slow-wave sleep and inhibition of rapid eye movement sleep), psychomotor retardation, fatigue, reduced exploratory behavior, impaired social behavior (e.g., reduction in the time spent by adult animals in social olfactory exploration of a juvenile conspecific), reduced libido (particularly in females), impaired sexual activity, altered pain perception, and anhedonia (the diminished capacity to experience pleasure and gratification from activities that previously brought enjoyment) [63,280]. Mediation of these symptoms by IL-1 has been indicated by the findings that: (1) Both humans and animals demonstrate correlations between the elevation in

IL-1 levels during various medical conditions and the prevalence and severity of the above-mentioned sickness behavior symptoms; (2) Pharmacological administration (either peripherally, or directly into the brain) as well as genetically-engineered transgenic overproduction of IL-1 produces sickness behavior symptoms; (3) IL-1 signaling inhibitors block the behavioral effects of sickness and cytokine elevations [9,142,218,226,263,265].

IL-1-induced sickness behavior is accompanied by HPA axis activation, and the behavioral symptoms were found to be correlated with ACTH and corticosterone levels. IL-1 doses that were shown to increase corticosterone levels (0.05 and 0.1 μg/mouse) also reduced the consumption of a sweet solution. Smaller doses, which did not alter corticosterone levels (0.025 μg/mouse), did not affect behavior either [35]. When an inefficient dose of IL-1 was co-administered with a similarly inefficient dose of TNFα, they synergistically induced both elevated corticosterone secretion and sickness behavior [35]. The decrease in locomotor activity and increase in shivering following peripheral IL-1 administration were found to be correlated with plasma ACTH levels, whereas the increase in body temperature was correlated with the levels of corticosterone [271].

Similar results to those demonstrating the bi-directional interaction between IL-1 and the HPA axis (see Section 2.1 above) were also found in behavioral studies. That is, both chronic stress and ADX facilitated the behavioral effects of IL-1: When IL-1 was administered following chronic (but not acute) stress, its detrimental effect on social exploration and appearance was significantly enhanced [254]. Several studies showed that both ADX and blockade of GC receptors by RU-38486 amplified and prolonged the behavioral effects of IL-1 administration: The decrease in social exploration and increase in body temperature, induced by either peripherally or centrally administered IL-1, were enhanced by ADX or RU-38486 [105], and, under these treatments, ICV administration of low IL-1 doses, which do not cause behavioral alterations in non-treated mice, resulted in reduced social exploration [104]. Corticosterone supplementation abolished the augmenting effect of ADX for low IL-1 doses, reduced it for moderate doses, and had no effect on higher doses [104,105]. Similar results were observed in rats: ADX prolonged and potentiated the detrimental effects of both IP and ICV IL-1 administration on social exploration and body weight, and under corticosterone supplementation, the potentiation was reduced, and no prolongation was observed [207].

Several lines of evidence implicate IL-1 in facilitation of pain responsiveness (hyperalgesia) [265]. Endogenous IL-1 was found to mediate the hyperalgesic effects of various inflammatory stimuli [56,164,220,242], and exogenous IL-1 administration usually produces hyperalgesia [87,195,267]. Furthermore, together with Shavit et al. [233,276], we recently demonstrated that the role of IL-1 in pain responsiveness is not restricted to inflammatory states, by showing lower basal pain sensitivity [276], as well as prolonged and potentiated morphine analgesia in mice with genetic impairments of IL-1 signaling as well as in IL-1ra-treated mice [233]. The fact that IL-1 is an important modulator of pain perception [234,265], together with its involvement in stress responses, suggests that IL-1 may mediate stress-induced pain modulation.

Pain perception, which normally promotes recuperative and defensive behaviors, may interfere with the ability of an organism to cope with threatening stimuli and conditions. Thus, it is often suppressed following exposure to a variety of stressors, a phenomenon termed stress-induced analgesia (SIA) [5]. Two studies investigated the role of IL-1 in SIA using different strategies. The first study examined the effect of ICV administration of IL-1ra on foot-shock-induced analgesia, reporting a transient blockade of SIA 10 min after shock administration [290]. In another study, we used two mice strains with impaired IL-1 signaling (IL-1 receptor-deficient mice- IL-1rKO, and IL-1ra over-expressing mice—IL-1raTG) to systematically examine the involvement of IL-1 in the analgesic responses produced by different stress intensities [277]. We showed that mild swim stress (2 min at 32 °C) induced analgesia and elevated corticosterone levels in WT mice, but not in IL-1rKO or IL-1raTG mice. In contrast, both WT and mutant strains displayed an analgesic response and elevated corticosterone secretion following severe stress (2 min at 15 °C).

3.2. Brain IL-1 underlies stress-induced memory impairment by modulating glucocorticoids secretion

Stress can profoundly modulate learning and memory functioning, as well as the neural plasticity mechanisms that underlie these processes. Acute stress can facilitate memory, particularly to stimuli associated with the stressful experience itself, and can be considered as an adaptive cognitive response that enables the organism to cope during the exposure to a stressor and on subsequent encounters with it. Conversely, stress can also impair subsequent learning, memory, and neural plasticity and can even induce profound amnesia [137]. These bi-directional effects of stress seem to involve GCs and are mainly related to the functioning of the hippocampus [52,137]. In view of the role of IL-1 in stress-induced GCs secretion, and based on recent demonstrations that IL-1 influences memory processes and hippocampal plasticity in a similar pattern to that induced by stress, it can be hypothesized that IL-1 mediates the effects of stress on memory and plasticity, possibly via of its effects on GCs production.

Over the last decade it became evident that IL-1 plays a dual role in memory processes. On the one hand, physiological levels of IL-1 are needed for memory formation and on the other hand any deviation from the physiological range, either by excess elevation in IL-1 levels or by blockade of IL-1 signaling, results in impaired memory [101,102]. Many studies have demonstrated the detrimental effect of excess IL-1 levels on memory formation using various doses (of either IL-1α or IL-1β), administration routs and species, in several memory testing paradigms [7,10,11,16,18,72,96,97,170,171,194,210,212,243,244,246]. All of these studies found the negative influence of IL-1 to be specific to memory tasks that depend on normal hippocampal functioning, whereas the performance of hippocampal-independent tasks was spared. Other studies also showed that IL-1 mediates the memory impairments caused by various inflammatory agents [97,98,200,208,209]. On the other hand, several studies by our research group as well as others demonstrated the pivotal role of low, "physiological" levels of IL-1 in hippocampal-dependent memory processes, using either pharmacological or genetic approaches [8,36,37,95,101,245,285]. The beneficial role of IL-1 in memory processes is further supported by recent reports of learning-induced induction of IL-1 gene expression in the hippocampus [72,101]. Together, these findings suggest that the influence of IL-1 on memory follows an inverted U-shape pattern, i.e., learning-associated increases in IL-1 levels are needed for memory formation; however, any deviation from the physiological range, either by excess elevation in IL-1 levels (induced by immunological, physical, or psychological stressors) or by blockade of IL-1 signaling, results in memory impairment. Similarly to the involvement of IL-1 in memory processes, an inverted U-curve pattern exists for its influence on hippocampal plasticity as well [154]; whereas some studies report a detrimental effect of elevated IL-1 levels on LTP (reviewed in [156,191], both *in vivo* and *in vitro* [22,53–55,57,59,127,130,193,260,261], others report that hippocampal IL-1 expression is induced by high frequency stimulation that also induces LTP [230] and that LTP is impaired when IL-1 signaling is blocked [8,55,154,217,230].

Many research studies examined the effects of endogenous (stress-induced) or exogenous GCs administration on hippocampal-dependent memory and plasticity, reporting that the effects of GCs on hippocampal-dependent memory and neural plasticity can be either inhibitory (particularly at high levels) or facilitatory (particularly at low levels) [41,65,66,137,138,173]. Thus, similarly to the finding on the involvement of IL-1 in hippocampal-dependent memory, GCs also exert an inverted U-shaped influence on memory and plasticity [52,73].

The findings that the influences of IL-1 and the influence of stress or GCs on memory follow the same inverted U-shape, and that stress can induce IL-1 production, which in turn activates the HPA axis, may lead to two hypotheses. First, IL-1 may mediate the effects of stress on memory, and second, adrenocortical activation may be involved in the influence of IL-1 on memory formation (both detrimental and beneficial), which is usually assessed in the context of stressful paradigms (e.g., the Morris water maze or fear-conditioning). Both hypotheses have been experimentally assessed, as described below.

Several studies assessed the hypothesis that IL-1 mediates the detrimental effects of psychological stress on memory. Maier and Watkins [163] were the first to demonstrate the role of IL-1 in stress-induced modulation of memory functioning, using the learned helplessness procedure, in which rats subjected to a severe inescapable tailshock stress displayed marked impairment in subsequent learning of an active avoidance task (i.e., they learned to be helpless) [161]. ICV administration of IL-1ra (100 μg/rat) before the inescapable shock administration blocked the development of learned helplessness [163]. The same group further showed the involvement of IL-1 in stress-induced memory impairment in the fear-conditioning paradigm, in which animals learned to associate an aversive stimulus (footshock) with either a novel context (an hippocampal-dependent memory task) or with an auditory cue (an hippocampal-independent memory task) [85,167,168]. Specifically, when rats were isolated for 5 or 6 h following fear-conditioning, contextual memory was impaired, whereas auditory-cued memory remained intact [17,210]. Mediation of this effect by IL-1 was evidenced by the increase in hippocampal IL-1β levels following social isolation, and by the rescue of the impaired contextual memory by ICV administration of IL-1ra before the isolation stress [210]. The detrimental effect of stress-induced IL-1 on hippocampal memory in this paradigm may be mediated by a reduction in BDNF levels, as isolation reduced BDNF expression in the dentate gyrus and CA3 regions of the hippocampus, but this reduction was blocked by ICV IL-1ra administration before isolation [17]. Recently, we showed the involvement of IL-1 in chronic isolation-induced memory loss [25]. We reported that chronically-isolated mice displayed impaired contextual fear-conditioning and reduced spatial memory in the water maze. Moreover, transplantation of neural precursor cells (NPCs), obtained from neonatal mice with transgenic over-expression of IL-1ra (IL-1raTG) [155] under the glial fibrillary acidic protein (GFAP) promoter (which chronically elevated hippocampal IL-1ra levels), completely rescued the stress-induced memory impairments [25].

The possible involvement of GCs in IL-1-induced memory impairment was demonstrated by two studies [243,244], reporting a concomitant modulation of the effects of IL-1 on memory and corticosterone secretion. These studies found a detrimental effect of ICV administered IL-1β on spatial memory in the water maze as well as on working memory in the radial arm maze, in which animals have to enter previously marked arms in order to get a food reward. Eight weeks of feeding with a diet enriched in the anti-inflammatory omega-3 fatty acid ethyl-eicosapentaenoic acid (E-EPA, 1%) attenuated the IL-1-induced memory impairment and blocked the IL-1-induced increase in serum corticosterone concentration [243,244], suggesting that this increase is involved in the effect of IL-1 on memory. This hypothesis was later substantiated by showing that IL-1-induced memory impairment in the radial arm maze was blocked when IL-1 was co-administered with the GC receptor antagonist RU486 [246].

The role of GCs in IL-1-induced memory improvement was directly assessed using GC receptor blockade: Song et al. [245] reported improved contextual passive avoidance response concomitantly with increased corticosterone secretion in rats that were ICV injected with IL-1β. However, when IL-1β was co-administered together with RU486, the beneficial effect on memory was eliminated, as was the increase in corticosterone levels [245]. Additionally, IL-1rKO mice, which displayed impaired memory performance [8], also showed diminished corticosterone secretion in response to mild stressors [103], suggesting that impaired HPA axis activation may mediate the poor memory performance of these mice.

To conclude, the findings reported to date show that on the one hand IL-1 mediates the detrimental effects of stress on memory, and on the other hand HPA axis activation, which affects memory in an inverted U pattern similarly to IL-1, may be involved in both the detrimental and the beneficial effects of IL-1 on memory formation (which were assessed using stressful paradigms). Based on all the data presented in this section, the following model may be proposed: Stressful stimuli induce an increase in brain IL-1 levels, which in turn contribute to the activation of the HPA axis. Subsequently, the secretion of GCs affects memory and plasticity processes in an inverted U-shaped pattern (Fig. 2).

3.3. Brain IL-1 mediates stress-induced depression via adrenocortical activation

One of the major deleterious consequences of chronic stress, in both human and animal models, is the development of depressed mood and behavior. Indeed, exposure to stressors in humans, particularly in individuals with genetic vulnerability, has a substantial causal association with major depression [47,133,136].

Over the last decade, several lines of evidence have implicated inflammatory processes in general, and IL-1 in particular, in the etiology and pathophysiology of depression associated with immunological stressors, including: (1) A high incidence of depression in medical conditions characterized by inflammation and IL-1 production, particularly within the brain [64,226,280]. (2) Induction of depressive symptoms in cytokine treated cancer and hepatitis-C patients, which can be reversed by antidepressant treatment [33,44,185] (3) Cytokine-related induction of depressed mood in normal subjects following experimental exposure to immune challenges [182,213,232]. (4) Studies in experimental animals, showing that exposure to various immune challenges, as well as exogenous administration of IL-1, either peripherally or directly into the brain, produce depressive-like symptoms, which can be attenuated by chronic treatment with antidepressant drugs [48,175,280–282], as well as by pretreatment with cytokine antagonists, particularly IL-1ra, and by manipulations in IL-1 family genes [62,113,204,284]. Taken together, these findings suggest that under conditions of immune activation due to physical illnesses, the production of IL-1 contributes importantly to the induction of depressive symptomatology.

Additional evidence indicates that the role of IL-1 is not restricted only to immune activation-associated depression. Specifically, elevated levels of inflammatory markers, particularly IL-1, were found in patients with major depression or minor depression (dysthymia), and those levels were correlated with the severity of depression, the duration of the current depressive episode, and the age of disease onset [6,34,113,150,158,199,226,255]. Furthermore, genetic association was demonstrated between genes of inflammatory factors, including polymorphisms in IL-1 family

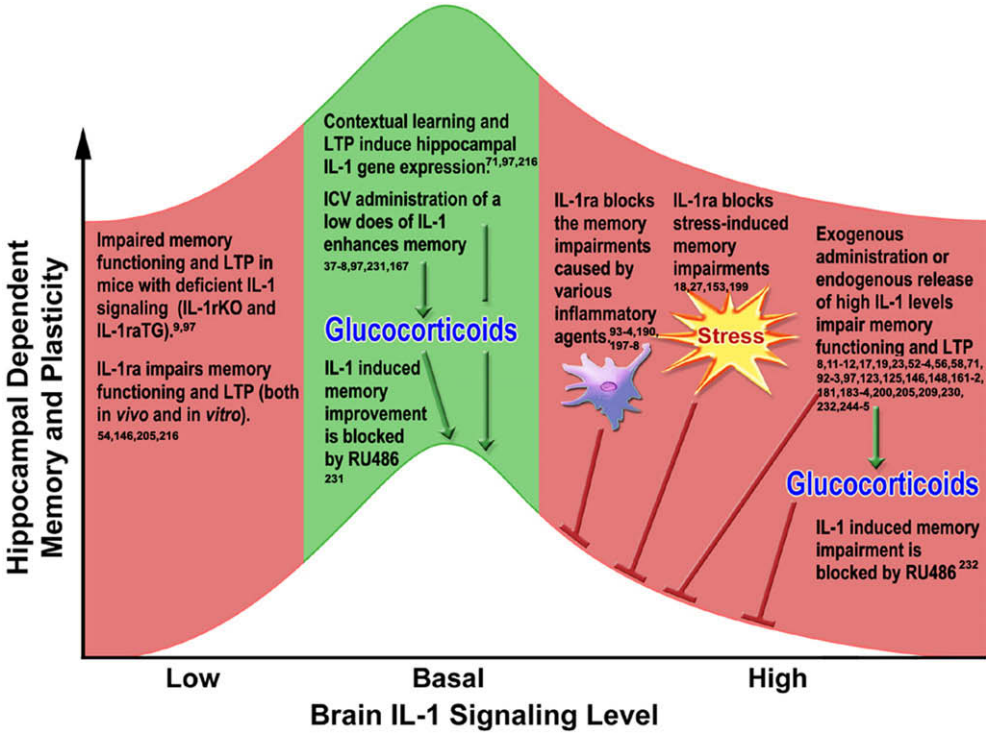

Fig. 2. The inverted U-shaped effect of IL-1 on memory and plasticity is mediated by glucocorticoids. The influence of IL-1 on memory and plasticity follows an inverted U-shape pattern, i.e., learning-associated increase in IL-1 levels is needed for memory formation (green), whereas any deviation from the physiological range, either by excess elevation in IL-1 levels or by blockade of IL-1 signaling, results in memory and plasticity impairment (red). Low dose GCs can also facilitate memory, whereas chronic or severe stressors, as well as high GC levels, can impair memory and neural plasticity. Studies on the implications of the interaction between stress, IL-1 and GCs on memory and plasticity show that IL-1 mediates the detrimental effects of stress on memory, and that GCs are involved in both the detrimental and the beneficial effects of IL-1 on memory formation. Based on these studies, the following model is proposed: stressful stimuli induce an increase in brain IL-1 levels, which in turn contributes to the activation of the HPA axis. Subsequently, the secretion of GCs affects memory and plasticity processes in an inverted U-shaped pattern.

genes, and severity of depression and its responsiveness to antidepressant treatment [287].

A direct involvement of IL-1 in stress-induced depression has been reported so far only in studies with animal models, which are always stress-related, i.e., the depressive-like symptoms appear as a consequence of exposure to either acute or chronic stress [188]. For example, in the chronic mild stress (CMS) model developed by Willner [272,273], and the chronic unpredictable stress (CUS) adapted from it, rodents are repeatedly exposed to a random set of relatively minor stressors (e.g., cage tilt, soiled cage, noise in the room, flashing light) for at least 4 weeks. These models resemble human depression in its long duration, the depressive-like symptoms that are induced, particularly anhedonia (diminished capacity to experience pleasure)) [63], and their responsiveness to chronic antidepressant therapy [272,273]. Other animal models of depression, such as learned helplessness, employ more severe uncontrollable stressors, which are administered acutely, assessing the consequent development of helplessness and despair several days later [161,169,198,231,236]. The forced swim test developed by Porsolt [205,206] examines the response to stress on an even shorter time scale (5 min).

The first demonstration of the involvement of IL-1 in stress-induced depression was provided by Maier and Watkins, who reported that shock-induced learned helplessness was reduced following ICV administration of IL-1ra [163]. We have recently demonstrated a critical role for IL-1 in chronic stress-induced depression. First, we showed that exposure to the CMS regime induced IL-1 protein secretion in the hippocampus [100], similarly to the increase in peripheral IL-1 levels found in depressed patients [150,199,255]. The physiological significance of this increase in IL-1 protein levels following CMS was demonstrated by the findings that IL-1rKO and IL-1raTG mice, which were previously shown not to respond to either exogenous or endogenous IL-1 [145,155], display no depressive-like symptoms such as decreased sucrose preference (reflecting anhedonia) or reduced social exploration, following exposure to CMS [100]. Because IL-1ra over-expression in IL-1raTG mice is under the GFAP promoter and therefore restricted to the CNS, it can be concluded that central, rather than peripheral IL-1 production and actions are mediating the depressive-like effect of CMS. A recent study found similar results using the CUS paradigm [141], reporting no CUS-induced decrease in sucrose consumption in IL-1rKO mice. Furthermore, they demonstrated the role of IL-1 in CUS-induced depression in rats using a pharmacological strategy, by showing that chronic ICV IL-1ra administration prevented CUS-induced anhedonia [141].

We also demonstrated that IL-1 is not only necessary, but also sufficient for the manifestation of depressive symptoms, as mice that were chronically administered with IL-1 via osmotic minipumps for 4 weeks, without any exposure to stressors, demonstrated depressive symptoms similar to those expressed in mice that were exposed to CMS [100]. The finding that chronic IL-1 induces a depressive-like condition coincides with previous research demonstrating that acute exogenous administration of IL-1 produces anhedonia in rodents, reflected by reduced preference for sweet solutions and reduced libido [9,175]. The relevance of these findings to depression is further demonstrated by the ability of chronic antidepressant therapy to block IL-1-induced anhedonia [175].

In humans, the relations between stress and depression are reflected by the marked activation of the HPA axis exhibited by depressed patients [15,45,81,157], which can be normalized following successful antidepressant therapy [116,214,228,286].

Furthermore, many patients with major depression exhibit hypersecretion of cortisol and its metabolites [94,219], and treatment with the GC antagonist mifepristone is effective in some forms of depression [28]. Other clinical observations show that patients with Cushing's syndrome, which results in hypercortisolemia, as well as patients with other diseases who are treated with high doses of GCs, often experience severe depression [76,99]. Using the CMS model of depression in mice, we examined the possibility that dysregulation of the HPA axis underlies the involvement of IL-1 in depression. We showed that WT mice exhibited increased corticosterone levels following CMS, similarly to the hypercortisolism found in depressed patients [15,45]; however, no such increase was observed in IL-1rKO mice, concomitant with their blunted behavioral depressive symptoms. The necessity of corticosterone in CMS-induced depression was further demonstrated by the lack of depressive symptoms in adrenalectomized mice [100]. Another recent study reported that administration of the GC receptor antagonist mifepristone (RU-486) eliminated the CMS-induced decrease in sucrose preference and open field exploration, and blocked the alterations in synapsin-1 in different hippocampal areas [279]. Together, these studies indicate that at least in the CMS model, GC secretion is causally related to the development of the depressive symptoms. This conclusion is further strengthened by the finding that chronic corticosterone administration results in depressive symptoms similar to those displayed by mice exposed to CMS [100]. The concomitant absence of CMS-induced depressive-like symptoms and corticosterone secretion in IL-1rKO, along with the findings that adrenalectomy blocked CMS-induced depression whereas chronic corticosterone mimicked the effects of CMS in both WT and IL-1rKO mice, demonstrates that chronic elevation in corticosterone levels are both necessary and sufficient for producing depressive symptoms, thus strongly implicating corticosterone as the downstream mediator of IL-1's involvement in CMS-induced depressive symptoms.

The data presented above suggest that elevated levels of brain IL-1 are causally related to various aspects of depression, including the behavioral symptomatology, adrenocortical activation, and reduced neurogenesis (see below). Based on these findings, two suggestions may be made: First, the elevated IL-1 levels observed in depressed patients who are not physically ill [150,199,255] are not merely a byproduct of the depressive symptomatology, but may be caused by chronic life stressors and play a direct role in the induction of depression. Second, antidepressant therapy may produce at least some of its beneficial effects on behavioral depression, as well as the normalization of the HPA axis functioning and neurogenesis, by modulating IL-1 signaling. Moreover, manipulations and interventions that directly modulate IL-1 signaling may provide novel preventive and therapeutic procedures for alleviating depression (Fig. 3).

3.4. Stress-induced IL-1 reduces hippocampal neurogenesis: implications for memory impairments and depressive behavior

The formation of new neurons in the adult brain, a process termed neurogenesis [109,111,132], was implicated in both cognitive functioning and depression. Impaired hippocampal neurogenesis has been reported following exposure to various acute and chronic stress protocols [75,78,92,108,180], as well as to corticosterone administration [123,278]. Adrenalectomy, on the other hand, induces a burst of hippocampal cell proliferation in the short term [42,143]. Similarly, immune activation was recently demonstrated to have a detrimental influence on neurogenesis, suggest-

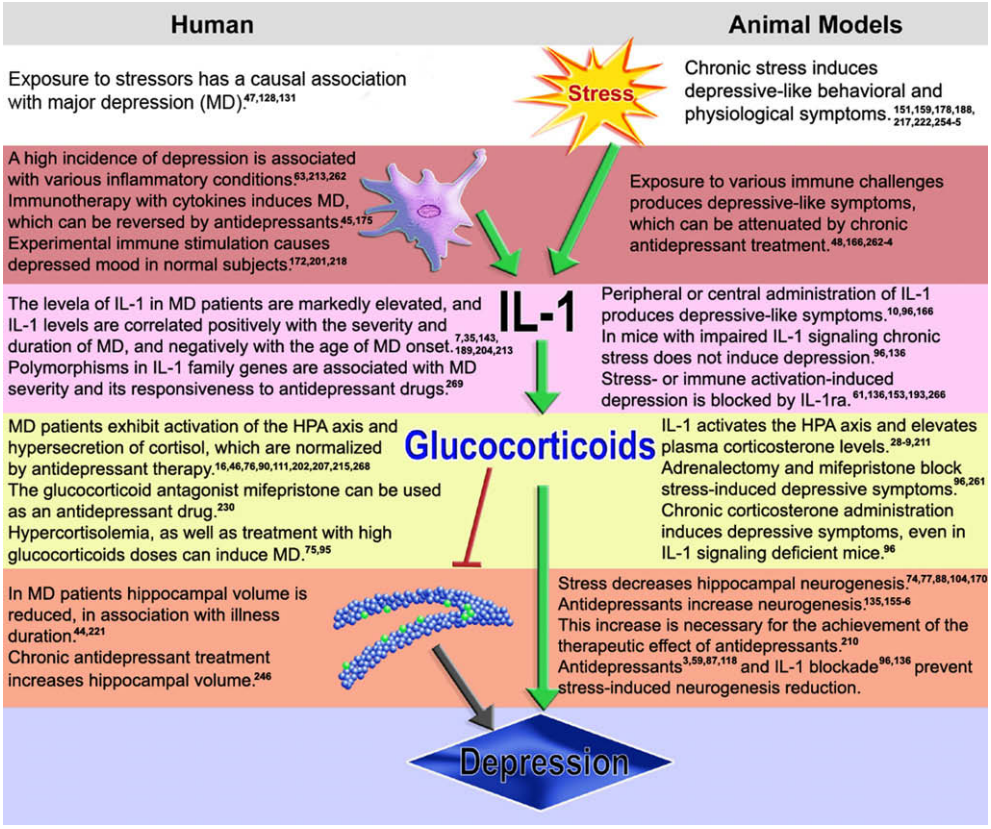

Fig. 3. Brain IL-1 mediates stress-induced depression via adrenocortical activation. One of the major deleterious consequences of chronic stress and immune activation is the development of depression, which involves IL-1-induced glucocorticoids secretion, and possibly decreased neurogenesis. The figure summarizes the literature showing that the interplay between stress, IL-1 and HPA axis activation underlies the development of depressive behavior, in both humans and animal models.

ing a negative role for pro-inflammatory cytokines on this process. Specifically, microglia, the macrophage-like cells within the brain, were suggested as the mediators of this detrimental effect [131]. Moreover, treatment with IL-1 inducers, including LPS and radiation, resulted in marked suppression of hippocampal neurogenesis [82,181]. We [100] as well as others [141] provided direct evidence for the influence of IL-1 on neurogenesis by showing that both acute and chronic IL-1 exposure (4 weeks via osmotic minipumps) results in impaired hippocampal cytogenesis and neurogenesis. The mechanisms underlying the effects of IL-1 on hippocampal neurogenesis were recently investigated [141]. It was found that IL-1RI is expressed *in vivo* by proliferating cells and neuronal progenitors in the sub-granular zone of the hippocampus. *In vitro*, IL-1RI is expressed by all the proliferating primary cultured adult hippocampal progenitors (AHPs), and activation of this receptor by IL-1β results in a decreased percent of proliferating AHPs in the culture. Furthermore, it was reported that this anti-neurogenic effect is mediated by activation of NfκB signaling pathway, and can be blocked by IL-1ra [141].

Based on the similar effects of stress and IL-1 on neurogenesis, and the induction of IL-1 by stress, it was hypothesized that IL-1 mediates the anti-neurogenic effect of stress, an hypothesis that was recently confirmed by several studies [25,100,141]. A role for IL-1 in mediating the effects of acute stress was recently demonstrated by showing that IL-1ra administration blocks the decrease in neurogenesis induced by two acute stressors (footshock and immobilization) in rats [141]. Similar protection from the anti-neurogenic affect of acute stress was found in IL-1rKO mice as well [141]. We have recently shown that IL-1 mediates the detrimental effect of isolation stress on hippocampal neurogenesis, and demonstrated its functional significance for memory processes. As detailed above, subjecting mice to chronic isolation stress elevated hippocampal IL-1 levels and impaired contextual fear-conditioning. Furthermore, chronic isolation stress produced a dramatic decrease in hippocampal neurogenesis [25], considered an important mechanism for hippocampal-dependent learning and memory [2,238]. However, intrahippocampal transplantation of IL-1raTG neural precursor cells, which chronically elevated the levels of IL-1ra throughout the stress exposure period, thus blocking IL-1 signaling, completely abolished the detrimental effect of isolation stress on neurogenesis, and blocked the cognitive impairment [25].

Impaired neurogenesis may also underlie the involvement of IL-1 in CMS-induced depression. In recent years, impaired hippocampal neurogenesis has been implicated in major depression [75,77,78,120,221], mainly based on studies in rodents, demonstrating that: (1) Chronic administration of antidepressants increased neurogenesis in the rat dentate gyrus [140,165,166]. (2) Antidepressants prevented the reduction in neurogenesis in models of stress-induced depression [3,60,91,122]. (3) Normal levels of neurogenesis are required for the behavioral effects of antidepressants [222]. These findings may be also related to the reduction in hippocampal volume in patients with major depression, which correlates with the length of illness [43,235], and the finding that chronic antidepressant treatment can increase hippocampal volume [262].

In support of a role for neurogenesis in stress-induced depression, we found that CMS reduced hippocampal cytogenesis and neurogenesis in WT mice, but not in IL-1rKO mice, concomitantly with the lack of depressive symptoms in these animals [100]. Similar findings of a simultaneous lack of anhedonia and protection from decreased neurogenesis in IL-1rKO mice was reported following CUS as well [141]. Furthermore, chronic ICV IL-1ra administration prevents the detrimental effect of chronic unpredictable stress on both hedonic behavior and neurogenesis in the hippocampal dentate gyrus [141]. Together with the findings on the effects of chronic IL-1 administration on neurogenesis [100,141] these findings demonstrate that IL-1 is both necessary and sufficient for chronic stress-induced suppression of hippocampal neurogenesis. Corticosterone probably acts as a downstream mediator for the effect of IL-1 on neurogenesis, as demonstrated by the finding that chronic corticosterone administration resulted in impaired neurogenesis in both WT and IL-1rKO mice [100] (Fig. 2).

4. The involvement of IL-1 in immunological and psychological stress: an evolutionary perspective

The relationships between immune activation, IL-1, and stress responses may best be viewed in an evolutionary context. The immune system, with its responsiveness to physical stressors such as injury and infection, exists even in the most primitive organisms and is probably more ancient in evolutionary terms than the fight or flight stress response systems [160]. Indeed, many phylogenetically ancient species, including sponges, mollusks, and insects produce IL-1 and related pro-inflammatory cytokines [274]. In these animals, IL-1 is produced by hemocytes, which are macrophage-like phagocytic cells that constitute the principal-host defensive response against microbial invaders [197]. At sites of injury and infection, hemocytes were shown to produce IL-1β [50,119], which plays a major role in promoting the inflammatory response [20]. Interestingly, molluscan hemocytes also produce stress-like hormones, including CRH, ACTH, GCs, and catecholamines [196]. In these cells, IL-1β seems to precede and induce the production of these hormones, which are all secreted by the same cell. During evolution, the relationship between immunologically-induced IL-1 and hormone production was adopted by neural systems that mediate the responsiveness to various physical and psychological stressors. Furthermore, even following the evolutionary development of a central nervous system that is separated from the periphery by a blood–brain barrier, which limits the ability of peripherally-produced IL-1 to influence neuroendocrine and behavioral systems, IL-1 still retained its intimate relationship with stress responsive systems. This was achieved by the development of immune-to-brain communication pathways that enable peripherally-produced IL-1 to induce the central production of IL-1, which in turn can activate the neuroendocrine and neurobehavioral responses to stress [160].

The behavioral and physiological components of the stress response (e.g., fight or flight) pose great metabolic challenges for organisms, requiring release of stored energy into the blood and its enhanced utilization by relevant tissues, such as the muscles and the brain. Preparation of the organism to meet these challenges and facilitation of the metabolic responses to stressors are primary functions of HPA activation and GC secretion. Specifically, GCs enhance and prolong the increase in blood glucose due to epinephrine and glucagon and enhance the cardiovascular activation induced by the sympathetic nervous system, promoting faster and more efficient distribution of glucose and oxygen to stress-relevant tissues [225]. As detailed above, in the context of immune activation as well as many physical and psychological stressors, IL-1 production and secretion seem to be upstream to HPA activation, and therefore may be considered a primary mechanism enabling the satisfaction of stress-associated metabolic and behavioral demands.

In addition to its metabolic influence via stress hormones, IL-1 was found to directly modulate metabolic processes. In particular, the local production of IL-1 stimulates glucose uptake, in an insulin-independent way [71]. This function may serve an important role because stress-induced GCs produce a general decrease in glucose uptake, which counter-regulates insulin's hypoglycemic effects. It is possible that IL-1-induced glucose uptake in tissues that are particularly relevant for the stress response (e.g., sites of

intense immune activation, muscles and brain) provides a means to counteract the effect of GCs on glucose uptake. Furthermore, a local increase of IL-1 levels seems to follow intense neural stimulation, as exemplified by the induction of IL-1 gene expression following the induction of LTP [230] and learning [101]. Thus, during stress, the secretion of IL-1 may constitute a mechanism for the coupling of the high metabolic demands of intense stress-induced neural activation in specific brain locations.

Although IL-1-mediated metabolic changes are adaptive under acute stress conditions, these changes may have deleterious consequences during chronic activation. Under such conditions, which may be due to chronic stress exposure or due to impairments in mechanisms that normally counteract stress-induced behavioral suppression, brain cells may be exhausted by the chronically elevated metabolic utilization, leading to impaired plasticity, reduced neurogenesis, and depression.

5. Summary and conclusions

Stress responses provide crucial and essential means for adaptation and survival in the constantly challenging and demanding environment that characterizes the life of most organisms. The physiological substrate that underlies the responsiveness to various stressors is quite complex. The present review demonstrates that IL-1 is one of the most critical molecules involved in neuroendocrine and neurobehavioral stress responses. Specifically, ample evidence from both human and experimental animal studies demonstrates that many types of stressors, including immunological, physiological and psychological challenges, induce the production of IL-1, both in the periphery and within the brain. The mechanisms underlying stress-induced IL-1 production are not fully elucidated but it is suggested that stress-induced stimulation of NE secretion within the brain, acting via β-adrenergic receptors, can trigger a rapid *de novo* production and/or secretion of pre-stored IL-1, and that the cellular source of both immunological and psychological stress-induced brain IL-1 is activated microglia.

Stress-induced IL-1 production affects many physiological and behavioral systems. Interestingly, many of these IL-1-mediated effects, including neuroendocrine modulation, fever, alterations in peripheral immune parameters, and sickness behavior symptoms, are shared by both immunological and psychological stressors. One of the primary effects of stress-induced elevation in brain IL-1 is the activation of the HPA axis. This activation seems to involve the effects of IL-1 on hypothalamic noradrenergic neurotransmission, suggesting that the relationship between brain IL-1 and noradrenergic systems is bi-directional. Stress-induced IL-1-mediated secretion of glucocorticoids alters various neurobehavioral processes. In particular, IL-1 plays an important role in stress-induced modulation of memory functioning. Specifically, low levels of brain IL-1 (which may be elicited by exposure to the stress-associated with aversive learning paradigms) promote memory consolidation whereas high levels of stress-induced IL-1, particularly in chronic situations, impair memory consolidation. These effects of IL-1 are specific to memory that depends on the integrity of the hippocampus and are associated with parallel alterations in hippocampal LTP. Elevation in IL-1 levels following chronic stress exposure induces depressive symptoms, also via the secretion of glucocorticoids. Finally, brain IL-1 mediates the effects of both chronic and acute stressors on hippocampal neurogenesis, which in turn may be involved in memory impairments and depressive behavior. The findings presented in this review suggest that whereas under some physiological conditions low levels of IL-1 promote the adaptive stress responses necessary for efficient coping, under severe and chronic stress conditions IL-1 mediates several detrimental cognitive and emotional effects of stress. Thus, blockade of IL-1 signaling can be used as a preventive and therapeutic procedure for alleviating stress-associated neuropathology and psychopathology.

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