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Review

Modulation of Neural Networks by Interleukin-1

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Abstract. Interleukin-1 (IL-1) is an inflammatory cytokine that has been shown to modulate neuronal signaling in homeostasis and diseases. In homeostasis, IL-1 regulates sleep and memory formation, whereas in diseases, IL-1 impairs memory and alters affect. Interestingly, IL-1 can cause long-lasting changes in behavior, suggesting IL-1 can alter neuroplasticity. The neuroplastic effects of IL-1 are mediated via its cognate receptor, Interleukin-1 Type 1 Receptor (IL-1R1), and are dependent on the distribution and cell type(s) of IL-1R1 expression. Recent reports found that IL-1R1 expression is restricted to discrete subpopulations of neurons, astrocytes, and endothelial cells and suggest IL-1 can influence neural circuits directly through neuronal IL-1R1 or indirectly via non-neuronal IL-1R1. In this review, we analyzed multiple mechanisms by which IL-1/IL-1R1 signaling might impact neuroplasticity based upon the most up-to-date literature and provided potential explanations to clarify discrepant and confusing findings reported in the past.

Keywords: Neurogenesis, LTP, synaptogenesis, IL-1RAPL1, neuroimmune

INTRODUCTION

Interleukin-1 (IL-1) is a master inflammatory cytokine that regulates all aspects of immunological responses of the host against infection and injury [1]. Its neuromodulatory role was first discovered in studies investigating the mechanisms of mammalian sickness symptoms, such as fever, lethargy, social withdrawal, anhedonia, hypophagia, increased secretion of glucocorticoids, and increased slow wave sleep [2]. Sickness symptoms are a set of auxiliary adaptive anti-infection changes controlled by the central nervous system (CNS) to conserve energy, avoid further opportunities of infection, and shift host's overall biology towards anti-infection metabolism and activity [2]. Even when sickness symptoms/behaviors are caused by immune activity confined to the periphery, the expression of IL-1 can be found in the brain, where it orchestrates many of these responses [3, 4]. For example, brain IL-1 can activate neurons of the preoptic area-raphe pallidus circuit to induce fever [5, 6], stimulate the paraventricular nucleus of the hypothalamus to activate the hypothalamus-pituitary-adrenal gland axis (HPA) to induce glucocorticoids secretion [7], and modulate the hypothalamic feeding control center to cause hypophagia [8, 9]. These neuromodulatory actions are also operative when there are inflammatory activities in the brain itself, such as those during brain injury [10] or after bacterial or viral infection of the CNS [4, 11, 12]. These evidences suggest neural functions of IL-1 are designed to coordinate immunological activities with physiological

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and behavioral outputs through its actions in the CNS. Interestingly, these adaptive changes may even occur under conditions that are not directly related to an immune activation. For example, acute [13] or chronic [14] psychological stress can also induce brain IL-1 expression, which causes some of the responses resembling sickness symptoms. Thus, neuromodulatory functions of IL-1 may be called upon under a broader set of circumstances that imply the presence of danger to produce a shared set of CNS-controlled host defense responses.

In general, the neural responses to acute sickness are brief and occur immediately when homeostasis is disturbed by infection or stress, suggesting IL-1 could serve as an additional input to neural circuits regulating the relevant physiological and behavioral systems to transiently alter their outputs, producing the protective sickness symptoms. Further investigation of the CNS functions of IL-1 revealed that IL-1 has neuroregulatory roles beyond transitory activities during isolated inflammatory or stressful events. For example, IL-1 levels were found to vacillate with circadian rhythm [15] and influence normal sleep [16, 17]. In addition, a sickness event can cause delayed and lasting changes in cognition and IL-1 was found to play a critical role in the altered processes of learning and memory [18], the consequences of which could affect the nervous system long after the initial triggering infectious or stressful events. For such temporally discontinuous neuromodulatory actions of IL-1 to occur, IL-1 cannot simply act as an additional input to be conducted through existing neuro-circuitries, it must be able to alter the structure of neurocircuitry itself. This possibility is highlighted by the fact that during development, a period when neurocircuits are built and extensively modified, induction of IL-1 causes profound changes in the trajectory of neurodevelopment, resulting in behavioral phenotypes resembling psychological disorders later in life [19–21]. Alteration of neural networks can also occur during adult life and this phenomenon has been termed neuroplasticity. How IL-1 might cause changes in neuroplasticity is the focus of this review.

BASICS OF NEUROPLASTICITY

Classical neuroplasticity was originally conceived by Hebb who suggested coordinated activity between the pre- and postsynaptic neurons strengthens their connection [22]. This "fire together, wire together" hypothesis suggests that certain types of neuronal activities can result in changes of neuronal networks such that dynamic responses of neurons are shaped by prior activation history. Since then, a large literature has been developed to investigate the molecular and structural underpinnings of neuroplasticity and to define the ways neuronal connectivity can be modified. Presently, neuroplasticity is examined from two perspectives: 1) functional plasticity—changes in neuronal excitability; 2) structural plasticity—anatomical changes to neuronal circuits, such as addition or removal of cells or synapses. Overall, neuroplasticity encodes pro-survival information, allowing organisms to learn, retain memories, and predict outcomes based upon prior experiences. It is critical for the maintenance of the learned behavior.

Birth and death of neurons

The founder of modern neuroscience, Ramon y Cajal, famously stated in 1928: "Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree [23]". This sentiment was held firm by neuroscientists for decades. However, breaking the historical status quo, Altman and Das showed incorporation of centrally injected thymidine-H^3 into the DNA of proliferating cells of adult rat dentate gyrus and suggested that new neurons can be generated in adult brain [24]. Later studies substantiated this notion of adult neurogenesis using other proliferation markers, such as Bromodeoxyuridine (BrdU) [25, 26]. These studies located adult neurogenesis in discrete areas of the CNS, neurogenic niches. The best-known neurogenic niches are located in the subventricular zone and the hippocampal subgranular zone. The newly generated neurons can migrate from the neurogenic niches to incorporate into existing neuronal networks [27], creating a form of structural neuroplasticity. This neuroplastic process may be crucial for cognitive and affective behaviors. Experimental studies have shown: 1) chemical or genetic ablation of neural progenitor cells (NPC) impairs learning of normal animals [28] and cognitive recovery in animals with brain injury [29]; 2) preservation or enhancement of neurogenesis ameliorates depressive-like behaviors in animal models of stress [30, 31] and enhanced learning in exercising animals [32]. Neurogenesis

is now confirmed in many species including fish, reptiles, birds, rodents, non-human primates and humans [40]. Thus far, neurogenesis has been implicated in the consolidation of new memories [33, 34], modification of cognition [35, 36], generation of positive affect [37], and reorganization of neural circuits after injury [38, 39]. Typically, neurogenesis is visualized by immunohistochemical labeling of proliferation markers, proliferation related proteins, immature cell markers, or by retroviral fluorescent labeling of dividing cells [41]. Although neuroplasticity is typically associated with the birth of new neurons, it is significantly influenced by the death of neurons as well because both addition and subtraction of neurons to neural networks alters neural structures. The loss of neurons via necrosis and apoptosis occur following traumatic brain injuries [42], excitotoxic injuries [43], substance abuse [44], and ischemia [45]. In animal models of disease and injury, presence of dying cells correlates with the deficits in regulation of memory and affect, implicating neuronal death in functions dependent on neuroplasticity.

Synaptic structure

Synapses are physical spaces between neurons that allow them to transmit chemical signals from one cell to the next. Synaptic communication or neurotransmission consists of pre-synaptic neurotransmitter production and release followed by a neurotransmitter receptor mediated response in the postsynaptic neuron. Synaptic plasticity is a driving force that contributes to dynamic changes in neurocircuitry that underlie complex cognitive behaviors [46, 47]. Aberrant changes to synaptic structures can be the cause of behavioral abnormalities, such as depression and anxiety [48, 49]. Enduring alterations in synaptic structure can occur in one of three ways: 1) creation and elimination of synapses, 2) alteration of synaptic morphology, and 3) changes to synaptic adhesion. Synaptogenesis, the generation of new synapses, which often manifests as newly formed synaptic spines, occurs on the timescale of days to weeks, thus providing a delayed and lasting effect on neural networks. The importance of proper synaptic network formation is exemplified in neurodevelopmental disorders such as autism spectrum disorder and X-linked mental retardation, where affected individuals have either vastly more [50, 51] or less dendritic spines [52], respectively. In addition, appropriate synaptic elimination, synaptic pruning, is critical to sculpt efficient neural circuits. For example, Huttenlocher et al. found experience-dependent visual learning requires elimination of under-used synapses [53]. Interestingly, synaptic pruning is modulated by glial cells. Recent studies have shown microglia actively engulf synapses in both health [54] and disease [55, 56] and was found essential for memory creation [57] and forgetting [47].

The morphology of synapses, especially spine morphology, can be visualized and analyzed. Dendritic spines can be classified as stubby, mushroom, thin, and filipodia. Each type of spine is suggestive of the maturity of a dendritic spine. Typically, mushroom spines are stable excitatory synapses whereas thin spines or filipodia are immature and unstable [58, 59]. Abnormal amount of certain type(s) of spine morphology have been observed in humans with neurodevelopmental disease, schizophrenia, and Alzheimer's disease [60, 61]. Another parameter of synaptic structure is synaptic adhesion. Synaptic adhesion proteins contribute to the formation and maintenance of synapses [62]. Perturbations of neuronal adhesion are associated with impaired [63, 64] or exaggerated synaptic growth [65] which have been found in brains of patients with mental health diseases like addiction [66] and schizophrenia [67]. Synapses can be visualized by immunolabeling of synaptic proteins, by viral or genetic neuronal expression of reporter fluorescent proteins, and by electron microscopy. Synaptic adhesion has been studied in cultured cells expressing synaptic adhesion molecules.

Neuronal excitability

From the functional perspective, neuroplasticity is measured by the altered relationship between presynaptic inputs and postsynaptic responses — amplified or diminished excitability. Classic examples of functional plasticity are long term potentiation (LTP) and long term depression (LTD). During LTP the postsynaptic response is enhanced by a prior tetanus stimulus, a high frequency stimulation. Following the tetanus stimulation, influx of high levels of calcium is induced in the postsynaptic neuron to activate downstream signaling and change the postsynaptic receptor composition, especially AMPA receptors (AMPAR) and NMDA receptors (NMDAR), resulting in increased excitability of the postsynaptic membrane. During LTD, on the other hand, the postsynaptic response is suppressed after a low frequency stimulus conditions the postsynaptic neuron to hyporespond to input stimulation. Influx of low levels

of calcium following the low frequency stimulation causes phosphatases in the postsynaptic neuron to inhibit pathways that recruit AMPAR, thus causing decreased postsynaptic responses [68]. LTP and LTD play crucial roles in the generation of lasting memory, in cognitive function, and in mood disorder [69]. Beyond LTP and LTD, changes in resting membrane potential, ion channels, surface receptors, and rate of neurotransmitter clearance can also influence neuronal excitability. These influencers of excitability are clinically significant. Treatment for bipolar disorder alters resting neuronal membrane potential [70]; mutations in ion channels are known to contribute to the etiology of epilepsy [71]; alterations of AMPA/NMDA receptor ratio influences memory [72]; and abnormal neurotransmitter clearance is implicated in both depression [73] and excitotoxic injury [74]. Traditionally, LTP and LTD are measured using electrophysiological recordings in a slice preparation or *in vivo*. Other electrophysiological methods, such as whole cell patch clamp, are used to measure neuronal excitability. Additionally, imaging techniques have been employed to visualize neuronal calcium influx *in vitro* and *in vivo* [75].

INTERLEUKIN-1 AND NEUROPLASTICITY

Several lines of research suggest IL-1 modulates neuroplasticity. Under physiological conditions, IL-1 levels are known to oscillate throughout the day [15]. Deletion of IL-1 receptor decreases sleep while central administration of IL-1, at low picogram levels, increases slow wave sleep in rodents [76, 77]. IL-1 has been found to be induced by learning processes [78] and is critical for spatial [79], but not associative learning [80], suggesting specific neural circuits are susceptible to modulation by IL-1. Furthermore, blockade of IL-1 signaling has been shown to impair memory consolidation [78, 81]. Therefore, these findings support a role for IL-1 in regulating physiological neuroplasticity in the generation of memory. In contrast, in models of severe stress [14, 82], brain injury [83, 84], or IL-1 overexpression [85], IL-1 was found to impair memory. These conditions are associated with significantly induced brain IL-1 expression, suggesting IL-1 at pathological levels might exert opposite effects on memory versus its physiological effects. At nanogram levels, central IL-1 elicits robust neuroinflammatory responses, such as leukocyte infiltration, microglial activation, and additional cytokine production [86]. Interestingly, mental

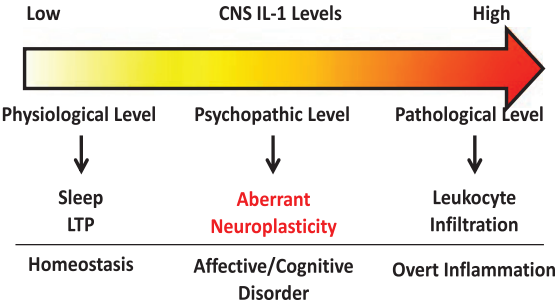

Fig. 1. Schematic of concentration dependent IL-1 signaling within the CNS.

health diseases like chronic fatigue [87, 88], depression [89, 90], anxiety [91, 92], and panic disorder [93] have all been linked with elevated brain IL-1. However, in these diseases overt neuroinflammatory responses are often not found, but above normal IL-1 levels are present [90]. Thus, a spectrum of IL-1 activities may exist depending on its concentration. We propose that very low IL-1 concentrations regulate normal physiological functions whereas very high IL-1 concentrations cause overt neuroinflammation. In between, chronically elevated IL-1 above physiological levels may alter neuronal plasticity and is important for the pathogenesis of psychopathology (See Fig. 1). In this review, we will dissect the diverse modalities by which IL-1 regulates neuroplasticity.

Essential to understanding how IL-1 influences neuroplasticity, it is important to understand how IL-1 mediates intracellular signaling and how IL-1 receptors are distributed in the brain. IL-1 exists in two isoforms, IL-1α and IL-1β. They both bind to a single receptor, the type 1 Interleukin-1 Receptor (IL-1R1) to mediate signaling. IL-1/IL-1R1 complex recruits IL-1R1 accessory proteins (IL-1RAcP). IL-1RAcP also exists in two isoforms, IL-1RAcP and IL-1RAcPb. IL-1RAcP is known to recruit the adaptor protein, MyD88, which initiates activation of pathways such as NFκB and p38-MAPK. IL-1RAcPb prevents the recruitment of MyD88 and IL-1R1/IL-1AcPb complex signals through pathways such as AKT [94] or Src [95]. Interestingly, IL-1RAcPb is expressed specifically in neurons [96] and is up to 1000 times more sensitive to IL-1 than IL-1RAcP [95]. Therefore, IL-1 could stimulate neurons and non-neuronal cells very differently via different downstream signaling pathways and elicit dramatically different sensitivities on these cell types. Originally, IL-1R1 expression was thought to be ubiquitously expressed throughout the CNS

[97]. However, using advanced genetic reporter we showed that IL-1R1 expression is restricted to specific endothelial cells, ventricular cells, astrocytes, and neurons in discrete subpopulations of the CNS [86, 98]. Restricted neuronal IL-1R1 expression suggests direct neuronal modulation by IL-1 is limited to select neuronal circuits. In this review, we will utilize this new information to analyze the direct versus indirect mechanisms by which IL-1 alters neuroplasticity.

IL-1 and neurogenesis

In non-neuronal cells, IL-1 can induce the proliferation of bone marrow derived mesenchymal stem cells [99, 100]. In neural tissue, on the contrary, *in vitro* data shows IL-1 is a potent inhibitor of NPC proliferation [101–104] suggesting the action of IL-1 is anti-neurogenic. Indeed, CNS IL-1 induction by bacterial [105, 106] and viral [11] infection, stress [107, 108], radiation [109, 110] and neurodegeneration [111] is correlated with decreases in brain NPCs. Furthermore, direct stimulation with IL-1 in the hippocampal neurogenic niche decreases neurogenesis [85, 86, 112]. The potent anti-neurogenic actions of IL-1 can be inhibited with IL-1R antagonist (IL-1Ra) [11, 111, 113], abrogated by IL-1R1 knockout [86, 114], or suppressed by voluntary exercise which reduced IL-1 expression [115, 116]. Surprisingly, neurogenesis is inhibited in transgenic mice that overexpresses IL-1Ra [117], but not in IL-1R1 knockout mice [86]. It is possible that the anti-neurogenic effect of transgenic overexpression IL-1Ra is due to mechanisms independent of IL-1R1.

Two mechanisms have been proposed to explain IL-1-mediated inhibition of neurogenesis: 1) inhibition of NPC proliferation, and 2) alteration of the cell fate of NPCs. The first mechanism is supported by the following evidences: 1) IL-1 was found to decrease incorporation of thymidine analogues in NPC [11, 86, 107]; 2) IL-1 activates signaling pathways associated with cell cycle arrest [118, 119]; and 3) IL-1 decreases the number of immature neurons [85, 86, 112]. The second mechanism is supported by: 1) *In vitro* stimulation of NPCs with IL-1α and IL-1β caused an increase in the amount of astroglia-like cells and a decrease of differentiated neurons [120, 121]; 2) *In vivo*, in a disease model of West Nile Virus, an increase in proliferating astrocytes and a decrease in neurogenesis were found in an IL-1R1 dependent manner [11].

Recently we have found IL-1R1 expression in dentate granule neurons near the hippocampal subgranular zone, but not in the adjacent NPCs, suggesting the anti-neurogenic effect of IL-1 must be indirect [86]. Indeed, conditional knockout of NPC MyD88 did not attenuate IL-1-induced suppression of neurogenesis [85]. Furthermore, Liu et al. showed that IL-1 induced anti-neurogenesis can be mediated indirectly via endothelial and myeloid IL-1R1 [86].

IL-1 and neuronal cell death

Historically, IL-1 was first found to alter neural networks by distorting neuronal connectivity via neuronal death, especially in brain injury and neurodegenerative diseases. Under these conditions, the expression of IL-1 coincides with loss of neurons. In *in vitro* studies, high levels of IL-1 can directly induce neuronal apoptosis [118, 122–124]. However, in these studies, neurons were cultured in the presence of glial cells and it is possible that IL-1 promoted neuronal death indirectly through glial cells. Indeed, Thornton et al. found the neurotoxic effect of IL-1 was abrogated when glial cells were removed from the culture [124, 125]. Consistently, IL-1 was found to stimulate glial production of both reactive oxygen and nitrogen species (ROS and NOS) which are harmful to neurons [124, 126]. In contrast, other studies found IL-1 can stimulate glial cells to produce nerve growth factor that is potentially neuroprotective [127, 128]. These *in vitro* results suggest IL-1 is capable to produce opposite effects on neuronal survival via glial cells.

Surprisingly, intracerebral administration of IL-1 *in vivo* does not affect neuronal survival [86, 129–131], suggesting IL-1 alone does not cause neuronal death even in the presence of glial cells *in vivo*. However, blockade of IL-1 signaling by genetic deletion of IL-1R1 or over-expression of IL-1Ra reduced neuronal damage in animal models of stroke [84] and epilepsy [132], suggesting that the neurotoxic effect of IL-1 will manifest if other injurious factors are present. Indeed, when IL-1 was administered during CNS injury [133], stroke [134], or co-administered with excitotoxins [130, 135], neuronal apoptosis was exacerbated.

One mechanism for the exacerbation of neuronal death could be IL-1-mediated leukocyte infiltration into the CNS. In experimental models of neurodegeneration, such as epilepsy [136], ischemia [137], and experimental autoimmune encephalomyelitis (EAE) [138], IL-1 recruits leukocytes to the brain

and is crucial for disease progression. Blockade of recruitment of leukocytes reduces neuronal death in these conditions. A second mechanism by which IL-1 exacerbates neuronal death is the induction of inflammatory factors such as ROS, NOS, and prostaglandins. Multiple studies found glial ROS and NOS induced by IL-1 cause neuronal death [124–126]. Interestingly, IL-1-induced endothelial prostaglandin E_2 production is neurotoxic whereas IL-1 induced prostacyclin produced from neurons is neuroprotective [139]. The third mechanism is IL-1 could make neurons vulnerable by reducing neuronal viability. The maintenance of neuronal survival is associated with the presence of neurotrophic factors, such as brain derived neurotrophic factor (BDNF). BDNF is known to promote neuronal survival and a decrease of BDNF levels can make neurons more susceptible to injury [140]. IL-1 has been shown to impair the production of BDNF mRNA *in vivo* [141] and BDNF protein *in vitro*. IL-1 also interferes with BDNF-mediated signaling in cortical neurons, which results in decreased neuronal survival [123]. In addition, IL-1 can induce upregulation of neuronal excitatory neurotransmitter receptors thus conferring an increased sensitivity to excitotoxin [142]. Therefore, both the immunological (leukocyte recruitment and induction of inflammatory factors) and the neurological (enhancement of neuronal vulnerability) effects of IL-1 may converge to account for IL-1 mediated exacerbation of neuronal death during tissue injury. We have diagrammed these interactions in Fig. 2. The neurotoxic effects of IL-1 are most likely mediated by the canonical IL-1R1 signaling pathway. Blockade of NFκB and p38 abrogated neuronal death in models of injury [143, 144]. Recently a new IL-1R-mediated pathway has been discovered. In this pathway IL-1R1 is associated with IL-1RAcPb, not IL-1RAcP. Current studies indicate the IL-1R1/IL-1RAcPb signaling is neuroprotective because deletion of IL-1RAcPb enhanced neuronal death after excitotoxic [145] or immunological challenges [96]. IL-1RAcPb is neuronal specific; therefore, the IL-1-mediated neuroprotective effects would occur only in IL-1R1 and IL-1AcPb expressing neurons. We recently found IL-1R1 expression is limited to discrete subpopulations of neurons, suggesting the neuroprotective effects of IL-1 signaling in neurons is not universal. The balance between the canonical IL-1R1/IL-1RAcP and the alternative IL-1R1/IL-1RAcPb signaling could determine whether IL-1 exerts a neurotoxic or neuroprotective effect. Indeed during aging, where neurons are more susceptible to injury, increased IL-1RAcP/IL-1RAcPb ratio is correlated with increased inflammatory signaling and neuronal death [145].

Synaptic changes and IL-1

IL-1 has been shown to impact three aspects of synaptic structure: 1) neurotransmitter receptor composition, 2) spine density, and 3) synaptic adhesion. *In vitro*, IL-1 was shown to induce an increase expression of NMDARs [146] and reduced expression of AMPARs [147]. These IL-1 induced changes were confirmed in an *in vivo* model of hyperammonemia. Furthermore, these IL-1-induced changes in neurotransmitter receptor composition can be abrogated *ex vivo* in hippocampal slices by treatment with IL-1Ra [148]. Only three studies have investigated the effect of IL-1 on the density of synapses. In one study, IL-1 applied to cultured primary hippocampal neurons at a high concentration (3 ng/mL for 24 hrs) caused a decrease in postsynaptic densities measured by PSD95 immunolabeling [149]. In another, low levels (0.05 ng/mL for 30 mins) of IL-1β did not alter synaptic density [146]. In the third study, IL-1R1 deletion resulted in an increase of postsynaptic markers, suggesting endogenous IL-1 acts to reduce the amount of postsynaptic sites [150]. In terms of synaptic adhesion, Yoshida et al. found IL-1RAcP and IL-1RAcPb can couple, trans-synaptically, with protein tyrosine phosphatase receptor type delta (PTPRδ) to serve as synaptic adhesion molecules thus guiding synaptic formation [151]. In a cell culture system, expression of IL-1RAcP increased the protein expression of presynaptic markers, Bassoon and VGLUT1 and knockdown of IL-1RAcP reduced synapse formation. Interestingly, these two isoforms of IL-1RAcP appear to play distinct roles in synaptogenesis: whereas IL-1RAcP is important for presynaptic differentiation, IL-1RAcPb is important for postsynaptic differentiation [152]. Related to IL-1RAcP, Interleukin-1 Receptor Accessory Protein-Like 1 (IL-1RAPL1) is known to be critical in the formation of synapses. IL-1RAPL1 shares key features of the extracellular domains, transmembrane domain and signaling domain with IL-1RAcPb and is known to mediate synaptogenesis modulated by IL-1 [153]. Similar to IL-1RAcPb, IL-1RAPL1 also contains an extended intracellular C-terminus domain that prevents the activation of NFκB [154]. Mutations or genetic deletions in IL-1RAPL1 cause learning disabilities and autism-like syndromes in humans and mice in association with abnormal synaptic morphology [153,

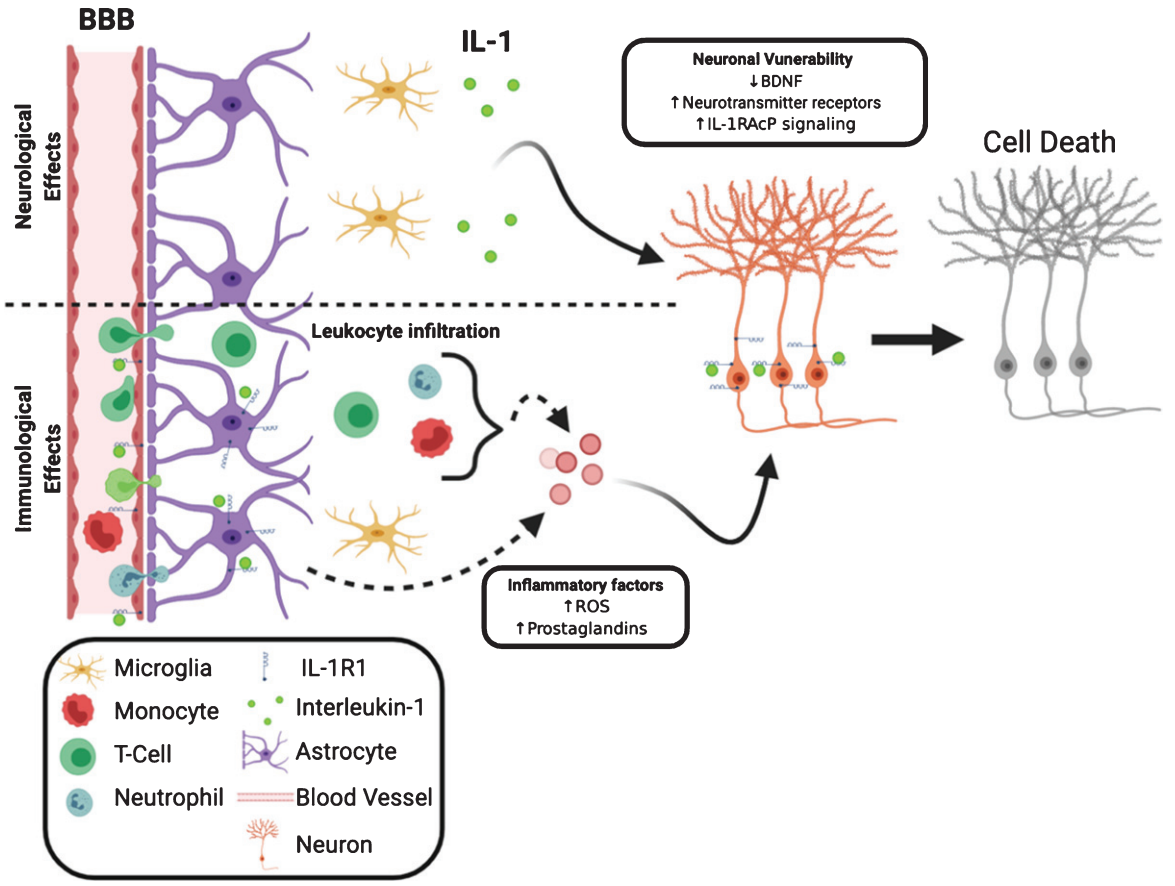

Fig. 2. Neurological and immunological IL-1 effects converge to influence neuronal survival. IL-1R1 can directly influence neuronal viability via decreasing neurotrophic factors, increasing membrane-bound neurotransmitter receptor and increasing inflammatory signaling. The decreased neuronal viability is coupled with increased release of neurotoxic inflammatory factors from non-neuronal cells, such as leukocytes, astrocytes and endothelia.

155]. Neurons with IL-1RAPL1 knockdown or neurons from IL-1RAPL1 knockout mice have decreased dendritic arborization, decreased spine density, and decreased excitatory synapses [151, 156]. IL-1AcP knockout mice show decreased in synaptic spines within the cortex and hippocampus [152], however, it is unknown whether deletion of IL-1RAcPb could cause similar effects and whether IL-1 is involved in the regulation of synaptic adhesion.

LTP/LTD and IL-1

Influence of IL-1 on functional synaptic plasticity, such as LTP and LTD, has also been studied. Katsuki et al. were the first to show IL-1 can inhibit LTP in the CA3 neurons of the hippocampus [157]. Since this seminal finding, others studies have also shown IL-1 can inhibit LTP in the neurons of the CA1 [158, 159], CA3, and dentate gyrus of the hippocampus [160–163].

On the contrary, others suggest that IL-1 is critical for induction of LTP and its maintenance. When LTP was induced with electrical stimulation of hippocampal slices or *in vivo*, an increase in IL-1 was observed [164, 165]. Likewise, the act of learning was found to induce IL-1 production in the hippocampus suggesting learning associated neuronal activation can drive IL-1 expression. The level of IL-1 induction was correlated to the reduction of errors in a memory test suggesting IL-1 aids in the learning process [78, 164]. In addition, when IL-1R1 signaling was pharmacologically blocked by IL-1Ra, LTP maintenance was reduced and learning was impaired [165, 166]. In line with these findings, Avital et al. found LTP in dentate gyrus or CA1 neurons was not inducible in IL-1R1 KO mice [81]. IL-1 may also modulate LTD. In

one study, application of IL-1 reduced basal neuronal responsiveness, preventing subsequent induction of LTD [167].

Several confounding factors need to be considered when assessing the role of IL-1 in LTP and LTD. Firstly, most electrophysiology studies are done in acute slices that are known to induce the expression of endogenous IL-1 in the injured slices. This injury associated increase in IL-1 may mask the effect of physiological levels of IL-1 in the slice. To reduce this potential artifact, two methods have been employed: 1) lower the incubation and recording temperatures and 2) increase the pre-test incubation duration. Ross et al. studied LTP in slice preparation at room temperature because injury related IL-1 release is higher at physiological temperature [166]. Schneider et al. incubated the slice for more than 5 hours before LTP recording to allow for injury-induced IL-1 to diminish [165]. Therefore, results from *in vitro* studies done at different temperatures or incubation preparations may be divergent. Secondly, the use of IL-1Ra to verify the effect of IL-1 could be confounded by the off-target effects. This unexpected possibility was suggested by Loscher et al. after showing application of IL-1Ra impaired LTP in synaptosomes from IL-1R1 deficient mice [168].

Most recent analysis suggests that IL-1 may modulate LTP in a synapse-specific manner. In hippocampal neurocircuitry, dentate gyrus granule neurons project to CA3 neurons via mossy fibers and CA3 neurons project to CA1 neurons via Schaffer collaterals. IL-1 has been shown to inhibit Schaffer/CA1 LTP, but not dentate/CA3 LTP [159]. Our studies have revealed that neuronal IL-1R1 expression is restricted to dentate granule cells in hippocampus. Therefore, the effects seen by Hoshino et al. in the CA1 cells are most likely indirect because CA3 and CA1 neurons do not express IL-1R1. The same conclusion may apply to most of the aforementioned studies because LTP is recorded in neurons in brain regions that do not express neuronal IL-1R1. Indirect mechanisms of modulation of LTP by IL-1 have been examined in previous literature. For example, IL-1-induced ROS has been found to mediate LTP impairment, which is rescued with antioxidant treatments [163].

Neuronal excitability and IL-1

The influence of IL-1 on neuronal excitability has been studied extensively; but the reported results are discrepant and confusing. Numerous studies have shown IL-1 suppresses neuronal excitability. IL-1 has been found to hyperpolarize neurons in the amygdala [169], anterior hypothalamus [170], dorsal motor nucleus [171], and hippocampus [81, 167], suggesting IL-1 can reduce the excitability of neurons. In support, IL-1 has been found to enhance the hyperpolarizing chloride [172, 173] and potassium currents [94] and inhibit the depolarizing sodium [174–176] and calcium currents [173, 176–179]. In addition, IL-1 has been shown to reduce the release of the excitatory neurotransmitter glutamate [163, 178, 180] and enhance the release and signaling of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [172, 173, 181–183]. These findings are consistent with studies that show IL-1 can reduce excitatory postsynaptic potentials [169]. Finally, IL-1 suppressed spreading depolarization in a model of cortical ischemia-reperfusion [184]. Taken together this set of evidences suggests IL-1 is inhibitory for neuronal excitability.

Conversely, evidences exist to support that IL-1 can enhance neuronal excitability. IL-1 has been shown to induce depolarization in neurons in the hypothalamus [170, 185], subfornical organ [186], and trigeminal ganglion [187]. IL-1 has been shown to suppress the inhibitory chloride [188] and potassium currents [189, 190] and increase excitatory sodium currents [187]. In addition, IL-1 was found to increase neuronal intracellular calcium [142, 191, 192]. In models of three different diseases IL-1 was also found to increase neuronal excitability. In epilepsy, IL-1 suppressed GABA induced inhibitory currents [193]; in a prion disease model, IL-1 depolarized CA1 neurons [194]; and in multiple sclerosis, elevated IL-1 cerebrospinal fluid (CSF) level was correlated with an increased response to transcranial magnetic stimulation, suggesting the neurons are hyperexcitable [195]. The increased neuronal activity can be blocked by IL-1Ra suggesting IL-1R1 signaling mediates the neuronal excitability increase in these diseases [195–197]. Taken together this evidence suggest IL-1 is excitatory.

Beyond the apparent contradictory evidences reviewed above, Zhu et al. found that under basal conditions, IL-1 increased glutamate and GABA release, but suppressed neurotransmission once neurons were activated [198]. This suggests IL-1 modulates neuronal activity depending on state of activation.

Here we propose three possible explanations for the discrepancy in the literature. Firstly, IL-1 signaling may differentially influence neuronal excitability due to concentration-dependent activities of IL-1.

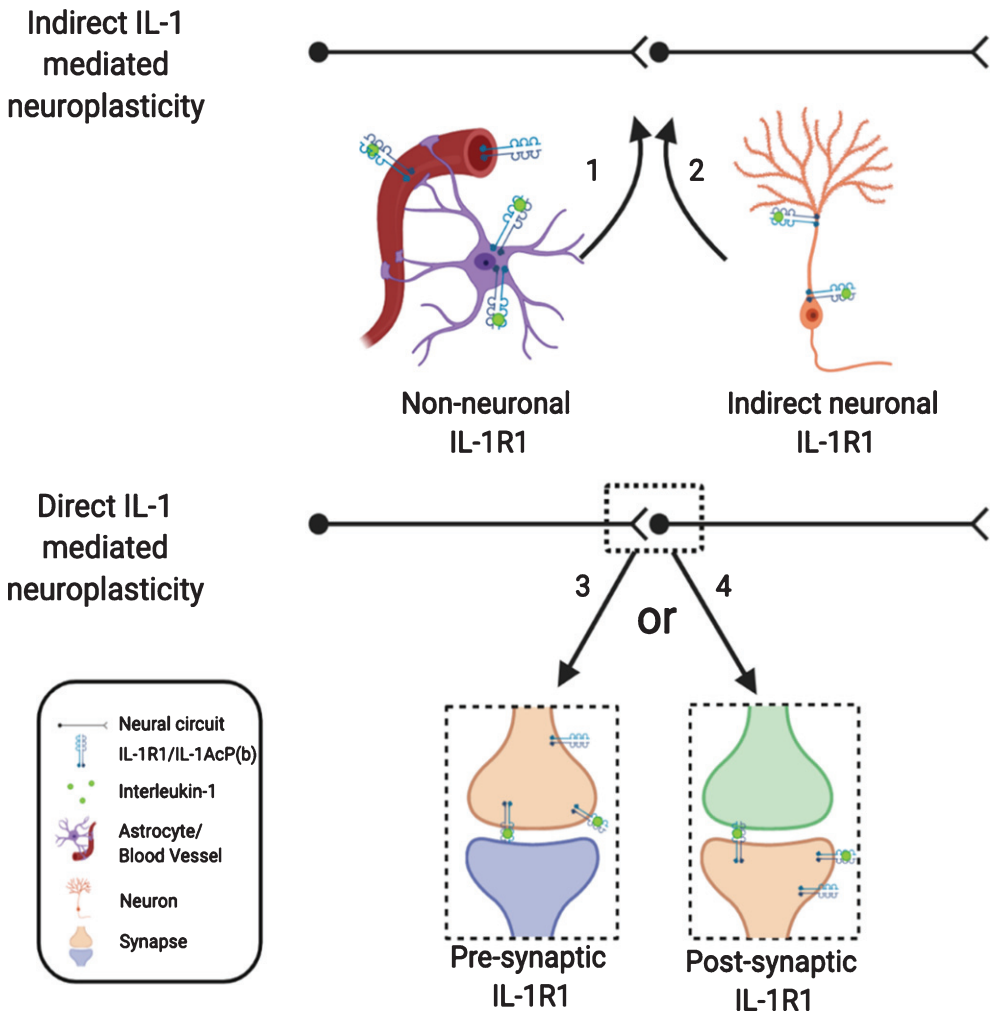

Fig. 3. Nonconventional IL-1R1 mediated neuroplasticity. IL-1 may exert its effect indirectly via non-neuronal IL-1R1 or via IL-1R1 on outlying neurons. IL-1 may mediate its effect directly on neurons with IL-1R1, however, IL-1R1 signaling may initiate various responses depending on whether IL-1R1 is expressed pre- or postsynaptically.

Multiple studies found the kinetics of IL-1 signaling on neuronal excitability acts as a U-shaped curve, such that low and high concentrations of IL-1 exert opposite effects on neuronal excitability. This is demonstrated by two studies showing low concentrations of IL-1 and high concentrations of IL-1 causes opposite effects on neuronal excitability [177, 186]. In addition, neuronal IL-1R1 has been shown to have higher sensitivity to IL-1 compared to non-neuronal IL-1R1 [86, 199]. Therefore, different levels of IL-1 present during recording could engage different biochemical and cellular targets. Secondly, the presence or absence of non-neuronal IL-1R1 signaling could confound the interpretation of IL-1-mediated changes in neuronal excitability. For example, IL-1 induced hyperpolarization of dorsal motor neurons was found to be dependent on prostaglandin synthesis [171] and hyperpolarization of hypothalamic [170] or amygdala neurons [181] was shown to be dependent on MyD88 signaling. These signaling cascades are typically observed downstream of IL-1R1 activation in non-neuronal cells such as endothelia and astrocytes, suggesting non-neuronal cells near the recorded neurons could be the main driver of the observed IL-1 effects in these studies. Thirdly, previous studies were hindered by the lack of identification of IL-1R1 on the recorded neurons. Even assuming non-neuronal IL-1R1 does not participate in the IL-1 induced fast electrophysiological effects, the recorded effects on a neuron without IL-1R could still be resulted from changes occurred in a nearby neuron that does have IL-1R. This notion is sup-

ported a previous data that showed in certain brain regions, such as the striatum, neuronal activity was not altered by IL-1 [200]. We have observed in our IL-1R1 reporter mice, neuronal IL-1R1 is absent in the striatum (unpublished data). Future studies need to clarify the role of IL-1 on modulating neuronal excitability by identifying the precise cellular IL-1R involved in the studied effects.

Influence of IL-1 on neuronal excitability could impact neuroplasticity. Recent literature describes a new paradigm of non-Hebbian neuroplasticity where the alteration of neuronal excitability can influence how apt a circuit is to undergo plasticity, which is termed intrinsic plasticity. For example, quick calcium influx in hippocampal CA1 neurons can elicit place cell formation without repeated wiring of the circuit to produce rather instant spatial memory [201]. Whether IL-1 can alter intrinsic neuroplasticity has yet to be determined.

SUMMARY/CONCLUSION

In this review, we analyzed the role of IL-1 in modulating neuroplasticity from the current literature. While the significance of IL-1-mediated changes in neuroplasticity is becoming increasingly clear in neurophysiology, neuropathology, and the pathogenesis of psychological and psychiatric disorders, how IL-1 causes these changes are complex and multi-faceted. Indirect pathways utilizing non-neuronal IL-1R1, which have been somewhat discounted in the past, could play predominant roles in shaping neuroplasticity. The direct influence of IL-1 on neuroplasticity through neuronal IL-1R1 is also more intricate than previously thought, due to restricted and discrete expression of neuronal IL-1R1 in subpopulations of neurons. How presynaptic IL-1R1 and postsynaptic IL-1R1 differentially modify neuroplasticity remains to be determined. In addition, different levels of IL-1 produced under physiological, psychopathological, and inflammatory conditions could modulate neuroplasticity through different modalities by engaging different IL-1R1 expressing cell types or different IL-1R1 expressing neurons. These conceptualizations are diagramed in Fig. 3.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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