Acta Physiologica Sinica, August 25, 2005, 57 (4): 414-420
http://www.actaps.com.cn

Brief Review

Role of the central interleukin-1 in stress responses

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Abstract: The molecules of interleukin-1 (IL-1) system are widely distributed in central nervous system. As a classical pro-inflammatory factor, central IL-1 has diverse biological functions and plays a pivotal role in a number of important physiological and pathophysiological processes. During the past few years, particular attentions have been directed to the stress mediator actions of central IL-1. This paper reviews some recent findings in the studies of central IL-1 functions in stress responses, including the effects of stress on central IL-1, the roles of IL-1 in the initiation of stress responses, the neural circuitries and intracellular signal transduction pathways involved in the central IL-1 mediated stress responses, as well as the actions of central IL-1 on brain high function and behavior under stressful conditions.

Key words: interleukin-1; central nervous system; stress

中枢白细胞介素 -1 在应激反应中的作用

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摘　要：白细胞介素 -1(interleukin-1, IL-1)系统分子广泛分布于中枢神经系统。中枢 IL-1 具有极其丰富的生物学功能，作为经典炎性细胞因子，在多种生理、病理生理过程中起重要作用。近几年来，中枢 IL-1 的应激介质作用备受关注。本文综述了中枢 IL-1 在应激反应中作用的最新进展，包括应激对中枢 IL-1 系统的影响，中枢 IL-1 对应激反应的启动和介导作用；参与中枢 IL-1 应激介导作用的神经环路和细胞信号转导通路，以及中枢 IL-1 对应激时脑高级功能和行为反应的影响。

关键词：白细胞介素 -1 ；中枢神经系统；应激
中图分类号：Q426；Q427；R338；R74

With recent advancements in genomics and proteomics, as well as intensive study on the functions of the central interleukin-1 (IL-1), new members of IL-1 system have been discovered and more information has been gained on the mechanisms of IL-1 as well as its intracellular signal transduction. The IL-1 family, the IL-1 receptor family and the molecules related to IL-1 receptors are collectively referred to as the "IL-1 system". IL-1 family consists of IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra); IL-1 receptor family has ten members, including IL-1RI, IL-1RII, IL-1RacP, T1/ST2, IL-1Rrp, IL-1Rrp-2, IL-1RAPL, IL-1γRAP, TIGIRR (IL-1RAPL-2) and SIGIRR. The molecules of central IL-1 system are widely distributed in the central nervous system (CNS), and have diverse biological functions[1,2]. Recently, there have been a lot of studies in the field of physiology and pathophysiology. Several lines of evidence demonstrate that the central IL-1 is not only a classical pro-inflammatory factor, but also a key cytokine

Received 2004-09-15　Accepted 2005-06-03

This work was supported by the National Basic Research Priorities Programme of China (No. G2000056908) and the National Natural Science Foundation of China (No. 3980047, 30370557).

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that has diverse roles in many physiological regulatory functions and some important pathological processes; especially, the role of the central IL-1 in stress responses has received many attentions. In the present society with an accelerated rhythm of life, the incidence rate of stress disorders rises gradually, therefore, exploring the stressful mediator functions of central IL-1 may have great theoretical and clinical significance.

Influences of stress on central IL-1 system

In stressful conditions, nearly all members of central IL-1 system have been reported to be elevated in the brain. For example, non-intermittent electric footshock can activate central IL-1 system; immobilization stress increases the mRNA expression, protein levels and biological activities of IL-1 in the hypothalamus, as well as enhances the expression of IL-1ra mRNA[3]. Increase in IL-1β mRNA expression in the hypothalamus and hippocampus of rats is elicited by intravenous lipopolysaccharide (LPS) stimulation. Similarly, intracerebroventricular (ICV) administration of bacterial endotoxin also rapidly and significantly elevates IL-1β levels in the brain[4]. Electric tail-shocks can quickly increase IL-1β content in the hypothalamus, hippocampus and pituitary. Social isolation stress can enhance IL-1β levels in the hippocampus and cerebral cortex [5]. Laparotomy stress increases IL-1β receptor levels in mouse pituitary. Infectious stress induced by intravenous LPS stimulation (30 μg/mouse) can promote the binding of IL-1β and IL-1α to their receptors in mouse pituitary. Inflammatory or non-inflammatory stress elicited by intraperitoneal injection of LPS remarkably increases IL-1β mRNA expression in the hypothalamus, hippocampus, and cerebral cortex of rats[6]. Footshock stress can rapidly elevate the expression of *c-fos* and IL-1 mRNA/protein levels in the neurons of paraventricular nucleus and limbic endbrain, as well as in sensory neurons linked to alertness, noxious stimulation, and visceral sensation.

Although changes of central IL-1 levels can be induced by various stressful stimulations, these changes are obviously as distinct as their corresponding stressors. During inescapable electric tailshock, IL-1β levels were remarkably elevated in hypothalamus, hippocampus, cerebellum, posterior cortex, and the nucleus of solitary track in rats at the beginning of the stimulus, and then declined as the stimulus continued. In contrast, sustained high level of IL-1β was observed in most of the brain areas in rats throughout the process of LPS stimulation (1 mg/kg, i.v.)[1,2].

There have been many reports on the sources of central IL-1β in stress. In inflammatory stress, infectious stress or injury of the CNS, the primary source of IL-1 is microglia. The astrocytes usually secrete IL-1 later than microglia. Microglia stores pro-IL-1 in a constitutive fashion, the early rapid increment of IL-1 may due to the cleavage of pre-existing pro-IL-1 by caspase-1 (cysteinyl aspartate-specific protease-1, also termed interleukin-1β converting enzyme, ICE) in microglia. Notably, mature IL-1β can be produced from pro-IL-1β by caspase-1 action in less than 7.5 min. In addition, central IL-1 is also synthesized and released by oligodendroglia, neurons, cerebrovascular cells, and circulating immune cells which might invade brain during inflammatory conditions. IL-1ra expression is usually induced by the same stimuli that result in the production of IL-1, which occurs mainly in neurons and at a later timepoint (1~3 h after IL-1 elevation)[1]. A recent report indicates that production of IL-1 in metabolic stress is associated with AMP-activated protein kinase (AMPK), and that the activator of AMPK can effectively inhibit IL-1 synthesis in microglia cells under metabolic stress. Besides, purine receptors $P2X_7$ can regulate the cleavage and release of IL-1β from microglia. Further studies have shown that central or peripheral administration of adrenal glucocorticoid can significantly suppress the synthesis and release of central IL-1β. Inescapable electric tail-shock-evoked increase in central IL-1β level is remarkably higher in adrenalectomized rats than that in intact ones[4], which means that the production of central IL-1β is related to adrenal cortical hormones in such stress condition.

In summary, stress may elicit responses of the central IL-1 system in a regional and cellular fashion. Although the production of IL-1 can be produced by all of cells in the CNS, the glia cells are the main source of IL-1β in stress.

Central IL-1 participates in the initiation, mediation and regulation of stress responses

The central IL-1 system plays an important role in initiating, mediating and regulating stress responses. In stab lesion stress, the expression of IL-1 receptor-I (IL-1RI) and the synthesis/release of IL-1β in cerebral glia cells increase rapidly; the increased IL-1 activates hippocampal pyramidal cells that are related to the initiation of stress responses. In stress responses to LPS, the fever response and activation of immune system were accompanied by increased level of central IL-1β mRNA, protein, and bioactivity. These stress responses induced by LPS can be attenuated by central administration of IL-1ra. Central IL-1β mediates intestinal response and intestinal dysfunction in acute immobilization stress. Footshock stress significantly enhances IL-1 levels as well as the expressions of some early genes

including *c-fos*, NGFI-B and expression of corticotrophin releasing hormone (CRH) mRNA in paraventricular nucleus of adult male Sprague-Dawley rats or Fisher-344 rats. The expressions of *c-fos*, NGFIB and CRH can be mimicked by ICV injection of IL-1β (100 ng/10 μl). The expression of *c-fos* can be blocked by ICV injection of IL-1ra, suggesting that the activation of central IL-1 is not only prior to some early gene such as *c-fos* in stress, but also possibly mediates the activation of these early genes[7].

Notably, a large number of reports indicate that elevation of IL-1β mRNA and protein levels are only observed in the hypothalamus of animals with immobilization stress. This is different from the results obtained in other stresses in which the IL-1β mRNA and protein levels are elevated in multiple brain regions. Oxidative stress from brain injury is closely related to central IL-1 system. The 8-hydroxydeoxyguanosine, a marker of ultra-oxidative DNA damage of the CNS, is significantly increased in wild type mice after transient middle cerebral artery occlusion (tMCAO), but not in IL-1α or IL-1β knockout mice, indicating that central IL-1 may be involved in the mediation of oxidative stress during brain injury[8]. Immobilization stress can induce the production of an immune-suppressive protein in the serum of rats. This effect was dose-dependently antagonized by ICV injection of IL-1ra and enhanced by ICV injection of IL-1β, whereas no such effect was observed by intraperitoneal injection (i.p.) of IL-1β or IL-1ra, suggesting that central IL-1β may play an important role in the production of immune-suppressive protein during immobilization stress[9,10].

It has been generally accepted that central IL-1 may regulate behavioral responses to stress by means of influencing learning and memory. For instance, central IL-1 can inhibit memory by suppressing long-term potentiation (LTP) of hippocampal neurons. It is reported that latency of arriving at the invisible platform in IL-1RI knockout mice was significantly longer than that in wild type mice in water maze test. Electrophysiological studies indicate that LTP cannot be elicited in neurons of dental gyrus or hippocampal CA1 region in IL-1RI knockout mice. In conditioned fear stress, the fear-like behavior was remarkably attenuated in IL-1RI knockout mice. However, in test for non-hippocampus-dependent memory, the fear-like behavior of IL-1RI knockout mice was similar to that of the wild type mice[11]. In contextual fear conditioning, the microinjection of IL-1β into dorsal hippocampus of rats abolished freezing behavior and increased motor activity, which implies that central IL-1 may impair the memory for contextual fear condition by influencing the dorsal hippocampal neurons. However, ICV injection of IL-1β or IL-1ra cannot affect the behavior of rats in auditory-cue conditioned fear stress[12]. In social isolation stress, rats manifested increment of motor activity and diminution of freezing behavior, accompanied by significant raise of IL-1β level in hippocampus and cerebral cortex; whereas such behavioral responses were effectively attenuated by ICV injection of IL-1ra. These results suggest that the increment of central IL-1β protein level may suppress the memory for fear in social isolation stress[5]. In general, different psychological stress responses may depend on different mechanisms of high-level brain functions; hence the actions of central IL-1 in different psychological stress responses may also vary. In addition, central IL-1 directly induces the behavioral changes of rats in stress conditions. Our previous studies demonstrated that ICV injection of anti-IL-1β antibody specifically decreased motor activity of rats in novelty stress[13]. Central administration of low dose of IL-1 (non-fever-inducing) significantly inhibited social behavior and exploration behavior in rats, whereas central administration of high dose of IL-1 (fever-inducing) decreased motor activity. Elevated plus maze test showed that central administration of low dose of IL-1 remarkably reduced the anxiety behavior of rats, in contrast, higher dose of IL-1 could increase such behavior[14].

IL-1 receptor accessory protein-like molecule (IL-1RAPL) expressed in human hippocampal neurons may play roles in learning, memory, and some other brain functions. Expression of IL-1RAPL in hippocampus was severely decreased in patients with mental retardation. This disables central IL-1 from activating stress activated protein kinases (SAPK) intracellular signal pathways, which results in decreased release of neurotransmitters and dysfunction of synaptic plasticity[1].

Central IL-1 system is involved in the central regulation of cardiovascular responses to stress. Stress elicited by different stimuli, including immobilization stress, electric tail-shock, acute or chronic electric footshock stress, novel conditional stress, and conditioned fear stress, *etc*., may induce cardiovascular responses such as increased heart rate and blood pressure. Correspondingly, tachycardia and hypertension can also be observed in human during stress (fear, tension, depression, anxiety and angry, *etc*.). In addition, IL-1 immune-positive neurons and innervations were reported to exist in cardiovascular regulatory centers such as hypothalamus and hippocampus[15,16].

We demonstrated that central IL-1 mediated cardiovascular responses to stress. ICV injection of IL-1ra inhibited pressor response evoked by conditioned fear stress or

immobilization stress. ICV injection of IL-1β induced the hypertensive response of rats, which consisted with the reports of other authors[17,18]. Our study further revealed that central IL-1 might also mediate the pressor response induced by restraint stress via rostral ventrolateral medulla (RVL): both restraint stress and ICV administration of IL-1β could increase mean arterial blood pressure (mABP) as well as enhance discharges of RVL neurons in rats, in a correlated fashion. Moreover, ICV injection of IL-1ra effectively attenuated the pressor responses induced by restraint stress or by ICV injection of IL-1β[19]. Blockade of P38-SAPK pathway remarkably decreased the pressor response to footshock stress or central IL-1β administration. Therefore, it is likely that central IL-1 mediates the hypertensive response to footshock stress via P38-SAPK pathway[20]. As far as present knowledge goes, intracellular signal transduction pathways such as IL-1 – IL-1RI – NF-κB, IL-1 – IL-1RI – JNK-SAPK, and IL-1 – IL-1RI – P38-SAPK are the key pathways involved in the mediating actions of central IL-1 to stress.

Until recently, the mechanism of the central IL-1 mediation in the cardiovascular responses to stress remains to be fully elucidated. Several studies suggest that central IL-1 may mediate cardiovascular response to stress in two ways: (1) directly and rapidly increasing the secretion of CRH from magnocellular neuroendocrine neurons in the paraventricular nucleus of hypothalamus, which initiates the complicated neuroendocrine reactions that in turn induce the cardiovascular responses to stress; (2) through the classical stress mediating circuitry, i.e. the limbic-hypothalamic-pituitary-adrenal (LHPA) axis, with the former more physical and the latter more psychological.

Central IL-1 related neuroendocrine pathways in stress responses

The central IL-1 system and other central neuroendocrine factors coordinately initiate, mediate, and regulate stress responses. Several studies showed that IL-1 immune-positive neurons as well as the IL-1 receptors exist in brain regions regulating stress response. In the central regulatory process of stress responses, IL-1, in concert with CRH, activates or modulates hypothalamic-pituitary-adrenal (HPA) axis, which in turn induces complex stress responses[1,7,21]. In acute restrain stress, central IL-1β and CRH together initiate and mediate the gastrointestinal responses such as histamine secretion from gastrointestinal mast cells in stress rats, whereas such response can be significantly and specifically suppressed by central administration of IL-1ra or CRH receptor antagonists. Similar gastrointestinal response was mimicked by ICV administration of IL-1β or CRH in stressless rats. Furthermore, it is especially noteworthy that stress-like responses induced by central IL-1β are effectively blocked by antagonist of CRH receptor, however, stress-like responses elicited by central CRH cannot be affected by IL-1ra, suggesting that central IL-1 may initiate and regulate gastrointestinal stress response prior to CRH. Intraperitoneal LPS administration resulted in a significant increase in IL-1RI mRNA levels in the pituitary of wild-type mice; such increment was attenuated in the pituitary of CRH knockout mice. The up-regulation of IL-1 receptors in pituitary induced by CRH is severely suppressed by dexamethasone. Further researches indicate that up-regulation of IL-1 receptors in pituitary induced by stress or CRH treatment is related to intracellular cAMP. Somatostatin or dexamethasone can effectively inhibit the actions of CRH on cAMP production and IL-1α binding to IL-1R. In addition, ACTH levels in serum are not increased by adrenalectomy in IL-1 knockout mice or mice intracerebroventricularly transfected with IL-1ra gene, but not in wild type mice. If wild type mice are affected by high concentration of IL-1ra in embryonic period, adrenalectomy in mature period will not result in elevated serum ACTH levels. These studies imply that central IL-1 are closely related to rising levels of ACTH in adrenalectomized mice, and central IL-1 may not only be involved in the activation of HPA axis in stress, but also regulate the development of HPA axis. However, it is worth that molecules of central IL-1 system do not always coordinate with CRH in stress. For instance, a significant increase in IL-1 receptor expression and a significant decrease in CRH receptor expression in the pituitary were seen in laparotomy stress. This suggests that a complicated relationship between central IL-1 system and HPA axis may exist in stress[22]. In some types of moderate stress, such as auditory stress or stimulation with low dose of 2-deoxydextrose, the release of corticosterone in IL-1 knockout mice is lower than that in wild type mice. In contrast to mild stress, severe stress can significantly boost the level of corticosterone in serum of IL-1 knockout mice, suggesting that compensative mechanism may exist for initiating stress response in the absence of central IL-1, and central IL-1 may work coordinately with other stress mediators[23]. It has been known that activation of the central IL-1 system in stress is related to brain nitric oxide (NO). ICV injection of NO synthase (NOS) inhibitor effectively suppresses the rising of central IL-1 protein level as well as *c-fos* and IL-1 mRNA expressions in the paraventricular nucleus induced by peripheral LPS stimulation. This implies that central NO may

be an important factor related to the activation and mediative actions of central IL-1 in stress. On the other hand, ischemia stress upregulates the expression of members of the central IL-1 system, which results in an enhanced production of NO and reactive oxygen species (ROS), these exacerbate the injury of nervous cells in tMCAO[1,2]. Central IL-1 mediates stress responses coordinately with other cytokines. Physiological or psychological responses induced by immobilization stress are linked to central IL-1 and IL-6. In immobilization stress, there is a specific correlation between the changes of peripheral IL-6 and the changes of IL-1 mRNA in the hypothalamus[24].

Central IL-1 mediates stress responses via specific neural circuits in the brain. The brain areas linked to stress regulation include hypothalamus, some thalamic nuclei, amygdala, hippocampus, nucleus accumbens, and some nuclei of brain stem and locus coeruleus. The generally accepted neural mechanism for initiating, mediating and regulating stress by central IL-1 are as follows: (1) One or some of the major neural circuits including the HPA axis, limbic-HPA neural circuit, and sympathetic adrenal medulla neural pathways are activated by some stressful signals through complex processes. (2) Through neural and humoral pathways, the activated neural circuits elicit integrative and diverse responses to stress. During these processes, the central IL-1 system exerts the stress mediator functions through HPA or LHPA neural circuitries. Specifically, central IL-1 can indirectly activate HPA axis via limbic system, or act on hypothalamus to activate HPA axis for mediating stress responses. For instance, elevated IL-1 in the cerebral cortex, amygdala and hippocampus significantly activate HPA circuit in stress, which further activate neuroendocrine system to initiate stress responses. These actions together accomplish the psychological stress responses associated to high brain functions such as learning and memory. (3) Central IL-1 can also act on CRH neurons in the hypothalamus to rapidly and directly initiate stress response[25,26]. It is reported that central IL-1 can regulate the synaptic plasticity of CRH neurons in paraventricular nucleus, which is represented by hyperresponsiveness of CRH neurons to stress-elicited LTP[7,19]. ICV injection of IL-1ra can attenuate the activation of HPA axis of mice in stress, whereas such attenuation can be blocked by sympathectomy[27]. This implies that the sympathetic nervous system is related to the role of central IL-1 as a stress mediator.

In summary, the molecules of central IL-1 system as a collection of stress mediators are closely related to intracerebral CRH, NO, and some cytokines. Central IL-1 system mediates stress responses via some neural circuitries including HPA, LHPA and sympathetic nervous pathway. The central IL-1-related stress neural circuits are illustrated in Fig. 1.

Future perspectives

In the past few years, attentions have been focused on new functions of the central IL-1 system under physiological and pathophysiological conditions. Recent studies have established that the components of central IL-1 system are not only a group of pleiotropic physiological

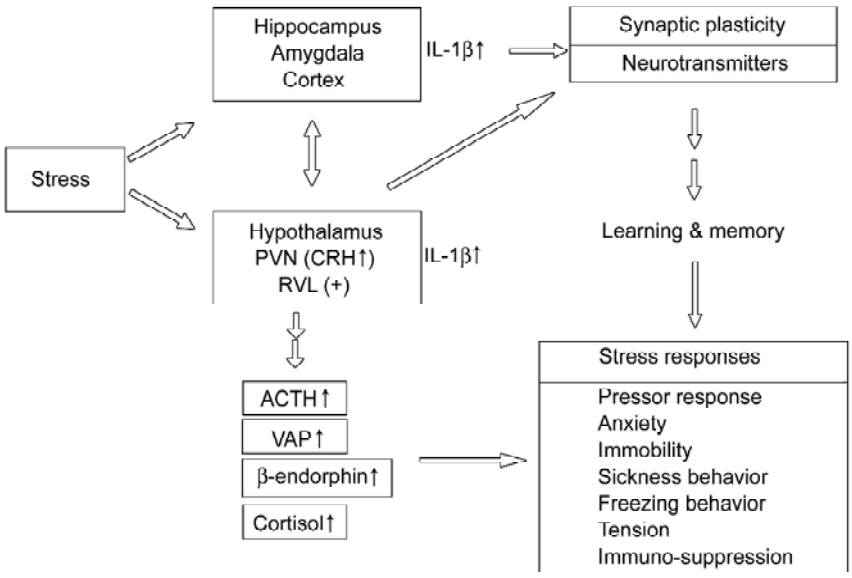

Fig. 1. Neural circuits of stress mediated by central interleukin-1. +, activation; ↑, increase.

cytokines, but also initiators, mediators and regulators for stress responses. In addition, there are close correlations between physiological functions and stress initiating/mediating/regulating actions of central IL-1. However, the details of how these molecules are involved in stress responses remain obscure, especially in some important aspects such as the intracellular signal transduction pathways, neural circuitries, *etc*., for the central IL-1-related stress. Although lots of issues remain to be resolved, it is very promising that investigations on the stress-mediating actions of the central IL-1 system will contribute well to both our understandings of the brain and clinical therapies in stress disorders.

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ACKNOWLEDGEMENTS: We thank Dr. friends FENG Jia-Wu and WANG Xiu-Jie, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, China, for their kind help in the writing.

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