Interleukin-1 β with learning and memory

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Abstract: Interleukin-1 β (IL-1 β) is one of the first cytokines ever described. It has long been recognized to play an important role in mediating inflammation and orchestrating the physiological and behavioral adjustments that occur during sickness. Recently, accumulating evidence has indicated that IL-1 β also adversely affects cognitive function. Nevertheless, there are also some reports showing no effects or even beneficial effects of IL-1 β on learning and memory. The relationship between IL-1 β and cognitive impairment has not been clearly elucidated. Here we reviewed the evidence of both negative and positive effects of IL-1 β on learning and memory, and the key factors that may affect the effects of IL-1 β on learning and memory were discussed.

Keywords: interleukin-1 β ; learning; memory; dose; age; memory type; memory stage

1 Introduction

Interleukin-1 (IL-1) is a pro-inflammatory cytokine that orchestrates inflammatory and host defense responses in the body^[1]. In the periphery, IL-1 is mainly secreted by activated macrophages. IL-1 regulates a series of immune and inflammatory responses. It can increase the expression of adhesion factors on endothelial cells, enabling transmigration of leukocytes to the sites of infection and inducing a number of pro-inflammatory cytokines, chemokines and inflammation-associated molecules to form an amplified cascade to stimulate an immune response^[2]. The 2 forms of IL-1, IL-1 α and IL-1 β , share partial sequence homology and a similar structure^[3]. They both bind to the functional IL-1 receptors and exert largely the same physiological effects^[4,5]. mRNAs of both isoforms are translated to produce precursor proteins, which are then cleaved to yield the mature forms. Pro-IL-1 α

is cleaved to yield the mature form by cell surface-bound calpain, and pro-IL-1 β is cleaved by an intercellular enzyme, IL-1 β converting enzyme (ICE), also known as caspase-1. In the healthy central nervous system (CNS), IL-1 β is present in the brain, at a low level^[6]. Microglia, the principal endogenous immune effector cell of the CNS, expresses caspase-1 and seems to be the earliest and a major source of IL-1 β after experimental CNS injury, infection, or inflammation^[7]. Indeed, various studies have consistently detected IL-1 β in the CNS after brain injury or peripheral immune activation. For example, IL-1 β bioactivity^[8-10], immunoreactivity^[11-13], mRNA^[14-16], and protein^[17] have been shown to be present in brain after peripheral administration of lipopolysaccharide (LPS). Apart from its role in orchestrating inflammatory and host defense responses, IL-1 β has also been implicated in learning and memory. Many studies have reported that immune activation has detrimental effects on learning and memory and IL-1 β seems to be a key mediator in this process^[18-24], since IL-1 receptor antagonist (IL-1ra) or anti-IL-1 β antibody administration can reverse the detrimental effects^[18,21,22,24]. However, there are also some reports showing no effects or even ben-

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eficial effects of IL-1 β on learning and memory. Complete elucidation of the relationship between IL-1 β and cognitive impairment still needs further investigations.

2 Detrimental effects of IL-1 β on learning and memory

2.1 Impacts of direct IL-1 β administration on learning and memory The effects of immune stimulation on cognitive processes in rodents have been widely studied. The first study examining the effects of IL-1 β on learning and memory was conducted in 1993. In this study, intracerebroventricular (i.c.v.) injection of IL-1 β (100 ng) one hour before the spatial water maze training could result in an impairment in performance of spatial navigation in the first trial on the following day^[25]. In a subsequent set of experiments, similar results were obtained. Mice receiving peripheral injection of IL-1 β (100 ng, i.p.) on the first and the second day of spatial water maze training showed impaired spatial learning^[21]. Furthermore, IL-1 β was found to impair learning in random start point version of water maze (hippocampus-dependent spatial memory), but not in fixed start point version of water maze (hippocampus-independent non-spatial memory)^[26]. Besides, lower dose (15 ng) of IL-1 β (i.c.v.) can also induce the detrimental effects on spatial memory^[27], and similarly, IL-1 β could impair the performance of rats in the hippocampus-dependent spatial version of water maze, but not in the hippocampus-independent visually guided version of water maze.

Apart from the water maze paradigm, studies on fear conditioning have also indicated the detrimental effects of IL-1 β on memory. It has been reported that when injected (i.c.v.) immediately following conditioning, IL-1 β (10 or 20 ng) can impair contextual (hippocampus-dependent) but not auditory-cued (hippocampus-independent) fear conditioning^[28]. Also, bilateral intra-hippocampal injection of IL-1 β (10 ng/side) impairs the contextual fear conditioning^[29]. In a different version of fear-conditioning paradigm in which rats are pre-exposed to the context before the conditioning session, researchers find that rats receiving bilateral intra-hippocampal injection of IL-1 β (1 ng/side) after pre-exposure to the context show less freezing than do the vehicle-treated

rats^[30]. These studies indicate that IL-1 β interferes with the hippocampus-dependent memory, without affecting the hippocampus-independent memory.

Studies using other memory testing paradigms have also shown the detrimental effects of IL-1 β on learning and memory. In an autoshaping task, rats injected with IL-1 β (4 μ g, i.p.) show learning impairment, compared with the saline-injected controls^[31]. In the three-panel runway task, intra-hippocampal injection of IL-1 β (32 and 100 ng/side, but not 10 ng/side) is shown to impair the working memory of rats^[32,33]. In addition, the win-shift radial arm maze has revealed that administration of IL-1 β (10 and 50 ng, i.c.v.) can cause working memory impairment in rats^[34].

To sum up, the above findings strongly suggest that IL-1 β exerts detrimental effects on the performance in memory tasks that are specifically dependent on normal hippocampal functioning, but not in hippocampus-independent memory tasks. Similar results can be obtained using different doses, administration routes, and species (Table 1).

2.2 Impacts of disrupting IL-1 β signaling pathway on learning and memory Due to the detrimental effects of IL-1 β on learning and memory, it is naturally supposed that blocking the signaling pathway of IL-1 β may have some beneficial effects on learning and memory. However, some studies have come to the opposite results, showing that disrupted IL-1 β signaling may actually impair learning and memory.

One important method to block the IL-1 β signaling pathway is through pharmacological approach. It has been reported that rats with i.c.v. injection of IL-1 receptor antagonist (IL-1ra, 100 μ g) at the end of the training day showed impaired spatial memory when tested 24 h later in water maze. In the same study, injection of IL-1ra (100 μ g, i.c.v.) at the end of the passive avoidance training impaired rats' memory when tested 8 d later^[35]. In another study, i.c.v. injection of IL-1ra (100 μ g) immediately after fear conditioning impaired mice's memory when tested 48 h later^[36]. Another way to modify signaling pathways is genetic manipulation. Avital *et al.* have reported that IL-1 receptor type I knockout (IL-1rKO) mice that show no responsiveness to exogenous IL-1 β ^[37], display a lower rate of learning in spatial memory paradigm, but are similar to the controls in the non-spatial visible plat-

Table 1. Summary of the studies on the effect of IL-1 β on learning and memory by direct administration of IL-1 β

Agent	Species	Dose	Route	Memory testing paradigm	Time	Effect on memory	Reference
IL-1 β	Rat	100 ng	i.c.v.	Water maze spatial	1 h before training	Impairment	[25]
					Immediately before training	No effect	[25]
IL-1 β	Mouse	100 ng	i.p.	Water maze spatial	During training	Impairment	[21],[26]
IL-1 β	Rat	15 ng	i.c.v	Water maze spatial	During training	Impairment	[27]
IL-1 β	Rat	10 or 20 ng	i.c.v	Fear-conditioning contextual	Immediately following conditioning	Impairment	[28]
IL-1 β	Rat	10 ng/side	Intrahippoc-ampal	Fear-conditioning contextual	Immediately following conditioning	Impairment	[29]
IL-1 β	Rat	1 ng/side	Intrahippoc-ampal	Fear-conditioning contextual	Immediately, 3 h and 24 h following pre-exposure to context	Impairment	[30]
					48 h following pre-exposure to context	No effect	[30]
IL-1 β	Rat	4 μ g	i.p.	Autoshaping	45 min before day 2 of training	Impairment	[31]
IL-1 β	Rat	32 or 100 ng/side	Intrahippoc-ampal	Three-panel runway	10 min before training	Impairment	[32],[33]
IL-1 β	Rat	10 ng/side	Intrahippoc-ampal	Three-panel runway	10 min before training	No effect	[33]
IL-1 β	Rat	10 or 50 ng	i.c.v.	Radial arm maze	5 min after training 45 min before testing	Impairment	[34]
IL-1 β	Rat	10 ng	i.c.v.	Water maze spatial	Immediately after the last trial	No effect	[35]
IL-1 β	Rat	10 ng	i.c.v.	Passive avoidance	Immediately after the shock (testing 1 d after)	No effect	[35]
IL-1 β		10 ng	i.c.v.	Passive avoidance	Immediately after the shock (testing 5 d after)	Enhancement	[35]
IL-1 β	Mouse	1 ng	i.c.v.	Fear-conditioning contextual	Immediately following conditioning	Enhancement	[36]
IL-1 β	Mouse	10 ng	i.c.v.	Fear-conditioning contextual	Immediately following conditioning	Impairment	[36]
IL-1 β	Rat	2 μ g/kg	i.p.	Water maze spatial	Before training, after training, before testing	No effect	[86]
IL-1 β	Rat	0.1, 2, 4, or 100 μ g/kg	i.p.	Fear-conditioning contextual	Immediately following conditioning	No effect	[87]
IL-1 β	Mouse	100 ng	i.p.	Water maze spatial	2 h before training (3 d $\times$ 5 trials/d, water 23 $^{\circ}$ C)	No effect	[88]
					2 h before training (2 d $\times$ 9 trials/d, water 23 $^{\circ}$ C)	Impairment	[88]
					2 h before training (2 d $\times$ 9 trials/d, water 18 $^{\circ}$ C)	No effect	[88]
IL-1 β	Rat	15 ng	i.c.v.	Passive avoidance	50 min before conditioning and 50 min before testing	Enhancement	[89]
IL-1 β	Rat	1 or 3 μ g/kg	i.p.	Active avoidance	24 h before training	Enhancement	[90],[91]
IL-1 β	Rat	6 μ g/kg	i.p.	Active avoidance	24 h before training	No effect	[90]

form version of water maze^[38]. Besides, the IL-1rKO mice show impaired contextual fear conditioning, but normal auditory-cued fear conditioning 48 h after the conditioning trial^[38]. Similar results are obtained in IL-1ra transgenic (IL-1raTG) mice, in which the human IL-1ra gene is overexpressed specifically within the CNS and the response to exogenous IL-1 β administration is abolished^[39]. These mice show descending learning ability in the spatial memory paradigm, but not in the non-spatial memory paradigm, and impaired contextual but normal auditory-cued fear conditioning^[36].

In summary, both pharmacological (IL-1ra) and genetic (IL-1rKO, IL-1raTG) studies suggest that low or physiological levels of IL-1 β may be required for normal physiological regulation of memory processes, especially for hippocampus-dependent memory (Table 2).

2.3 Effects of IL-1 β on long-term potentiation (LTP) IL-1 β precursor protein, IL-1 β converting enzyme, IL-1 β and IL-1 receptors are all localized in the brain^[40,41], especially at a high density in the hippocampus^[42]. There is evidence suggesting that IL-1 β may be required for normal physiological regulation of hippocampal plasticity and memory processes. LTP, a persistent increase in synaptic efficacy following high-frequency stimulation of that synapse, is believed to be a major mechanism underlying many types of learning and memory. It has been reported that LTP in the hippocampus is accompanied by a long-lasting increase of IL-1 β gene expression, and exposure to IL-1ra can impair the maintenance of LTP^[43]. These results indicate a role of low levels of IL-1 β in modulating the physiological processes underlying LTP. In contrast, high levels of IL-1 β can impair LTP, as demonstrated by several research groups. It has been shown that elevated levels of IL-1 β can inhibit the expression of LTP in the CA₃ region of the hippocampus^[44]. Similar results have been obtained in the CA1 region of the hippocampus^[45] and in the dentate gyrus^[46,47]. The impairment of LTP is believed to be caused by IL-1 β , because IL-1ra strongly attenuates the inhibitory effects of IL-1 β on LTP expression. Moreover, IL-1rKO mice exhibit no LTP, either *in vivo* or *in vitro*, and display severely impaired hippocampus-dependent but normal hippocampus-independent memory^[38].

2.4 Association of IL-1 β with infection- and stress-induced impairments of learning and memory It has been suggested that infection and stress can lead to the stimulation of common neuronal pathways^[48,49]. Both of them can induce the productions of cytokines, including IL-1 β , IL-6, *etc.*^[17,50,51]. LPS are large molecules found in the outer membrane of gram-negative bacteria. They act as endotoxins, stimulating the immune system in animals as well as in human. Extensive studies have examined the effects of LPS on learning and memory and the role of IL-1 β in this process. It has been shown that LPS can selectively impair hippocampus-dependent contextual fear conditioning, while having no effects on hippocampus-independent auditory fear conditioning^[18]. LPS administration at the dose of 0.125 mg/kg (but not 0.25 mg/

Table 2. Summary of the studies on the effect of IL-1 β on learning and memory by disrupting the IL-1 β signaling pathway

Agent	Species	Dose	Route	Memory testing paradigm	Time	Effect on memory	Reference
IL-1ra	Rat	100 μ g	i.c.v.	Water maze spatial	Immediately after the last trial	Impairment	[35]
IL-1ra	Rat	100 μ g	i.c.v.	Passive avoidance	Immediately after the shock (testing 1 d later)	No effect	[35]
IL-1ra	Rat	100 μ g	i.c.v.	Passive avoidance	Immediately after the shock (testing 8 d later)	Impairment	[35]
IL-1ra	Mouse	100 μ g	i.c.v.	Fear-conditioning contextual	Immediately following conditioning	Impairment	[36]
IL-1R	Mouse	—	Knockout	Water maze spatial	—	Impairment	[38]
				Fear-conditioning contextual	—	Impairment	[38]
IL-1ra	Mouse	—	Transgenic	Water maze spatial	—	Impairment	[36]
				Fear-conditioning contextual	—	Impairment	[36]

kg or 0.5 mg/kg) immediately after the conditioning impairs contextual fear conditioning, but not auditory-cued fear conditioning in juvenile rats. Similar results are obtained in adult rats, only at the dose of 1 mg/kg. Besides, administration of IL-1ra (100 mg/kg, i.h.) immediately following LPS injection can reverse the detrimental effects on contextual fear memory. Moreover, LPS has been indicated to cause memory impairment in the passive avoidance paradigm^[52] and induce deterioration of spatial learning in the water maze paradigm^[19]. By using a fixed start location version of water maze, researchers show that LPS can impair spatial learning in rats^[53]. The effects of LPS on learning and memory have also been examined in another paradigm—two-way active avoidance, and results show that LPS (250 μ g/kg, i.p.) can impair two-way active avoidance conditioning in C57BL/6J mice^[20].

The effects of some other inflammatory agents on learning and memory have also been investigated. It has been reported that mice inoculated with the bacterium *Legionella pneumophila*, which increases IL-1 β level in mice^[54], one day before training in the spatial water maze task show impaired learning. However, injection of anti-IL-1 β antibodies 2 h before training can block these detrimental effects on spatial memory^[21,22]. The role of HIV coat protein gp120 in AIDS-related memory impairment has also been studied. It is found that rats with i.c.v. injection of HIV gp120 (4, 6, or 8 μ g) exhibit increased IL-1 β level in the hippocampus and impaired contextual, but not auditory-cued fear conditioning^[24]. Similarly, when IL-1ra or alpha melanocyte stimulating hormone (α MSH), an endogenous hormone and transmitter that inhibits the actions of IL-1 β , is injected (i.c.v.) before administration of HIV gp120, these detrimental effects are abolished. Apart from these agents, chronic brain inflammation has also been found to impair memory and elevate IL-1 β level in the brain. It has been reported that infusion of LPS (0.25 μ g/h) into the 4th ventricle for 4 weeks results in an increase of IL-1 β mRNA level within the basal forebrain region and the hippocampus, and a significant impairment in spatial memory in T-maze test^[55]. Another chronic neuroinflammation model is established based on a delayed-type hypersensitivity (DTH) response to the bacterium *Bacillus Calmette-Guerin* in the hippocampus of rats. By using

this model, researchers have found that hippocampal DTH response produces elevated IL-1 β level in the infected hippocampus and memory impairment in Y-maze^[56]. Moreover, IL-1 β is shown to mediate this DTH-induced memory impairment, because when IL-1ra is chronically administered for 10 d before testing, the memory impairment would be abolished.

Interestingly, animals show impaired memory not only when immune system is stimulated, but also when psychological stress is exerted. This was demonstrated in an early study in 1995^[57]. In this study, rats subjected to inescapable shock 24 h before training in an active avoidance task exhibited impaired learning compared to the controls. Furthermore, the learning impairment could be blocked by i.c.v. administration of IL-1ra before inescapable shock. Using another form of stressor—social isolation, researchers find that isolation for 5 h following fear conditioning impairs contextual, but not auditory-cued memory in rats^[28]. Besides, hippocampal IL-1 β level is increased following social isolation, and i.c.v. administration of IL-1ra before isolation can block the detrimental effects of social isolation on contextual memory.

In conclusion (Table 3), both activation of immune system and psychological stress can affect learning and memory, with elevations in IL-1 β level. Lines of evidence show that infection and stress interact with each other, exerting their effects on learning and memory^[58-60], and IL-1 β seems to be an important intermediary in these processes.

2.5 Involvement of IL-1 β in memory impairments associated with aging and disease Although a majority of studies are carried out in rodents, some evidence indicates the involvement of IL-1 β in memory impairments associated with aging and diseases in human. Aged people often have atrophic hippocampus and exhibit symptoms of dementia^[61,62]. It is supposed that the increase of IL-1 β during aging is implicated in the changes of brain function associated with normal aging^[63]. Alzheimer's disease (AD) is the most common form of dementia occurring in aged people. The typical pathologic characteristics of AD in human brain include amyloid plaques and neurofibrillary tangles^[64]. Recent evidence suggests that AD is always accompanied by chronic inflammation that may contribute to the progression of this disease^[65]. Epidemio-

Table 3. Summary of the studies on the effect of IL-1 β on learning and memory by infection and stress

Agent	Species	Dose	Route	Memory testing paradigm	Time	Effect on memory	Reference
LPS	Rat (juvenile)	0.125 mg/kg	i.p.	Fear-conditioning contextual	Immediately following conditioning	Impairment	[18]
		0.25 or 0.5 mg/kg	i.p.	Fear-conditioning contextual	Immediately following conditioning	No effect	[18]
LPS	Rat (adult)	1 mg/kg	i.p.	Fear-conditioning contextual	Immediately following conditioning	Impairment	[18]
		0.5 or 2 mg/kg	i.p.	Fear-conditioning contextual	Immediately following conditioning	No effect	[18]
LPS	Mouse	50 μ g	i.p.	Passive avoidance	Immediately after the shock	Impairment	[52]
LPS	Mouse	600 μ g/kg	i.p.	Water maze spatial	During training	Impairment	[19]
LPS	Rat	100 μ g/kg	i.p.	Water maze spatial	Day 1 of training 5 d of training daily	Impairment No effect	[53] [53]
LPS	Mouse	250 μ g/kg	i.p.	Active avoidance	During training	Impairment	[20]
Bacteria (<i>Lp</i>)	Mouse	8 $\times$ 10 ⁶ bacteria/mouse	i.p.	Water maze spatial	1 d before training	Impairment	[21],[22]
Protein (gp120)	Rat	4, 6, or 8 μ g	i.c.v.	Fear-conditioning contextual	Immediately following conditioning	Impairment	[24]
LPS	Rat	0.25 μ g/h	i.c.v.	T-maze	Infusion for 4 weeks	Impairment	[55]
Bacteria (<i>E. coli</i>)	Rat (24 months)	2.5 $\times$ 10 ⁹ CFU	i.p.	Water maze spatial	7 d prior to training (testing 1 h after the last training)	No effect	[95]
					7 d prior to training (testing 48 h after the last training)	Impairment	[95]
				Fear-conditioning contextual	4 d prior to conditioning (testing 1 h following conditioning)	No effect	[95]
					4 d prior to conditioning (testing 48 or 72 h following conditioning)	Impairment	[95],[96]
Bacteria (<i>E. coli</i>)	Rat (3 months)	2.5 $\times$ 10 ⁹ CFU	i.p.	Water maze spatial	7 d prior to training (testing 1 or 48 h after the last training)	No effect	[95]
				Fear-conditioning contextual	4 d prior to conditioning (testing 1 or 48 h following conditioning)	No effect	[95]
Shock	Rat	stress	—	Active avoidance	24 h before training	Impairment	[57]
Social isolation	Rat	stress	—	Fear-conditioning contextual	Immediately following conditioning	Impairment	[28]

logical studies show that persons who have taken anti-inflammatory drugs have a lower risk of developing AD^[66-70]. Moreover, there are clinical studies indicating the protective effects of anti-inflammatory drugs in AD patients^[71,72]. IL-1 β plays an important role in chronic inflammation in AD patients. Firstly, IL-1 β levels are significantly higher in the temporal lobe^[73], frontal cortex^[74], hippocampus^[75,76], and cerebrospinal fluid (CSF)^[75] in AD patients, compared with the age-matched controls. Secondly, IL-1 β is highly expressed by microglia within hours of head trauma^[77] which is a high risk factor for the development of dementia and AD. Thirdly, IL-1 β is found in the regions surrounding amyloid plaques^[73,78]. IL-1 β immunoreactive microglia are abundant in neuritic plaques, but rare in non-neuritic plaques^[79]. Besides, IL-1 β may promote the development of AD. Amyloid precursor protein (APP) is a ubiquitous membrane-bound protein, from which amyloid beta peptides are derived. Several studies show that IL-1 β has some effects on the expression and processing of APP. Through stimulating APP promoter^[80], IL-1 β increases the expression of APP mRNA^[81,82]. IL-1 β also stimulates protein kinase C to process APP into amyloid beta peptides^[83]. Interestingly, LPS has similar effects by increasing IL-1 β level^[84]. Approximately half of AIDS patients develop the symptoms of AIDS-related dementia complex (ADC), and IL-1 β is supposed to be involved in ADC-related learning impairment, because high IL-1 β levels are observed in the CSF of AIDS patients and by post-mortem brain examination, especially in demented AIDS patients^[85].

3 No effects or even beneficial effects of IL-1 β on learning and memory

Despite the findings of detrimental effects of elevated IL-1 β level on memory processes discussed above, other studies using somewhat different schedules of IL-1 β administration and test procedures, have shown no effects or even beneficial effects of IL-1 β on learning and memory. It has been reported that IL-1 β (2 μ g/kg, i.p.) has no effects on learning and memory of rats in the MWM^[86]. In another study, at the dose of 2 μ g/kg, LPS can impair hippocampus-dependent memory consolidation, which however, could not be replicated by injecting IL-1 β systemically, even at a wide

range of doses (0.1, 2, 4 and 100 μ g/kg)^[87]. Besides, injection of IL-1 β (100 ng, i.c.v.) immediately before training does not impair the performance of rats on day 2 in the water maze^[25]. It has also been shown that young female mice treated with IL-1 β (100 ng, i.p.) and trained in the water maze (5 trials each day for 3 d) find the platform with the same pathlength as controls. Moreover, at a higher dose (1000 ng, i.p.), IL-1 β may actually facilitate learning in the water maze (9 trials each day for 2 d)^[88]. When rats are bilaterally injected with IL-1 β (1 ng/side) directly into the hippocampus 48 h after pre-exposure to the context, no effects on fear conditioning can be observed^[30]. In the three-panel runway, intra-hippocampal IL-1 β injection (10 ng/side) does not impair the working memory of animals^[33]. Rats injected with IL-1 β (10 ng/rat, i.c.v.) at the end of passive avoidance training show no impairment in memory when tested one day after training. Furthermore, when tested 5 d after training, rats exhibit facilitated memory^[35]. In another spatial form of the passive avoidance test, i.c.v., injection of IL-1 β (15 ng) 50 min before the conditioning and then 50 min before the testing can enhance conditioned fear memory in rats^[89]. Also, i.p. injection of low doses of IL-1 β (1, 3 μ g/kg but not 6 μ g/kg) 24 h before training can result in better performance in active avoidance^[90,91].

To sum up, elevated IL-1 β level seems to be necessary for the impairment of learning and memory, but whether it is sufficient to induce the impairment of learning and memory still needs to be further explored.

4 Key factors mediating the effects of IL-1 β on learning and memory

More recently, the role of immune activation induced by LPS or IL-1 β in causing deficits in learning and memory has been critically reviewed, with a specific focus on multiple confounding factors such as decreased motivation, reduced locomotor activity and swimming speed, conditioned taste and place aversion, increased stress responses and thigmotaxis, and state-dependent effects^[92]. Here we focused on some important factors that may affect the effects of IL-1 β on learning and memory, including dose, age, memory type and memory stage.

4.1 Dose An inverted U-shaped model of the influence of IL-1

on memory has been proposed, that is, physiological levels of IL-1 are necessary for memory formation, while any deviation from the physiological range, either excessive elevation or blockade of IL-1 signaling, may result in impairment in memory^[93]. Therefore, dose is a key factor that influences the effects of IL-1 β on learning and memory. It has been reported that IL-1 β gene expression is induced in the hippocampus 24 h following fear-conditioning in mice^[36]. Furthermore, when mice are injected with IL-1 α (100 μ g, i.c.v.) or IL-1 β (1 or 10 ng) immediately after conditioning and tested 48 h later, they show a significant difference in fear conditioning. Specifically, mice injected with either IL-1 α or a high dose of IL-1 β exhibit impaired contextual fear conditioning, while mice injected with a low dose of IL-1 β exhibit improved contextual fear conditioning^[36]. These data indicate that on one hand, elevated IL-1 β levels are likely to impair learning and memory, on the other hand, low levels of IL-1 β may facilitate learning and memory.

4.2 Age As mentioned above, increased IL-1 β levels are associated with memory impairment in aged people. Age is a critical factor for memory impairment not only during normal aging, but also at pathological conditions. It has been shown that for rats at different ages, different doses of LPS are required to produce detrimental effects on contextual fear conditioning^[18]. A low dose of LPS (0.125 mg/kg) can impair contextual fear conditioning in juvenile rats, while in adult rats, a higher dose (1 mg/kg) is needed to produce the same effect. Also, the same dose of LPS (250 μ g/kg) may have different effects on water maze performance in 2-month-old and 12-month-old female C57BL/6J mice^[94]. The 12-month-old female mice treated with LPS spent more time and swam longer distance to find the platform, as compared with 2-month-old LPS-treated mice. These findings indicate that older animals are more adversely affected by LPS treatment. Moreover, *Escherichia coli* (*E. coli*) has been revealed to be capable of impairing contextual fear responses and long-term memory in water maze in old rats (24-month-old), but not in young ones (3-month-old)^[95]. Similar results have been obtained in another study^[96]. These data indicate that aging rats are more vulnerable to memory disruption following injection of *E. coli* than young rats. This discrepancy can usu-

ally be attributed to the age-related modulation of Brain-Endocrine-Immune Axis after activation of immune system. It has been reported that IL-1 β level in the hippocampus increases in response to LPS stimulation in 24-week-old mice, but not in 3-week-old ones^[97]. Aged mice are more sensitive to endotoxic shock after LPS administration^[98,99]. Exaggerated neuroinflammation and sickness behavior are found in aged mice after peripheral immunostimulation^[100]. After peripheral LPS administration, aged mice show prolonged sickness behavior including anorexia, depressed activity, reduced social behavior, *etc.*, and lose more weight than adult mice. Microarray analysis has revealed increased inflammation in the brain of LPS-treated aged mice, compared to the LPS-treated adult mice. Besides, exaggerated and prolonged elevations of LPS-induced inflammatory cytokines including IL-1 β and oxidative stress are found in aged brain. Furthermore, it has been illustrated that the exaggerated neuroinflammation and prolonged sickness behavior are due to a hyperactive microglia response associated with higher induction of inflammatory IL-1 β and anti-inflammatory IL-10^[101]. Similar results have been obtained when LPS is administered intracerebroventricularly^[102]. In conclusion, age is a significant factor mediating Brain-Endocrine-Immune Axis. Aged brain is more sensitive and vulnerable to immunity activation, which may be responsible for the severe behavioral deficits that frequently occur in older adults with infections, including impaired learning and memory ability.

4.3 Learning or memory An early study showed that IL-1 β (100 ng/rat, i.c.v.) did not affect the acquisition of spatial learning in the first day, but caused a transient memory impairment in the first trial of the following day^[25]. Subsequent experiments in mice came to similar results^[88]. Young female mice with i.p. injection of IL-1 β (100 ng) could find the platform equally well as controls in the training. However, the probe test that examines the accurate memory of animals revealed that at the end of training, control mice searched predominantly in the target quadrant, while IL-1 β -treated mice did not. These results indicate that although both groups learned to locate the platform, only the control mice remembered the location of the platform well in relation to the extra-maze spatial cues. It seems that memory, rather than learning,

is selectively affected by IL-1 β . This may be related to the characteristics of the hippocampus, since IL-1 β has a close relation with the hippocampus-dependent memory, as shown previously. It has been demonstrated that the ventral hippocampus is not necessary for the acquisition of spatial learning^[103-105], but lesions of the ventral hippocampus are sufficient to cause retrograde amnesia in a previously learnt spatial task^[106]. Using contextual fear conditioning, researchers have shown the detrimental effects of elevated IL-1 β on memory consolidation^[18,23,28]. The impairment of memory appears to be caused particularly by interference with the processes that construct a representation of the features of the context rather than the processes that associate this representation with the aversive consequences of shock, because pre-exposure to the context before the conditioning can eliminate the impairment in contextual fear caused by LPS^[18].

4.4 Specific types and stages of memory Memory appears to be more selectively affected by IL-1 β than learning. It has also been shown that IL-1 β specifically affects hippocampus-dependent memory, but not the hippocampus-independent memory. Moreover, it seems that IL-1 β interferes with specific stages of memory. It has been reported that peripheral injection of *E. coli* could produce a marked increase of IL-1 β level in the hippocampus^[96]. Aged rats treated with *E. coli* 7 d prior to the training in the water maze did not show deficits in acquisition of learning or in short-term retention probe testing, but did show impairment in long-term retention probe testing^[95]. In the same study, injection of *E. coli* 4 d prior to conditioning could impair long-term, but not short-term memory in contextual fear conditioning in aged rats^[95]. In another study^[35], rats were injected with IL-1 β immediately after conditioning and tested at days 1 and 5 post conditioning, or injected with IL-1 α immediately after conditioning and tested at days 1 and 8 post conditioning in the passive avoidance paradigm. IL-1 β induced time-dependent memory improvement, that is, there was a significant difference in latency between IL-1 β -injected group and control group on the fifth day, but not on the first day post-injection. IL-1 α significantly impaired long-term memory of the rats, as shown by much shorter latencies to touch the drinking spout on the eighth day post-injection, compared with saline-in-

jected rats. These data suggest that IL-1 β may significantly influence the long-term memory rather than the short-term memory. Several studies on other species also show that immune activation does not impair short-term working memory. It has been reported that LPS-induced immune activation can impair attention but not short-term working memory in pigeons^[107]. In human, 0.8 ng/kg LPS can induce an improvement in working memory, but an impairment in declarative memory^[108]. Subsequent studies show that 0.2 ng/kg LPS produces little effect on working memory, executive function or attention^[109]. In upper respiratory tract infection patients, researchers find no decrements in accuracy of episodic memory or in quality of working memory, but a major decrease in speed of cognitive processing, particularly in retrieval of memory^[110]. The hippocampus is essential for consolidation of information from short-term to long-term memory^[111,112]. IL-1 β may be involved in this process and exert its influence on long-term memory.

To sum up, IL-1 β may affect specific types and particular stages of memory in cognitive activities. Apart from that, through the Brain-Endocrine-Immune Axis, the time and duration of IL-1 β action on learning and memory need to be considered. It has been shown that i.c.v. injection of IL-1 β one hour, but not immediately before training causes memory impairment in rats. The authors conclude that these animals injected directly before training have achieved both the acquisition and consolidation of the memory before IL-1 β 's effects on these processes take hold^[25]. It has also been reported that IL-1 β (i.p.) has no effects on water maze learning when mice are subjected to a spaced learning protocol (5 trials per day for 3 d), but impairs the performance of mice in a massed learning protocol (9 trials per day for 2 d)^[88]. This lack of effect may be attributed to the kinetics of IL-1 β in the sickness response, as spaced learning protocol offers more time for rest and a longer interval between injection and learning episodes. In another study^[30], IL-1 β was bilaterally injected into the hippocampus at different time points after pre-exposure to the context. The animals were shocked one day after microinjection and tested for contextual fear response one day after conditioning. Rats injected with IL-1 β immediately or 3 h after pre-exposure showed a 50% reduc-

tion in contextual fear conditioning, while injection of IL-1 β 24 h following pre-exposure only induced a 20% decrease in fear response, compared with the controls. Moreover, no effects on the fear response were observed when IL-1 β was injected 48 h after pre-exposure.

Taken together, time is a key factor influencing the effects of IL-1 β on learning and memory. Time points for stimulation and detection are critical in studying the effects of IL-1 β on learning and memory.

5 Conclusion

The present evidence suggests that IL-1 β is involved in learning and memory. On one hand, physiological level of IL-1 β is essential for learning and memory. On the other hand, elevated IL-1 β level may have detrimental effects on learning and memory. Dose, age, time are the key factors modulating the effects of IL-1 β on learning and memory. Also, species, strain, testing paradigm, and even environment are probable influencing factors. These may explain some inconsistencies on the effects of IL-1 β on learning and memory in different studies. Nevertheless, IL-1 β has been implicated and hypothesized to be a critical mediator in memory impairments associated with aging, stress, infection, AD, and ADIS-related dementia complex. Therefore, in addition to its role in mediating inflammation and coordinating the sickness behavior, IL-1 β also plays an important role in cognitive function, especially in hippocampus-dependent cognitive activities.

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白介素 1 β 与学习和记忆

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摘要: 白介素 1 β 是最早被研究的细胞因子之一。白介素 1 β 调节炎症以及在病态时协调生理和行为变化的重要作用早已研究者认可。最近越来越多的研究表明白介素 1 β 可能会损害认知功能, 但也有些研究报道白介素 1 β 对学习记忆没有损伤甚至有促进作用。因此, 白介素 1 β 与认知损伤之间的关系尚不十分清楚。本文对白介素 1 β 损害或促进学习记忆的实验数据进行了综述, 并对可能影响白介素 1 β 对学习记忆作用的一些关键因素进行了讨论。

关键词: 白介素 1 β ; 学习; 记忆; 浓度; 年龄; 记忆类型; 记忆阶段