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Research Report

Interleukin-1β inhibits the differentiation of hippocampal neural precursor cells into serotonergic neurons

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ABSTRACT

Interleukin-1 beta (IL-1β) is one of pro-inflammatory cytokines. Recent studies have shown that IL-1β impairs hippocampal neurogenesis, mediates proliferation and differentiation of multipotent neural precursor cells (NPCs), and exerts effects of anti-proliferation, anti-neurogenesis, and pro-gliogenesis on embryonic hippocampal NPCs. The aim of this study was to examine the effect of IL-1β on the differentiation of hippocampal NPCs into functional serotonergic neurons, which play important roles in the pathophysiology and treatment of depression. Hippocampal NPCs were prepared from the hippocampus of neonatal rats (within 24 h after birth). After three passages and phenotyping, hippocampal NPCs were cultured in a differentiating medium with various concentrations (5, 10, and 20 ng/mL) of IL-1β for 7 days. At the endpoint, the serotonergic differentiation of hippocampal NPCs in IL-1β-treated cultures decreased in a dose-dependent manner and this effect was blocked by IL-1ra, an IL-1 receptor antagonist capable of blocking the effects of IL-1 by binding to the same receptor (IL-1R1) without triggering signaling; serotonin in the lysate of the differentiated hippocampal NPCs decreased in IL-1β-treated cultures; and levels of Bcl-2 and phosphorylated extracellular-regulated kinase (pERK) were also lower in differentiated hippocampal NPCs with IL-1β treatment. These results support the hypothesis that IL-1β is an important factor in the stress-associated neuropathology and psychopathology and has relevance to the treatment of depressive symptoms in patients with depression.

1. Introduction

Interleukin-1 (IL-1) is a prototypal cytokine with pleotropic effects. It comes from many types of cells including immune cells in the periphery as well as glia and neurons within the brain (Dinarello, 1996). The action of IL-1 involves various ligands and receptors: IL-1α and IL-1β activate the IL-1 receptor type I (IL-1RI) (Sims et al., 1993); whereas IL-1

Abbreviations: 5-HT, serotonin; bFGF, basic fibroblast growth factor; DIV, days in vitro; DMEM, Dulbecco's modified eagle's medium; DMSO, dimethyl sulphoxide; EGF, epidermal growth factor; ERK, extracellular-regulated kinase; FBS, fetal bovine serum; GFAP, glial fibrillary acidic protein; HPA, hypothalamic pituitary-adrenal axis; IL-1, interleukin-1; IL-1β, interleukin-1 beta; IL-1RI, IL-1 receptor type I; IL-1ra, IL-1 receptor antagonist; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa B; NPC, neural precursor cell; pERK, phosphorylated ERK

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receptor antagonist (IL-1ra) serves to block the effects of IL-1 by binding to the same receptor (IL-1R1) without triggering signaling (Seckinger et al., 1987). IL-1 signaling is mediated by multiple pathways including the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NFκB) cascades, translocation of transcription factors into the nucleus, and transcription of immediate-early genes like *c-jun* and *c-fos* (McCulloch and Downey, 2006).

IL-1 is the first cytokine that has been associated with modulation of neuroendocrine systems, particularly the hypothalamic pituitary-adrenal axis (HPA) (Berkenbosch et al., 1987; Bernton et al., 1987; Sapolsky et al., 1987). Production of brain IL-1 is an important link in stress-induced activation of the HPA axis and secretion of glucocorticoids, which mediate the effects of stress on memory functioning and neural plasticity. Moreover, IL-1 signaling and the resultant glucocorticoid secretion mediate the development of depressive symptoms associated with exposure to acute and chronic stressors, at least partly via suppressing hippocampal neurogenesis (Goshen and Yirmiya, 2009). These previous findings suggest that IL-1 is a critical mediator of adaptive stress responses as well as stress-associated neuropathology and psychopathology.

There is an accumulating array of data linking IL-1β up with the stress-associated neuropathology and psychopathology. First, IL-1β increased following various stressors in animals and humans (Goshen and Yirmiya, 2009); second, depressed mood was associated with serum elevations of IL-1β in subjects without a psychiatric history (van den Biggelaar et al., 2007); third, higher concentrations of IL-1β inhibited learning, memory and long-term potentiation (Depino et al., 2004; Nolan et al., 2005; Yirmiya et al., 2002); fourth, levels of depression, anxiety, and memory impairment in human volunteers were positively correlated with serum IL-1β (Yirmiya et al., 2000). Moreover, hippocampal IL-1β-mediated cognitive impairment was associated with stress (Goshen and Yirmiya, 2009; Vereker et al., 2001) and depression (Goshen et al., 2007).

The hippocampus has been linked with some psychiatric disorders including clinical depression. Stem cells have been shown to reside in this brain region and to differentiate under a variety of conditions into neural cells. Recent studies have shown that high levels of IL-1β impairs hippocampal neurogenesis in aged mice (Kuzumaki et al., 2010), mediates proliferation and differentiation of multipotent neural precursor cells (NPCs) (Wang et al., 2007), and exerts effects of anti-proliferation, anti-neurogenesis and pro-gliogenesis on embryonic hippocampal NPCs (Green et al., 2012).

Although effects of IL-1β on the proliferation and differentiation of hippocampal NPCs have been studied, little is known about the influence of IL-1β on embryonic hippocampal NPC lineage restriction and differentiation. The aim of this study was to examine the effect of this pro-inflammatory cytokine on the differentiation of embryonic hippocampal NPCs into functional serotonergic neurons, which play important roles in the pathophysiology and treatment of depression (Jans et al., 2007; Mann, 1999). IL-1β in the present study was shown to inhibit the differentiation of embryonic hippocampal NPCs into serotonergic neurons in a dose-dependent manner and this effect was blocked by IL-1ra. In the differentiated hippocampal NPCs, IL-1β treatment decreased levels of serotonin (5-HT), which was accompanied with lower Bcl-2 and phosphorylated extracellular-regulated kinase (pERK).

2. Results

2.1. *IL-1β inhibits cell proliferation and decreases the survival rate of hippocampal NPCs*

IL-1β exposure has been shown to decrease the total cells of cultured NPCs, inhibit cell proliferation and reduce viability

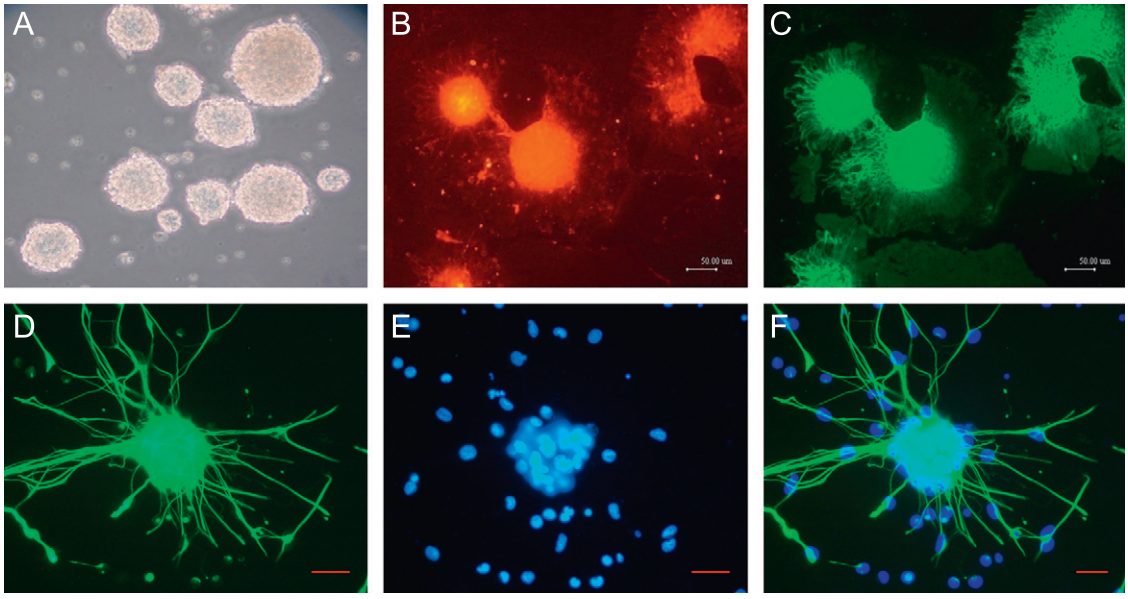

Fig. 1 – Neural precursor cells in neurospheres. (A) Typical neurospheres at passage 2. (B) and (C) Immunofluorescence images of neurospheres showing III-Tubulin (B) and GFAP positive (C) staining. (D) and (E) A neurosphere showing Nestin positive staining (D) and nuclei of all cells identified by DAPI (E). (F) The merged image of (D) and (E).