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BRAIN RESEARCH

Research Report

Interleukin-1β interferes with signal transduction induced by neurotrophin-3 in cortical neurons

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ARTICLE INFO

Article history:
Accepted 13 October 2007
Available online 26 October 2007

Keywords:
IL-1β
NT-3
Signal transduction
Cortical neuron

ABSTRACT

It was previously observed that IL-1β interferes with BDNF-induced TrkB-mediated signal transduction and protection of cortical neurons from apoptosis evoked by deprivation from trophic support [Tong L., Balazs R., Soiampornkul R., Thangnipon W., Cotman C.W., 2007. Interleukin-1beta impairs brain derived neurotrophic factor-induced signal transduction. Neurobiol. Aging]. Here we investigated whether the effect of the cytokine on neurotrophin signaling is more general. The influence of IL-1β on NT-3 signaling was therefore studied under conditions when NT-3 primarily activated the TrkC receptor. The cytokine reduced NT-3-induced activation of MAPK/ERK and Akt, but did not interfere with Trk receptor autophosphorylation. IL-1β reduced tyrosine phosphorylation of the docking proteins, IRS-1 and Shc, which convey receptor activation to the downstream protein kinase cascades. These are the steps that are also inhibited by IL-1β in BDNF-induced signal transduction. The functional consequences of the effect of IL-1β on NT-3 signaling were severe, as NT-3 protection of the trophic support-deprived cortical neurons was abrogated. In view of the role in the maintenance and plasticity of neurons of ERK, Akt and CREB, which are activated by neurotrophins, elevated IL-1β levels in the brain in Alzheimer's disease and other neurodegenerative diseases might contribute to the decline in cognitive functions before the pathological signs of the disease develop.

1. Introduction

Neurotophins are a family of structurally related proteins that regulate the survival, differentiation and maintenance of different populations of peripheral and central neurons and they are also essential for modulating neuronal plasticity (Bibel and Barde, 2000; Huang and Reichardt, 2001; Leingartner et al., 1994; Segal et al., 1992). BDNF and NT-3 support the survival and differentiation of select populations of neurons in a partially redundant manner (Minichiello and Klein, 1996). The effects are primarily mediated through high affinity Trk receptors: BDNF signals by activating TrkB, whereas NT-3 is more promiscuous (Huang and Reichardt, 2003), but activates preferentially TrkC (Lamballe et al., 1991). Even if neurons expressing both Trk receptors, BDNF and NT-3 may have specific biological effects (Ip et al., 1993; Leingartner et al.,

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doi:10.1016/j.brainres.2007.10.051

1994; McAllister et al., 1999; Segal et al., 1992) and there is convincing evidence that in vivo, at least in the inner ear, NT-3 signals exclusively through the TrkC receptor (Stenqvist et al., 2005), indicating that TrkB and TrkC are not functionally redundant even when coexpressed in individual neurons.

We have been studying the influence of factors that may contribute to neuronal dysfunction in early stages of Alzheimer's disease (AD), when pathological changes are not yet manifest (Tong et al., 2004, 2001). Recently we examined the effect of the proinflammatory cytokine IL-1β on BDNF signaling and function (Tong et al., 2007). IL-1β levels are elevated in the brain with aging and even more so in neurodegenerative disorders, such as AD. We observed that IL-1β, under conditions when it does not compromise neuronal viability, interferes with BDNF signaling by reducing activation of the docking proteins that convey the signal from the activated Trk receptors to the Ras/MAPK and PI3-K/Akt pathways, and thus elicits a type of neurotrophin resistant state (Tong et al., 2007). The functional consequences were severe, as neuronal vulnerability was increased. The neuroprotective function of IGF-1 that is another important neurotrophic factor is similarly compromised in cerebellar granule cells by another proinflammatory cytokine TNFα that elicits a reduction of the activation of the docking protein IRS-2 (Venters et al., 1999).

In order to test how general is the proinflammatory cytokine-induced neurotrophic factor resistance, we have

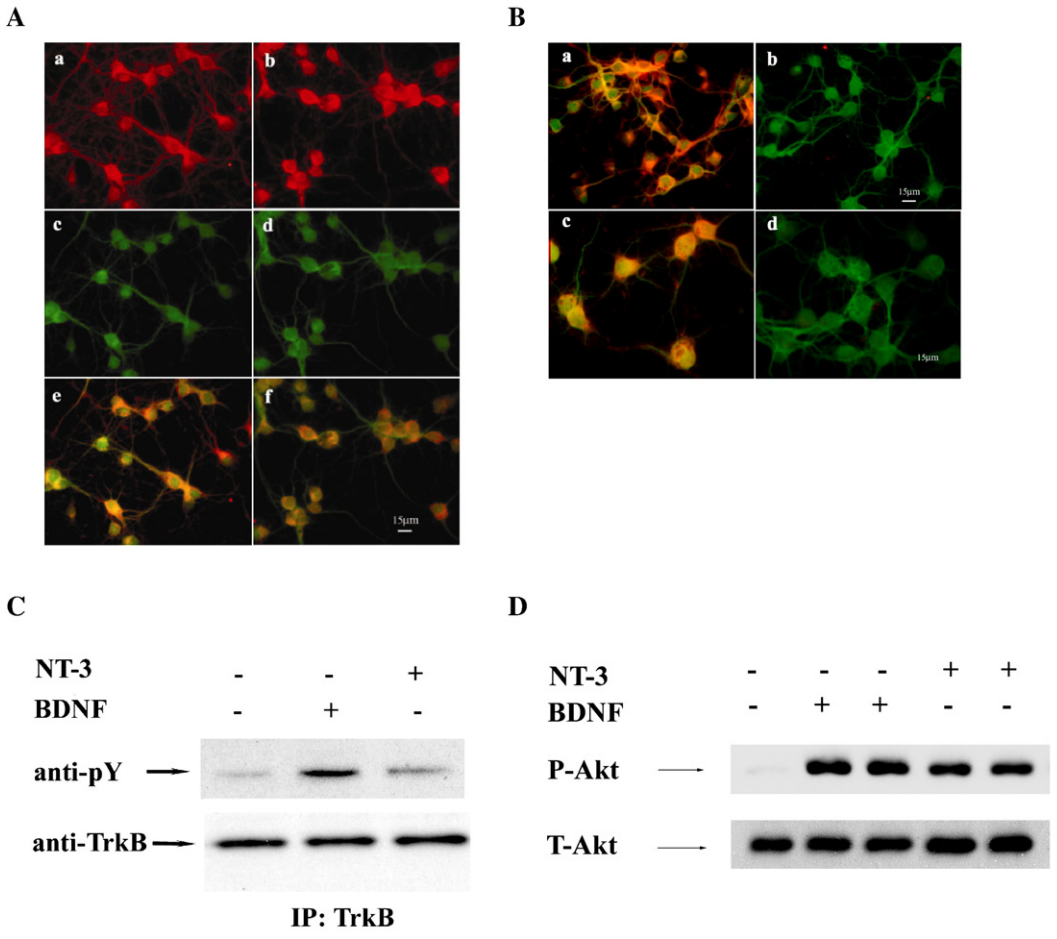

Fig. 1 – Virtually all cultured cortical neurons express both TrkB and TrkC receptors. (A) Immunocytochemical detection of TrkB (a) and TrkC (b) receptors using specific antibodies (red). Neurons were detected using MAP-2 antibodies (c and d) (green). The merged images (orange) show that almost all neurons express TrkB (e) as well TrkC (f) receptors. In independent experiments (not shown), an additional staining with Hoechst 33342 dye showed that virtually all the live nerve cells expressed these receptors. (B) Specificity of the Trk antibodies. Merged images (orange) are shown after double staining with antibodies recognizing MAP-2 (green) and Trk receptors (red) using antibodies to TrkB (a) and TrkC (c). Double staining with Trk antibodies preabsorbed with peptides used for the antibody production and specific for C-terminal sequences of TrkB (b) and TrkC (d) showed only green images (MAP-2). (C) Compared with the autophosphorylation of the TrkB receptor induced by BDNF, the effect of NT-3 is low (25±8%, $n=3$). Cultures were exposed to 10 ng/ml of BDNF or NT-3 for 15 min. Immunoprecipitates obtained with TrkB antibody were blotted with phosphotyrosine antibodies (anti-pY) and TrkB antibodies. (D) In spite of the relatively low activation of TrkB receptor by NT-3, the degree of NT-3-induced activation of Akt was only slightly less than that obtained with BDNF (cells were treated with the neurotrophins at 10 ng/ml for 15 min), consistent with NT-3 predominantly activating TrkC-mediated signaling.