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Stimulation of production of glial cell line-derived neurotrophic factor and nitric oxide by lipopolysaccharide with different dose-responsiveness in cultured rat macrophages

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ABSTRACT

To understand the molecular basis of inflammation-induced neurotrophic influences, we investigated the effects of lipopolysaccharide (LPS) on production of glial cell line-derived neurotrophic factor (GDNF) in the injured rat spinal cord or in cultured rat macrophages in comparison with the effects on synthesis/secretion of inducible nitric oxide synthase (iNOS) and nitric oxide (NO). We found that GDNF mRNA expression lasted longer than that of iNOS mRNA in the injured spinal cord after injection of the high-dose LPS that had improved locomotor function, suggesting that the GDNF expression and its balance with NO generation were critical for injury regeneration. Therefore, we next investigated the effects of LPS on cultured macrophages. Levels of iNOS mRNA and secreted NO were enhanced by LPS at lower concentrations (10 ng/mL and above), whereas mRNA expression and secretion of GDNF were elevated only at higher concentrations (100 ng/mL and above). The culture medium of macrophages treated with 10 ng/mL of LPS was actually neurotoxic against cultured cortical neurons, whereas that conditioned at 1000 ng/mL was not. These observations suggest that neurotoxicity partly based on NO is induced by a lower degree of inflammation, whereas neurotrophic effects based on GDNF are manifested at a higher degree of inflammatory activity.

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