

newer results with dexamethasone will spark an interest in the development of potent and specific NF- κ B inhibitors. Since NF- κ B is involved in the production of a large number of cytokines, acute phase response proteins, and adhesion molecules, it is an ideal target for inhibitors of an inflammatory reaction.

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Neurotrophins and Excitotoxicity

The results obtained by Jae-Young Koh *et al.* (1) on neurotrophin-mediated potentiation of excitotoxic necrosis are not consistent with other findings (2), but are consistent with our previous observation (3). We found that glutamate neurotoxicity is increased in cerebellar neurons pretreated with neurotrophins such as brain-derived neurotrophic factor (BDNF) or neurotrophin-3 (NT-3), but not by nerve growth factor (NGF).

This toxicity in cerebellar neurons might be comparable to the excitotoxic necrosis characterized by Koh *et al.*; it is prevented by *N*-methyl-D-aspartate (NMDA) receptor antagonists (4, 5), and spontaneous toxicity in cerebellar neurons after glucose deprivation can be delayed by NMDA receptor antagonists (6). The latter result is consistent with the finding that cultured cerebellar neurons release endogenous excitotoxins that induce NMDA receptor-mediated neurotoxicity (5, 7) and agrees with data presented by Koh *et al.* on the role of NMDA receptors in necrosis after glucose and oxygen deprivation in cultured cortical neurons.

Thus, NMDA receptor-mediated excitotoxic necrosis probably underlies the potentiation of neurotoxicity by neurotrophins that we observed. Such potentiation may not be selective for NMDA receptor-mediated necrosis. NT-3 but not BDNF or NGF potentiated non-NMDA receptor-mediated domoate toxicity in cerebellar neurons (3), suggesting a specific action of BDNF on NMDA receptor-mediated toxicity, while NT-3 may also affect neurotoxicity via non-NMDA receptors.

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Response: We admire the study of Fernández-Sánchez and Novelli, which focused on the neuroprotective effect of basic Fibroblast growth factor (bFGF) on cultured cerebellar granule cells exposed to glutamate agonists (1). We are intrigued by their additional observation that BDNF and NT-3 increased glutamate agonist-induced granule cell death, and agree that it provides additional general challenge to the conventional wisdom that neurotrophins are beneficial (or at least not harmful) for injured neurons, regardless of injury type. However, further study will be needed to determine the exact relationship between this observation and our recent report (2).

Our study was focused on a new proposal that the neuroprotective effects of neurotrophins may be restricted to apoptosis,

with the factors potentiating necrosis death. Fernández-Sánchez and Novelli did not originally address the nature of the glutamate-induced death they observed (1). Their favored explanation for the protective effects of bFGF on this death was enhancement of Ca^{2+} influx, an idea most consistent with the death being apoptosis. Apoptosis is easily evoked in cerebellar granule cell cultures, and can be blocked by depolarization or other methods for raising the concentration of Ca^{2+} ions ($[\text{Ca}^{2+}]_i$) (3). In our neocortical cultures, excitotoxins induce a Ca^{2+} -overload necrosis death that is increased by measures which increase Ca^{2+} influx of $[\text{Ca}^{2+}]_i$.

Mediation by NMDA receptors does not resolve whether apoptosis or necrosis occurs, as both forms of death can be triggered by glutamate receptor activation (4). Understanding the relationship between our recent study and that of Fernández-Sánchez and Novelli is also complicated by the finding of Lindholm *et al.* that BDNF did protect cerebellar granule cells against glutamate-induced death (5). NT-3 increased death associated with domoic acid exposure in the study of Fernández-Sánchez and Novelli, whereas neurotrophins did not affect AMPA- or kainate-induced excitotoxicity in our cortical cultures.

In any case, we hope that our collective in vitro observations will spur further examination of a potential "dark side" of neurotrophins in animal models of brain or spinal cord injury. In recent experiments, we have found that intracerebral injection of NT-4/5 in adult rats increases the volume of brain infarction after transient middle cerebral artery occlusion (6).

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