Mammalian neuronal cells are susceptible to injury and death due to oxygen radicals, ischemia, axotomy, glucose deprivation, excitotoxins, and other noxious agents. Even under normal physiological conditions, these cells are subject to naturally occurring programmed cell death. Protecting neurons against injury from these and other insults, and promoting their growth, differentiation and survival during development, are several groups of neurotrophic factors (1–3). Foremost among these are the classical neurotrophins, a family of small ($\sim$ 13 kD), highly basic proteins, of which nerve growth factor is the prototype. Other neurotrophins include brain-derived growth factor (BDGF), neurotrophin 3 (NT3), and NT 4/5. Additional compounds with neurotrophic properties include a variety of cytokines such as ciliary neurotrophic factor (CNF), leukemia inhibitory factor (LIF), and various interleukins; fibroblast growth factor (FGF); insulin-like growth factor 1 (IGF-1); transforming growth factor β (TGF β) and related factors; and glial-derived neurotrophic factor (GDNF). Gene knockout studies of neurotrophic factors and their receptors have helped define their functions and the specific target populations of their actions. In general, specific neurotrophic factors support specific populations of neurons, although there is overlap in the trophic support of individual neurons in the central nervous system (4). There is much hope that neurotrophic factors may prove useful in the treatment of neurological diseases and nerve injury. Clinical trials in Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, AIDS-related neuropathy, diabetic neuropathy, and other disorders, have been initiated (5).

Despite the variety of neurotrophic factors already characterized, the identification of novel factors with proven effectiveness must be welcome news. In this issue of *The Journal*, Brenneman and Gozes (6) describe the purification of a neuroprotective 14-kD protein, called activity-dependent neurotrophic factor (ADNF), which is secreted by astroglial cells in the presence of vasoactive intestinal peptide (VIP). A 14–amino acid residue peptide, contained within ADNF (ADNF-14), prevented neuronal cell death caused by glycoprotein 120, the envelope protein of the human immunodeficiency virus, by excitotoxin *N*-methyl-D-aspartate (NMDA), by β-amyloid peptide, a neurotoxin associated with the pathogenesis of Alzheimer's disease, and by the neurotoxin tetrodotoxin. The findings are all the more remarkable in that the VIP-induced neurotrophic peptide was active in the surprisingly low concentration range of 10^{-17}–10^{-12} M! Biological activity at such low concentrations is known for toxins such as those of *Clostridium botulinum* and *C. tetani*, but not for physiologically acting hormones or neurotransmitters in mammalian systems. Although the full sequence of ADNF is not presented, the chemical identification of the highly potent ADNF-14 should prompt additional investigation and confirmation of its biological effects.

The induction of ADNF by astroglial cells may be an important mechanism by which VIP exerts its neuroprotective action. A widely distributed neuropeptide, VIP is richly present in neurons of the cerebral cortex and hippocampus and often localized in cholinergic neurons (7). VIP, and a more potent lipophilic analog, [stearyl-norleucine[17]] VIP (8), have been shown to protect cortical and hippocampal neurons in several experimental models of injury that are relevant to Alzheimer's disease (6, 9). In that disease, neuronal loss leads to deficits in three neuronal systems: cholinergic, hippocampal, and cortical neurons (10). Like other neurotrophic factors, VIP also promotes the survival and differentiation of developing neuronal cells (11, 12). The administration of a VIP antagonist in neonatal mice resulted in neuronal damage and retardation of behavioral development (13).

The protective effect of VIP extends beyond neuronal tissues. In isolated, perfused lungs, the peptide prevents, attenuates or delays acute oxidant injury induced by the herbicide paraquat, by the combination of xanthine and xanthine oxidase, and by glutamate receptor agonist NMDA (14). VIP is similarly protective in an in vivo model of septic shock and acute lung injury, caused by infusion of cobra venom factor. In isolated rat hearts perfused by the Langendorff technique, VIP dose-dependently enhances left ventricular function and coronary flow, and reduces myocardial tissue injury, intracellular Ca^{2+} transients, and the level of hydroxyl radical detected in the ischemic reperfused heart (15).

In these preparations as in neuronal systems, the protective effect of VIP is exhibited at considerably higher concentrations than reported for the glial-derived ADNF peptide. Two distinct receptor-second messenger systems appear to be involved: a Ca^{2+} pathway in the glial-mediated action observed at strikingly low concentrations (16), and adenylyl cyclase stimulation in almost all other VIP effects elicited at higher concentrations (7). An increase in intracellular $[Ca^{2+}]$ seems an unlikely mechanism of neuroprotection since it is an essential step in the initiation of central neuronal excitotoxicity due to intense NMDA receptor activation (17). On the other hand, an increase in intracellular $[Ca^{2+}]$ may be necessary for prevention of neuronal cell death under certain circumstances (18).

VIP may be a physiological modulator of neuronal and other cell injury. Such a role is suggested by the augmented production of the peptide and increases in its mRNA in response to injury, demonstrated in the lungs and airways (19), and its increased expression following axotomy (20). Finally, the promising results reviewed here suggest that it may be appropriate to consider beginning clinical trials of VIP, of more potent, longer-acting analogs such as stearyl-Nle17-VIP, and perhaps, as we learn more, of the newly identified ADNF-14, in neurological and other conditions where tissue protection or rescue of injured tissue is indicated.

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