Transforming Growth Factor-β

A Neuroprotective Factor in Cerebral Ischemia

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Abstract

Transforming growth factor-β (TGF-β) has diverse and multiple roles throughout the body. This review focuses on the evidence supporting its functions in the central nervous system, with a particular emphasis on its purported role in cerebral ischemia. Numerous studies have documented that TGF-β1 levels are enhanced in the brain following cerebral ischemia. As evidence that such an upregulation is beneficial, agonist studies have demonstrated that TGF-β1 reduces neuronal cell death and infarct size following middle cerebral artery occlusion (MCAO), while conversely, antagonist studies have shown increased neuronal cell death and infarct size after MCAO. These studies suggest that TGF-β1 has a neuroprotective role in cerebral ischemia. Recent work with adenoviral-mediated overexpression of TGF-β1 in vivo in mice has further implicated a neuroprotective role for TGF-β1 in cerebral ischemia, as evidenced by a reduction in neuronal cell death, infarct size, and neurological outcome. Additionally, numerous in vitro studies have documented the neuroprotective ability of TGF-β1 in neurons from a variety of species, including rats, mice, chicks, and humans. Of significant interest, TGF-β1 was shown to be protective against a wide variety of death-inducing agents/insults, including hypoxia/ischemia, glutamate excitotoxicity, β-amyloid, oxidative damage, and human immunodeficiency virus. The mechanism of TGF-β1-mediated neuroprotection remains to be resolved, but early evidence suggests that TGF-β1 regulates the expression and ratio of apoptotic (Bad) and antiapoptotic proteins (Bcl-2, Bcl-x1), creating an environment favorable for cell survival of death-inducing insults. Taken as a whole, these results suggest that TGF-β1 is an important neuroprotective factor that can reduce damage from a wide array of death-inducing agents/insults in vitro, as well as exert protection of the brain during cerebral ischemia.

Index Entries: Transforming growth factor-β; neuroprotection; stroke; ischemia; excitotoxicity; central nervous system; brain; hippocampus; cerebral cortex.
INTRODUCTION

Transforming growth factor-βs (TGF-βs) represent a large family of growth factors that contains over 30 members, including over 20 bone morphogenetic proteins (BMPs), 4 activins/inhibins, and three TGF-β proteins (1). Most of the members of the TGF-βs family share seven cysteine residues that comprise a characteristic cysteine knot motif in the three-dimensional structure. Furthermore, most share the feature of being synthesized as a larger precursor structure, from which the mature, active segment is derived. TGF-βs also have a wide expression pattern, which suggests multiple and diverse functions for its family members. Indeed, more than 16,000 published studies have appeared in the literature in just the past 10 yr alone that have implicated TGF-βs in varied and diverse processes such as development, disease, transformation, wound healing, extracellular matrix synthesis, cell proliferation, inflammatory cell infiltration, immunosuppression, chemoprotection, neurotropism, and neuroprotection (1–5). To maintain focus, this review will center on the central nervous system (CNS) actions of TGF-βs, with a special emphasis on its potential neuroprotective role in cerebral ischemia. An overview of the TGF-β signaling system is provided, followed by a description of CNS localization, actions and implications of the TGF-β system in CNS function and neurodegeneration, and potential mechanisms of action.

TRANSFORMING GROWTH FACTOR-β ISOFORMS, RECEPTORS, AND SIGNAL TRANSDUCTION: AN OVERVIEW

Transforming Growth Factor-β Isoforms and Transforming Growth Factor-β Receptors

Of the 30-plus members of the TGF-β superfamily, TGF-β was the first member identified over 20 yr ago and is perhaps the best known. TGF-β exists as three isoforms in mammals—designated TGF-β1, TGF-β2, and TGF-β3; each of which is the result of a separate gene (1,6). It has also been proposed that there are two additional isoforms that are homologs to the mammalian TGF-β isoforms, e.g., TGF-β4 in chicken and TGF-β5 in Xenopus. The three mammalian TGF-β isoforms share similar basic structures and have an approx 65–80% homology in the mature region. An additional important caveat is that the TGF-β1–3 proteins exist in both active and latent forms (6–8). TGF-β is secreted in an inactive form, noncovalently linked to a latency-associated peptide, which is covalently bound to a latent TGF-β binding protein. The latent TGF-β protein is thought to play a role in storage, secretion, and activation of TGF-β. The release/activation of TGF-β from the latent precursor is achieved by the action of proteases, such as plasmin, cathepsins B and D, calpain and glycosidases, or through the action of binding proteins (e.g., thrombospondin-1; 7,8).

With regard to mediation of TGF-β actions, three different TGF-β receptors have been identified, the type I, type II, and type III TGF-β receptor (9). The type I and II receptors mediate high-affinity binding and signal transduction, whereas the role of the type III receptor is unknown, although several reports suggest it may present TGF-β to the type I and II receptors. Both the type I and II receptors have been shown to contain a serine-threonine kinase domain in the cytoplasmic C-terminus. TGF-β binds directly the type II receptor, which forms a heteromeric dimer of the type I and type II receptors (10). This interaction results in a unidirectional phosphorylation event in which the type II receptor phosphorylates the type I receptor, activating its kinase domain. The activated type I receptor then signals to a variety of intracellular mediators, with the Smad family being the best characterized.

Transforming Growth Factor-β Signal Transduction

The Smads represent a crucial discovery in unraveling the TGF-β-mediated signal transduction system. Smads were initially discov-