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Serum Growth Factors and Neuroprotective Surveillance

Focus on IGF-I

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Abstract

The adult brain requires a constant trophic input for appropriate function. Although the main source of trophic factors for mature neurons is considered to arise locally from glial cells and synaptic partners, recent evidence suggests that hormonal-like influences from distant sources may also be important. These include not only relatively well-characterized steroid hormones that cross the brain barriers, but also blood-borne protein growth factors able to cross the barriers and exert unexpected, albeit specific, trophic actions in diverse brain areas. Insulin-like growth factor I (IGF-I) is until now the serum neurotrophic factor whose actions on the adult brain are best-characterized. This is because IGF-I has been known for many years to be present in serum, whereas the presence in the circulation of other more classical neurotrophic factors has only recently been recognized. Thus, new evidence strongly suggests that IGF-I, and other blood-borne neurotrophic factors such as Fibroblast Growth Factor (FGF-2) or the neurotrophins, exert a tonic trophic input on brain cells, providing a mechanism for what we may refer to as neuroprotective surveillance. Protective surveillance includes "first-line" defense mechanisms ranging from blockade of neuronal death after a wide variety of cellular insults to upregulation of neurogenesis when defenses against neuronal death are overcome. Most importantly, surveillance should also encompass modulation of homeostatic mechanisms to prevent neuronal derangement. These will include modulation of basic cellular processes such as metabolic demands and maintainance of cell-membrane potential as well as more complex processes such as regulation of neuronal plasticity to keep neurons able to respond to constantly changing functional demands.

Index Entries: Neuroprotection; neurotrophic factors; blood–brain barriers; insulin-like growth factor I; brain physiology.

Introduction

All tissues require a homeostatic balance for proper function. Nerve tissue appears to have a dedicated set of cells, glial cells, to keep tight control of ion and nutrient input to neurons

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(1). Although hormones are classical homeostatic modulators in all tissues, endocrine control of brain function has been implicitly considered less important than paracrine modulation by neurotrophic factors and other local cell-to-cell messengers. This is likely owing to the existence of functional and anatomical brain barriers that have been considered an unsurmountable obstacle for blood-borne macromolecules with neuroactive potential *(2).* With the exception of lipid-soluble molecules, such as hormonal steroids, passage of molecules through the brain barriers is mostly restricted to ions and nutrients *(3).* Thus, brain cells have been considered out of reach of serum-protein hormones and circulating trophic messengers in general. In addition, both neurons and glial cells synthesize many different growth factors, which argues against the idea that the same molecules that are locally available need to be recruited from the periphery. Based on these observations, it is currently accepted that local messengers are the principal trophic input to neurons.

However, a number of apparently unrelated observations suggest that normal brain function relies on a peripheral neurotrophic network that provides constant protective surveillance against functional derangement. This article focuses on the major observations supporting this notion.

Circulating Growth Factors and Central Nervous System Diseases

Brain growth factors and cytokines are drastically altered in the course of all types of brain lesions *(4).* The complex array of changes found for each particular disease and cell type makes it difficult to establish the pathological significance of these alterations. However, it is widely assumed that local changes in neurotropic proteins reflect adaptive responses to neuronal death. Whether these responses help or otherwise hinder recovery of function is controversial, although it is probable that both beneficial and detrimental effects occur *(5).*

In search of possible markers of neurodegeneration, clinically oriented studies have begun to determine levels of different neurotrophic factors in the cerebrospinal fluid (CSF) of patients afflicted with different neurodegenerative diseases. The relative ease in obtaining serum samples from these patients, as compared to CSF, prompted evaluation of serum levels of neurotrophic factors even though synthesis of these factors in organs other than the brain *(6–8)* makes it difficult to establish a relationship between changes in serum levels of neurotrophins and the neurodegenerative process. Many neurotrophic factors, including the neurotrophins, FGFs, insulin-like growth factors (IGFs), and so on, have detectable serum and CSF levels that in many instances are changed in neurodegenerative diseases *(9–18).* Although for most neurotrophic factors information relative to serum and CSF levels in different neurodegenerative conditions is scarce, in the case of IGFs detailed information is already available (*see 19* for a review). The major conclusion is that all neurodegenerative diseases studied so far, including major illnesses such as Alzheimer's disease (AD), multiple sclerosis (MS), or stroke, as well as many types of inherited and idiopatic neurodegenerative diseases, show changes in serum IGFs levels, and in many cases also in the CSF. Although the relationship of these changes to the pathogenesis of the different diseases remains to be established, these observations lead to the following question: Do changes in serum levels of neurotrophic factors relate to changes in brain levels?

Serum Neurotrophic Factors Cross the Blood–Brain Barriers

For years, it has been considered that neurotrophic factors should be locally synthesized by brain cells because the blood–brain barriers isolate the brain from blood-borne macromolecules. Furthermore, neurotrophic factors, such as the neurotrophins, have long been considered to be biologically relevant only in brain physiology even though the first known biological source of nerve growth factor, the founding member of

the family, was the male mouse submandibular gland *(6).* However, new evidence is gradually changing this conception. First, all trophic factors active in the brain are also present in the periphery; second, and most important, many of them, including insulin, IGF-I, FGF-2, Epidermal Growth Factor (EGF), the neurotrophins, and so on, cross the blood-brain barriers *(20–26).* The main route of entrance into the brain appears to be the blood-CSF pathway through the choroid plexus (CP). Although the underlying mechanisms are not yet known, transport of neuroactive growth factors across the CP epithelium includes a receptor-specific process, similar to what is well-established for other blood-borne proteins, such as transferrin or albumin *(27).* Once in the CSF, growth factors reach specific targets throughout the brain parenchyma by unknown mechanisms, possibly including binding to carrier proteins and/or retrograde transport from the ventricular surface *(28,29).* At any rate, potent biological effects of blood-borne neurotrophic factors on different brain areas indicate that they can target specific neuronal populations *(21,30–33).* The diversity of effects reported support a physiological role for this novel route of action of blood-borne growth factors. However, little is known about the physiological conditions under which serum growth factors access the brain, or whether this process is constitutive or regulated. Nevertheless, changes in the blood-CSF growth factor pathway have already been suggested to be involved in brain pathology *(3,21,32).*

Circulating IGF-I is a Physiological Neuroprotective Agent

IGF-I circulates in blood at high concentrations, forming stable, long-lived protein complexes with several IGF-binding proteins *(34).* Although all types of tissues synthesize IGF-I, the main source of blood-borne IGF-I is the liver *(35).* Since the establishment of the "somatomedin hypothesis" *(34),* IGF-I has been considered the principal effector of growth-hormone actions in somatic growth. For this reason, the endocrine role of circulating IGF-I has been extensively studied in past years *(34).* However, recent observations indicate that major disruptions in the IGF-I endocrine system do not alter somatic growth *(7,35,36),* leaving liver-derived serum IGF-I without a clear physiological function.

Parallel to this questioning of the classical endocrine role of serum IGF-I, several reports started to show that serum growth factors can enter into the brain crossing the brain barriers (*see* above). Original studies focused on the passage of serum insulin into the brain because both insulin and insulin receptors are present in brain tissue, but no local synthesis of insulin, if any, could account for the levels of protein found in brain *(37).* While insulin passes from the blood to the brain likely through the blood–brain barrier present in the capillary endothelium *(38,39),* other growth factors cross at a much higher rate through the blood–choroid plexus interface *(21,33).*

Initially, these observations met considerable resistance because the brain barriers, sealed by tight junctions, were considered to impede passage of serum macromolecules *(2).* However, recent views on the functional role of the CP propose an active role of this specialized epithelium in the controlled transfer of neuroactive signals, including neuroactive growth factors from the blood into the brain *(3).* Although the mechanisms involved in this transport are not yet clear, we know they include a receptor-dependent stage. Indeed, receptors for IGFs, FGFs, and the neurotrophins, to name a few, are present either in the capillary endothelium, the choroid plexus epithelium, or both *(3,40–42).* Preliminary evidence from our laboratory indicates that at least for IGF-I, transcytosis via specific subcellular compartments within the choroid epithelium appears as a likely mechanism of passage to the CSF for this growth factor. Transcytosis through the CP of proteins such as transferrin or transthyretin is well-known *(3,43).* Once in the CSF, IGF-I may bind to different IGF-binding proteins abundant in the CSF *(29)* that serve both as carriers and biological reservoirs of IGFs. In turn, the ventricular surfaces contain cells expressing IGF-I

receptors *(44).* Thus, CSF-borne IGF-I can rapidly gain access to widely separated target areas throughout the brain *(3).* Indeed, blood-injected digoxigenin-labeled IGF-I reaches target cells in the hippocampus, cerebellum, or brainstem within minutes after its injection *(21).*

Evidence that the passage of serum IGF-I to the brain bears functional significance comes from different sources. First, IGF-I receptors are distributed diffusely throughout the entire brain even though the sites of IGF-I synthesis are restricted to circumscribed areas such as the olfactory bulb, hippocampus, cerebellum, or spinal cord *(45).* Besides this apparent mismatch between receptor localization and ligand availability, levels of IGF-I in the brain remain relatively stable throughout development and adulthood, whereas levels of IGF-I mRNA gradually decrease along development to reach low levels in the adult *(46–48).* An extracerebral source for brain IGF-I would easily explain these discrepancies. Second, tranport of blood-borne IGF-I into the brain appears to be regulated by physiological stimuli, such as physical exercise *(21).* For example, we have gathered evidence (Trejo, Carro, and Torres-Aleman, 2001, in press), that an increased transport of serum IGF-I into the brain mediates the stimulatory effects of exercise on brain neurogenesis *(49)* and c-fos activation *(21).*

Additional evidence in support of a physiological role of circulating IGF-I in the brain comes from the variety of central effects exerted by systemic administration of IGF-I. Thus, a bolus intravenous injection of IGF-I produces a protracted increase in neuronal excitability both under basal conditions as well as after afferent stimulation (*21,* and our unpublished observations). This procedure also results in increased hippocampal BDNF expression (*21*), an effect also produced by physical exercise *(50).* Furthermore, serum IGF-I is essential for adult hippocampal neurogenesis (*30,* and Trejo, Carro, and Torres-Aleman, 2001, in press). IGF-I shows also strong neuroprotective effects when given peripherally *(51)* through upregulation of antiapoptotic and growth-promoting proteins *(31,32,52).*

A Neuroprotective Surveillance Network

Based on the observations previously, outlined, we propose that circulating neuroactive growth factors such as IGF-I or FGF-2 (and probably others as well) form part of a surveillance mechanism developed by the body to maintain brain homeostasis. We envisage this surveillance as a two-armed process. First, serum neurotrophic factors will be involved in what we may term "preemptive measures" designed to help neurons adapt to constantly changing functional needs. Modulation of homeostatic mechanisms underlying basic cellular processes such as energy demands and membrane excitability will be a first priority. Indeed, glucose accumulation and consumption, oxygen availability, membrane ion-channel activity, calcium-flux levels, and many other basic processes are all targets of growth-factor actions in the brain *(53).* Other known actions of neurotrophic factors including their ability to modulate neurotransmitter receptor function, synaptic strength, or cytoskeleton dynamics that form the basis of neural plasticity events will also importantly contribute to keep neuronal function within appropriate physiological limits *(54,55).* This type of process may explain the common observation that administration of neurotrophic factors prior to brain damage results in reduced neuronal death; i.e., neurons are "tuned-up" by neurotrophic factors to cope better with homeostatic derangements.

A second essential component of this surveillance network will include protection from pathological disturbances when preventive mechanisms are overcome. Neurotrophic factors protect neurons against an extraordinary variety of threats such as oxidative stress, excitotoxicity hypoxia, hypoglycemia, and other insults normally occurring along the life of the neuron. Furthermore, when these protective effects fail, ultimate approaches such as neuron replacement through growth factor-regulated neurogenesis may also take place *(30,33).*

Neuroprotective serum factors may in this way be included in a surveillance network

similar to the immunogical surveillance network of which circulating cytokines form a part. At first glance this may look like just a new name for a well-known role of neuroactive serum hormones. After all, that gonadal and adrenal steroids play important roles in neuronal survival has long been known. However, our view suggests a functional relationship between peripheral protein growth factors and brain homeostasis more important than previously considered. Specifically, we propose that the tonic trophic input that appears to be essential for proper brain function derives not only from local factors present in the neuronal microenvironment but also from blood-borne neurotrophic signals such as IGFs, FGFs, the neurotrophins, and others. As previously noted, all these factors are also synthesized by brain cells. So, what might be the reason for this apparent redundancy?

Trophic Redundancy as a Neuroprotective Strategy

There are many apparently redundant processes in brain physiology. During neurogenesis, approx 50% of neurons die at different stages along development *(56).* From neuropathological studies in the adult brain, we know that neurological deficits appear only after the function of a substantial number of neurons is compromised. Can we infer from these observations that the developing brain produces excess neurons or that the adult brain needs only a subset of its cells for appropriate functioning? It is obvious that what we may interpret as redundant processes only reflects a lack of knowledge of the biological significance of our observations. In the case of blood-borne neurotrophic factors, should we consider them redundant?

A first possibility is that redundancy of trophic inputs truly exists and is a strategy to assure neuronal survival. If a source of trophic input disappears owing to pathological derangement (for example, after cell death-induced deafferentation), alternative sources will continue providing trophic input to keep target neurons functional. A second possibility is that redundancy is only apparent. For example, different sources of a same neurotrophic factor may merely reflect compartmentalization of trophic signaling. This will result in a distinct functional significance for each source of trophic factor. In other words, it is the anatomical location of the trophic signal together with its identity that confers biological relevance. Because functional compartmentalization is the rule rather than the exception in classical neurotransmission, we will use a comparative approach between neurotransmitters and growth factors to illustrate this notion, i.e., the IGF-I and glutamate inputs received by Purkinje cells in the cerebellar cortex. Adult Purkinje cells, albeit at lower levels than during development, synthesize IGF-I *(57),* so they are exposed to IGF-I secreted by neighboring cells. In addition, they receive and depend for proper functioning on IGF-I input from climbing fiber afferents *(58,59).* Finally, they can also accumulate blood-borne IGF-I *(21).* Glutamate is the neurotransmitter used by the two main afferents to Purkinje cells, i.e., parallel fibers and climbing axons. However, Purkinje cells distinguish the two signals, despite some possible perisynaptic leakage of glutamate *(60),* because the glutamate signal is anatomically constrained. Similarly, IGF-I synthesized by Purkinje cells may signal a subpopulation of Purkinje cells or other neighboring cells different from those cells receiving IGF-I input from climbing axons or from those Purkinje cells that accumulate blood-borne IGF-I. Although no colocalization studies have been performed, the subpopulation of Purkinje cells that express IGF-I receptors may be different from the subpopulation that synthesizes IGF-I. Furthermore, IGF-I receptors are localized only in synapses that in turn show different anatomical distribution in subpopulations of Purkinje cells *(61).* Thus, compartmentalization strategies developed for neurotransmitter signaling may also underlie neuroprotective signaling.

Conclusions

Recent observations suggest that blood-borne neurotrophic factors play a role in brain homeostasis more important than previously expected. Serum levels of an increasing list of neurotrophic factors are changed in many neurodegenerative diseases. Blood-borne neurotrophic factors cross the blood–brain barriers and modulate brain function. Based on these observations we propose that circulating neurotrophic factors form part of a neuroprotective surveillance network. Surveillance mechanisms include preventive as well as defensive processes. The former allow neurons to adapt to normal functional demands. The latter permit neurons to cope with harmful situations. Although the subject of this review has focused on IGF-I, it is reasonable to assume that other neurotrophic factors present in serum are involved in similar mechanisms. After all, the trophic effects of IGF-I on brain cells are indistinguishable from those exerted by other neurotrophic factors.

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References

1. Walz W. (1989) Role of glial cells in the regulation of the brain ion microenvironment. *Prog. Neurobiol.* **33,** 309–333.
2. Rubin L. L. and Staddon J. M. (1999) The cell biology of the blood-brain barrier. *Annu. Rev. Neurosci.* **22,** 11–28.
3. Strazielle N. and Ghersi-Egea J. F. (2000) Choroid plexus in the central nervous system: biology and physiopathology. *J. Neuropathol. Exp. Neurol.* **59,** 561–574.
4. Isackson P. J. (1995) Trophic factor response to neuronal stimuli or injury. *Curr. Opin. Neurobiol.* **5,** 350–357.
5. Morganti-Kossman M. C., Lenzlinger P. M., Hans V., Stahel P., Csuka E., Ammann E., et al. (1997) Production of cytokines following brain injury: beneficial and deleterious for the damaged tissue. *Mol. Psychiatry* **2,** 133–136.
6. Murphy R. A., Saide J. D., Blanchard M. H., and Young M. (1977). Nerve growth factor in mouse serum and saliva: role of the submandibular gland. *Proc. Natl. Acad. Sci. USA* **74,** 2330–2333.
7. Sjogren K., Liu J. L., Blad K., Skrtic S., Vidal O., Wallenius V., et al. (1999) Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. *Proc. Natl. Acad. Sci. USA* **96,** 7088–7092.
8. Nakahashi T., Fujimura H., Altar C. A., Li J., Kambayashi J., Tandon N. N., and Sun B. (2000) Vascular endothelial cells synthesize and secrete brain-derived neurotrophic factor. *FEBS Lett.* **470,** 113–117.
9. Gilmore J. H., Jarskog L. F., Lindgren J. C., McEvoy J. P., and Xiao H. (1997) Neurotrophin-3 levels in the cerebrospinal fluid of patients with schizophrenia or medical illness. *Psychiatry Res.* **73,** 109–113.
10. Hock C., Heese K., Muller-Spahn F., Huber P., Riesen W., Nitsch R. M., and Otten U. (2000) Increased CSF levels of nerve growth factor in patients with Alzheimer's disease. *Neurology* **54,** 2009–2011.
11. Kossmann T., Stahel P. F., Lenzlinger P. M., Redl H., Dubs R. W., Trentz O., et al. (1997) Interleukin-8 released into the cerebrospinal fluid after brain injury is associated with blood-brain barrier dysfunction and nerve growth factor production. *J. Cereb. Blood Flow Metab.* **17,** 280–289.
12. Laudiero L. B., Aloe L., Levi-Montalcini R., Buttinelli C., Schilter D., Gillessen S., and Otten U. (1992) Multiple sclerosis patients express increased levels of beta-nerve growth factor in cerebrospinal fluid. *Neurosci. Lett.* **147,** 9–12.
13. Malek A. M., Connors S., Robertson R. L., Folkman J., and Scott R. M. (1997) Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. *Pediatr. Neurosurg.* **27,** 182–189.
14. Mizuno Y., Takada H., Urakami K., Ihara K., Kira R., Suminoe A., et al. (2000) Neurotrophin-3 levels in cerebrospinal fluid from children with bacterial meningitis, viral meningitis, or encephalitis. *J. Child. Neurol.* **15,** 19–21.
15. Mogi M. and Nagatsu T. (1999) Neurotrophins and cytokines in Parkinson's disease. *Adv. Neurol.* **80,** 135–139.

16. Patterson S. L., Grady M. S., and Bothwell M. (1993) Nerve growth factor and a fibroblast growth factor-like neurotrophic activity in cerebrospinal fluid of brain injured human patients. *Brain Res.* **605,** 43–49.
17. Tham A., Nordberg A., Grissom F. E., Carlsson-Skwirut C., Viitanen M., and Sara V. R. (1993) Insulin-like growth factors and insulin-like growth factor binding proteins in cerebrospinal fluid and serum of patients with dementia of the Alzheimer type. *J. Neural Transm. Park Dis. Dement. Sect.* **5,** 165–176.
18. Torres-Aleman I., Barrios V., Lledo A., and Berciano J. (1996) The insulin-like growth factor I system in cerebellar degeneration. *Ann. Neurol.* **39,** 335–342.
19. Busiguina S., Fernandez A. M., Barrios V., Clark R., Tolbert D. L., Berciano J., and Torres-Aleman I. (2000) Neurodegeneration is associated to changes in serum insulin-like growth factors. *Neurobiol. Dis.* **7,** 657–665.
20. Banks W. A., Jaspan J. B., and Kastin A. J. (1997) Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. *Peptides* **18,** 1257–1262.
21. Carro E., Nunez A., Busiguina S., and Torres-Aleman I. (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J. Neurosci.* **20,** 2926–2933.
22. Deguchi Y., Naito T., Yuge T., Furukawa A., Yamada S., Pardridge W. M., and Kimura R. (2000) Blood-brain barrier transport of 125I-labeled basic fibroblast growth factor. *Pharm. Res.* **17,** 63–69.
23. Pan W., Banks W. A., and Kastin A. J. (1998) Permeability of the blood-brain barrier to neurotrophins. *Brain Res.* **788,** 87–94.
24. Pan W. and Kastin A. J. (1999) Entry of EGF into brain is rapid and saturable. *Peptides* **20,** 1091–1098.
25. Poduslo J. F. and Curran G. L. (1996) Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Brain Res. Mol. Brain Res.* **36,** 280–286.
26. Reinhardt R. R. and Bondy C. A. (1994) Insulin-like growth factors cross the blood-brain barrier. *Endocrinology* **135,** 1753–1761.
27. Stewart P. A. (2000) Endothelial vesicles in the blood-brain barrier: are they related to permeability? *Cell Mol. Neurobiol.* **20,** 149–163.
28. Ferguson I. A., Schweitzer J. B., Bartlett P. F., and Johnson E. M., Jr. (1991) Receptor-mediated retrograde transport in CNS neurons after intraventricular administration of NGF and growth factors. *J. Comp Neurol.* **313,** 680–692.
29. Ferry R. J., Jr., Katz L. E., Grimberg A., Cohen P., and Weinzimer S. A. (1999) Cellular actions of insulin-like growth factor binding proteins. *Horm. Metab Res.* **31,** 192–202.
30. Aberg M. A., Aberg N. D., Hedbacker H., Oscarsson J., and Eriksson P. S. (2000) Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus. *J. Neurosci.* **20,** 2896–2903.
31. Armstrong C. S., Wuarin L., and Ishii D. N. (2000) Uptake of circulating insulin-like growth factor-I into the cerebrospinal fluid of normal and diabetic rats and normalization of IGF-II mRNA content in diabetic rat brain. *J. Neurosci. Res.* **59,** 649–660.
32. Pulford B. E., Whalen L. R., and Ishii D. N. (1999) Peripherally administered insulin-like growth factor-I preserves hindlimb reflex and spinal cord noradrenergic circuitry following a central nervous system lesion in rats. *Exp. Neurol.* **159,** 114–123.
33. Wagner J. P., Black I. B., and DiCicco-Bloom E. (1999) Stimulation of neonatal and adult brain neurogenesis by subcutaneous injection of basic fibroblast growth factor. *J. Neurosci.* **19,** 6006–6016.
34. Jones J. I. and Clemmons D. R. (1995) Insulin-like growth factors and their binding proteins: biological actions. *Endocr. Rev.* **16,** 3–34.
35. Yakar S., Liu J. L., Stannard B., Butler A., Accili D., Sauer B., and LeRoith D. (1999) Normal growth and development in the absence of hepatic insulin-like growth factor I. *Proc. Natl. Acad. Sci. USA* **96,** 7324–7329.
36. Ueki I., Ooi G. T., Tremblay M. L., Hurst K. R., Bach L. A., and Boisclair Y. R. (2000) Inactivation of the acid labile subunit gene in mice results in mild retardation of postnatal growth despite profound disruptions in the circulating insulin-like growth factor system. *Proc. Natl. Acad. Sci. USA* **97,** 6868–6873.
37. Schechter R., Holtzclaw L., Sadiq F., Kahn A., and Devaskar S. (1988) Insulin synthesis by isolated rabbit neurons. *Endocrinology* **123,** 505–513.
38. Pardridge W. M. (1993) Transport of insulin-related peptides and glucose across the blood-brain barrier. *Ann. NY Acad. Sci.* **692,** 126–137.
39. Poduslo J. F., Curran G. L., and Berg C. T. (1994) Macromolecular permeability across the blood-

nerve and blood-brain barriers. *Proc. Natl. Acad. Sci. USA* **91,** 5705–5709.
40. Bondy C. A., Werner H., Roberts C. T., Jr., and LeRoith D. (1990) Cellular pattern of insulin-like growth factor-I (IGF-I) and type I IGF receptor gene expression in early organogenesis: comparison with IGF-II gene expression. *Mol. Endocrinol.* **4,** 1386–1398.
41. Golden P. L., Maccagnan T. J., and Pardridge W. M. (1997) Human blood-brain barrier leptin receptor. Binding and endocytosis in isolated human brain microvessels. *J. Clin. Invest.* **99,** 14–18.
42. Timmusk T., Mudo G., Metsis M., and Belluardo N. (1995) Expression of mRNAs for neurotrophins and their receptors in the rat choroid plexus and dura mater. *Neuroreport* **6,** 1997–2000.
43. Moos T. and Morgan E. H. (2000) Transferrin and transferrin receptor function in brain barrier systems. *Cell Mol. Neurobiol.* **20,** 77–95.
44. Aguado F., Rodrigo J., Cacicedo L., and Mellstrom B. (1993) Distribution of insulin-like growth factor-I receptor mRNA in rat brain. Regulation in the hypothalamo-neurohypophysial system. *J. Mol. Endocrinol.* **11,** 231–239.
45. Bondy C. A. and Lee W. H. (1993) Patterns of insulin-like growth factor and IGF receptor gene expression in the brain. Functional implications. *Ann. NY Acad. Sci.* **692,** 33–43.
46. Bach M. A., Shen-Orr Z., Lowe W. L., Jr., Roberts C. T., Jr., and LeRoith D. (1991) Insulin-like growth factor I mRNA levels are developmentally regulated in specific regions of the rat brain. *Brain Res. Mol. Brain Res.* **10,** 43–48.
47. Pons S., Rejas M. T., and Torres-Aleman I. (1991) Ontogeny of insulin-like growth factor I, its receptor, and its binding proteins in the rat hypothalamus. *Brain Res. Dev. Brain Res.* **62,** 169–175.
48. Torres-Aleman I., Pons S., and Arevalo M. A. (1994) The insulin-like growth factor I system in the rat cerebellum: developmental regulation and role in neuronal survival and differentiation. *J. Neurosci. Res.* **39,** 117–126.
49. van Praag H., Christie B. R., Sejnowski T. J., and Gage F. H. (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. USA* **96,** 13,427–13,431.
50. Neeper S. A., Gomez-Pinilla F., Choi J., and Cotman C. W. (1996) Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res.* **726,** 49–56.
51. Fernandez A. M., de la Vega A. G., and Torres-Aleman I. (1998) Insulin-like growth factor I restores motor coordination in a rat model of cerebellar ataxia. *Proc. Natl. Acad. Sci. USA* **95,** 1253–1258.
52. Fernandez A. M., Gonzalez de la Vega A. G., Planas B., and Torres-Aleman I. (1999) Neuroprotective actions of peripherally administered insulin-like growth factor I in the injured olivocerebellar pathway. *Eur. J. Neurosci.* **11,** 2019–2030.
53. Mitchell J. J., Paiva M., Walker D. W., and Heaton M. B. (1999) BDNF and NGF afford in vitro neuroprotection against ethanol combined with acute ischemia and chronic hypoglycemia. *Dev. Neurosci.* **21,** 68–75.
54. Black I. B. (1999) Trophic regulation of synaptic plasticity. *J. Neurobiol.* **41,** 108–118.
55. Schuman E. (1997) Growth factors sculpt the synapse. *Science* **275,** 1277, 1278.
56. Purves D. (1980) Neuronal competition. *Nature* **287,** 585, 586.
57. Lee W. H., Javedan S., and Bondy C. A. (1992) Coordinate expression of insulin-like growth factor system components by neurons and neuroglia during retinal and cerebellar development. *J. Neurosci.* **12,** 4737–4744.
58. Nieto-Bona M. P., Busiguina S., and Torres-Aleman I. (1995) Insulin-like growth factor I is an afferent trophic signal that modulates calbindin-28kD in adult Purkinje cells. *J. Neurosci. Res.* **42,** 371–376.
59. Torres-Aleman I., Pons S., and Garcia-Segura L. M. (1991) Climbing fiber deafferentation reduces insulin-like growth factor I (IGF-I) content in cerebellum. *Brain Res.* **564,** 348–351.
60. Satake S., Saitow F., Yamada J., and Konishi S. (2000) Synaptic activation of AMPA receptors inhibits GABA release from cerebellar interneurons. *Nat. Neurosci.* **3,** 551–558.
61. Garcia-Segura L. M., Rodriguez J. R., and Torres-Aleman I. (1997) Localization of the insulin-like growth factor I receptor in the cerebellum and hypothalamus of adult rats: an electron microscopic study. *J. Neurocytol.* **26,** 479–490.