THE SOMATOTROPHIC AXIS IN BRAIN FUNCTION
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IN BRAIN FUNCTION

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During the past decade studies have shown that growth hormone (GH) may exert profound effects on the central nervous system (CNS). The hormone thus appears to display an important role in many functions related to the CNS. GH deficiency is known to result in a reduction of several dimensions related to quality of life. However, exogenous compensation of the hormone may counteract these disabilities. For instance, GH replacement therapy is found to improve the psychological capabilities in adult GH-deficient (GHD) patients. Beneficial effects of the hormone on certain functions, including memory, mental alertness, motivation, and working capacity, have been reported. GH treatment of GHD children has also been observed to produce significant improvement in many behavioral problems seen in these individuals. Studies also indicated that GH replacement therapy affects the cerebrospinal fluid (CSF) levels of various hormones and neurotransmitters. Further support for CNS being a target for GH emerges from observations indicating that the hormone may cross the blood–brain barrier (BBB) and from studies confirming the presence of GH receptors (GHR) in the brain. Many effects of GH are mediated through the release of insulin-like growth factor-I (IGF-I). Therefore, studies on effects induced by IGF-I on brain function have been applied in order to obtain increased understanding of the mechanism by which GH exerts effects on brain areas related to various behaviors seen to be affected during GH replacement. The aim of this book is to summarize and highlight some recent knowledge in this area. This includes clinical observations of patients with a reduced ability to produce the hormone along with successful outcomes of GH replacement therapy in GHD patients and neuroprotective effects involving the somatotrophic axis, as well as animal models to explore the mechanisms at the neurochemical level by which the hormone induces its effects.

The first two chapters deal with some fundamental concepts regarding the biosynthesis and chemical nature of GH and IGF-I, focusing on mechanisms behind the regulation of secretion of these hormones to give the reader a brief background of events taking place in the body before the hormones interact with their receptors. The following two chapters describe basic mechanisms of how GH and IGF-I interact with receptors on their target cells. This includes text on receptor structure and mechanisms involved in signal transduction to finally give the GH or IGF-I response. Subsequent to these introductory chapters, the book content addresses questions related to the CNS.

Chapters 5 and 6 discuss mechanisms by which GH and IGF-I may reach their targets in the CNS. Also, methods for quantification and analysis of the two hormones in the CSF and their application in clinical studies are highlighted. Models used to study the transport of GH over the BBB are described. It seems that although there is strong evidence that GH may cross the BBB, as judged from human studies, it is difficult to demonstrate an active transport mechanism for the hormone using animal models. In human subjects, administration of GH causes a dose-dependent increase of the hormone in the CSF, whereas in models using rats or cell lines, penetration of the hormone across the BBB seems limited. As for IGF-I, it is demonstrated that this growth factor in conformity with insulin and prolactin may be transported over the BBB through a receptor-mediated mechanism.

An important part of the book content is given in Chapters 7–9, dealing with GH and IGF-I receptors in the brain regarding their regional distribution along with their chemical nature. Data on purification of GH receptors from human brain tissues, as well as description of the characteristic of GHR gene transcripts, are included in these chapters.
The outline of a procedure combining affinity chromatography and zone electrophoresis for the recovery of a purified preparation of GHR from the human choroid plexus is described in Chapter 8, and Chapter 9 deals with the characteristics of the GHR message in various regions of the rat brain. A comprehensive review on the localization of GH and IGF-I receptors is given in Chapter 7.

In the next section of the book there are a series of chapters (10–15) dealing with functional aspects of the role of the somatotrophic axis in the brain. Various types of animal models and cell systems have been used to establish a comparatively deep knowledge in functions that GH and IGF-I have in CNS injury, neurogenesis, and cognitive behaviors. Also, the interaction in various brain circuits of GH with prolactin is highlighted.

A major part of this book (Chapters 16–23) is directed to clinical studies. Hence, the role of the somatotrophic axis in acromegaly, life quality, psychiatric diseases, aging, and neurodegenerative diseases, e.g., Alzheimer's disease, is discussed. Also, the beneficial effects of hormone replacement GHD in children and GH-induced improvement on cognitive functions in elderly GHD patients are highlighted.

Finally, the remaining chapters focus on future perspectives, e.g., on the potential use of GH antagonists as possible pharmacological tools in future therapy and on future perspectives with respect to GH replacement therapy and life quality. Taken together, it has been interesting to see that it has been possible to get contributors to this book with such a good representation of geographical districts around the world, but also a good representation of the research around the world on the somatotrophic axis in relation to CNS.

It is believed that with the current advances in research on GH and IGF-I, this volume will represent a timely book that contributes an important topic that will be of interest to a variety of scientists from students and medical practitioners to basic and clinical researchers.

I am grateful to all my colleagues who have contributed such excellent chapters to this volume. As editor, I would like to point out that all these chapters were submitted within a time period of 6–7 months and should therefore contribute the very recent knowledge in the respective field covered within the volume.

Fred Nyberg
Uppsala in June, 2005
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Herbert McLean Evans is one of the most recognized endocrinologist in the field of growth hormone. In the early 1920-ies he demonstrated the presence of growth promoting material in adeno-pituitary extracts. In 1944 he published for the first time the isolation of growth hormone from bovine pituitaries. In addition to his pioneering work on growth hormone, Dr. Evans has contributed fundamental discoveries within a broad area of physiology but particularly in the field of endocrinology. His remarkable career as scientist is reflected by his development of the dye for cytological staining known as “Evans blue” and by the widely used “Long-Evans” rat strain.

Herbert Evans was born in 1882 in Modesto, California. He received his B.S. from the University of California at Berkley in 1904 but moved to Baltimore in 1905 to continue his medical studies. Evans obtained his M. D. at John Hopkins University in 1908 and received a chair as Professor in Anatomy in 1915 at Berkley, where he remained until his retirement in 1952. During this time he spent a lot of time visiting a large number of laboratories in the United States and also abroad. Dr. Evans remained active in his research until he passed away in 1971.

In addition to his pioneering work on growth hormone together with Joseph Long he was recognized for his brilliant work on the estrous cycle in the rat. In 1930 he created the Institute of Experimental Biology and several capable researchers joined his laboratory; Drs W.R. Lyons and Choh Hao Li with whom Dr. Evans carried out considerable work on pituitary hormones, e.g. lactogenic hormones, gonadotrophins as well as adrenocorticotropic hormone. He has contributed more than 600 scientific papers. One excellent example is his last written article a review chapter on growth published in the Pituitary Gland in 1966.

Dr. Evans presented a personality characterized by independence of thought, subtle powers of persuasion and an unfruffled demeanor, which made him appear as a figure of mystery to his colleague. He was essentially a forceful character with an underlying tenacity of purpose with a splendid intellect, which carried him forward in the pursuit of truth as he saw it. His memory will remain for many years to come.
Paul Roos was born in 1928 in Alingsås not to far from Gothenburg in western Sweden. He obtained his B.S. at the University in Lund in 1952 and in 1954 he went to Uppsala to perform his PhD studies in the laboratory of Professor Arne Tiselius (a Nobel Prize Laureate for his development of electrophoresis.) In 1958 he received a Licentiate in Biochemistry and a doctoral degree in the same subject in 1967, all at the University in Uppsala. Paul Roos was promoted to Professor in Biochemistry at Uppsala University in 1972 and remained on this chair until he retired in 1994.

When Paul Roos arrived in Uppsala he focused his research on pituitary hormones. Together with Professor Jerker Porath, at the same Department, he directed studies on the melanocyte-stimulating hormone. At Cambridge University, in collaboration with Dr. Ievan Harris, he determined the primary sequence of this hormone. However, his major contribution to the field of endocrinology came from his outstanding work on the isolation and characterization of growth hormone and gonadotrophins. Paul Roos was the first to outline a procedure for the recovery and isolation of growth hormone from human pituitaries under mild conditions. His highly purified preparation was subsequently used in a number of clinical studies. The procedure of Dr. Roos was used by AB KABI (Stockholm, Sweden) to prepare growth hormone (trade name: Crescormon) from human pituitaries for clinical use. A growing international interest for treatment of pituitary dwarfism prompted the KABI’s research director to get this growth hormone preparation registered as a new pharmaceutical drug and the Roos preparation of growth hormone was registered under the trade name Crescormon in 1971. Unlike most other preparations of growth hormone available for clinical use at that time Crescormon prepared according to the Roos procedure did not give rise to any antibodies against the hormone.

Professor Roos also became recognized for his development of excellent methods for the purification of human pituitary FSH, TSH, LH and prolactin. His FSH preparation was also successfully used in clinical therapy in well-recognized studies he did in collaboration with the gynaecologist Professor Carl Gemzell. All the work carried out by Paul Roos was done with high accuracy and skillfulness. All hormone products leaving his laboratory for clinical purpose were proven to be of a high quality and could successfully be used in various clinics in Sweden and abroad.
Introduction

FRED J. NYBERG

Growth hormone (GH) has received a distinct profile among all other hormones produced in the pituitary gland. It represents one of the most extensively characterized proteins within the area of biomedical science. In the biochemical perspective GH consists of a single amino acid chain of around 190 amino acids stabilized by two sulfide bridges. It has a molecular weight around 22,000 daltons and exhibit a comparatively high metabolic stability. Its growth-promoting effects have been attractive not only for basic hormonal research but also in clinical therapy.

Although most the biological actions attributed to GH relates to its effects on peripheral organs and tissues, the hormone may induce profound effects on functions linked to the central nervous system (CNS). This has become evident from recent studies directed to investigation of GH-induced effects on psychological functions that have seen to be affected and improved during GH replacement therapy.

In 1982 I was involved in studies indicating that rat GH given at physiological concentration may affect the catecholamine turnover in the rat hypothalamus (Andersson et al., 1983). It was suggested that rGH inhibits its own secretion partly via reduction of DA synthesis and release in the median eminence leading to increased somatostatin release and partly via reduced noradrenaline synthesis and turnover in the median eminence leading to reduced secretion of a GH releasing factor. Similar observations were made for prolactin (Andersson et al., 1981). At this time studies suggesting that both lactogenic and somatogenic binding sites are present in the brain appeared in the literature (DiCarlo et al., 1985; Posner et al., 1983). These investigations revealed that GH binding sites were present in brain areas such as hypothalamus, pituitary and the choroid plexus. Subsequent research carried out in my laboratory identified specific binding sites for the hormone not only in these brain regions but also in brain regions not directly connected to the hypothalamo-pituitary axis.

In the late 1980-ies and early 1990-ies clinical researchers observed decreased ratings on psychological well-being in studies of GH deficient patients and that GH replacement therapy reduced this symptom (Bengtsson et al., 1993; McGauley et al., 1990). Of special interest was the observation that GH may improve learning and memory capabilities. However, the mechanisms underlying these effects were not known. We identified and characterized specific binding sites for the hormone in various areas of the human brain (Lai et al., 1991 and 1993) and found that the density of these sites were sex dependent and declined with aging. We suggested that these sites are involved in the mediation of the GH effects on the brain (Nyberg, 1997, 2000). Also, we cloned the GH receptor in various tissues of the rat brain, including choroids plexus, hippocampus, hypothalamus and the spinal cord (see Thörnwall-Le Grevés, 2001 and chapter 9), but also in the human choroid plexus (Nyberg et al., 2000). These studies indicated that the nucleotide sequence of these receptor gene transcripts were almost identical with the liver variant of the GH receptor.

Studies on the distribution of GHR protein and message in the brain revealed the presence of the GH receptors in many tissues related to the functional anatomy of various behaviors known to be associated with the hormone.
Important and expanding area of research both in basic and clinical sciences. Evidence for rapid and discrete reductions in dopamine and noradrenaline levels and turnover in the median eminence of the hypophysectomized male rat. Proc Natl Acad Sci USA. 99, 7119–7123.


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Biosynthesis of Growth Hormone and Insulin-like Growth Factor-I and Regulation of Their Secretion
I. Introduction

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) are important regulatory factors of animal growth. Both of them are involved in multiple physiological functions ranging from controlling cell cycle progression to changing the overall metabolic status of the organism. Because of their vital roles, their biosynthesis, as well as secretion, is tightly regulated. It is now known that the expression and release of GH and IGF-I from their production sites are results of an orchestration among various factors, including hormones, metabolic status, and external stimuli. This chapter briefly reviews our current understanding of how GH and IGF-I biosynthesis and secretion are regulated. The discussion is mainly focused on GH biosynthesis and secretion in the pituitary and on IGF-I biosynthesis in the brain. The important factors involved in these processes are described as well as the mechanisms where known.

I. INTRODUCTION

Growth is an important process that occurs naturally in every organism. It is a universal event resulting from a series of physiological changes in the body, including increases in mass, size, and complexity of the organism. Numerous factors are involved in orchestrating this complex process in which growth hormone (GH) and insulin-like growth factor-I (IGF-I) are among the key elements mediating this vital event.

The GH is a polypeptide hormone predominantly synthesized and secreted from the anterior pituitary. Since its discovery in the 1940s (Li et al., 1945), numerous investigations have been performed to study its biological functions. It is now recognized that GH is involved in multiple physiological events that regulate growth, body composition, energy metabolism, bone metabolism, cardiac functions, and immune functions, among others. It has also been demonstrated that GH not only exerts its actions on peripheral tissues, but also on the central nervous system (CNS), where it modulates appetite, cognitive functions, energy metabolism, memory, mood, neuroprotection, and sleep (reviewed in Nyberg, 2000). Early studies on the mechanisms of the growth process have revealed that GH probably does not stimulate somatic growth directly but acts through mediators called somatomedins, which are now known as insulin-like growth factors (IGFs).

The presence of these mediators was first proposed in 1957 by Salmon and Daughaday, and the subsequent isolation of human IGF-I revealed that it shares significant structural homology with insulin (Rinderknecht and Humbel, 1978). IGF-I also possesses multiple functions, including the stimulation of myogenesis, inhibition of apoptosis, mediation of cell cycle progression, and modulation of immune response and sex steroid production (reviewed in Le Roith et al., 2001).