



Ribosomal Protein S6 Phosphorylation in the Nervous System: From Regulation to Function

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Since the discovery of the phosphorylation of the 40S ribosomal protein S6 (rpS6) about four decades ago, much effort has been made to uncover the molecular mechanisms underlying the regulation of this post-translational modification. In the field of neuroscience, rpS6 phosphorylation is commonly used as a readout of the mammalian target of rapamycin complex 1 signaling activation or as a marker for neuronal activity. Nevertheless, its biological role in neurons still remains puzzling. Here we review the pharmacological and physiological stimuli regulating this modification in the nervous system as well as the pathways that transduce these signals into rpS6 phosphorylation. Altered rpS6 phosphorylation observed in various genetic and pathophysiological mouse models is also discussed. Finally, we examine the current state of knowledge on the physiological role of this post-translational modification and highlight the questions that remain to be addressed.

Keywords: rpS6 phosphorylation, mRNA translation, ribosome, mTOR, S6K, PP-1, brain, signaling cascades

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INTRODUCTION

The eukaryotic ribosome is composed of the small 40S and the large 60S subunits, comprising together 4 ribosomal RNA species and 79 ribosomal proteins (Kressler et al., 2010). In many organisms, ribosomal proteins undergo various post-translational modifications, including phosphorylation, acetylation, methylation, O-linked β -N-acetylglucosaminylation, and ubiquitylation (Xue and Barna, 2012). Historically, the phosphorylation of the 40S ribosomal protein S6 (rpS6) was the first post-translational modification described (Gressner and Wool, 1974). The presence of phospho-rpS6 (p-rpS6) at different levels in a 2D gel provided the first evidence that rpS6 phosphorylation could occur at several residues (Lastick et al., 1977). Ensuing studies identified five evolutionary conserved and clustered carboxy-terminal phospho-sites, which undergo phosphorylation in an ordered manner, beginning with Ser236 and followed sequentially by Ser235, Ser240, Ser244, and Ser247 (Martin-Pérez and Thomas, 1983; Wettenhall et al., 1992; Meyuhas, 2008, 2015). Intriguingly, the exact function of the post-translational modification of this indispensable ribosomal protein remains enigmatic. Despite the large debate regarding its physiological role, rpS6 phosphorylation is commonly used as a marker for neuronal activity and a readout of mammalian target of rapamycin complex 1 (mTORC1) activity (Meyuhas, 2008, 2015; Mahoney et al., 2009; Knight et al., 2012). This review summarizes our current knowledge regarding the molecular mechanisms as well as the variety of stimuli modulating rpS6 phosphorylation in the nervous system.

Protein Phosphorylation In The Nervous System

Michael Brown



Protein Phosphorylation In The Nervous System:

Protein Phosphorylation in the Nervous System Eric J. Nestler, Paul Greengard, 1984-06-14 Considers the role of protein phosphorylation in neuron specific phenomena Comprehensively treats the enzymes and molecular biology of phosphorylation and dephosphorylation reactions examines evidence for the obligatory role of these reactions in neuronal function and extensively reviews the large number of phosphorylation pathways and their interactions Original schematic diagrams illustrate principles of the biochemical basis of cell regulation

The Cell Cycle in the Central Nervous System Damir Janigro, 2008-01-23 Cell Cycle in the Central Nervous System overviews the changes in cell cycle as they relate to prenatal and post natal brain development progression to neurological disease or tumor formation Topics covered range from the cell cycle during the prenatal development of the mammalian central nervous system to future directions in postnatal neurogenesis through gene transfer electrical stimulation and stem cell introduction Additional chapters examine the postnatal development of neurons and glia the regulation of cell cycle in glia and how that regulation may fail in pretumor conditions or following a nonneoplastic CNS response to injury Highlights include treatments of the effects of deep brain stimulation on brain development and repair the connection between the electrophysiological properties of neuroglia cell cycle and tumor progression and the varied immunological responses and their regulation by cell cycle

Protein Phosphorylation in the Nervous System Huiai Yang, 2000

Receptors in the Nervous System Abel Lajtha, 2013-06-29 A major advance in the biological sciences in the past decade has been the biochemical identification of cell membrane receptors The existence of receptor substances on the surface of cells that recognize and bind to extracellular molecules was proposed at the beginning of the century by the pharmacologist and immunologist Paul Ehrlich and the physiologist J N Langley Since then receptors have been found to play an important role in numerous physiological and pathological processes Over the years many attempts have been made to physically isolate and chemically characterize receptors but because of the receptors extremely low concentration and membrane localization these efforts have met with limited success Yet despite the failure to characterize receptor substances the concept of the presence of such molecules has had considerable heuristic value Using pharmacological physiological and immunologic approaches researchers have identified several specific receptors e g α and adrenergic nicotinic and muscarinic cholinergic and histaminergic With the characterization of various types of receptors on cell membranes many drugs were developed that proved to be experimentally and therapeutically useful It was only in the early 1970s that methods for the specific measurement chemical characterization and physical isolation of cell membrane receptors were developed These advances were made possible by the availability of ligands with high specific radioactivity that retained their biological activity and of experimental procedures that differentiated between specific and non specific binding of ligands

Glycobiology of the Nervous System Robert K. Yu, Cara-Lynne Schengrund, 2014-08-23 A thorough introduction is provided to the variety and complexity of the

roles that glycoconjugates play in the cells of the nervous system Basic information as well as the latest developments in neural glycobiology are discussed Topics covered range from the structure and metabolism of the saccharide chains and current approaches used in their study to changes glycoconjugates undergo during development and aging of the nervous system and the roles they have in neurological disease The breadth and depth of topics covered make it an essential reference for those new to the field as well more seasoned investigators

Nucleotides and their Receptors in the Nervous System P. Illes,H. Zimmermann,1999-08-31 The study of purinergic mechanisms has for long been focused on the actions of the nucleoside adenosine whereby the contribution of nucleotides to the signaling systems has been underestimated Based on the proceedings of a IUPHAR Satellite Conference held in Leipzig Germany this book offers a comprehensive update and overview of nucleotide release the structure and function of nucleotide receptors nucleotide metabolizing ecto enzymes as well as the physiological functions of nucleotides in the nervous system The physiology and molecular biology of receptors for ATP and other nucleotides are examined as are the physiology and molecular biology of enzymes that hydrolyze extracellular nucleotides At present a pharmacology of the nucleotide signaling system is being developed Of particular interest is the production of receptor subtype specific antagonists and of drugs that selectively affect the extracellular lifetime of the nucleotide An excellent source of reference for institutes of pharmacology biochemistry neurology zoology and physiology and for the pharmaceutical industry

Basic Neurochemistry R. Wayne Albers,Donald L. Price,2005-11-11 Basic Neurochemistry Molecular Cellular and Medical Aspects a comprehensive text on neurochemistry is now updated and revised in its Seventh Edition This well established text has been recognized worldwide as a resource for postgraduate trainees and teachers in neurology psychiatry and basic neuroscience as well as for graduate and postgraduate students and instructors in the neurosciences It is an excellent source of information on basic biochemical processes in brain function and disease for qualifying examinations and continuing medical education Completely updated with 60% new authors and material and entirely new chapters Over 400 fully revised figures in splendid color

Basic Neurochemistry Scott T. Brady, PhD,George J. Siegel, MD,R. Wayne Albers,Donald L. Price,2012 Includes bibliographical references and index

Research Awards Index ,1989

Neural Mechanisms of Conditioning D.L. Alkon,C.D. Woody,2012-12-06 This is the second volume to be based on a series of symposia being held periodically on the neurobiology of conditioning The first entitled Conditioning Representation of Involved Neural Functions was based on a symposium held in Asilomar Cali fornia in October 1982 Woody 1982 The present volume is based on a symposium organized by D Alkon and C Woody held at the Marine Biological Laboratory in Woods Hole Massachusetts in November 1983 This series of symposia and their publication are more than justified by the extraordinary progress being made during recent years in all branches of neuroscience and its application to our understanding of some of the basic neuronal mechanisms of conditioning and learning Invertebrate models of conditioning have been used by many in the attempt to obtain a more thoroughly controlled analysis at the single cellular

and synaptic level of the mechanisms involved in elementary conditioning in a simple nervous system. Examples of this approach are presented in this volume and utilize insects grasshopper crustacea crayfish and particularly the relatively simple nervous systems of mollusks *Aplysia* and *Hermissenda*. In such preparations it is possible to carry out precise electrophysiological and neurochemical studies of single identified cells and synapses involved in such simple processes as habituation and sensitization as well as simple forms of associative conditioning usually using simple aversive or withdrawal reflexes.

Journal of Rehabilitation Research & Development, 1988 Molecular Mechanisms of Neuronal Responsiveness Yigal H. Ehrlich, Robert H. Lenox, Elizabeth Kornecki, William O. Berry, 2013-03-13

The interaction of neurotransmitters neuromodulators and neuroactive drugs with receptors localized at the cell surface initiates a chain of molecular events leading to integrated neuronal responses to the triggering stimuli. Major advancements in the characterization and isolation of receptor molecules have answered many questions regarding the nature of the elements that determine the specificity in these interactions. At the same time recent studies have provided evidence that delicate regulation by intracellular enzymatic systems determines the efficiency of the stimulus response coupling process. The interaction between receptors operates in feedback control mechanisms and transduces signals from the receptors to various effector sites in a highly coordinated fashion. These studies are at the focus of the present volume which is an outcome of a symposium held at the University of Vermont College of Medicine on March 21-23 1986 in conjunction with the seventeenth annual meeting of the American Society for Neurochemistry. The symposium has demonstrated clearly that the concerted efforts of investigators in neurophysiology biochemistry pharmacology cell biology molecular genetics neurology and psychiatry are required to achieve better understanding of the processes underlying neuronal responsiveness. This volume includes contributions provided by prominent investigators in all these research areas. We hope that the readers will find here a useful source of information and ideas for stimulating further studies which may serve to narrow the gap between basic neuroscience research and its clinical implications.

Comparative Invertebrate Neurochemistry G. G. Lunt, R. W. Olsen, 2012-12-06

The attractions of invertebrate nervous systems have long been appreciated by neurophysiologists. Indeed some of the milestones in our understanding of nervous systems have their foundations in experiments done on invertebrate preparations typified by the role of the squid axon in dissecting the events that constitute the action potential. More recently we have seen how the relatively simple nervous system of *Aplysia* has permitted new insights into the molecular mechanisms of memory and learning. Neurochemists however have not been enthusiastic about invertebrate tissues as their experimental material. Much of the biochemical information on invertebrate nervous systems that has accrued has been incidental almost as a by-product of what were primarily physiological investigations. Fortunately the field is changing and research groups are making a positive choice to turn to invertebrate tissues. Two important factors have contributed to this. First the study of analogous systems in invertebrates and vertebrates can tell us much about the

evolution of nervous systems The application of the techniques of molecular genetics to the study of such molecules as receptors and ion channels can provide detailed information about their composition that in turn allows us to better understand their function By extending such studies to the invertebrates we should be able to understand how such systems have developed Secondly invertebrate pests are responsible for enormous losses of agricultural crops and are major vectors of disease in man

Pharmacological Effects of Ethanol on the Nervous System Richard A. Deitrich, V. Gene Erwin, 1995-12-21 This book dissects the effects of ethanol on the major neurotransmitter systems affected by ethanol and correlates these actions with the behavioral consequences The subject is approached first from the perspective of the neurochemical system and the behaviors resulting from ethanol's effects on that system The behaviors themselves are discussed in later chapters Some older theories of the effects of ethanol such as the membrane fluidization hypothesis are evaluated in light of new and updated information Fetal Alcohol Syndrome FAS as well as the structural damage in the brain by long term ethanol exposure are also discussed

Glial Interfaces in the Nervous System Håkan Aldskogius, John Fraher, 2002 Glial cells are commonly viewed as subordinate players to the functional requirements of neighbouring neurons in normal as well as pathological conditions These neuron glial interactions are crucial for the development maintenance plasticity and repair of the nervous system They are also dependent upon and/or influenced by interactions between glial cells themselves

Bibliography of Medical Reviews, 1976

Direct and Allosteric Control of Glutamate Receptors Michael G. Palfreyman, Ian J. Reynolds, Phil Skolnick, 1994-08-16 Direct and Allosteric Control of Glutamate Receptors describes in detail recent research that has demonstrated that glutamate receptors are subject to numerous modulatory controls Significant new insights into the physiology and pathophysiology of the nervous system have been obtained by these discoveries The sites on the receptor proteins where modulation occurs have provided a platform of opportunities for medicinal chemists to design new therapeutic modalities These new drugs will be of major significance in treating diseases such as stroke Alzheimer's epilepsy Parkinson's Huntington's neurotrauma schizophrenia pain and anxiety associated with abnormal excitatory amino acid neurotransmission and function

Fast and Slow Chemical Signalling in the Nervous System Leslie L. Iversen, Elisabeth C. Goodman, 1986 Papers presented at the Inaugural Symposium for the Merck Sharp Dohme Research Laboratories Neuroscience Research Centre Harlow

Calcium and Cell Physiology D. Marme, 2012-12-06 The purpose of the present volume is to give a comprehensive and up to date survey of the nature and role of calcium ions Ca in the regulation of cellular function Since Ca has gained in interest over the past years as a cellular messenger in signal transduction and since the discovery of its cellular receptor protein calmodulin has helped in understanding its mode of action in molecular terms we felt that an interdisciplinary selection of topics from the calcium field could provide a good source of information for all those interested in calcium mediated physiology The volume begins with an overview on the synarchic nature of the two cellular messengers cyclic AMP and Ca The next three chapters deal with the various

transport mechanisms for Ca The biochemistry and molecular biology of calmodulin as well as the cellular localization of calmodulin and calmodulin binding proteins are reviewed Calcium regulation of smooth muscle contraction introduces the pharmacology of calcium antagonists The Crustacean Nervous System Konrad Wiese, 2013-04-17 Crustacean preparations have been successfully used for more than 50 years to investigate the principles which enable nerve cells and neural circuitry to perform in a wide variety of functions The proud record of information of general significance obtained from crayfish and lobster nervous systems testifies that the use of an experimental system precisely matching theoretical and experimental requirements of a measurement is an essential part of the success In some respects the secondarily diversified vertebrate and mammalian nervous systems pose severe obstacles to experimentation and measurement whereas the crustacean nervous system recommends itself by being composed of individual neurons of unique morphology and physiology which can be used repeatedly in several preparations Moreover a restricted number of invariantly displayed behaviors enable the experimenter to correlate neuron activity with parts of the behavior easier Experts use these advantages to focus on a well defined neuron and mechanism and to take a convincing measurement within a minimum amount of time In this book distinguished neurobiologists the leading experts in the field have joined efforts to present research using crustacean experimental systems Thus they have contributed comprehensive information regarding a nervous system other than that of vertebrates and mammals that of crustaceans The accumulated knowledge on the crustacean nervous system shows that it is clearly divergent in evolution but functions in a similar way to neuronal circuitry found in the vertebrate system and can be used to interpret it

The Top Books of the Year Protein Phosphorylation In The Nervous System The year 2023 has witnessed a remarkable surge in literary brilliance, with numerous captivating novels captivating the hearts of readers worldwide. Lets delve into the realm of top-selling books, exploring the engaging narratives that have charmed audiences this year. Protein Phosphorylation In The Nervous System : Colleen Hoover "It Ends with Us" This heartfelt tale of love, loss, and resilience has captivated readers with its raw and emotional exploration of domestic abuse. Hoover masterfully weaves a story of hope and healing, reminding us that even in the darkest of times, the human spirit can triumph. Protein Phosphorylation In The Nervous System : Taylor Jenkins Reids "The Seven Husbands of Evelyn Hugo" This captivating historical fiction novel unravels the life of Evelyn Hugo, a Hollywood icon who defies expectations and societal norms to pursue her dreams. Reids captivating storytelling and compelling characters transport readers to a bygone era, immersing them in a world of glamour, ambition, and self-discovery. Protein Phosphorylation In The Nervous System : Delia Owens "Where the Crawdads Sing" This captivating coming-of-age story follows Kya Clark, a young woman who grows up alone in the marshes of North Carolina. Owens weaves a tale of resilience, survival, and the transformative power of nature, captivating readers with its evocative prose and mesmerizing setting. These popular novels represent just a fraction of the literary treasures that have emerged in 2023. Whether you seek tales of romance, adventure, or personal growth, the world of literature offers an abundance of engaging stories waiting to be discovered. The novel begins with Richard Papen, a bright but troubled young man, arriving at Hampden College. Richard is immediately drawn to the group of students who call themselves the Classics Club. The club is led by Henry Winter, a brilliant and charismatic young man. Henry is obsessed with Greek mythology and philosophy, and he quickly draws Richard into his world. The other members of the Classics Club are equally as fascinating. Bunny Corcoran is a wealthy and spoiled young man who is always looking for a good time. Charles Tavis is a quiet and reserved young man who is deeply in love with Henry. Camilla Macaulay is a beautiful and intelligent young woman who is drawn to the power and danger of the Classics Club. The students are all deeply in love with Morrow, and they are willing to do anything to please him. Morrow is a complex and mysterious figure, and he seems to be manipulating the students for his own purposes. As the students become more involved with Morrow, they begin to commit increasingly dangerous acts. The Secret History is a exceptional and gripping novel that will keep you wondering until the very end. The novel is a warning tale about the dangers of obsession and the power of evil.

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