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Cerebral Signal Transduction

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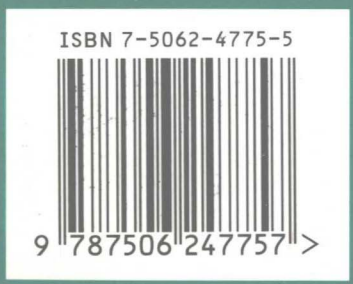

ISBN 7-5062-4775-5
定价：260.00元

—— 英文重印版 ——

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From First to Fourth Messengers

Edited b

Maarten E. A. Reith

College of Medicine, University of Illinois, Peoria, IL

Humana Press

Totowa, New Jersey

世界图书出版公司

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999 Riverview Drive, Suite 208
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This publication is printed on acid-free paper. ♾
ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Cover design by Martin E. A. Reith, Karen Schultz, and Patricia F. Cleary.

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Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data

Cerebral signal transduction : from first to fourth messengers / edited by Maarten E. A. Reith.
p. cm. -- (Contemporary neuroscience)
Includes bibliographical references and index.
ISBN 0-89603-608-1 (alk. paper)
1. Molecular neurobiology. 2. Cellular signal transduction.
3. Nervous system--Diseases--Molecular aspects. 4. Nervous system-Degeneration--Molecular aspects. 5. Second messengers (Biochemistry) I. Series.
[DNLM: 1. Signal Transduction--physiology. 2. Apoptosis--physiology. 3. Depressive Disorder--physiopathology. 4. Memory--physiology. 5. Nerve Degeneration--physiopathology. 6. Signal Transduction--drug effects. QH 601 C4139 2000]
QP356.2.C475 2000
612.8--dc21
DNLM/DLC
for Library of Congress 99-38476
CIP

Preface

Since the pioneering discovery of cyclic AMP four decades ago, a multitude of signaling pathways have been uncovered in which an extracellular signal (first messenger) impacts the cell surface, thereby triggering a cascade that ultimately acts on the cell nucleus. In each cascade the first messenger gives rise to the appearance of a second messenger such as cyclic AMP, cyclic GMP, or diacylglycerol, which in turn triggers a third messenger, a fourth messenger, and so forth. Many advances in elucidating such pathways have been made, including efforts to link messenger molecules to brain processes operative in health or disease. However, the latter type of information, relating signaling pathways to brain function, is scattered across a variety of publication media, which makes it difficult to integrate the multiple roles of different signaling cascades into our understanding of brain function in health and disease.

The primary aim of *Cerebral Signal Transduction: From First to Fourth Messengers*, therefore, is to offer a comprehensive picture of the recent advances made in the signaling field as it relates to neuronal and cerebral function. The current state of progress provides an exciting opportunity for such a comprehensive focus because molecular tools have become available to selectively remove, reduce, or enhance specific components in the signaling pathways, e.g., by interfering with the genes encoding key proteins. In addition, the increased awareness of crosstalk between different signaling cascades has revealed many possibilities for changes in gene expression underlying long-term changes in brain function.

Normal cerebral functions, such as memory or apoptosis during development, may be compromised in disease, as seen in Alzheimer's, in such neurodegenerative diseases as Parkinson's, Huntington's, or amyotrophic lateral sclerosis, or in stroke and brain trauma. In addition, there has been recent progress in elucidating the role of signaling messengers in depression and in the action of drugs of abuse. Accordingly, *Cerebral Signal Transduction: From First to Fourth Messengers* is organized around four themes involving brain functions: memory,

neurotrophic factor signaling pathways thought to be important in the development and treatment of mood disorders. Stress and the development of depression are linked through cAMP/PKA (Chap. 9) and neurotrophic factor pathways (Chaps. 9 and 10) potentially involved in the novel, nonconvulsive treatment of repeated transcranial magnetic stimulation (Chap. 10). A strong connection between signaling messengers in mood disorders and clinical findings is continued in Chap. 11 focusing on components of the cAMP/PKA and DAG/PKC cascades. In the section *Drug Dependence*, Chaps. 12–15 discuss DAG/PKC signaling pathways and other cascades regulating the production of transcription factors implicated in the development and expression of drug dependence. Various signaling pathways in opiate (Chap. 12) and psychostimulant (Chaps. 13–15) dependence are discussed involving cyclic AMP, protein kinases, and transcription factors. Chapters 12 and 13 review the wealth of information that has come from recent studies with knockout mice lacking genes for the production of various key signaling messengers or receptor proteins acted upon by messengers. Chapters 14 and 15 discuss the role of the dopamine transporter in regulating the first messenger dopamine involved in the action of psychostimulant drugs, in particular that of cocaine. Phosphorylation of the dopamine transporter by the DAG/PKC signaling pathway is described (Chap. 14) and the transcriptional regulation of the dopamine transporter is reviewed (Chap. 15). Additionally, the latter chapter links pharmacodynamic mechanisms operative in human cocaine dependence with those studied in animal models.

The choice of authors for each chapter reflects the editor's identification of investigators who have been instrumental in developing these new frontiers in neuroscience. I thank the authors for their patience, during the process of putting this book together. I deeply appreciate the opportunity offered by Paul Dolgert and Tom Lanigan at Humana Press to produce this book in recognition of the importance of cerebral signal transduction in both health and disease.

Maarten E. A. Reith

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Contents

Part I

Introduction

1

From First to Fourth Messengers in the Brain

An Overview

Maarten E. A. Reith

INTRODUCTION

This volume attempts to review *cerebral* signal transduction in health and disease under four different topics: memory, neurodegeneration/apoptosis, depression, and drugs of abuse. Research on intracellular signaling was initiated four decades ago by the pioneering discovery of Sutherland, Rall, and Wosilait of cyclic adenosine monophosphate (cAMP) (*see* ref. *1*). Since then, a multitude of signaling pathways have been uncovered in a wide variety of cells and tissues from yeasts to humans. In general, these pathways are initiated by extracellular signals impacting the cell surface, triggering a cascade that ultimately acts on the cell nucleus. Each cell type expresses a subset of receptors and messenger proteins. *Neuronal* cells many times express unique cell-surface proteins that recognize specific extracellular signals. These surface proteins can be different from, for example, those in *yeast* cells, although they link to similar kinases and phophatases that make up the signaling cascade or effectors in a given subcellular compartment. Such differences have been amply documented. For example, photoreceptors along with their G-proteins and effectors reside in the same outer segment compartment of the rod photoreceptor cell *(2)*, whereas receptors and G-proteins are asymmetrically distributed in neuronal growth cones *(3)* and rat Sertoli cells *(4)*. There is also evidence that protein–tyrosine kinases produce distinct cellular responses as a function of subcellular location *(5)*. Not only is location important, but different cell types are known to express different complements of receptors, G-proteins, and effectors. With regards to G-proteins, there are more than 20 distinct α-subunits, 5 β-subunits, and 10 γ-subunits. These subunits are capable of producing a multitude of combinations to form heterotrimers linked to heptahelical receptors. Different cell types and different effector systems use different subunit combinations, and many receptor subtypes can be linked to more than one G-protein at a time *(2)*.

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Edited by: M. E. A. Reith © Humana Press Inc., Totowa, NJ

Other examples of cell-dependent differences in components of signaling systems can be found in the family of calmodulin (CaM)–phosphodiesterases (PDEs), which are involved in cyclic nucleotide breakdown. CaM–PDE1A is the only CaM–PDE isozyme expressed in kidney medulla, whereas brain cells can express CaM–PDE1A, B, and C with distinct regional patterns of distribution *(6)*. Within the Ras subfamily of small G-proteins, Rab3A is found only in cells with regulated secretion, including neuronal cells. Evidence suggests a role of Rab3A in Ca^{2+}-dependent exocytosis, in conjunction with rabphilin-3A, which is expressed only in the brain *(7)*. It is clear that cell specificity in signaling pathways can arise from different subtypes or subcellular locations of the individual signaling components. Crosstalk among various signaling cascades, and the cell-dependent differences in ligand, receptor, G-protein, and effector interactions adds to the complexity and yields many different cascading scenarios.

Despite the complex interactions, general signaling mechanisms used by many cell types can be described. For example, the growth-factor-triggered mitogen-activated protein kinase (MAPK) signaling cascade has a basic pattern in both the yeast *S. cerevisiae* and in vertebrates. However, different MAPK isoforms serve at a given level for each signaling pathway. MAPK isoforms serve in *S. cerevisiae* as FUS3 and KSS1 and in vertrebrates as extracellular regulated kinases ERK-1 and -2 *(8)*. The STE11 protein at the MAP3K (i.e., two kinase levels upstream from MAPK) level in *S. cerevisiae* is homologous to mitogen-activated, ERK-activating kinase (MEK) kinase (MEKK) in vertebrates *(8)*.

Growth-factor-initiated signaling pathways in the brain have been shown to be involved in the action of drugs of abuse *(9)*. In addition, signaling pathways in brain lead, via phosphorylation of the transcription factor cAMP response element-binding protein (CREB), to the expression of immediate early genes (IEGs) such as *c-fos (10–14)* (*see also* Chapters 2, 8, 9, 10, 12, and 13). Regulation of the expression of CRE-bearing genes through CREB binding is not limited to the brain *(15)*.

The purpose of this chapter is to briefly summarize the major signaling pathways. Signaling information will be compared from a variety of systems, mostly but not limited to the brain. It is hoped that this review will assist the reader to place the detailed signaling information in the following chapters in a larger context and help to explore potential interfaces between pathways. First, the messengers are treated in a "horizontal" manner, categorized by their placement as first, second, third, and fourth in the sequence of events across cascades. Second, the messenger cascades are described in a "vertical" way, for each cascade separately. Third, potential points of

crosstalk between the cascades are presented as an important mechanism for multiple cellular responses to a given extracellular signal.

MESSENGERS USED IN SIGNAL TRANSDUCTION: HORIZONTAL APPROACH

First Messengers

First messengers are extracellular signals impacting the cell surface, thereby setting in motion a sequence of signaling events. Extracellular signals capable of triggering signaling cascades include neurotransmitters, neuromodulators, or hormones acting upon receptors. In addition, nerve impulses can serve as extracellular signals. Certain receptors can be ionotropic, so that activation by a first messenger triggers influx of a second messenger such as Ca^{2+} (Table 1). Receptors can also be linked to G-proteins coupled to an ion channel or to other second-messenger systems via adenylate cyclase, phospholipase C (PLC), nitric oxide (NO) synthase, or phospholipase A_2 (PLA_2) (Table 1). Examples of signaling pathways that differ from the classic synaptic point-to-point transmission are becoming more and more numerous. Neuromodulators, such as peptides and small molecules like adenosine, can act as first messengers in the brain. Hormones such as progesterone and adrenal steroids can also exert effects on plasma membrane receptors. Classically studied steroid hormone effects involve intracellular receptors (*see* Third Messengers). Finally, nerve impulses can act as first messengers by depolarization-induced Ca^{2+} channel opening allowing influx of the second messenger Ca^{2+} (Table 1).

Second Messengers

The mechanism by which the first messenger triggers the appearance of the second messenger depends on the event that links the two (Table 1). In the case of the second messengers cAMP, cyclic guanosine monophosphate (cGMP), diacylglycerol (DAG), inositol triphosphate (IP_3), and arachidonic acid (AA), the link between the activation of a receptor by the first messenger and the stimulation of a second messenger occurs via G-proteins. The G-proteins (G_s, G_i, G_o, $G_{i,o}$, G_q) make up a complex family with many different combinations of the various α-, β-, and γ-subunits (*see* Chapters 5 and 11 for G-protein changes in Alzheimer's disease and bipolar affective disorder, respectively). Stimulation of the G_s subfamily increases adenylate cyclase activity, inhibits Na^+ channels, and opens Ca^{2+} channels, whereas G_i subfamily activation has the opposite effect and can also promote cGMP phosphodiesterase. G_o protein activation closes Ca^{2+} channels, whereas $G_{i,o}$ proteins inhibit adenylate cyclase and stimulate the β isoform of PLC. G_q

Table 1
Messenger Pathways: A Horizontal View

Messengers with links	Ca^{2+}/CaM pathways	cAMP/PKA pathways	DAG/PKC pathways[a]	NO/PKG pathways	AA pathways	Steroid receptor pathways
First messenger	Neurotransmitter or nerve impulse	Neurotransmitter, modulator, or hormone	Neurotransmitter, modulator, or hormone	Neurotransmitter	Neurotransmitter	Neurotransmitter
Link	Cation channel of NMDA receptor, receptor linked by G-protein to Ca^{2+} channel, or voltage-sensitive Ca^{2+} channel	G_s, G_i, or $G_{i,o}$ protein-coupled receptor → adenylate cyclase	G_q protein-coupled receptor → PLC	Cation channel of NMDA receptor → Ca^{2+}/CaM → NO synthase	Cation channel of NMDA receptor → Ca^{2+} → PKC → PLA_2	G_s protein-coupled receptor → adenylate cyclase
Second messenger	Ca^{2+}	cAMP	DAG, IP_3	NO	AA	cAMP
Link	CaM KI, II, IV	PKA	PKC (guanylate cyclase)[a]	Guanylate cyclase	K^+ channels, cannabinoid receptors, glutamate transporters, dopamine transporters	PKA → phosphorylation steroid receptor
Third messenger	CREB, SRF, SIF	CREB, SRF, SIF, IRBP	IRBP, Raf (cGMP)[a]	cGMP		Phosphorylated steroid receptors as transcription factors
Link	Binding to CRE, SRE, SIE	Binding to CRE, SRE, SIE, IRE	Binding to IRE; MAPK	PKG		Binding to RE
Fourth messenger	Fos, prodynorphin	Fos, prodynorphin, Jun B, Zif/268, Fos B[b], ΔFosB[b], Fras[b], Jun[b]	Jun B, Fos[c], Jun[c]			

Note: In composing the table, the following sources were used: refs. *8,13,16–18,21–26,40–45,* and *71*. The information is not meant to be exhaustive, especially on the transcription factors, which are subject of active ongoing research.

[a] Activity/compound in parentheses are less well studied.

[b] Possible fourth messengers resulting from PKA stimulation but third messenger unknown.

[c] Expression known to be stimulated by PKC activation but third messenger unknown.

protein activation can enhance PLC activity, which results in an increase of IP_3 and DAG. DAG can stimulate protein kinase C (PKC) and increase cGMP, as does the unique messenger nitric oxide (NO) (Table 1). AA has been reported to modulate neurotransporter function for glutamate *(16–18)*, glycine *(19)*, γ-aminobutyric acid *(20)*, and dopamine *(21)*.

The second messenger Ca^{2+}, in addition to being generated by influx through G-protein-coupled Ca^{2+} channels, can be increased intracellularly by activation of the *N*-methyl-D-aspartate (NMDA) receptor. Voltage-dependent Ca^{2+} channels can also increase Ca^{2+} by opening upon depolarization. The NMDA receptor plays an additional role in the production of the second messenger NO by Ca^{2+}/CaM stimulation of NO synthase activity (Table 1).

Third Messengers

Third messengers are generally transcription factors that are phosphorylated by protein kinases, which are, in turn, under the influence of various second-messenger systems (*see* Table 1). For example, the second messenger Ca^{2+} (produced intracellularly by either Ca^{2+} influx through the NMDA receptor, Ca^{2+} channels coupled to G-proteins, or voltage-sensitive Ca^{2+} channels) stimulates Ca^{2+}/CaM-dependent kinase (CaM K) I, II, or IV, which phosphorylates the third messengers such as CREB, serum response factor (SRF), and *sis*-inducable factor (SIF). These third messengers bind to the cAMP response element (CRE), SRF response element (SRE), and SIF response element (SIE), respectively *(13,22)*. Another example is the second-messenger cAMP stimulation of protein kinase A (PKA), which phosphorylates CREB, SRF, SIF, or the inverted repeat element (IRE) binding protein (IRBP) *(23)*. DAG, which is formed by activation of receptors linked to the phospholipid signaling system, activates PKC. Endogenous PKC is available in the nucleus to affect the phosphorylation state and activity of several transcription factors. Activated PKC can also stimulate the Ras (small G-protein) pathway, which leads from Ras and Raf (a cytoplasmic serine/threonine protein kinase) to MAPK (Table 1). Finally, several members of the steroid receptor family (i.e., for progesterone or vitamin D, or the orphan receptor chicken ovalbumin upstream promotor [COUP-TF]) can be regarded as third messengers, as these receptors can be phosphorylated by PKA, which is stimulated by cAMP. These cytoplasmic receptors then function as ligand-regulated transcription factors upon translocation to the nucleus (Table 1).

Fourth Messengers

The third messenger CREB, itself a transcription factor, induces the expression of IEGs that encode transcription factors such aş Fos (the protein of the *c-fos* gene). These transcription factors then act as a fourth messengers (*see*