

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,

neurodegeneration/apoptosis, mood disorders, and drug dependence. This book advances understanding of the mechanistic underpinnings for complex behavioral processes and clinically relevant brain diseases, and will be of interest to scientists, graduate students, and advanced undergraduates seeking a comprehensive overview of the cerebral signaling field. Selected chapters will also be of interest to physicians carrying out postmortem measurements related to cerebral signaling and who wish to study in more detail the mechanisms underlying brain diseases and the actions of pharmacotherapeutics. Most therapeutic drugs target the effect of first messengers (neurotransmitters) by either interfering with or mimicking their receptor action or altering their levels by acting on enzymes involved in their synthesis, degradation, or storage. The future will undoubtedly see new drugs targeting events downstream in the cascade of second, third, and fourth messengers, and we believe that *Cerebral Signal Transduction: From First to Fourth Messengers* will contribute to progress towards such novel pharmacotherapeutics.

Each chapter in *Cerebral Signal Transduction: From First to Fourth Messengers* is not simply a review of the work carried out in the author's laboratory, but rather presents a critical survey and synthesis of achievements in that area. Chapter 1 offers an overview of the various signaling cascades and their crosstalk, with the intent to provide basic resource material for reading the more specialized subsequent chapters. Under the section *Memory*, Chapters 2–4 discuss cAMP/PKA, Ca^{2+} /calmodulin-dependent protein kinase, DAG/PKC, and NO/PKG signaling pathways operative in learning and memory. The coverage includes simpler model systems for learning and memory such as *Aplysia californica* (Chap. 2) and *Drosophila* (Chap. 3) as well as more complicated systems including the honeybee (Chap. 3) and the mammalian hippocampus (Chaps. 2 and 4). Under the section *Neurodegeneration and Apoptosis*, Chaps. 5–8 describe cAMP/PKA, DAG/PKC, NO/PKG, and neurotrophic factor signaling cascades involved in these processes. Chapter 5 focuses on receptor–G protein interactions in Alzheimer's disease and Chap. 6 on NO signaling involved in neural injury, neurological disorders, and aggression. Chapter 7 discusses pro- and anti-apoptotic neurotrophic factor signaling pathways involving Ras, and Chap. 8 focuses on pathways in neurodegeneration that utilize Ca^{2+} . Both Chaps. 5 and 8 connect signaling messengers in neurodegeneration with clinical findings in or implications for humans. Under the section *Depression*, Chaps. 9–11 cover cAMP/PKA, DAG/PKC, and

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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Reith, M. (Ed.)

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