

Preface

Neural membranes are highly dynamic and interactive structures composed of glycerophospholipids, sphingolipids, cholesterol, and transmembrane and peripheral proteins of various shapes, molecular masses, and functions. The binding between phospholipids and proteins is necessary for vertical positioning and tight integration of proteins into the membrane. Phospholipids and sphingolipids contribute to the lipid bilayer asymmetry, whereas cholesterol and sphingolipids form lipid rafts, which act as platforms for molecular sorting, trafficking, and signal transduction processes. Lipid mediators are chemical messengers that are released in response to cell stimulation or injury from membrane phospholipids, sphingolipid, and cholesterol. Lipid mediators play important roles in internal and external communication and modulate cellular responses such as the growth arrest, differentiation, adhesion, and migration. These processes are modulated by eicosanoids (prostaglandins, leukotrienes, thromboxanes, and lipoxins) and docosanoids (resolvins, protectins, neuroprotectins, and maresins), which are generated by the action of phospholipases A₂, cyclooxygenases, and lipoxygenases on arachidonic and docosahexaenoic acids (ARA and DHA), respectively. The non-enzymic lipid mediators of ARA and DHA metabolism include isoprostanes, neuroprostanes, isoketals, neuroketals, isofurans, 4-hydroxynonenal, and 4-hydroxyhexanal. Action of sphingomyelinases on sphingomyelin generates ceramide, a metabolite closely associated with apoptotic cell death. Further degradation of ceramide generates sphingosine, which in its phosphorylated form induces cell proliferation, and thus produces the balance between cell death and cell survival. In the brain, cholesterol is hydroxylated into oxysterols or hydroxysterols (24(*S*)-hydroxysterol, 25-hydroxysterol, 27-hydroxysterol, 22-hydroxysterol) by cytochrome P450-dependent oxygenases. Conversion of cholesterol to hydroxysterols is a major mechanism for the elimination of cholesterol from the brain. Collective evidence suggests that under normal conditions low levels of lipid mediators are needed for signal transduction, gene expression, and neural cell proliferation and differentiation, resulting in neural cell survival but high levels of enzymic and non-enzymic lipid mediators may cause neurodegeneration through the induction of oxidative stress, neuroinflammation, and apoptosis. Thus, neural membranes are not only

simple inert barrier, but a Pandora's box of lipid mediators; many of which have powerful neurochemical effects on cell growth, proliferation, differentiation, survival, and apoptosis. Levels of lipid mediators in neural and non-neural tissues are partly regulated by diet. The high intake of food enriched in ARA (vegetable oils) elevates levels of eicosanoids and upregulates the expression of proinflammatory cytokines. ARA and its metabolites have prothrombotic, proaggregatory, and proinflammatory properties. In contrast, diet enriched in DHA (fish and fish oil) generates docosanoids, which not only downregulate proinflammatory cytokines but also have antiinflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and vasodilatory effects. At present, the threshold concentrations of lipid mediators that promote and facilitate neural cell injury and death are not known. In neurological disorders, cell death not only depends upon elevated levels of lipid mediators, but also on cross-talk (interplay) among glycerophospholipid-, glycosphingolipid-, and cholesterol-derived lipid mediators. Studies on lipid-derived mediators fall in a fast-paced research area related to neurodegeneration and provide opportunities for target-based therapeutic intervention using inhibitors of lipid mediator synthesizing enzymes.

The goal of this monograph is to present readers with cutting edge and comprehensive information on lipid mediators in a manner that is useful not only to students and teachers, but also to researchers and physicians. This monograph has 11 chapters. Chapters 1 and 2 describe metabolism, roles, and involvement of eicosanoids and docosanoids in neurological disorders. Chapters 3 and 4 describe cutting edge information on the synthesis, degradation, roles, and association of lyso-glycerophospholipids and platelet activating factor in neurological disorders. Chapter 5 describes metabolism and roles of cannabinoids in brain and their relationship with neurological disorders. Chapters 6 and 7 are devoted to the metabolism of nonenzymic lipid mediators of arachidonic acid metabolism (4-hydroxynonenal and isoprostanes) and docosahexaenoic acid metabolism (4-hydroxyhexanal and neuroprostanes). Chapters 8 and 9 describe metabolism, roles, and involvement of ceramide, ceramide-1-phosphate, sphingosine, and sphingosine-1-phosphate, respectively, in neurological disorders. Chapter 10 describes metabolism, role, and association of cholesterol and hydroxycholesterols with neurological disorders. Finally, Chap. 11 provides readers and researchers with perspective that will be important for future research work on bioactive lipid mediators. My writing style and demonstrated ability to present complicated material on lipid mediators makes this monograph particularly accessible to neuroscience graduate students, teachers, and fellow researchers. It can be used as supplement text for a range of neuroscience courses. Clinicians and pharmacologists will find this book useful for understanding molecular aspects of lipid mediators in neurodegeneration in acute neural trauma (stroke, spinal cord trauma, and head injury) and neurodegenerative diseases (Alzheimer disease, Parkinson disease, and Huntington disease). To the best of my knowledge no one has written a monograph on the role of lipid mediators in the brain. This monograph will be the first to provide a comprehensive description of glycerophospholipid, sphingolipid, and cholesterol-derived mediators, their interactions with each others in normal brain and in brain tissue from neurological disorders. I also hope that this

monograph will provide senior researchers some guidance for overcoming problems on lipid mediator research that they are encountering in their laboratories.

One of the hallmark of this monograph is the presentation of a unifying concept of lipid mediator-mediated signal transduction processes associated with excitotoxicity, oxidative stress, and neuroinflammation. The presentation of this monograph is based on uniformity and logical progression of subject from one topic to another with an extensive bibliography. For the sake of explanation, simplicity, and uniformity a large number of figures and line diagrams of signal transduction pathways with chemical structures of lipid mediators are also presented. It is hoped that my attempt to integrate and consolidate the knowledge of lipid mediators and signal transduction processes in normal and diseased brain will provide the basis of more dramatic advances and developments on the determination, characterization, and roles of glycerophospholipid-, sphingolipid-, and cholesterol-derived lipid mediators in neurological disorders.

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