Eicosanoids in Reproduction

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PREFACE

For many years during the 1960s and early 1970s interest in prostaglandins was focused heavily on the area of reproduction. In particular, the luteolytic action of prostaglandin $F_{2a}$ in domestic ruminants and small animals gave hope of a potential for a new contraceptive for women. It is interesting to note that the greatest impact of prostaglandins in "clinical" practice has often been in the field of veterinary medicine. The impact of prostaglandins in obstetric practice continues to expand and grow, yet, in the 1960s, interest was centered on their ability to induce uterine contractions. Research grew from these beginnings to include not only many new areas of investigation such as cardiovascular and renal physiology but also to encompass other products of arachidonic acid metabolism (eicosanoids) such as prostacyclin, thromboxanes, leukotrienes, etc. In so doing we have gained new appreciation of the breadth of importance of eicosanoid actions and have made great strides in our understanding of the regulation of arachidonic acid metabolism. We are becoming acutely aware of the importance of integrating such information into wider mechanisms of hormone action and intracellular signaling. The interactions between tissues, cells, and different bioactive substances are now of critical importance in understanding the true roles of eicosanoids in physiological and pathological mechanisms. All these advances have fed back to research in reproduction to enhance our ability to understand more fully the mechanisms of ovulation, luteolysis, parturition, etc. We must understand the position of eicosanoids in these mechanisms rather than try to explain mechanisms completely by eicosanoid actions alone. In this book we have attempted to draw together an up-to-date account of knowledge of eicosanoid participation in many areas of reproduction. It is intended that this book aid students by supplying considerable basic information and an idea of the scope of eicosanoid research in reproduction, while satisfying investigators with the latest information available in these areas.
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Dr. Mitchell obtained his M.A. and D. Phil degrees in 1977 from the University of Oxford and later in the same year was elected to the Staines Medical Research Fellowship at Exeter College. He was awarded a Medical Research Council (U.K.) Senior Fellowship in 1979. He moved to the University of Texas Southwestern Medical School as a Research Associate Professor of Biochemistry in 1981 and he was appointed an Associate Professor in 1983. In 1984 he moved his work to the University of California, San Diego, where he was appointed Professor and Director of the Division of Biological Sciences, Department of Ophthalmology and Professor of Reproductive Medicine. Dr. Mitchell joined the University of Utah in 1988 where, in addition to his primary appointment, he is Adjunct Professor of Cellular, Viral, and Molecular Biology.

Dr. Mitchell is a member of many societies including the Biochemical Society, Royal Society of Chemistry (Fellow), Society for Endocrinology, Society for the Study of Fertility, American Society for Biochemistry and Molecular Biology, American Chemical Society, American Institute of Chemists (Fellow), Endocrine Society, and the Society for Gynecologic Investigation.

Dr. Mitchell is presently on the editorial boards of Prostaglandins, Leukotrienes and Essential Fatty Acids, the Journal of Clinical Endocrinology and Metabolism, and Placenta. In 1988 he was appointed to a 4-year term on the Human Embryology and Development Study Section of the National Institutes of Health.

Dr. Mitchell’s research interests are based broadly on the biochemical mechanisms of growth and differentiation of tissues at the molecular, cellular, organ, and whole animal level. Attention is focused on the development of fetal tissues and uterine tissues that play a part in the mechanism(s) of parturition. In these studies he concentrates particularly on the regulation of arachidonic acid metabolism.

Dr. Mitchell has participated as a guest lecturer at seminars throughout the world on numerous occasions. He has been the recipient of research grants from the Medical Research Council (U.K.) and the National Institutes of Health; he has authored more than 200 peer-reviewed papers and over 50 review articles.
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TABLE OF CONTENTS

Chapter 1
Pathways of Arachidonic Acid Metabolism ......................................................... 1
Murray D. Mitchell

Chapter 2
Regulation of the Arachidonic Acid Cascade and PAF Metabolism
in Reproductive Tissues ......................................................................................... 5
John M. Johnston, Noriei Maki, Marlane J. Angle, and Dennis R. Hoffman

Chapter 3
Eicosanoid Binding Sites in Ovarian and Uterine Tissues ......................... 39
Ch. V. Rao

Chapter 4
Prostaglandins and Semen ............................................................................... 55
R. W. Kelly

Chapter 5
Placental PGE2 and the Initiation of Parturition in the Sheep ..................... 73
G. D. Thorburn and G. E. Rice

Chapter 6
The Role of Eicosanoids in Menstruation and Disorders of Menstruation .... 87
S. K. Smith

Chapter 7
Eicosanoids and the Uterine Cervix ................................................................. 103
Keith Hillier

Chapter 8
Eicosanoids and Blastocyst Implantation ....................................................... 123
T. G. Kennedy

Chapter 9
Eicosanoids and the Regulation of Uteroplacental Hemodynamics .......... 139
Ronald R. Magness and Charles R. Rosenfeld

Chapter 10
Placental Biosynthesis, Metabolism, and Transport of Eicosanoids ............ 169
Leslie Myatt

Chapter 11
Eicosanoids in Human Pregnancy and Parturition ........................................ 199
Marc J. N. C. Keirse

Chapter 12
Clinical Use of Eicosanoids for Cervical Ripening before Induction of Labor 223
Marc J. N. C. Keirse
Chapter 1

PATHWAYS OF ARACHIDONIC ACID METABOLISM

Murray D. Mitchell

Products of arachidonic acid metabolism (eicosanoids, e.g., prostaglandins, leukotrienes, etc.) have important roles in reproductive processes in all mammalian species that have been studied. For instance, there is overwhelming evidence that prostaglandins (PGs) play critical parts in the mechanisms that regulate oviposition, ovulation, menstruation, and uterine contractions, to name but a few examples. It is now well established that products of arachidonic acid metabolism by way of lipoxygenase pathways (hydroperoxyeicosatetraenoic acids [HPETEs], hydroxyeicosatetraenoic acids [HETEs], and leukotrienes [LTs]) have potent biological activities, and are more important than products of the cyclooxygenase pathway in many biological mechanisms. In this introductory chapter, I shall attempt briefly to provide a simplified outline of the pathways of arachidonic acid metabolism. More detailed and specialized reviews are available on the basic pathways of arachidonic acid metabolism and should be consulted for specific information concerning the enzymes involved and their regulation. In this introduction only a brief outline of these pathways and the products formed will be presented. Arachidonic acid (all \( \text{cis-}5,8,11,14 \)-eicosatetraenoic acid) is a carbon-20 polyunsaturated fatty acid that is the precursor of what is presently the most important group of eicosanoids (derivatives of carbon-20 polyunsaturated fatty acids). Formation of these eicosanoids requires that arachidonic acid be in the nonesterified form. Arachidonic acid is a typical polyunsaturated fatty acid in that it is present in cells predominantly in an esterified form, usually in the \( sn-2 \) position of a glycerophospholipid. Hence, the liberation of arachidonic acid is a key event in the biosynthesis of eicosanoids and, indeed, it has been thought to be the rate-limiting step in this process. The release of arachidonic acid from glycerophospholipids is accomplished either directly, by the action of phospholipase A2, or indirectly, by the action of phospholipase C; the latter mechanism requires the subsequent actions of diacylglycerol lipase and monoacylglycerol lipase (Figure 1).

Arachidonic acid liberated by these reactions can be metabolized by way of at least three major pathways (Figure 1). The most recently discovered pathway is that designated as the epoxygenase pathway. In this pathway, arachidonic acid is metabolized by way of cytochrome \( P_{450} \)-linked monooxygenase enzymes into biologically active epoxides and thence to various vicinal diols and trihydroxy acids. This metabolic pathway was originally described in liver and kidney, but may be present in many other tissues. Information concerning this pathway, its products and the possible roles of such products in fetal and neonatal life is still limited. Hence, hereafter, attention will be focused on the other two major pathways of arachidonic acid metabolism, i.e., the cyclooxygenase and lipoxygenase pathways (Figure 1).

An outline of the enzymes involved in arachidonic acid metabolism is presented in Figure 1 and the major products of such metabolism are given in Figure 2. The formation of prostaglandins (cyclooxygenase pathway) begins with the action of prostaglandin endoperoxide synthase, synonymous with fatty acid cyclooxygenase, on arachidonic acid. There is an inherent peroxidase activity in the holoenzyme such that the \( \text{PGG}_2 \) (15-hydroperoxy derivative) formed is rapidly converted to \( \text{PGH}_2 \) (15-hydroxy derivative). Although these substances are short-lived intermediates, they do possess intrinsic biological activity. It is the formation of these endoperoxide intermediates that is inhibited by non-steroidal anti-inflammatory agents. Thus, the biosynthesis of all prostaglandins and thromboxanes is
Eicosanoids in Reproduction

FIGURE 1. A simplified schematic representation of the enzymatic pathways of arachidonic acid metabolism.

FIGURE 2. A simplified outline of the pathways of arachidonic acid metabolism.

inhibited by such drugs. The endoperoxide intermediates are metabolized further to prostaglandins by the actions of various isomerases. Evidence for a specific reductase to form PGF\textsubscript{2α} is still limited and it is likely that this conversion is often nonenzymatic. The enzymes of prostaglandin biosynthesis are located in the microsomal fraction of the cell with the exception of PGD\textsubscript{2} (11-keto-) isomerase, which is a cytosolic enzyme.
The first step in the catabolism of prostaglandins is catalyzed by 15-hydroxyprostaglandin dehydrogenase (PGDH), which is a cytosolic enzyme. The 15-keto-derivatives so formed are substantially biologically inactive and are rapidly converted to the 13,14-dihydro-15-keto-derivatives that are the major circulating forms. A major site of such metabolism is the lung; almost all biologically active prostaglandins are metabolized during one passage through the lungs. Such metabolism occurs, first, by uptake into pulmonary cells and second, by the action of PGDH. Elimination of biologically active prostaglandins is completed by a series of beta oxidations and omega oxidation that result in the formation of a wide variety of products that are excreted in the urine. It should be noted that exceptions exist to the preceding description of prostaglandin catabolism. For instance, PGD$_2$ is an extremely poor substrate for PGDH and prostacyclin may not be metabolized completely by the lungs since it is not a good substrate for the uptake mechanisms that transport prostaglandins into the pulmonary cells for subsequent metabolism.

Lipoxygenase enzymes are found in several subcellular fractions and catalyze the formation of hydroperoxyeicosatetraenoic acids (HPETEs) from arachidonic acid (Figures 1 and 2). These derivatives are biologically active and are converted rapidly to their hydroxy (HETE) derivatives which also have biological activity. Other pathways of metabolism exist for the HPETEs, of which the leukotriene pathway is presently considered the most important. This pathway derives from the 5-lipoxygenase pathway and the key step is the conversion of 5-HPETE to leukotriene A$_4$. Thereafter, leukotriene A$_4$ is metabolized either by addition of water at C-12 leading to the opening of the epoxide at C-6 and the formation of leukotriene B$_4$ or by nucleophilic opening of the epoxide at C-6 by the sulfhydryl group of glutathione and the formation of leukotriene C$_4$. The latter compound may be metabolized further by the sequential elimination of glutamic acid and glycine to form leukotriene D$_4$ and leukotriene E$_4$. Conversion of leukotriene E$_4$ to leukotriene F$_4$ occurs by addition of a $\gamma$-glutamyl residue to the amino group. The further metabolism of leukotrienes is complex and described in detail elsewhere.$^3$
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