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Arachidonic acid cascade in endothelial pathobiology

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Abstract

Arachidonic acid (AA) and its metabolites (eicosanoids) represent powerful mediators, used by organisms to induce and suppress inflammation as a part of the innate response to disturbances. Several cell types participate in the synthesis and release of AA metabolites, while many cell types represent the targets for eicosanoid action. Endothelial cells (EC), forming a semi-permeable barrier between the interior space of blood vessels and underlying tissues, are of particular importance for the development of inflammation, since endothelium controls such diverse processes as vascular tone, homeostasis, adhesion of platelets and leukocytes to the vascular wall, and permeability of the vascular wall for cells and fluids. Proliferation and migration of endothelial cells contribute significantly to new vessel development (angiogenesis). This review discusses endothelial-specific synthesis and action of arachidonic acid derivatives with a particular focus on the mechanisms of signal transduction and associated intracellular protein targets.

Keywords: Arachidonic acid; Eicosanoids; Endothelial cells

Contents

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Review outline

This review is focused on the role of endothelium in eicosanoid-induced alteration of vascular function. Two aspects will be selectively examined here, namely, (a) the contribution of endothelium to eicosanoid generation and (b) endothelial-specific action of eicosanoids. In the first section, the review will provide background information about endothelial functions and the major signaling pathways that control them. The next section will analyze the mechanisms of AA release, uptake, and conversion, with the particular focus on the action of unconverted AA and AA amide derivative. Subsequent specific sections will discuss the synthesis and action of cyclooxygenized, lipoxygenized, and monooxygenized AA products. Each section will review the molecular mechanisms of endothelial response to AA metabolites, focusing on the nature of signaling pathways involved. In a few cases where data are available, this review will provide information about cytoskeleton-directed effects of AA metabolites. Multifaceted effects of eicosanoids on vascular functions are summarized in Table 1.

Introduction

Arachidonic acid (AA) and its metabolites are well-known modulators of inflammation that are synthesized and/or released by living cells in response to various factors. Inflammation, which can be acute or chronic in nature, is usually characterized by local erythema, heat generation, and swelling (Gil, 2002; Yoshikai, 2001). Each of these symptoms is caused by the increased blood flow and vascular permeability that result in the production of tissue edema (Larsen and Holt, 2000). Since the endothelium modulates vascular tone and functions as a semi-permeable barrier between the vascular lumen and interstitium (Fig. 1A), it is a key participant in inflammation

Table 1
Effects of AA derivatives on vascular functions

AA metabolite	Vascular tone	PMN adhesion	Monocyte adhesion	Endothelial permeability	EC migration	EC proliferation	EC viability	Mechanism of action
Anandamide	↓1, 2				↑3		↓4	Ca↑, PI3 kinase, Akt, MAP kinases, NO↑ 3–6
TX	↑7			↑8–10	↑↓11–12	↑13	↓14–15	Ca↑, cAMP↑, cAMP↓, PKA, Akt 14, 16–17
PGD2	↓↑18, 19			↑18				cAMP↑ 16–18
PGF2	↑20			↑21				Ca↑ 16–17
PGE2	↓22–23			↑↓21, 24	↑11		↑23	Ca↑, cAMP↑, VEGF↑ 16–17, 25
PGI2	↓22	↓22, 26		↓↑24, 27–28		↓13		Ca↑, cAMP↑ 16–17
cPGs			↓29–30		↓31	↓31	↓↑29, 32–37	PPAR, NF-κB, NO↑, glutathione↑ 36–40
LTB4		↑22, 41		weak↑ 42		↑43		Ca↑, cAMP↓, PPAR 44–45
CysLTs	↓46			↑47, 48		↑43		Ca↑, PGI2↑ 44, 49
12-HETE		↑50	↑51–52	↑50, 53	↑54–55	↑54–55		PKC, direct effect on adhesion molecules 53, 56
15-HETE		↓57–59	↓59	↑50				Direct effect on adhesion molecules 56
LX	↓60	↓61–64		↓63–64		↓65	↓66	Ca↑, cAMP↓, PGI2 release 44, 63, 64, 67
EETs	↑↓68–70	↓71		↑69, 72	↑73	↑74	↑75	cAMP↑, hyperpolarization, Ca↑, PKA, Akt, tyrosine kinases 5, 73, 74, 76–84
20-HETE	↑↓85–86				↑87–88	↑87–88		PKC, depolarization, VEGF↑, PGI2↑ 80, 87, 89, 90

1. Randall et al., 1996; 2. Chaytor et al., 1999; 3. Mo et al., 2004; 4. Yamaji et al., 2003; 5. Mombouli et al., 1999a,b; 6. Zoratti et al., 2003; 7. Shibamoto et al., 1995; 8. Teixeira et al., 1995; 9. Turnage et al., 1997; 10. Valentin et al., 1997; 11. Kuwano et al., 2004; 12. Ashton et al., 1999; 13. Cheng et al., 2002; 14. Gao et al., 2000; 15. Zou et al., 2002; 16. Breyer et al., 2001; 17. Tsuboi et al., 2002; 18. Nishimura et al., 2001; 19. Liu et al., 1996; 20. Lonigro and Dawson, 1975; 21. Mark et al., 2001; 22. Gaetano et al., 2003; 23. Bouchard et al., 2000; 24. Ma and Pedram, 1996; 25. Pai et al., 2001; 26. Lindemann et al., 2003; 27. Bentzer and Grande, 2004; 28. Murata et al., 1997; 29. Zernecke et al., 2003; 30. Jackson et al., 1999; 31. Xin et al., 1999; 32. Bishop-Bailey and Hla, 1999; 33. Erl et al., 2004; 34. He et al., 2002; 35. Taba et al., 2003; 36. Ohno et al., 1991; 37. Levonen et al., 2001; 38. Ricote et al., 1998; 39. Rossi et al., 2000; 40. Calnek et al., 2003; 41. Nohgawa et al., 1997; 42. Lewis and Granger, 1988; 43. Walker et al., 2002; 44. Brink et al., 2003; 45. Yoshikai, 2001; 46. Busse, 1998; 47. Kanaoka et al., 2001; 48. Maekawa et al., 2002; 49. Geirsson et al., 1998; 50. Waldman et al., 1989; 51. Patricia et al., 1999; 52. Reilly et al., 2004; 53. Tang et al., 1993; 54. Tang et al., 1995a; 55. Nie et al., 2000; 56. Buchanan et al., 1998; 57. Takata et al., 1994a; 58. Takata et al., 1994b; 59. Huang et al., 1997; 60. Von der Weid et al., 2004; 61. Scalia et al., 1997; 62. Papayianni et al., 1996; 63. Takano et al., 1998; 64. Gronert et al., 2001; 65. Fierro et al., 2002; 66. Bratt et al., 1995; 67. Brezinski et al., 1989; 68. Zhu et al., 2000; 69. Alvarez et al., 2004; 70. Fang et al., 1999; 71. Node et al., 1999; 72. Ivey et al., 1998; 73. Michaelis et al., 2003; 74. Potente et al., 2003; 75. Yang et al., 2001; 76. Campbell et al., 1996; 77. Hu and Kim, 1993; 78. Hoebel et al., 1998; 79. Fleming, 2004; 80. Kroetz and Zeldin, 2002; 81. Li et al., 1999; 82. Fukao et al., 2001; 83. Graier et al., 1995; 84. Watanabe et al., 2003; 85. Fuloria et al., 2004; 86. Zhu et al., 2002; 87. Amaral et al., 2003; 88. Jiang et al., 2004; 89. Obara et al., 2002; 90. Pratt et al., 1998.