REVISTA ESPAÑOLA DE FISIOLOGIA, 46 (1), 47-56, 1990

Effect of Glucocorticoids on Arachidonate Metabolism and Prostaglandin Secretion

D. Duval

Department of Pharmacology
School of Medicine Necker
Enfants Malades
156 Rue de Vaugirard
75015 Paris (France)

(Received on December 19, 1989)

D. DUVAL. *Effect of Glucocorticoids on Arachidonate Metabolism and Prostaglandin Secretion.* Rev. esp. Fisiol., 46 (1), 45-54, 1990.

The effects of glucocorticoids on eicosanoid synthesis are briefly summarized and issues that remained unresolved or controversial are described. It is also suggested, in view of the present knowledge about the effects of sex steroids on uterine prostaglandin production, that common features may exist between these actions and those of anti-inflammatory steroids.

Key words: Glucocorticoids, Lipocortins, Arachidonate, Metabolism.

Background to the mechanism of glucocorticoid action

Since the early demonstration that glucocorticoids inhibit the release of prostaglandins (36, 44, 46), it has been progressively accepted that inhibition of eicosanoid synthesis represents the basis of their antiinflammatory effects (98, 101). Despite this assumption, the subcellular mechanisms of the glucocorticoid action has long remained obscure. It was first believed that steroids exert their effect on the synthesis of arachidonic acid metabolites via membrane stabilization (112), but it is now accepted that this effect is a classical receptor-mediated event and requires macromolecular synthesis. This conclusion is based on the following elements: There is a good correlation between the affinity of a given molecule for glucocorticoids receptors and its inhibitory action on PG synthesis (91, 106); the effects of glucocorticoids on PG formation can be blocked by a specific receptor antagonist RU 486 (55); the occurence of a lag phase of 1-2 h between the glucocorticoid treatment and the onset of the inhibition (32, 90); and the effect of dexamethasone on PG synthesis is abolished in the presence of inhibitors of either RNA or protein synthesis (17, 91).

Several characteristics of the metabolism of arachidonic acid, the major fatty acid precursor of eicosanoids, are important for the understanding of the glucocorticoid effect. It was demonstrated long ago, that only the free form of arachidonic acid can be converted into eicosanoids

(66), and that availability of free arachidonate is the rate limiting step in the biosynthesis of eicosanoids (4, 107). Since most of the cell arachidonate is found esterified in position 2 of membrane phospholipids (22, 37), it is generally accepted that arachidonate supply is controlled by the activity of phospholipase A_2 or the activities of phospholipase C plus diglyceride lipase (63).

Many results strongly suggest that glucocorticoids may act at the level of phospholipases: In numerous cell types, glucocorticoids have been shown to decrease both basal and stimulated arachidonate liberation from cellular stores (80, 100); In contrast with NSAID, which usually inhibit only the cyclooxygenase pathway, glucocorticoids block in parallel both cyclooxygenase and lipoxygenase pathways (38, 49, fig. 1). The inhibitory action of glucocorticoids on prostaglandin synthesis can be abolished by addition of exogenous arachidonic acid (16, 56).

Several explanations can be proposed to take into account this body of information: Glucocorticoids may either inhibit the synthesis of phospholipase A_2, induce the secretion of a phospholipase inhibitor or decrease the formation of an activator of phospholipase A_2. In fact, Hirata and coworkers, Flower et al. and Russo-Marie and Duval described the presence in the supernatants of dexamethasone-treated cells of proteins able to inhibit arachidonate release (6, 54, 89).

Nature and role of lipocortins

The discovery of these phospholipase inhibitory proteins which possibly represent second messengers of the glucocorticoid action has stimulated intensive investigations.

In a cooperative study it was first demonstrated that the various proteins discovered in rabbit neutrophils, in rat peritoneal macrophages or in cultures of rat renomedullary cells are very similar, if not identical. These proteins share indeed many common characteristics: they exhibit similar immunological determinants being recognized by the same monoclonal antibody; they are similarly induced by glucocorticoid treatment; they all decrease the release of fatty acids from membrane phospholipids; they present identical biochemical features: a molecular weight of approximately 40 Kd, a phosphorylation site and the ability to be cleaved by proteolytic enzymes in active fragments of 30 and 15 Kd (53).

This protein or this family of proteins was named Lipocortin.

Recently, lipocortin has been purified to homogeneity, sequenced (59) and its gene cloned and expressed in *E. Coli* (109). Using specific probes, it was demonstrated by Northern blot hybridisation that lipocortin mRNA was in fact expressed constitutively in a large variety of tissues (macrophages, lung, thymus and spleen, liver, heart, brain, kidney...) and in various cell lines (9). It was also confirmed that lipocortin can be phosphorylated and is a substrate for the tyrosine kinase activity of the Epidermal Growth Factor receptor (8).

Huang and coworkers have however purified from human placenta two proteins, lipocortin I and II, with the same ability to inhibit phospholipase but which only share a 50 % sequence homology (60). By further sequence homology analyses it was then established that lipocortins belong to the vast family of the calcium and lipids binding proteins and are in fact very similar to calpactins (39).

From this sum of results a mechanism of action was proposed where lipocortins inhibit phospholipase activity through a stoechiometric 1:1 interaction with the enzyme, this interaction being controlled by the phosphorylation status of the lipocortin (fig. 2). More recent experiments however, suggest that the effects of lipocortin on phospholipase activity is indirect rather than direct, and likely occurs by

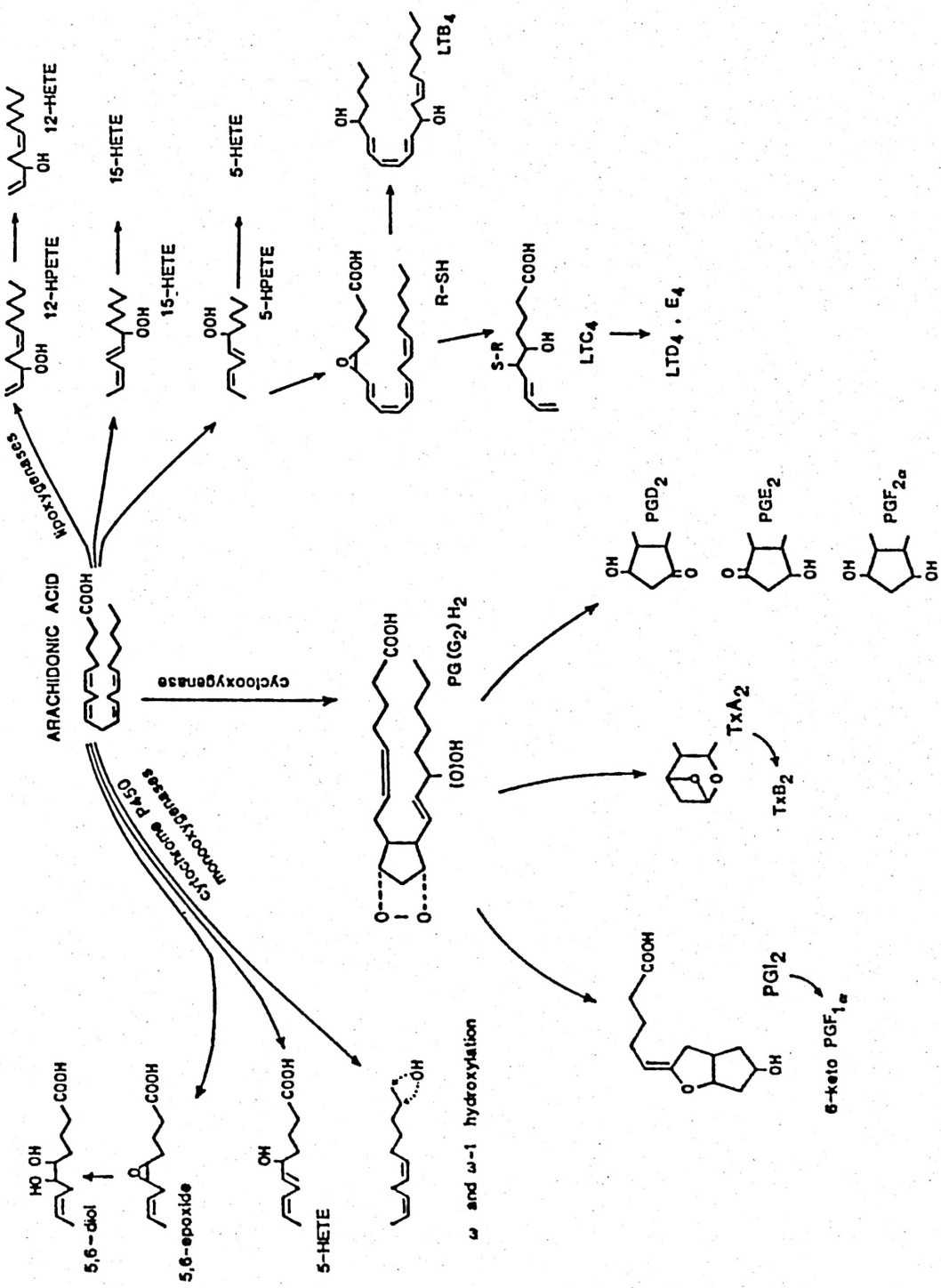

Fig. 1. *Three major pathways of arachidonate metabolism.*

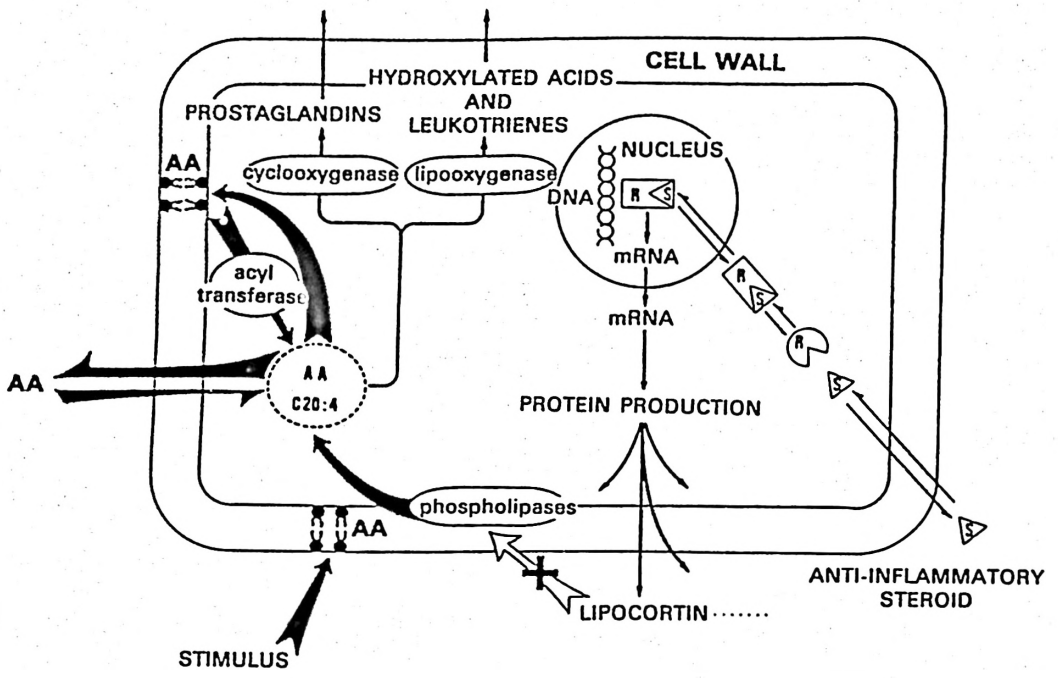

Fig. 2. *Mechanism of action of glucocorticoids on phospholipase activity.*

competition with the enzyme for the phospholipid substrates (18).

Although it has been now demonstrated that purified and recombinant lipocortins inhibit prostaglandin and leucotrienes synthesis and mimick some of the *in vitro* and in vivo anti-inflammatory effects of glucocorticoids (33, 111), there are now several results which do not support the hypothesis of a lipocortin-mediated mechanism of action of glucocorticoids.

Uncertainties and contradictions

In vitro *experiments.* — Some of the experiments carried out in cell cultures have produced results that are hard to combine with the lipocortin mechanism described above.

In contrast to that is observed with non steroidal anti-inflammatory drugs, glucocorticoids do not completely inhibit the synthesis of eicosanoids nor the liberation of arachidonic acid. Even at supramaximal concentrations of glucocorticoids, sufficient to saturate glucocorticoid receptors it is observed that the percentage inhibition is generally between 70 and 90 % and never exceeds this value. No satisfactory explanation of this residual synthesis has been provided up to now (89).

In addition, some authors have shown that in a given cell population glucocorticoids may inhibit to a different extent the synthesis of the various eicosanoids produced by the cells. Durant *et al.* have shown in cultures of mouse embryo fibroblasts that dexamethasone treatment led to a 70-80 % inhibition of PGE 2 and PGI 2 synthesis but only to a 30 % reduction of $PGF_{2\alpha}$ secretion (25). Similarly, Robin and coworkers described in cultures of mouse bone marrow derived mast cells that glucocorticoids inhibit the

formation of leucotrienes but enhances the synthesis of PGD_2 (86).

Finally, it appears in different systems, that glucocorticoids which inhibit the synthesis of prostaglandins triggered by a given signal, do not affect the secretion induced in the same cells by another stimulus nor the basal secretion (20, 52).

In order to account for these deviations from the model, it was proposed that different metabolic pools of arachidonate exist and are not coupled with the same efficiency to membrane receptors (58, 62), whereas some authors have also described the existence of different phospholipases with distinct characteristics and tissue specificities (88).

Furthermore, observations have been made which are in complete contradiction with the proposal of lipocortin-mediated action of steroids.

Different paradoxical situations can be observed with regards to the action of glucosteroids on arachidonate metabolism and prostanoid synthesis: in some cell lines or in some tissues, glucocorticoids may markedly enhance prostaglandin synthesis (30, 57, 69); as stated above, dexamethasone may in the same cell line enhance PGD_2 synthesis and inhibit leucotriene formation (86); DUVAL and coworkers described in U 937 cells that steroid treatment led to a significant stimulation of arachidonate release (28). It was also observed that steroids inhibit prostaglandin synthesis while stimulating arachidonate liberation (27).

These effects have been explained by a stimulation of PG synthetase activities associated in some cases with an inhibition of the fatty acid reacylation step (28, 69).

On the other hand, using specific probes to detect the level of expression of lipocortins and their intracellular content, several authors recently demonstrated that inhibition of eicosanoid synthesis may occur in the absence of any detectable effect of glucocorticoids on the synthesis of lipocortins (5, 61, 81).

In vivo *experiments.* — Given the results showing in many cell types an inhibition of prostaglandin formation by glucocorticoids, several groups have attempted to determine in vivo the effects of steroid treatment on the plasma concentration or on the urinary excretion of prostaglandin and prostaglandin metabolites.

Although these experiments have been carried out in different species, including man, using highly variable steroid concentrations and treatment schedules it is now obvious that the effects of glucocorticoids in vivo on prostaglandin formation remain elusive. Despite some results showing a moderate inhibition of urinary excretion in rats (7, 51), most of the studies done showed either no influence or even a stimulation of plasma levels and urinary excretion (76-78, 87, 104 and 26 for a review).

On the other hand, it is important to remember that therapeutic treatment by cortisol or methylprednisolone is known for almost 40 years to induce profound alterations on body fats and to induce a significant stimulation of the plasma concentrations of non esterified fatty acids including the prostaglandin precursor arachidonic acid (43, 64).

It thus appears that the effects of glucocorticoids on arachidonate metabolism and eicosanoid formation are more complex than previously claimed. Indeed, it is obvious from a literature survey that glucocorticoids may affect directly or indirectly many parameters which influence more or less the metabolism of arachidonic acid and its transformation.

POSSIBLE REGULATORY EFFECTS OF GLUCOCORTICOIDS ON ARACHIDONATE METABOLISM

Effects on lipid metabolism. — Glucocorticoids have been described to exert numerous effects on lipid metabolism. Many of these effects could contribute directly or indirectly to modulate arachi-

donate availability and prostaglandin levels.

Changes in eicosanoid levels may derive for example from changes in cyclooxygenase and/or PG synthetase activities (31) or from modification of the prostaglandin degrading enzyme (73).

Many different pathways of lipid metabolism are controlled in part by glucocorticoids and may either enhance or decrease the circulating arachidonate concentration.

These include regulation of the lysophospholipid acyl transferase activity (28), control of the transfer of acyl groups from phospholipids to triglycerides (105) or to cholesterylesters, alteration of the clearance of plasma arachidonic acid (3), enhanced TG hydrolysis (30), stimulation or inhibition of lipoprotein lipase levels (10, 50) and control of several of the steps involved in the turnover of phospholipid backbones (45, 85).

In addition, glucocorticoids may also regulate the synthesis of fatty acids at the level of fatty acid synthetase (108), or at the enzymes controlling elongation and desaturation of fatty acids (19).

Indirect effects mediated via proteins other than lipocortin. — Various proteins have been described to affect fatty acid availability in different ways:

Albumin for example may exert a striking effect on arachidonate release and transformation simply because of its capacity to bind large amounts of free fatty acids (27, 99).

Some plasma proteins such as haptoglobin, orosomucoid, and a circulating lipoprotein are known to exert an action on phospholipase activity and fatty acid release (21, 72, 84, 92).

Similarly, uteroglobin, a protein which can represent up to 40 % of the proteins secreted by uterine cells during pregnancy, is known to inhibit phospholipase activity (103, 110). Several authors have also described in various tissues the existence of a protein identical to uteroglobin (70).

Moreover, it is well known that peptides and proteins that exert a major role in cell to cell interactions often stimulate the arachidonic acid cascade (i.e. kinins and in particular bradykinin, immunological signals such as interleukin 1 and interleukin 2, cachectin, γ interferon, and non specific mediators such as proteases 14, 23, 42, 68, 113).

It is thus striking to observe that each of the factors listed above and probably others, are under glucocorticoid regulation (24, 75). This regulation could affect the synthesis of the factors mentioned above (41), the number of their receptors (15), or even the synthesis of an inhibitory protein. Several authors have now demonstrated that glucocorticoids enhance the production of a protein inhibitor of tissue plasminogen activator (40, 96) as well as of other antiproteases (TIMP, 71).

Thus, as emphasized previously by Claman (13), steroids act at a bewildering number of sites and it is not possible to find out a single steroid-induced protein or a single action which fully explains the clinical effects observed.

Multiplicity of the antiinflammatory actions of steroids

Since the demonstration of the anti-inflammatory effects of adrenal extracts 40 years ago, hydrocortisone and synthetic glucocorticoids represent the most potent class of anti-inflammatory and immunosuppressive agents.

Indeed they constitute the only drugs capable to abolish all the symptoms of an acute inflammatory reaction. Although non steroidal agents such as salicylates, indomethacin... inhibit the synthesis of prostaglandins, they are, by far, less potent than glucocorticoids as anti-inflammatory drugs. This difference was attributed to the property of steroids to block simultaneously cyclooxygenase and lipoxygenase pathways, but as already under-

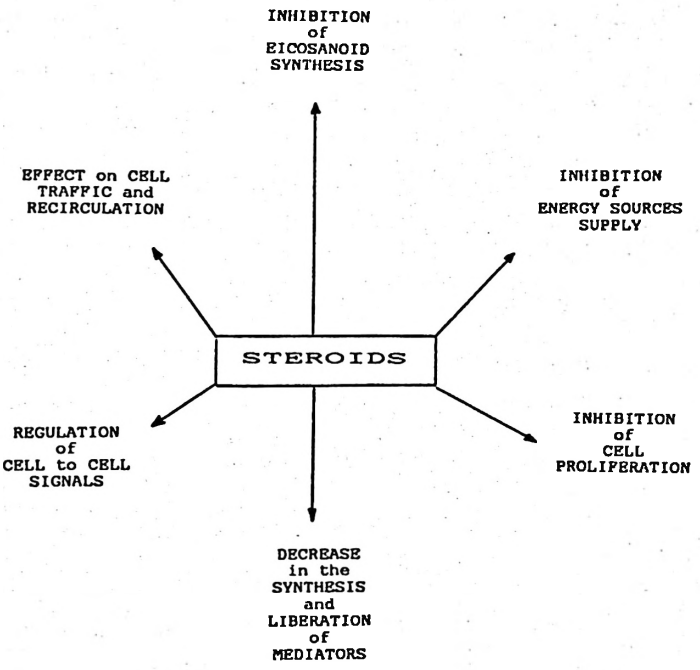

Fig. 3. *Mechanisms of the anti-inflammatory effects of glucocorticoids.*

lined by FAMAEY 10 years ago (34), the anti-inflammatory action of glucocorticoids is not due solely to their effect on eicosanoid synthesis. In fact, a complete description of the whole spectrum of effects of glucocorticoids on inflammatory reactions would constitute an extensive task. In the present paper (fig. 3) we have only briefly summarized the principal mechanism involved in these anti-inflammatory actions (24, 35, 74, 75, 95), just to stress that it is unrealistic to postulate that lipocortins may replace glucocorticoids as anti-inflammatory agents.

CONCLUDING REMARK: SEX STEROIDS AND PROSTAGLANDIN PRODUCTION

Numerous studies have now demonstrated that sex steroids, essentially estrogens and progesterone, exert a significant effect on prostaglandin synthesis in various tissues including cells of the vascular wall (82, 97), but particularly uterine cells (1, 12, 67, 79, 94, 102). In most of the cases, estradiol has been described to enhance the synthesis of PGE_2 and PGF_2 whereas progesterone inhibits their secretion.

This antagonist effect of sex steroids on PG secretion is considered to play an important role in pregnancy and labour (11, 65, 93).

In view of the large amount of information obtained in the last few years about the mechanisms of action of glucocorticoids on eicosanoid synthesis, it is surprising to see how little is known concerning the effects of sex steroids on arachidonate availability and metabolism.

Nevertheless, estradiol has been described in some experimental models:

To enhance the overall turnover of uterine cell phospholipids (2), to increase phospholipase activity and arachidonate liberation (83), to stimulate prostaglandin synthetase (48).

However, no real insight has been obtained on the mechanism by which estrogens control phospholipase activity.

Progesterone which inhibits PG synthesis, does in fact reduce lipocortin synthesis and metabolism in uterine cells (47). However, uteroglobin which is markedly induced by progesterone treatment in uterine cells has been suggested by several groups to play a role as anti-phospholipase protein (103, 110).

We believe that, taking into account the results obtained for glucocorticoids, major improvements in our knowledge of the effects of sex steroids on eicosanoid synthesis can be realized in the next few years.

Resumen

Se resumen brevemente los efectos de los glucocorticoides sobre la síntesis del eicosanoide y se describen los temas que permanecen sin solución o controvertidos. También se sugiere, a la vista de los conocimientos actuales de los efectos de los esteroides sexuales sobre la producción uterina de la prostaglandina, que puedan existir características comunes entre estas acciones y las de los esteroides antiinflamatorios.

Palabras clave: Glucocorticoides, Lipocortina, Metabolismo del araquidonato.

References

1. Abel, M. H. and Baird, D. T.: *Endocrinology* 106, 1.599-1.606, 1980.
2. Aizawa, Y. and Mueller, G. C.: *J. Biol. Chem.*, 236, 381-386, 1961.
3. Araki, H., Peck, R. C., Lefer, A. M. and Smith, J. B.: *Prostaglandins*, 21, 387-399, 1981.
4. Bell, R. L., Kennerly, D. A., Stranford, N. and Majerus, P.: *Proc. Natl. Acad. Sci. USA*, 76, 3.228-3.241, 1979.
5. Bienkowski, M. J., Petro, M. A. and Robinson, L. J.: *J. Biol. Chem.*, 264, 6.536-6.544, 1989.
6. Blackwell, G. J., Carnuccio, R., Di Rosa, M., Flower, R. J., Parente, L. and Persico, P.: *Nature*, 287, 147-149, 1980.
7. Blajchman, M. A., Senyi, A. F., Hirsh, J., Surya, Y., Buchanan, M. and Mustard, J. F.: *J. Clin. Invest.*, 63, 1.026-1.035, 1979.
8. Blake-Pepinsky, R. and Sinclair, L. K.: *Nature*, 321, 81-84, 1986.
9. Blake-Pepinsky, R., Sinclair, L. K., Browning, J. L. *et al.*: *J. Biol. Chem.*, 261, 4.239-4.244, 1986.
10. Brindley, D. N.: *Clin. Sci.*, 61, 129-133, 1981.
11. Casey, M. L., McDonald, P. C. and Mitchell, M. D.: *J. Clin. Invest.*, 75, 1.852-1.857, 1985.
12. Castracane, V. D. and Jordan, V. C.: *Prostaglandins*, 12, 243-251, 1976.
13. Claman, H. N.: *Clin. Immunol. Allergy*, 4, 317-329, 1984.
14. Clark, M. A., Bomalaski, J. S., Conway, T. M., Wartell, J. and Crooke, S. T.: *Prostaglandins*, 32, 703-708, 1986.
15. Crabtree, G. R., Munck, A. and Smith, K. A.: *Nature*, 279, 338-339, 1979.
16. Crutchley, D. J., Ryan, U. S. and Ryan, J. W.: *J. Pharm. Exp. Ther.*, 233, 650-655, 1985.
17. Danon, A. and Assouline, G.: *Nature*, 273, 552-554, 1978.
18. Davidson, F. F., Dennis, E. A., Powell, M. and Glenney, J. R.: *J. Biol. Chem.*, 262, 1.698-1.705, 1987.
19. De Gomez Dumm, I. N. T., De Alaniz, M. J. T. and Brenner, R. P.: *J. Lipid. Res.*, 20, 834-839, 1979.
20. De Nucci, G., Astbury, P., Read, N., Salmon, J. A. and Moncada, S.: *Eur. J. Pharm.*, 126, 11-20, 1986.
21. Denning-Kendall, P. A., Butt, N. M., Saed, S. A. and Collier, H. O. J.: *Biochem. Soc. Trans.*, 8, 79-80, 1980.
22. Dennis, E. A.: *Biotechnol.*, 5, 1.294-1.300, 1987.
23. Dinarello, C. A.: *TIPS*, 5, 420-422, 1984.
24. Durant, S., Duval, D. and Homo-Delarche, F. *Endocr. Rev.*, 7, 254-269, 1986.
25. Durant, S., Homo-Delarche, F., Duval, D., Papiernik, M., Smets, P. and Zalisz, R.: *Int. J. Tiss. Reac.*, 7, 117-122, 1985.
26. Duval, D.: *Presse Med.*, 15, 433-435, 1986.
27. Duval, D., Huneau, J. F. and Homo-Delarche, F.: *Prost. Leuk. Med.*, 23, 67-83, 1986.
28. Duval, D., Lynde, P., Hatzfeld, A. and Hatzfeld, J.: *Biochim. Biophys. Acta*, 887, 204-213, 1986.
29. Erman, A., Hassid, A. Baer, P. G. and Nasjletti, A.: *J. Pharm. Exp. Ther.*, 239, 296-301, 1986.
30. Erman, A., Baer, P. G., Nasjletti, A.: *J. Biol. Chem.*, 260, 4.679-4.683, 1985.

31. Erman, A. and Nasjletti, A.: *Biochem. Biophys. Res. Comm.*, 121, 255-260, 1984.
32. Errasfa, M., Rothhut, B., Fradin, A., Billardon, C., Junien, J. L., Bure, J. and Russo-Marie, F.: *Biochim. Biophys. Acta*, 847, 247-254, 1985.
33. Errasfa, M., Rothhut, B. and Russo-Marie, F.: *Biochem. Biophys. Res. Comm.*, 159, 53-60, 1989.
34. Famaey, J. P.: *Gen. Pharmacol.*, 9, 155-161, 1978.
35. Fauci, A. S.: *J. Immunopharmacol.*, 1, 1-25, 1979.
36. Floman, Y. and Zor, U.: *Prostaglandins*, 12, 403-416, 1976.
37. Flower, R. J. and Blackwell, G. J.: *Biochem. Pharm.*, 25, 285-291, 1976.
38. Fuller, R. W., Kelsey, C. R., Cole, P. J., Dollery, C. T. and MacDermot, I.: *Clin. Sci.*, 67, 653-656, 1984.
39. Geisow, M. J.: *Febs Letters*, 203, 99-103, 1986.
40. Gelehrter, T. D., Barouski, Miller, P. A., Coleman, P. L., Cwikel, B. J.: *Mol. Cell. Biochem.*, 53, 11-21, 1983.
41. Gillis, S., Crabtree, G. R. and Smith, K. A.: *J. Immunol.*, 123, 1.624-1.631, 1979.
42. Godfrey, R. W., Johnson, W. J., Newman, T. and Hoffstein, S. T.: *Prostaglandins*, 35, 107-114, 1988.
43. Gold, E. W., Fox, O. D., Weissfeld, S. and Curtiss, P. H.: *Clin. Orth. Rel. Res.*, 135, 272-280, 1978.
44. Greaves, M. W. and McDonald-Gibson W.: *Brit. Med. J.*, 2, 83-84, 1972.
45. Grove, R. I., Willis, W. D. and Pratt, R. M.: *Biochem. Biophys. Res. Comm.*, 110, 200-207, 1983.
46. Gryglewski, R. J., Panczenko, B., Korbut, R., Grodzinska, L. and Ocetkiewicz, A.: *Prostaglandins*, 10, 343-355, 1975.
47. Gurpide, E., Markiewicz, L., Schatz, F. and Hirata, F.: *J. Clin. Endocr. Metab.*, 63, 162-166, 1986.
48. Ham, E. A., Cirillo, V. J., Zanetti, M. E. and Kuehl, F. A.: *Proc. Natl. Acad. Sci. USA*, 72, 1.420-1.424, 1975.
49. Hammarström, S., Hamberg, M., Duell, E. A., Stawiski, M. A., Anderson, T. F. and Voorhees, J. J.: *Science*, 197, 994-996, 1977.
50. Hamosh, M., Yeager, H., Shechter, Y. and Hamosh, P.: *Biochim. Biophys. Acta*, 431, 519-525, 1976.
51. Handa, M., Kondo, K., Suzuki, H. and Saruta, T.: *Clin. Sci.*, 65, 37-42, 1983.
52. Heiman, A. S. and Crews, F. T.: *J. Pharm. Exp. Ther.*, 230, 175-182, 1984.
53. Hirata, F., Notsu, Y., Iwata, M., Parente, L., Di Rosa, M. and Flower, R. J.: *Biochem. Biophys. Res. Comm.*, 109, 223-230, 1982.
54. Hirata, F., Schiffmann, D., Venkatasubramanian, K., Salomon, D. and Axelrod, J.: *Proc. Natl. Acad. Sci. USA*, 77, 2.533-2.536, 1980.
55. Homo-Delarche, F., Duval, D. and Papiernik, M.: *J. Immunol.*, 135, 506-512, 1985.
56. Hong, S. C. and Levine, L.: *Proc. Natl. Acad. Sci. USA*, 73, 1.730-1.734, (1976).
57. Honma, Y., Kasukabe, T., Hozumi M. and Koshihara, Y.: *J. Cell. Physiol.*, 104, 349-357, 1980.
58. Hsueh, W., Desai, U., González-Crussi, F., Lamb, R. and Chu, A.: *Nature*, 290, 710-712, 1981.
59. Huang, K. S., McGray, P., Mattaliano, R. J. et al.: *J. Biol. Chem.*, 262, 7.639-7.645, 1987.
60. Huang, K. S., Wallner, B. P., Mattaliano, R. J. et al.: *Cell*, 46, 191-199, 1986.
61. Hullin, F., Raynal, P., Ragab-Thomas, J. M. F., Fauvel, J. and Chap, H.: *J. Biol. Chem.*, 264, 3.506-3.513, 1989.
62. Humes, J. L., Sadowski, S., Galavage, M., Goldenberg, M., Subers, E., Bonney, R. J. and Kuehl, F. A.: *J. Biol. Chem.*, 256, 2.329-2.335, 1981.
63. Irvine, R. F.: *Biochem. J.*, 204, 3-16, 1982.
64. Jeanrenaud, B. and Renold, A. E.: *J. Biol. Chem.*, 235, 2.217-2.223, 1960.
65. Keirse, M. J. N. C., Mitchell, M. D. and Turnbull, A. C.: *Brit. J. Obstet. Gynaecol.*, 84, 743-746, 1977.
66. Lands, W. E. M. and Samuelsson, B. *Biochim. Biophys. Acta*, 164, 426-429, 1968.
67. Leaver, H. A. and Richmond, D. H.: *Prost. Leuk. Med.*, 13, 179-196, 1984.
68. Levine, L. and Hassid, A.: *Biochem. Biophys. Res. Comm.*, 76, 1.181-1.187, 1977.
69. Lewis, R. A., Robin, J. L. and Austen, K. F.: *Int. Arch. Allergy Appl. Immun.*, 77, 121-125, 1985.
70. López de Haro, M. S. and Nieto, A.: *Biochem. J.*, 225, 255-258, 1985.
71. McGuire, M. B., Murphy, G., Reynolds, J. J. and Russel, R. G. G.: *Clin. Sci.*, 61, 703-710, 1981.
72. Miwa, M., Ichihashi, T., Motojima, H., Onodera-Kubota, I. and Matsumoto, M.: *J. Biochem.*, 98, 157-165, 1985.
73. Moore, P. K. and Hoult, J. R. S.: *Nature*, 288, 269-270, 1980.

74. Morris, H. G.: *Chest*, 88, S, 133S-141S, 1985.
75. Munck, A., Guyre, P. M., Holbrook, N. J.: *Endocr. Rev.*, 5, 25-44, 1984.
76. Naray-Fejes-Toth, A. and Fejes-Toth, G.: *Endocrinol.*, 119, 2.856-2.860, 1986.
77. Naray-Fejes-Toth, A., Fejes-Toth, G., Fischer, C. and Fröhlich, J. C.: *J. Clin. Invest.*, 74, 120-123, 1984.
78. Nasjletti, A., Erman, A., Cagen, L. M. and Baer, P. G.: *Endocrinology*, 114, 1.033-1.040, 1984.
79. Neulen, J., Zahradnik, H. P., Flecken, U. and Breckwoldt, M.: *Prostaglandins*, 37, 587-595, 1989.
80. Newcombe, D. S., Fahey, J. V. and Ishikawa, Y.: *Prostaglandins*, 13, 235-244, 1977.
81. Northup, J. K., Valentine-Braun, K. A., Johnson, L. K., Severson, D. L. and Hollenberg, M. D.: *J. Clin. Invest.*, 82, 1.347-1.352, 1988.
82. Ohtsu, A., Saitoh, N., Okada, N., Chang, W. C. and Murota, S.: *Thromb. Res.*, 32, 567-574, 1983.
83. Pakrasi, P. L., Cheng, H. C. and Dey, S. K.: *Prostaglandins*, 26, 991-1.009, 1983.
84. Pearson, J. D.: In «Cardiovascular Pharmacology of the Prostaglandins», A. G. Herman, P. M. Vanhoutte, H. Denolin and A. Goosens, eds.). Raven Press, New York, 1982, pp. 23-33.
85. Post, M., Barsoumian, A. and Smith, B. T.: *J. Biol. Chem.*, 261, 2.179-2.184, 1986.
86. Robin, J. L., Seldin, D. C., Austen, F. and Lewis, R. A.: *J. Immunol.*, 135, 2.719-2.726, 1985.
87. Rosenkrantz, B., Naray-Fejes-Toth, A., Fejes-Toth, G. *et al.*: *Clin. Sci.*, 68, 681-685, 1985.
88. Ross, M. I., Deams, R. A., Jesaitis, A. J., Dennis, E. A. and Ulevitch, R. J.: *Arch. Biochem. Biophys.*, 238, 247-258, 1985.
89. Russo-Marie, F. and Duval, D.: *Biochim. Biophys. Acta*, 712, 177-185, 1982.
90. Russo-Marie, F., Paing, M. and Duval, D.: *Agents & Actions*, S4, 49-62, 1979.
91. Russo-Marie, F., Paing, M. and Duval, D.: *J. Biol. Chem.*, 254, 8.498-8.504, 1979.
92. Saed, S. A., McDonald-Gibson, J., Cuthbert, J., *et al.*: *Nature*, 270, 32-36, 1977.
93. Satoh, K. T., Yasumizu, T., Fukuoka, H., *et al.*: *Am. J. Obstet. Gynaecol.*, 133, 886-890, 1979.
94. Schatz, F., Markiewicz, L. and Gurpide, E.: *J. Steroid, Biochem.*, 20, 999-1.003, 1984.
95. Schleimer, R. P.: *Ann. Rev. Pharmacol. Toxicol.*, 25, 381-412, 1985.
96. Seifert, S. C. and Gelehrter, T. D.: *Proc. Natl. Acad. Sci. USA*, 75, 6.130-6.133, 1978.
97. Seillan C., Ody, C., Russo-Marie, F., Duval, D.: *Prostaglandins*, 26, 3-12, 1983.
98. Stevenson, R. D.: *Lancet*, 225-226, 1977.
99. Stuart, M. J., Gerrard, J. M. and White, J. G.: *Blood*, 55, 418-423, 1980.
100. Tam, S., Hong, S. C. and Levine, L.: *J. Pharm. Exp. Ther.*, 203, 162-168, 1977.
101. Tashjian, A. M., Voelkel, E. F., McDonough, J. and Levine, J.: *Nature*, 258, 739-741, 1975.
102. Tawfik, O. W., Huet, Y. M., Malathy, P. V., Johnson, D. C. and Dey, S. K.: *Prostaglandins*, 34, 805-815, 1987.
103. Torkkeli, T., Krusius, T. and Jänne, O.: *Biochim. Biophys. Acta*, 544, 578-592, 1978.
104. Tsai, M. Y.: *Prost. Leuk. Med.*, 28, 119-125, 1987.
105. Tsai, P. Y. and Geyer, R. P.: *J. Biol. Chem.*, 253, 5.087-5.089, 1978.
106. Tsurufuji, S., Sugio, K. and Takemasa, F.: *Nature*, 280, 408-410, 1979.
107. Vogt, W.: In «Advances in Prostaglandin and Thromboxane Research» (C. Galli, *et al.*, eds.). Raven Press, New York, 1978. Vol. 3, pp. 89-95.
108. Volpe, J. J. and Marasa, J. C.: *Biochim. Biophys. Acta*, 380, 454-472, 1975.
109. Wallner, B. P., Mattaliano, R. J., Hession, C. *et al.*: *Nature*, 320, 77-81, 1986.
110. Warren Levin, S., Butler, J., Schumacher, U. K., Wightman, P. D. and Mukherjee, A. B.: *Life Sci*, 38, 1.813-1.819, 1986.
111. Weber, K. and Johnsson, N.: *Febs Letters*, 203, 95-98, 1986.
112. Weissmann, G. and Thomas, L.: *J. Clin. Invest.*, 42, 661-669, 1963.
113. Yaron, M., Yaron, I., Gurari Rotman, D., Revel, M., Lindner, H. R., Zor, U.: *Nature*, 267, 457-459, 1977.