THE EFFECT OF CYCLIC AMP ON MEMBRANE PERMEABILITY

Joseph S. Handler

Laboratory of Kidney and Electrolyte Metabolism, National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland 20014

It is generally agreed that cyclic AMP is the intracellular mediator of the permeability effects of vasopressin on anuran skin and urinary bladder, and on the mammalian distal nephron (1). The experimental basis for the conclusion (2–4) that the site of the permeability change elicited by the hormone is the cell membrane at the urinary (outer, mucosal, apical) surface of the cell was reviewed. The urinary membrane obviously differs from the cell membrane at the blood (inner, serosal, basal) and lateral surface of the epithelial cell and is a relatively small portion of the total cell membrane, a factor that will make isolation of the urinary membrane difficult. The idea (5) that vasopressin alters a porous barrier in the urinary membrane is supported by four types of experimental observations: 1) Hydraulic conductivity greatly exceeds the diffusional permeability to water in vasopressin-treated anuran skin (5) and urinary bladder (6). 2) Vasopressin causes an increase in pore size of anuran skin estimated by the probing molecule technique (7). 3) There is solvent drag for certain solutes in vasopressin treated skin (8) and urinary bladder (9). 4) In the absence of vasopressin, the activation energy for the diffusion of water across the toad bladder is high, indicating interaction of water molecules with the membrane, whereas the activation energy is low, similar to that of water diffusing in water, in vasopressin-treated bladders (10). Theoretical predictions that unstirred layers of solution adjacent to a membrane can cause quasiporous behavior of a nonporous membrane (11–13) led to the demonstration of such an effect of unstirred layers on thin lipid bilayer membranes (14). Recent reports indicate that when unstirred layers adjacent to the toad bladder and in the stroma of the bladder are minimized by vigorous stirring of the bulk solutions and by other manipulations, the following occur: 1) The diffusional permeability to water of the vasopressin-treated bladder rises markedly; the permeability of the epithelial cell layer of the bladder is estimated to rise even further (15) (hydraulic conductivity is not altered by stirring nor is diffusional permeability to water in the absence of vasopressin). 2) There is no increase in apparent pore size estimated by the probing molecule technique (16). 3) Solvent drag is not demonstrable (17). 4) The activation energy for the diffusion of water across the epithelial cells is estimated to be high (11 kcal/mole) in control and in vasopress-treated bladders (18). These studies and others (19) have led to the interpretation that cyclic AMP does not alter permeability in these tissues by increasing pore size in a rate limiting barrier. It remains to be determined whether water moves across the limiting barrier via aqueous channels or by diffusion through a nonaqueous phase of the membrane.

Journal of Supramolecular Structure
© 1973 Alan R. Liss, Inc., 150 Fifth Avenue, New York, N.Y. 10011

It is reasonable to propose (but far from established) that cyclic AMP alters permability and transport in vasopressin-sensitive tissues by activating cyclic AMP-dependent protein kinase. The enzyme has been found in kidney (20) and in the epithelial cells of anuran urinary bladder (21). Although it has been shown that the enzyme will catalyze the phosphorylation of a membrane-rich fraction prepared from bovine renal medulla (22), and from other tissues (23–25), it remains to be determined whether the urinary membrane is a substrate for the kinase in vivo and what the consequences of such phosphorylation would be. It is possible that cyclic AMP-dependent protein kinase is involved in the permeability effect of cyclic AMP but that other steps are interposed between activation of the kinase and the changes that occur in the urinary membrane that result in the permeability and transport phenomena elicited by cyclic AMP.

REFERENCES

1. Orloff, J., and Handler, J., Amer. J. Med. 42:757–768 (1967).
2. MacRobbie, E. A. C., and Ussing, H. H., Acta Physiol. Scand. 53:348–365 (1961).
3. Peachey, L. D., and Rasmussen, H. J., Biophys. Biochem. Cytol. 10:529–553 (1961).
4. Ganote, C. E., Grantham, J. J., Moses, H. L., Burg, M. B., and Orloff, J., J. Cell Biol. 36:355–367 (1968).
5. Koefoed-Johnsen, V., and Ussing, H. H., Acta Physiol. Scand. 28:60–76 (1953).
6. Hays, R. M., and Leaf, A. J., Gen. Physiol. 45:905–919 (1962).
7. Whittembury, G. J., Gen. Physiol. 46:117–130 (1962).
8. Andersen, B., and Ussing, H. H., Acta Physiol. Scand. 39:228–239 (1957).
9. Leaf, A., and Hays, R. M., J. Gen. Physiol. 45:921–932 (1962).
10. Hays, R. M., and Leaf, A., J. Gen. Physiol. 45:933–948 (1962).
11. Teorell, T., Trans. Faraday Soc. 33:1020–1021 (1937).
12. Dainty, J., Adv. Bot. Res. 1:279–326 (1963).
13. Ginzburg, B. Z., and Katchalsky, A., J. Gen. Physiol. 47:403–418 (1963).
14. Cass, A., and Finkelstein, A., J. Gen. Physiol. 50:1765–1784 (1967).
15. Hays, R. M., and Franki, N. J., Mem. Biol. 2:263–276 (1970).
16. Hays, R. M., Harkness, S. H., and Franki, N., In "Urea and the Kidney," B. Schmidt-Nielsen, (Ed.), Excerpta Media, Amsterdam, p. 149 (1970).
17. Hays, Richard M., "Current Topics in Membranes and Transport," Vol. 3, Academic Press, New York, (1972).
18. Hays, R. M., Franki, N., and Soberman, R., J. Clin. Invest. 50:1016–1018 (1971).
19. Schafer, J. A., and Andreeli, T. E., J. Clin. Invest. 51:1264–1278 (1972).
20. Kuo, J. F., and Greengard, P., Proc. Nat. Acad. Sci., U.S. 64:1349–1355 (1969).
21. Jard, S., and Bastide, F., Biochem. Biophys. Res. Comm. 39:559–566 (1970).
22. Dousa, T. P., Sands, H., and Hechter, O., Endocrinology 91:757–763 (1972).
23. Johnson, E. M., Veda, T., Maeno, H., and Greengard, P., J. Biol. Chem. 247:5650–5652 (1972).
24. Rubin, C. S., and Rosen, O. M., Biochem. Biophys. Res. Commun. 50:421–429 (1973).
25. Guthrow, C. E., Jr., Allen, J. E., and Rasmussen, H. J., Biol. Chem. 247:8145–8153 (1972).