Phosphodiesterase Discoveries

(Laboratory of Benjamin Weiss)

1. First to report on the physical separation of several different forms of phosphodiesterase in mammalian brain:

Uzunov, P. and Weiss, B.: Separation of multiple molecular forms of cyclic adenosine 3',5'-monophosphate phosphodiesterase in rat cerebellum by polyacrylamide gel electrophoresis. Biochim. Biophys. Acta 284:220-226, 1972.

2. First to show that different cell types contain different forms of phosphodiesterase:

Uzunov, P., Shein, H.M. and Weiss, B.: Multiple forms of cyclic 3',5'-AMP phosphodiesterase of rat cerebrum and cloned astrocytoma and neuroblastoma cells. Neuropharmacology 13:377-391,1974.

3. First to show that the different forms of phosphodiesterase can be selectively inhibited by drugs:

Weiss, B.: Selective regulation of the multiple forms of cyclic nucleotide phosphodiesterase by norepinephrine and other agents. In: Frontiers in Catecholamine Research, eds. E. Usdin and S. Snyder, Pergamon Press, New York, pp. 327-333, 1973.

Weiss, B.: Regulation of the multiple forms of cyclic nucleotide phosphodiesterase. Life Sci. 13:R167-R169, 1973.

Weiss, B., Fertel, R., Figlin, R. and Uzunov, P.: Selective alteration of the activity of the multiple forms of adenosine 3',5'-monophosphate phosphodiesterase of rat cerebrum. Mol. Pharmacol. 10:615-625, 1974.

Fertel, R. and Weiss, B.: Properties and drug responsiveness of cyclic nucleotide phosphodiesterases of rat lung. Mol. Pharmacol. 12:678-687, 1976.

Weiss, B. and Fertel, R.: Pharmacologic control of the synthesis and metabolism of cyclic nucleotides. Adv. Pharmacol. Chemotherp. 14:189-283, 1977.

4. **First to suggest that drugs that selectively inhibit phosphodiesterase may be effective therapeutic drugs:**

Weiss, B. and Hait, W.N.: Selective cyclic nucleotide phosphodiesterase inhibitors as potential therapeutic agents. Ann. Rev. Pharmacol. Toxicol. 17:441-477, 1977.

Weiss, B. and Greenberg, L.H.: Physiological and pharmacological significance of the multiple forms of the cyclic nucleotide phosphodiesterase. In: Molecular Biology and Pharmacology of Cyclic Nucleotides, eds. E. Folco and R. Paoletti, Elsevier/North Holland Biomedical Press, pp. 69-84, 1978.

Weiss, B., Prozialeck, W.C. and Wallace, T.L.: Interaction of drugs with calmodulin: Biochemical, pharmacological and clinical implications. Biochem. Pharmacol. 31:2217-2226, 1982.

Weiss, B., Earl, C. and Prozialeck, W.C.: Biochemical and possible neuropsychopharmacological implications of inhibiting calmodulin activity. Psychopharmacol. Bull., 19:378-386, 1983.

Weiss, B., Prozialeck, W.C. and Roberts-Lewis, J.M.: Development of selective inhibitors of calmodulin-dependent phosphodiesterase and adenylate cyclase; in Design of Enzyme Inhibitors as Drugs, ed. M. Sandler and H.J. Smith, Oxford University Press, New York, pp. 650-697, 1989.

5. First to show that phosphodiesterase activity is altered in disease states:

Hait, W.N. and Weiss, B.: Increased cyclic nucleotide phosphodiesterase activity in leukemic lymphocytes. Nature 259:321-323, 1976.

Hait, W.N. and Weiss, B.: Characteristics of the cyclic nucleotide phosphodiesterases of normal and leukemic lymphocytes. Biochim. Biophys. Acta 497:86-100, 1977.

Levin, R.M. and Weiss, B.: Characteristics of the cyclic nucleotide phosphodiesterases in a transplantable pheochromocytoma and adrenal medulla of the rat. Cancer Res. 38:915-920, 1978.

Weiss,B. and Winchurch, R.A.: Analyses of cyclic nucleotide phosphodiesterases in lymphocytes from normal and aged leukemic mice. Cancer Res. 38:1274-1280, 1978.

Winchurch, R., Hait, W. and Weiss, B.: Cyclic AMP phosphodiesterase activity of murine T and B lymphocytes. Cell. Immunol. 41:421-426, 1978.

Hait, W.N. and Weiss, B.: Cyclic nucleotide phosphodiesterase of normal and leukemic lymphocytes: kinetic properties and selective alteration of the activity of the multiple molecular forms. Mol. Pharmacol. 16:851-864, 1979.

6. First to show that a single cell type may contain more than one form of phosphodiesterase:

Uzunov, P., Shein, H.M. and Weiss, B.: Cyclic AMP phosphodiesterase in cloned astrocytoma cells: norepinephrine induces a specific enzyme form. Science 180:304-306, 1973.

Uzunov, P., Shein, H.M. and Weiss, B.: Multiple forms of cyclic 3',5'-AMP phosphodiesterase of rat cerebrum and cloned astrocytoma and neuroblastoma cells. Neuropharmacology 13:377-391,1974.

7. First to show that the different forms of phosphodiesterase can be selectively induced:
Uzunov, P., Shein, H.M. and Weiss, B.: Cyclic AMP phosphodiesterase in cloned astrocytoma cells: norepinephrine induces a specific enzyme form. Science 180:304-306, 1973.

8. First to show that the different forms of phosphodiesterase can be selectively activated:
Weiss, B.: Differential activation and inhibition of the multiple forms of cyclic nucleotide phosphodiesterase. Adv. Cycl. Nucl. Res. 5:195-211, 1975.

9. First to report on the ontogenetic development of the different forms of phosphodiesterase and its endogenous activator:
Strada, S.J., Uzunov, P. and Weiss, B.: Ontogenetic development of a phosphodiesterase activator and the multiple forms of cyclic AMP phosphodiesterase of rat brain. J. Neurochem. 23:1097-1103, 1974.

10. First to show the mechanism by which drugs may selectively alter phosphodiesterase activity:
Levin, R.M. and Weiss, B.: Mechanism by which psychotropic drugs inhibit adenosine cyclic 3',5'-monophosphate phosphodiesterase of brain. Mol. Pharmacol. 12:581-589, 1976.

Levin, R.M. and Weiss, B.: Binding of trifluoperazine to the

calcium-dependent activator of cyclic nucleotide phosphodiesterase. Mol. Pharmacol. 13:690-697, 1977.

Levin, R.M. and Weiss, B.: Specificity of the binding of trifluoperazine to the calcium-dependent activator of phosphodiesterase and to a series of other calcium-binding proteins. Biochim. Biophys. Acta 540:197-204, 1978.

Weiss, B. and Levin, R.M.: Mechanism for selectively inhibiting the activation of cyclic nucleotide phosphodiesterase and adenylate cyclase by antipsychotic agents. Adv. Cycl. Nucl. Res. 9:285-304, 1978.

Levin, R.M. and Weiss, B.: Selective binding of antipsychotics and other psychoactive agents to the calcium-dependent activator of cyclic nucleotide phosphodiesterase. J. Pharmacol. Exp. Ther. 208:454-459, 1979.

Weiss, B., Prozialeck, W., Cimino, M., Barnette, M.S. and Wallace, T.L.: Pharmacological regulation of calmodulin. In: Calmodulin and Cell Functions, Ann. N.Y. Acad. Sci. 356:319-345, 1980.

Weiss, B., Prozialeck, W.C. and Wallace, T.L.: Interaction of drugs with calmodulin: Biochemical, pharmacological and clinical implications. Biochem. Pharmacol. 31:2217-2226, 1982.

Prozialeck, W.C. and Weiss, B.: Inhibition of calmodulin by phenothiazines and related drugs; structure-activity relationships. J. Pharmacol. Exptl. Therap. 222:509-516, 1982.

Sellinger-Barnette, M. and Weiss, B.: Interaction of beta-endorphin and other opioid peptides with calmodulin. Mol. Pharmacol. 21:86-91, 1982.

Prozialeck, W.C. and Weiss, B.: Inhibition of calmodulin by phenothiazines and related drugs; structure-activity relationships. J. Pharmacol. Exptl. Therap. 222:509-516, 1982.

Barnette, M.S. and Weiss, B.: Interaction of neuropeptides with calmodulin. A structure-activity study. Psychopharmacol. Bull., 19:387-392, 1983.

In sum, Weiss' laboratory showed that there are different forms of cyclic nucleotide phosphodiesterases in mammalian tissue, that these different forms of the enzyme are differentially distributed in the various tissue and that the different phosphodiesterases are selectively regulated by endogenous compounds and exogenous pharmacologic agents. As cyclic nucleotides play an important and varied role in biological processes, these studies suggested that the selective activation or inhibition of these enzyme forms could comprise a novel means of altering biological processes. Indeed, the selective inhibition of the different phosphodiesterases have now formed the basis for a new, important class of pharmacologic agents, ones that have been shown to treat a number of diseases.