62. SUTHERLAND, E. W. AND CORI, C. F.: Influence of insulin preparations on glycogenolysis in liver slices. J. biol. Chem. 172: 737-750, 1948.
63. SUTHERLAND, E. W. AND CORI, C. F.: Effect of hyperglycemic-glycogenolytic factor and epinephrine on liver phosphorylase. J. biol. Chem. 188: 531-543, 1951.
64. SUTHERLAND, E. W. AND RALL, T. W.: Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. J. biol. Chem. 232: 1077-1091, 1958.
65. WEBB, J. L. AND HOLLANDER, P. B.: The action of acetylcholine and epinephrine on the cellular membrane potentials and contractility of rat atrium. Circulation Res. 4: 332-336, 1956.
66. WEST, T. C., FALK, G. AND CERVONI, P.: Drug alteration of transmembrane potentials in atrial pacemaker cells. J. Pharmacol. 117: 245-252, 1956.
67. WOSILAIT, W. D. AND SUTHERLAND, E. W.: The relationship of epinephrine and glucagon to liver phosphorylase. II. Enzymatic inactivation of liver phosphorylase. J. biol. Chem. 218: 469-481, 1956.

DISCUSSION

THE RECEPTORS FOR EPINEPHRINE AND NOREPINEPHRINE

R. P. AHLQUIST

Medical College of Georgia, Augusta, Georgia

Dr. Furchgott has described several theories regarding the general nature of the adrenergic receptors. Most of these theories have been developed from observations of differential effector responses to one or more adrenergic substances, administered exogenously or caused to appear endogenously. These methods are limited primarily by the uncertainty of the exact relationship between the observed gross response and the effector response at the cellular level.

It might be of interest to present briefly the unpublished observations that led to the development of one of the current theories of adrenergic receptors. In a search for a substance that would effectively prevent the spasmogenic action of vasopressin on the myometrium, we studied several compounds related chemically to epinephrine. Although none was found suitable, some were noted to have effects that seemed contradictory to our naive ideas of the general relationship between chemical structure and adrenergic action. Phenylephrine was found to relax effectively the ileum, both intact and isolated; dioxyephedrine (*alpha*-methylepinephrine), an active depressor amine, was found to have relatively little activity as far as gut relaxation was concerned; and isoproterenol could induce contraction of the isolated rabbit myometrium. We were also surprised that racemic arterenol was less effective as a vasoconstrictor than racemic epinephrine. A systematic, comparative study of other adrenergic drugs suggested the following relatively simple postulate.

Consider a series of amines closely related to epinephrine and call them compounds A, B, C and D. If in this series the order of relative activity is the same on all structures having adrenergic receptors (for example, A > B > C > D on the smooth muscle of blood vessels, the gut, uterus, nictitating membrane, etc.), then the differences in activity could be due entirely to the differences in chemical structure. If, however, the order of activity varies from structure to structure (for example, A > B > C > D on blood vessels; D > C > B > A on gut; C > D > A > B on uterus), then these variations in relative activity must be due in part to actual differences in the receptors involved.

As we later published, only two orders of relative activity for the common catecholamines were found if the adrenergic effector responses were considered in the broadest sense and if some apparent species variations were disregarded. Another fundamental assumption had to be made: that all of the catecholethanolamines acted on the receptors in a manner at least qualitatively similar to epinephrine.

If it is true that the differences in effector response to various catecholamines are due to differences in receptors, then the simplest theory suggests that there are only two kinds

of receptors. The alternative theory must be, then, that each effector has its own unique receptor mechanism. Evidence based on differential effector response and the effect of adrenergic blocking agents can be adduced for either theory. In our opinion the greater weight must be given to the dualistic receptor theory.

The two effector organs that have caused the greatest controversy are the heart and gut; at present we are investigating the latter. We hope soon to publish our results that, unfortunately, can be interpreted as proof that the gut receptor is *alpha*, in our terminology, or *beta*, or something entirely different. However, since experimental design, deliberate or unconscious, can produce results that will support almost any theory it is obvious that we will favor our previous ideas and continue to support the proposition that the adrenergic receptor of the gut is closely related to the receptor for vasoconstriction.[1]

[1] *Author's note:* Since this discussion was presented further studies in this laboratory have indicated that the ileum of the dog has both *alpha* and *beta* receptors, both of which subserve relaxation and inhibition.