pronounced in SCS cells with prominent diastolic depolarization. These observations could be accounted for by a specific increase in K^+ conductance in cells in which the K^+ equilibrium potential is less than maximal diastolic potential. (Supported by U.S. Public Health Service Grants HE 08372-02, HE 05435-05, and MH 3477.)

46. Synthesis of New Isomers of Bradykinin. K. VOGLER (*Hoffmann-LaRoche, Inc., Basle, Switzerland*).

In this study the synthesis of new isomers of the natural hormone containing D-amino acids is reported. Both all-D-bradykinin and all-D-retro-bradykinin were obtained in a pure state. The former represents the first synthetic antipode of a polypeptide hormone. The biological properties of these new compounds are discussed in the light of stereochemical considerations.

47. Demonstration of the Presence in Human Plasma of Two Separate Kinin-Forming Systems. W. VOGT (*Medizinische Forschungsanstalt der Max Planck Gesellschaft, Göttingen, Germany*).

It is well established that human plasma contains plasma kallikrein which, by acting on "kininogen", liberates plasma kinin. In addition another kinin-forming enzyme is present for which the term "kininogenase II" is suggested. It acts specifically on a substrate different from that utilized by kallikrein. This substrate (kininogen II) is not attacked by plasma kallikrein (suggested name "kininogenase I") or by pancreas kallikrein or trypsin. Kininogenase II is present in plasma as an inactive precursor and is activated by trypsin or by contact with glass. Active kininogenase II activates kininogenase I and hastens the subsequent destruction of the latter in plasma.

It seems likely that kinonogenase I is not activated by glass contact (or by Hageman factor) directly, but only through activation of kininogenase II. This would explain why dog plasma cannot be induced to form kinins on contact with glass. Dog plasma contains kininogenase I but practically no kininogenase II. In contrast, rat plasma contains only the kinin-forming system II. It is therefore a poor substrate for trypsin but well activated by contact with glass.

After glass activation of human plasma (B-depletion) kininogenase II and kininogen I are left, kininogenase I being inactivated and kininogen II being used up. For this reason in such plasma no kinin can be formed on further incubation, although by different methods an enzyme as well as a substrate can be demonstrated.

48. Polypeptide Receptor Mechanisms; Influence of pH and Heat. EDWARD J. WALASZEK and DONALD C. DYER (*Dept. of Pharmacology, Kansas Univ. Medical Center, Kansas City, Kans., U.S.A.*).

The biological testing of polypeptides was carried out on the isolated guinea pig ileum in a modified Tyrode's solution at 35°. The effect of pH was studied on the contractile potency of four polypeptides: bradykinin, eledoisin, angiotensin, and substance P. The solution used was Tyrode's without $NaHCO_3$, the pH of the solution adjusted with 0·1 N HCl or 0·1 N NaOH. The pH values were varied from 5 to 10. When bradykinin, eledoisin, and angiotensin were tested together, a clear dichotomy could be seen: at low pH eledoisin was least potent, whereas bradykinin was the most potent, peptide. As the pH was increased eledoisin increased in potency very markedly, while bradykinin declined in potency. Angiotensin tended to remain reasonably constant. It was sometimes found that at pH 10 bradykinin had no effect, whereas eledoisin was still very active. We suggest that it is possible to differentiate eledoisin from bradykinin by this procedure. It would appear that the positive charge is more important for bradykinin activity than it is for eledoisin activity. This could then be interpreted that they are acting on two different receptors. Substance P resembled eledoisin in these studies.

In another phase of this study the effect of heat on actions of different polypeptides on the guinea pig ileum were observed. These results will be reported in detail.

49. The Physiological and Pathological Role of the Kallikrein–Kallidin System. MARION E. WEBSTER (*Laboratory of Cardiovascular Physiology, National Heart Institute, Bethesda, Md., U.S.A.*).

The biochemical characterization of the kallikrein–kallidin system has led to speculation that the endogenous release of these powerful vasodilator polypeptides may play a role in regulating local blood flow. Infusion of the polypeptides directly into the kidney, coronary circulation, skeletal muscle, etc., is associated with an increase in blood flow independent of any systemic effects. The demonstration, however, that infusion of a naturally occurring substance can influence local blood flow, does not necessarily indicate that it alters blood flow under physiological conditions. Thus, for example, the vasodilatation produced in skeletal muscle by muscle contraction, arterial occlusion, and lumbar cholinergic sympathetic nerve stimulation is not altered in the presence of carboxypeptidase B, although that produced by infused kallidin is effectively blocked. The kallidins, therefore, do not appear to contribute to the vasodilatation seen under these conditions.

However, activation of the kallikrein–kallidin system may be important in the etiology of three pathological conditions: (1) hereditary angioneurotic edema, which is associated with an inherited deficiency of a serum inhibitor to plasma kallikrein; (2) flushing in patients with carcinoid syndrome, which is associated with an elevation of blood kallidin; and (3) arthritides of various etiologies, in which kallidin levels are increased in synovial fluid.

50. The Role of Release of Acetylcholine in the Gut-Contracting Action of a Polypeptide from Brain. G. ZETLER (*Dept. of Pharmacology, Univ. of Kiel, Germany*).

Crude substance P preparations from cattle brain were separated by aluminum oxide chromatography into three pharmacologically active fractions (F_a, F_b, F_c). The active principles of these fractions lose their biological activity during incubation with chymotrypsin and are therefore probably polypeptides. F_a and F_b are of basic nature; they cause relatively fast smooth-muscle contractions and lower the blood pressure of the atropinized rabbit. F_c, however, is acidic, and resistant to trypsin. It causes a slow kinin-like contraction of the guinea pig ileum and is inactive on the atropinized rabbit blood pressure. On the isolated guinea pig ileum, F_c can easily be differentiated from F_a, F_b, and bradykinin, for its action is antagonized by morphine (10^{-9}- g/ml), atropine (10^{-8}- g/ml), and cocaine (10^{-5} g/ml), but enhanced by eserine (5×10^{-8}- g/ml). Higher concentrations of these drugs have only a very weak, if any, influence on the actions of F_a, F_b, and bradykinin. In the presence of F_c but not of F_b the isolated gut releases an increased amount of an active material, which stimulates the dorsal muscle of the leech and is antagonized by *d*-tubocurarine (5×10^{-6} g/ml). It is concluded that the polypeptide of fraction F_c releases acetylcholine from the postganglionic neurons in the intestinal wall.

51. Microcirculatory Action of Polypeptides. B. W. ZWEIFACH (*Dept. of Pathology, New York Univ. Medical Center, New York, N.Y., U.S.A.*).

A study was made of the vasoactive properties of polypeptides of biological origin together with some synthetic analogues. Vascular behavior was studied by direct microscopy of the mesentery in the rat and rabbit with the test substances added locally or intra-arterially into the mesenteric artery. The substances studied included bradykinin, substance P, angiotensin, vasopressin, eledoisin, PLV2, and a polypeptide from lysosomal granules. Constrictor and potentiating actions of the peptides directly were compared with their effects on the vascular response to catecholamines, serotonin, and histamine. The effects on vascular smooth muscle were not related to the permeability-increasing action of these principles. Some of the peptides such as bradykinin and vasopressin had a synergistic effect on small blood vessels in the presence of other vasoactive agents such as serotonin.

Although polypeptides have a direct effect on vascular endothelium, they also act indirectly through the release of other vasoactive agents. Their role in the genesis of tissue injury will be discussed on the basis of their locus of action in the terminal vascular bed.