Meetings

Hypotensive Peptides

Bradykinin, kallidin, eledoisin, physalaemin, substance P, gastrin, and some related substances were discussed at an international symposium on hypotensive peptides, held in Florence, Italy, 25–29 October 1965.

For the sake of convenience, the nonapeptide bradykinin and its decapeptide analog, kallidin, which stimulate smooth muscles, are somewhat inaccurately called plasma kinins. In the same vein, the plasma globulin precursor of kinins is called kininogen, and enzymes that release kinins such as kallikrein are called kininogenases. Eledoisin and physalaemin, which occur in some nonmammalian tissues, are among the most potent vasoactive peptides. Substance P is a peptide obtained chiefly from brain or gut.

The organic chemists opened the meeting. R. B. Merrifield (Rockefeller University) described the synthesis of the heptadecapeptide, angiotensinyl-bradykinin, by means of his automated, solid-phase method. The product of this coupling of a hypertensive with a hypotensive peptide was synthesized in 3 days. The same method was used by J. M. Stewart (Rockefeller University) to obtain most of his 46 analogues of bradykinin.

V. Erspamer (University of Parma), with the cooperation of A. Anastasi's biochemical and M. Bernardi's organic chemical group (Farmitalia), dealt with peptides of nonmammalian origin. In agreement with the finding of Lübke and Schröder (Schering, Berlin) many of the shorter analogs of the undecapeptides eledoisin and physalaemin are as active as or even more active than their parent compounds. That substance P may be related to eledoisin is suggested by the fact that 10 out of 11 amino acids of eledoisin are present in substance P. Most derivatives of peptides remain active when structural changes are introduced at the NH_2-terminal end. However, the derivatives become inactive when the COOH-terminal end is modified. In contrast, phyllokinin from amphibian skin has the structure of bradykinin plus two additional amino acids (isoleucine and tyrosine-*o*-sulfate) at the COOH-terminal end, but it is more hypotensive than bradykinin. J. L. Prado (Escola Paulista, São Paulo) and J. J. Pisano (NIH) analyzed one of the peptides that occur in a wasp venom. It is probably identical with Gly^1-kallidin, previously synthesized by Schröder.

E. Werle (University of Munich) indicated that the amino acid composition of a kinin which is released in the plasma of birds (ornitho-kinin) is different from mammalian kallidin.

J. Spragg and K. F. Austen (Harvard University) prepared H^3-acetyl bradykinin. The labeled peptide was bound to specific antibradykinin antibody. Replacements of labeled bradykinin in the complex with unlabeled peptide offers a sensitive method for measuring bradykinin.

Pepsin can break down bradykininogen to smaller, but still active, fragments (E. Habermann, University of Würzburg). One of these derivatives of kininogen has the sequence of Met-Lys-bradykinyl-Ser-Val-Glu-NH_2, as confirmed by synthesis by Schröder. Enzymes can release bradykinin or kallidin from this substrate.

W. Vogt (Max Planck Institute, Göttingen) described the existence of two separate, parallel kininogen-kinin systems in blood plasma of man and some animals.

E. G. Erdös and H. T. Yang (University of Oklahoma) found several enzymes that inactivate bradykinin in the microsomal fraction of the homogenized kidney. Two enzymes were partially purified from swine kidney cortex. One of them is a carboxypeptidase. Another, the most active one, inactivates bradykinin and some of its derivatives by cleaving the Pro^7-Phe^8 bond in the peptide. Repeated intravenous administration of purified pancreatic carboxypeptidase B blocks the effects of bradykinin in the cat for hours. A catheptic enzyme which can release a kinin from kininogen was extracted from leukocytes and from spleen by L. M. Greenbaum (Columbia University).

E. J. Walaszek (University of Kansas) can differentiate among the actions of various peptides by shifting the *p*H of the bath fluid of the isolated smooth muscle organ used for bioassay. He correlated the results with the ionization of some receptor sites.

Because kininogen occurs in relatively large quantities in blood and bradykinin has a variety of actions, the search is on to ascribe a physiological role to the kinin-kallikrein system and to explain some pathological conditions with the presence of the peptides or releasing enzymes. M. E. Webster (NIH) excluded the possibility that kallidin plays an important role in decreasing the vascular resistance which follows muscle contraction. She infused dogs with carboxypeptidase B to block the effect of kallidin, but this treatment did not influence the decrease in vascular resistance caused by a still-unknown factor.

M. Schachter (University of Alberta) and S. M. Hilton (University of Birmingham) continued their debate on whether or not the kallikrein-kallidin system is responsible for the vasodilatation in a salivary gland which follows the stimulation of the chordalingual nerve. Some investigators supported Schachter's negative conclusions.

Many participants discussed the various cardiovascular, vasodilator effects of the peptides, but some investigators (P. Guth, Tulane University and T. Shimamoto, Tokyo Medical University) stressed the importance of venoconstriction caused by bradykinin. Shimamoto correlates this action with the subsequent development of arteriosclerosis. He reports favorable results in patients treated with a new drug which blocks this venoconstriction.

According to F. Sicuteri (University of Florence), in myocardial infarction released serotonin may sensitize to bradykinin, and thus contribute to pain. In subarachnoid hemorrhage, the release of a kinin upon dilution of the blood in cerebrospinal fluid may also explain the accompanying intense pain.

Plasma fractions given in infusion sometimes contain a large amount of active kallikrein that could account for

side effects. In gouty arthritis urate crystals may adsorb Factor XII and thus trigger the release of bradykinin and aggravate symptoms (V. Eisen and C. A. Keele, Middlesex Hospital). I. Trautschold (University of Munich) attributed the beneficial effects of proteolytic inhibitor Trasylol in pancreatitis to the inhibition of serum kallikrein or to the inhibition of the activation of serum kallikrein. He also proposed a new unit for kallikrein activity.

Investigators tried to solve the problem of amino acid sequence of the substance P and to analyze its effect on the central nervous system. H. Meinardi and L. Craig (Rockefeller University) found in goat hypothalamus a good source of the peptide. Contrary to earlier reports, substance P is a pure peptidic material, possibly containing two or three different peptides. G. Zetler (University of Lübeck) discovered a peptide component in the substance which contracts smooth muscles by releasing acetylcholine.

Scientists of 14 countries participated in the meeting, which was sponsored by the University of Florence and by the State University of New York at Buffalo and supported by various pharmaceutical houses. F. Sicuteri and E. G. Erdös were cochairmen.

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Information and Control Processes in Living Systems

"Aids to biological communication: prosthesis and synthesis" was the theme at the second of a projected series of conferences on information and control processes in living systems held in Pacific Palisades, California, 27 February–2 March 1966.

Otto H. Schmitt (University of Minnesota) introduced the discussion of input-output relations in man-machine systems by suggesting that we are limited in the prosthesis and synthesis of human cognition of our own available figures of thought and stereotyped modes of perception. He emphasized the intellectual tyranny imposed by our notions of analog versus digital as a logical dichotomy in representing sensory information. He pointed out that it is quite possible for a bivalent system to make use of both forms of data representation interchangeably.

Marvin Minsky (Massachusetts Institute of Technology) offered the view that there was an even worse tyranny in biological computation, where the notion of analog processes had blurred differences between the concepts of "numeral" and "number." Either can deal with continuous variables. It is important to ask whether the biological problem resembles numeral processes in their information content or numbers in their formulation of magnitude.

For purposes of data compression Schmitt described a scheme for recording only the times at which a function changed significantly in an increasing or decreasing fashion, thus acheiving as much as a 100-to-1 data reduction. He also offered the view that we need to reevaluate man-machine coding relation currently in use. Our traditional use of the base 10 probably is the best way of encoding information for machine use. Possibly an octal representation would have more advantages for arithmetic operations in both the man and the machine. In exploring the concept of a spatially distributed transmission function, Schmitt suggested more extensive consideration of the nature of information transforms in a multidimensional space with special reference to significance to temporal factors. The time domain, for example, may be used to indicate only transitions from one state to another, and thus to draw attention to significant trends or altered states. Antoine Remond's (Hôpital de la Salpetrière, Paris) chronograms involve analyses and displays in accordance with this concept.

In discussing the role of heuristics in biological communication, Arthur L. Samuel (International Business Machines Corp.) suggested that, in attempting to model the brain, it may be more fruitful to abandon any descriptions of human behavior as a basis for stimulation of cognitive functions. It is possible to develop logical game-playing computer programs without taking into account the way in which humans may play these same games. He offered the view that computers can act as ancillary memories for humans and can serve as mnemonic aids. The search strategies employed by humans in playing games such as checkers can only be simulated economically on a computer through the use of techniques for pruning nonprofitable branches of the search tree structure such as that afforded by the Alpha-Beta heuristic.

Ruth M. Davis (Department of Defense) reviewed the history of sensorimotor automata that exhibited goal-seeking behavior. These early devices had both photo and tactile sensors. Most of the development of automata since 1961 has been theoretical, however. Warren S. McCulloch (Massachusetts Institute of Technology) described a visual sensor that his group is developing which weighs 0.7 kilogram and occupies the space of a 15-centimeter cube. He noted that this reduction in size of hardware is a very important aspect of developing artificial automata. He pointed out that the neural membrane in the ganglion cells of *Aplysia*, the California sea slug, have a capacitance on the order of 40 microfarads per square centimeter, and its physical stimulation is proving extremely difficult. Minsky remarked that increased miniaturization of circuit components is inherently associated with increased computational speeds. This was supported by Walter L. Wasserman (Philco Corp.) who noted that miniaturization is vitally important in any practical prosthesis for man. There was general agreement that any successful stimulation of an automation must take into account feedback from the environment. Remond introduced material on what he described as a typical visual automation. In the human electroencephalogram, lambda potentials appear after the gaze is shifted and might thus act as a substrate for altered cortical excitability associated with deflection of the gaze. Seymour Papert (Massachusetts Institute of Technology) thought these were merely transients and that the true transaction of visual information occurs later. Robert Galambos (Yale University) emphasized the need for studies in ontogeny to improve our understanding of "programming" in the human subject as the basis for known aspects of innate behavior.

V. A. Koshevnikov (Pavlov Institute of Physiology, Leningrad, U.S.S.R.) described in detail a model of speech perception and production formulated in his laboratory which involved the cochlea as an analyzer. The next level of sensory pathways was represented by a matrix of 28 bandpass filters. These filters interacted with linguistic and semantic analyzers and with genera-