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(Abstract)

HORMONES OF THE POSTERIOR PITUITARY

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Since the discovery of the blood pressure-raising activity of extracts of the posterior pituitary gland by Oliver and Schafer in 1895, numerous biological activities have been found to be associated with this gland. These include the contraction of the uterus—the so-called oxytocic action, noted by Dale in 1905—the antidiuretic activity, the milk let-down activity, and the avian vasodepressor activity. With the knowledge of these actions, it became of considerable interest to determine the nature of the active principle or principles in the posterior pituitary.

Beginning with the early part of this century, attempts were made by various investigators to isolate the principle or principles in pure form. In the late 1920's Kamm and co-workers effected extensive purification of the posterior pituitary material and were able to obtain fractions highly potent in pressor activity with very little oxytocic activity and *vice versa*.

The studies carried out by the author and his associates on the posterior pituitary hormones date back to 1932, when these hormones were studied as an outgrowth of some researches on the chemistry of insulin. The methods employed in the studies prior to 1942 involved mainly electrophoretic techniques and those in the later studies, countercurrent distribution. As a result of the countercurrent distribution studies, highly purified preparations of the oxytocic hormone, oxytocin, and the pressor-antidiuretic hormone, vasopressin, were obtained. The oxytocin was obtained in crystalline form as a flavianate, representing the first isolation of this principle as a crystalline derivative. Hydrolysis of oxytocin showed it to contain eight amino acid residues, namely leucine, isoleucine, tyrosine, proline, glutamic acid, aspartic acid, glycine, and cystine, in equimolar ratios to each other and ammonia in a molar ratio of three to any one amino acid. Vasopressin from beef glands was shown to have the same constituents except that leucine and isoleucine were absent and phenylalanine and arginine were present. The vasopressin isolated from hog glands was found to differ from that isolated from beef glands in that the hydrolysate contained lysine in place of arginine. No difference was detected in the oxytocins derived from beef and hog glands.

With these purified preparations, it has been shown that oxytocin possesses oxytocic activity on the isolated rat uterus, avian vasodepressor activity and a highly potent milk-let-down activity. It has also been demonstrated that this preparation of oxytocin possesses slight but definite pressor and antidiuretic

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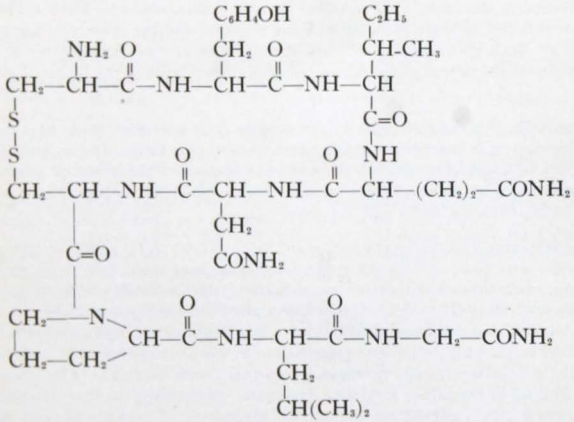
activity. The vasopressin possesses both pressor and antidiuretic activities. In addition, vasopressin has been shown to possess milk-let-down activity, avian vasodepressor activity, and oxytocic activity to a considerably less degree than that exhibited by oxytocin.

After the determination of the amino acid composition, the next step was to find out how the individual amino acids and ammonia were linked together to form the respective hormones. Degradative studies of oxytocin, including oxidation with performic acid, desulfurization with Raney nickel, determination of terminal groups, cleavage with bromine water, determination of sequence of amino acids by Edman degradation and partial hydrolysis with acid, led to the postulation of the following structure for the hormone.



Degradative studies on arginine-vasopressin resulted in the postulation of a similar type of structure for arginine-vasopressin, with phenylalanine replacing isoleucine in the ring and arginine replacing leucine in the side chain. The work on lysine-vasopressin indicated that it possessed a structure parallel to that of arginine-vasopressin, with lysine replacing arginine in the side chain.

As the final step in the determination of the structure of oxytocin, its synthesis was undertaken. This was accomplished by coupling N-carbobenzoxy-S-benzyl-L-cysteinyl-L-tyrosine with the heptapeptide amide L-isoleucyl-L-glutaminyl-L-asparaginyl-S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide, prepared in turn from tosyl-L-isoleucyl-L-glutaminyl-L-asparagine and the tetrapeptide amide S-benzyl-L-cysteinyl-L-prolyl-L-leucylglycinamide; the resulting protected nonapeptide amide was reduced in sodium-liquid ammonia and converted to the cyclic disulfide by aeration in aqueous solution. The synthetic octapeptide amide was compared with natural oxytocin as to potency, specific rotation, partition co-

efficients, amino acid composition, electrophoretic mobility, infrared pattern, molecular weight, enzymatic and acid inactivation, chromatography on the resin IRC-50, and cleavage with bromine water. The synthetic material and natural oxytocin were also compared with respect to milk ejection and induction of labor in the human as well as rat uterus contraction *in vitro*. Crystalline flavianates prepared from the synthetic material and from natural oxytocin were found to have the same crystalline form, melting point, and mixed melting point. All of these comparisons afforded convincing evidence of the identity of the synthetic product with natural oxytocin. This synthesis thus constitutes the first synthesis of a polypeptide hormone.

Comparable approaches to the synthesis of lysine-vasopressin and arginine-vasopressin have yielded encouraging results.