LETTER TO THE EDITOR

Prediction of α-Helices in Glucagon

Dear Sir:

In an earlier article (Schiffer and Edmundson, 1967) we described the use of helical wheels to predict which segments in a protein have α-helical potential. Alternative methods for such predictions (Schiffer and Edmundson, 1967; Prothero, 1966; Low, Lovell, and Rudko, 1968; Kotelchuck and Scheraga, 1969) have been compared for globular proteins for which the three-dimensional structures are known. In the present communication this comparison is extended to the peptide hormone, glucagon, which has 29 amino acid residues (Bromer, Sinn, and Behrens, 1957).

King (1965) proposed that glucagon was α-helical in crystals. From optical rotatory dispersion data and concentration-difference spectra, Blanchard and King (1966) concluded that the hormone also existed as associated helical molecules in concentrated solutions. When the solutions were diluted, the peptide dissociated into molecules of the random-coil type. Blanchard and King (1966) interpreted the results as evidence that the α-helices were labile in isolation but were stabilized by hydrophobic interactions between different molecules in the associated forms (probably trimers). This interpretation was supported by the observed stabilization of glucagon crystals by electrolytes. Moreover, the crystals were destroyed with organic solvents like 20% methanol, which is believed to decrease hydrophobic interactions.

Haugen and Lipscomb (1969) are currently determining the three-dimensional structure of glucagon by X-ray diffraction methods. At the Eighth International Congress of Crystallography, Lipscomb reported that the peptide is 75% helical, with two sections of helix. The C-terminal hexapeptide segment is not helical.

The wheels for the two helical segments we predict are shown in Fig. 1. The two helices have to be separate by our criteria, which include the necessity for hydrophobic residues to be located on one side of the wheel in an $n, n \pm 3, n \pm 4$ distribution. These residues, which are circled in Fig. 1, form a hydrophobic arc. The length of the segment connecting the helices cannot be accurately predicted, but the residues involved are probably derived from the group of Asp-15, Ser-16, Arg-17, and Arg-18 (numbered as in the linear sequence). These correspond to the last two residues in the first helix and the first two residues in the second helix depicted in Fig. 1.

A continuous helix encompassing residues 5–28 is not permitted under our rules because this group of polar side chains would interrupt the hydrophobic arc in the middle. A wheel for such a continuous helix is illustrated in Fig. 2.

Predictions based on four different methods (Schiffer and Edmundson, 1967; Prothero, 1966; Low et al., 1968; Kotelchuck and Scheraga, 1969) are presented in Table I. Our results

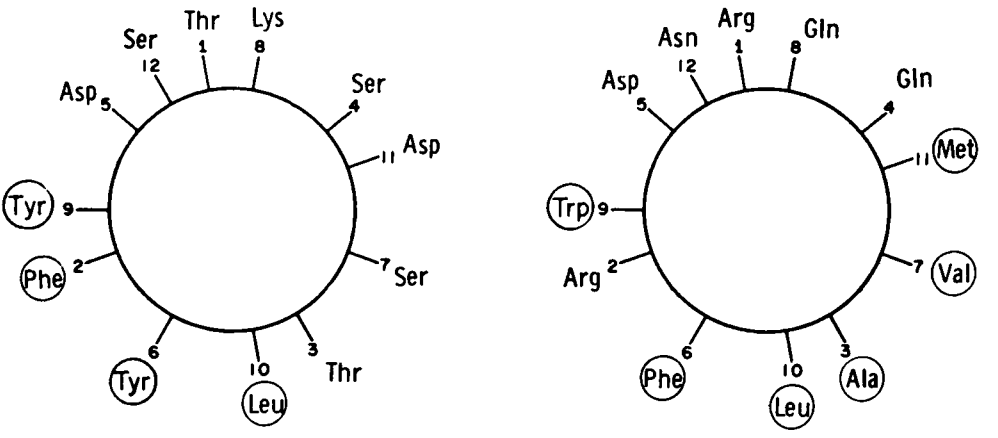

FIGURE 1 Helical wheels for porcine glucagon. The sequences (Bromer et al., 1957) are plotted on wheels which are projections of the amino acid side chains onto planes perpendicular to the long axes of α-helices (Schiffer and Edmundson, 1967). The external spokes of the wheel corresponds to the side chains, and the perimeter of the circle represents the backbone of the polypeptide chain. Adjacent side chains in the sequences are separated by 100° of arc on the wheels. Abbreviations for hydrophobic residues are circled.

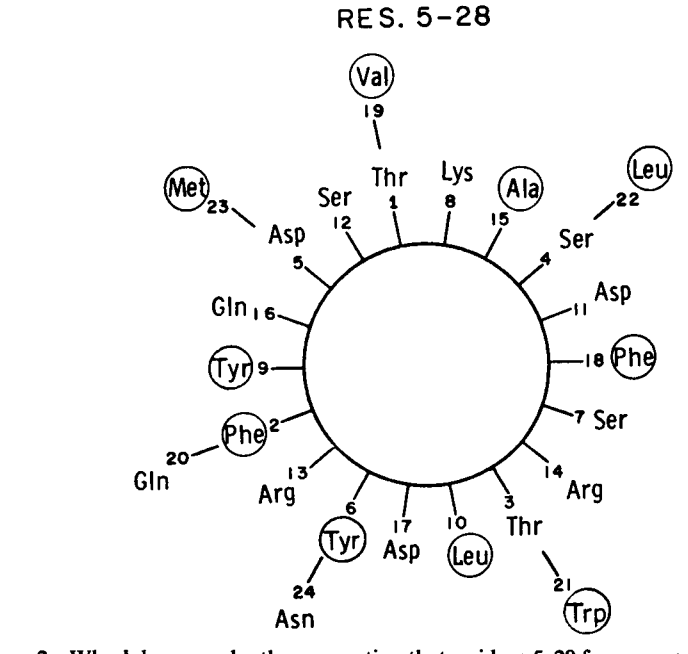

FIGURE 2 Wheel drawn under the assumption that residues 5–28 form one continuous helix. Note the two hydrophobic arcs on opposite sides of the wheel.

TABLE I

COMPARISON OF PREDICTIONS OF α-HELICES IN GLUCAGON

Authors	Helical segments		% helix
Prothero	None		0
Low, Lovell, and Rudko	None		0
Kotelchuck and Scheraga	—	17–27	38
Schiffer and Edmundson	5–16	17–28	83

are in closer agreement with the X-ray structure than the alternative procedures, although we do include five of the last six residues in our second proposed helix.

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