Neuropeptide Y (NPY) belongs to the pancreatic polypeptide fold (PP-fold) family of regulatory peptides. Analysis of circular dichroic spectra of NPY showed that it has a high degree of secondary structure in aqueous solution which is in agreement with the globular, folded crystal structure of PP. Using three different approaches with synthetic peptides, we have probed the importance of the PP-fold structure in the interaction of NPY with two types of binding sites, Y₁ and Y₂ receptors. First, stepwise construction of the NPY molecule from the C-terminal amidated end, showed that although C-terminal fragments encompassing most of the long α-helix reacted reasonably well with the Y₂ receptor, both Y₁ and Y₂ receptors required the presence of both ends of the PP-fold for full activity. Second, perturbation of the PP-fold by substitution with a helix-breaking proline residue, resulted in the loss of recognition of the N-terminal segment of the molecule by both types of receptors. Finally, a hybrid analog was constructed in which the essential, but by itself inactive, C-terminal segment of NPY was joined with the PP-fold motif of PP. This segment of PP is only 43% homologous to the similar motif in NPY, and most of the common residues cluster in the hydrophobic core of the fold. Nevertheless, the hybrid analog reacted with almost full potency on the Y₂ receptors. It is concluded that the antiparallel PP-fold is of structural importance for the receptor binding of NPY, and that its main function is to present the combined C- and N-terminal segments of the molecule to the receptors.

Neuropeptide Y (NPY) is an important regulator of neuronal function with a widespread distribution. In the central nervous system, NPY is involved mainly in the regulation of food intake, memory processing, and circadian rhythm. In the peripheral nervous system, NPY functions especially as a co- transmitter with norepinephrine in the regulation of vascular tone; a fact which has changed the concept of the function of the sympathetic nervous system. The neuroanatomy and physiology of NPY has recently been reviewed in a symposium volume (1).

The primary structure of NPY has been preserved well during evolution (2, 3). The 36-amino acid, amidated peptide belongs to the pancreatic polypeptide fold (PP-fold) family of peptides, characterized by a common tertiary structure, the so-called PP-fold (4, 5). In addition to NPY, the pancreatic hormone pancreatic polypeptide (PP) and the intestinal hormone peptide YY (PYY) belong to the family (6, 7). The PP-fold structure of avian PP has in great detail been studied by Blundell and coworkers (8, 9) by x-ray diffraction analysis down to 0.96 Å resolution. The PP-fold consists of a polypeptide-like helix and an amphiphilic α-helix which lies antiparallel with an angle of 152° between the helix axes (8). The two helices are joined by a type I β-turn and are held in the folded configuration through hydrophobic interactions between side chains of the α-helix interdigitating with the prolines in the N-terminal segment (Fig. 1). Circular dichroism studies of PP-fold peptides, including NPY, indicate that although the peptides do not have any stabilizing disulfide bridges, they do hold a considerable amount of secondary structure in aqueous solution (4, 9–13). This is true even for the monomeric form of NPY (13). As evaluated by Dobson and coworkers by two dimensional NMR the solution structure of at least one member of the family, bovine PP, appears to be very similar to the crystal structure of avian PP (14).

In the present investigation we have probed the importance of the PP-fold motif of NPY for the binding of this peptide to two types of NPY receptors (15–17). Three different approaches were employed: 1) The structure of the NPY molecule was built up stepwise from the essential C-terminal amidated end. 2) The PP-fold was perturbed through a single substitution. 3) The PP-fold motif of NPY was exchanged with the vastly different but structurally homologous PP-fold of PP itself.

**EXPERIMENTAL PROCEDURES**

**Peptide Synthesis**

Reagents—tert-Butyloxycarbonyl amino acid derivatives were purchased from Bachem (Switzerland). The p-methoxybenzhydrolamin resin (0.38 mmol of amine/g) were from Peptide Institute Inc., and dicyclohexylcarbodiimide and 1-hydroxy-benzotriazole from Fluka. All solvents were from Merck. Reagents were of analytical or HPLC grade.

Synthesis—[Pro-1(N)]NPY and the PP-(1-30)NPY-(31-36)-hybrid, which is equal to [Ile3,Gln3]PP, were synthesized by automated stepwise solid phase synthesis on an Applied Biosystems model 430A peptide synthesizer using the small scale t-butyloxycarbonyl chemistry (1 mmol of amino acid/20 mmol of peptidyl resin) according to the manufacturer's manual. NPY was synthesized as standard pro-
Neuropeptide Y

![Diagram of the structure of Neuropeptide Y and aligned sequences of the fragments used in the binding experiments.](image)

**Binding Experiments**

In the present study, the SK-N-MC cell line and its subline MC-IIXC were used as a general V1 receptor model and porcine hippocampal membranes were used as a general V2 receptor preparation (16, 17).

**Binding to Cells** The human primitive neuroectodermal cell line SK-N-MC (and the MCIX-C subclone of this) were kindly provided by Drs. June Biedler and Barbara A. Spengler, Sloan-Kettering Memorial Institute, New York (27, 28). All media and materials for tissue culture were from Gibco. As described in detail previously (15, 16), binding studies with cells were performed with 50,000 cpm of radioligand at 37°C using triplicates of 1.2 × 10^6 cells.

**Binding to Hippocampal Membranes**—Synaptic membranes were prepared from porcine hippocampal tissue according to the method of Gray and Whittaker (29), in which the P2 fraction was subfractionated on a discontinuous sucrose gradient and membranes from the interface between concentrations of 0.8 and 1.9 M sucrose were used (29). The binding was performed with 10,000 cpm of radioligand at 37°C in 0.5 ml of a 25 mM Hepes buffer, pH 7.4, containing CaCl_2 (2.5 mM), MgCl_2 (1 mM), bovine serum albumin (10 g/ml), and thimerosal (10 μM).

Circular Dichroism Spectroscopy

Circular dichroism (CD) spectra were recorded on a Jobin Yvon Dichrograph Mark V. The CD signal was calibrated with (+)-10-camphorsulfonic acid in a 1-cm cell assuming a ∆ε of 2.36 M^−1 cm^−1 at 290.5 nm. A spectral band width of 2.0 nm and a scan rate of 4 nm/min were used. The peptide samples were contained between cylindrical quartz windows with a nominal path length of 0.020 cm, dissolved to a final concentration of 0.1 mM acetic acid pH 4.5, except for NPY-(8-36)-peptide which was dissolved in distilled water at pH 5.9. Peptide concentrations were determined by amino acid analysis and all CD measurements were made at 26 ± 2°C. The final spectra were averaged from three scans prior to baseline subtraction and smoothing. The unit of ∆ε was based on the molar concentration of peptide bonds. The CD experiments were all performed at concentrations where NPY most likely is in a dimeric form (13). The secondary structure of the peptides was calculated from their spectrum using the methods of singular value decomposition and variable component analysis as described by Johnson and co-workers (23–25). We chose the calfskin collagen spectrum (26) as a reference spectrum for the polyproline II-like helix structure because this polymer resembles the sequence of the NPY polyproline-like segment more than for example poly-(l-proline) II does. Analysis of difference CD spectra of closely related proteins is a very sensitive method for studies on changes in secondary structure; in the present study the difference spectrum between the experimental spectra of NPY and NPY-(8-36)-peptide and between NPY and [Pro_3]NPY were calculated.

Indication of Peptides

[^3H]-Tyr(Me)Monoiido-NPY was prepared by indination of NPY using the oxidative agent 1,3,4,6-tetrachloro-3a,6a-diphenylglycoluril (Serva) and purified with isocratic elution on reverse phase HPLC using a Nucleosil 300-5 C_18 column, as described in detail previously (16).

Purification—The crude peptides were extracted into 50% acetic acid by hydrogen fluoride as described (20), and the fragments were freeze-dried and purified by reversed phase HPLC, on a C_18 column (1.6 × 20 cm, 7 μm particles) which was eluted at a flow of 6 ml/min with a gradient of acetonitrile from 30 to 45% in 0.2 M ammonium acetate, pH 3.5, over 45 min. Amino acid analysis, which was performed on the hydrolyzed peptides (6 M HCl, with 0.1% phenol for 18 h at 110°C) by ion exchange chromatography on a Kontron amino acid analyzer using the lithium citrate buffer system, gave results which were in good agreement with the theoretically expected values (Table I). The amino acid sequence of NPY, NPY-(8-36), [Pro_3]NPY, and [He_3,Gln_4]NPY were controlled by gas-phase sequencing on an Applied Biosystems model 470A Sequencer. The integrity of the C-terminal amide function was monitored by a radioimmunoassay, which is totally specific for this modification in NPY, using NPY antibody 8999 and[^3H]-Tyr(Me)monoiido-NPY (22). NPY-(13-36)-peptide was synthesized by Ferring and was a generous gift from Dr. Rolf Häkanson, University of Lund, Sweden.
bacitracin (0.5 g/liter), with a final synaptosome concentration of 100 mg of membrane protein/ml. Samples were incubated in triplicates at 37 °C for 1.5 h in a metabolic shaker. The incubation was stopped by the addition of 0.5 ml of ice-cold binding buffer before centrifugation at 3,500 x g for 10 min. The pellet was washed in 0.5 ml of the fragment, NPY-(8-36)-peptide, which was specifically bound to the receptors, both of the receptors requires the presence of even the far N-terminal segment of the molecule for full activity.

### RESULTS

**CD Analysis of NPY**—The CD spectrum of NPY and that of the fragment, NPY-(8-36)-peptide, which was specifically designed to lack the segment corresponding to the polyproline-like helix, are shown in Fig. 2A. The weighted difference spectrum between the experimental spectra of NPY and that of NPY-(8-36)-peptide, was compared to the spectrum of collagen (Fig. 2B). The similarity of both the shape and the intensity of these two spectra indicates that the 1-7 segment of NPY does adopt a polyproline-like structure. Computational analysis of the NPY spectrum was performed both after subtraction of one-fifth of the spectrum for collagen, corresponding to the 7 out of the 35 peptide bonds which according to the crystal structure of avian PP could be expected to be in a polyproline-like helix, and after subtraction of the difference spectrum between NPY and NPY-(8-36)-peptide. As shown in Table II, these analyses gave α-helical contents of 32 and 37%, respectively, which are only slightly less than the 43% found in the crystal structure of the homologous avian PP (4). The difference spectrum between NPY and NPY-(8-36)-peptide gave as a reference spectrum computational results for the structure of NPY which most closely resemble those of the PP crystal structure. This was most evident in the estimation of the amount of β-turn structure in NPY (Table I). In conclusion, the CD analysis supports the notion that NPY in aqueous solution holds a tertiary structure with a PP-fold similar to that found in the crystal structure of avian PP.

**Binding of C-terminal Fragments of NPY**—The C-terminal amide group is essential for the biological function of PP-fold peptides (30-32), and the free acid form of NPY was in our receptor preparations, as expected, devoid of any significant binding activity (data not shown). Thus, we decided to build the NPY molecule up stepwise from the C terminus. We chose to add sequences corresponding to turn after turn of the amphipathic α-helix to the C-terminal amidated hexapeptide (Fig. 1). In the last two fragments, sequences were added which corresponded to the β-turn, and finally half of the polyproline helix.

On the Y2 receptors the C-terminal hexapeptide itself did not displace the radiolabeled NPY. However, NPY-(23-36)-peptide and larger fragments bound to the Y2 receptors (Fig. 3). NPY-(19-36)-peptide displaced radiolabeled NPY from Y2 receptors with an ICso of 5.2 nM as compared to 0.74 nM for NPY. Further addition of the last turn of the helix, the β-turn, and half of the polyproline helix apparently did not increase the binding affinity of the fragments to the Y2 receptors. On the Y1 receptors, not even the longest fragment, NPY-(4-36)-peptide, bound significantly (Fig. 3). Thus, although the long C-terminal fragments of NPY encompassing most of the amphipathic α-helix bind rather well to the Y2 receptor, both of the receptors requires the presence of even the far N-terminal segment of the molecule for full activity.

### Structure and Binding of NPY with Perturbed PP-fold—
We decided to perform a single substitution of the tyrosine residue in position 20 with the helix-breaking imino acid, proline, to try to hinder as discretely as possible the formation of the α-helix and thus the PP-fold. The CD spectrum of [Pro20]NPY indicated that the solution structure of the analog is vastly different from that of NPY, as shown in Fig. 4. Since it was unknown whether the polyproline-like helix would be present or not in the structure of [Pro20]NPY, the calculations of secondary structural elements were performed for both cases, (Table II). In both analysis, a substantial reduction in α-helix content was found, from 32 or 37% in NPY to either 20 or 15%, dependent on the mode of calculation. This result was confirmed by analysis of the difference spectrum obtained from the experimental spectra of NPY and [Pro20]NPY (data not shown). Thus, the substitution had the desired deleterious effect on the structure of the NPY molecule.

In Y2 receptor preparations, the analog, [Pro20]NPY, displaced radiolabeled NPY with an ICso of 5.6 nM similar to that of NPY-(19-36)-peptide (Fig. 5). [Pro20]NPY did not bind at all to Y1 receptors (Fig 5). Thus, the analog in which the secondary structure in aqueous solution had been seriously disturbed reacted with both Y1 and Y2 receptors as the "corresponding" C-terminal fragment, NPY-(19-36)-peptide. The structural information, which is present in the intact N-terminal segment of the unfolded analog, apparently cannot be recognized by the receptors.
Tertiary Structure and Binding of NPY

Binding of NPY with a Functional but Altered PP-fold—
The C-terminal end of NPY is essential for the receptor binding but the C-terminal hexapeptide is by itself without potency (Fig. 3). Thus we decided to combine the C-terminal hexapeptide of NPY with the PP-fold of human PP and thereby create a hybrid molecule with the correct C terminus of NPY but a vastly different PP-fold motif (Fig. 1). Although the hybrid, PP-(1-30)-NPY-(31-36)-hybrid, had 17-amino acid substitution as compared to NPY it reacted with almost full potency on the Y₃ receptors (Fig. 6). The hybrid did, however, not bind to Y₁ receptors (Fig. 6). This is in accordance with the fact that the N-terminal sequence of the analog differs from that of NPY, and this part of NPY is essential for its binding to Y₁ type of receptors, as shown in Fig. 3, lower panel.

**DISCUSSION**

In the present study we provide evidence for the importance of the secondary and tertiary structure of NPY for its biological function. Kaiser and Kezdy (33) have made an ample case for the general importance of secondary structural elements in the binding and function of medium size peptides, 25-50 amino acids. They focused mainly on a series of peptides in which a spatial segregation of hydrophobic and hydrophilic residues creates a complementary amphiphilicity in a major segment of secondary structure (34). The peptides which they studied do not hold the ordered secondary structures in aqueous solution; however, the structures are believed to form in the amphiphilic environment of the cell surfaces. The formation and functional importance of especially amphiphilic helical segments have been probed in, for example, melittin (35), calcitonin (36), and β-endorphin (37). The experimental approach was to replace a segment of the hormone with a nonhomologous model peptide which preserved the general secondary structure, e.g. an amphiphilic α-helix composed of d-amino acids. Thus, by minimizing the sequence homology, even including nonpeptide elements (38), and still reproducing the biological response, it has been possible to provide evidence for the functional importance of segments of amphiphilic secondary structure (33, 34).

This "peptide engineering" approach could not directly be applied to NPY. Although peptides have been produced which had the desired physiochemically properties, these analogs bound with less than 1% of the potency of NPY to brain receptors (13). Nevertheless, the observation in the present study, that partial disruption of the central helix in NPY through the introduction of a single proline residue secludes the N-terminal sequence from receptor recognition, supports the conjecture that secondary structure is important for the function of the peptide. It should be emphasized, however, that NPY differs from endorphin, calcitonin, etc. in holding a globular, tertiary structure in aqueous solution; a structure

**TABLE II**

Secondary structure of NPY and [Pro²⁸]NPY as calculated from analysis of their circular dicroic spectra

| Secondary structure | Polyproline helix | α-Helix | Antiparallel β-strand | Parallel β-strand | β-Turn | Random coil |
|---------------------|------------------|--------|-----------------------|------------------|--------|-------------|
| NPY (I)             | 20 (20)          | 37 (43)| 7 (0)                 | 2 (0)            | 12 (11)| 22 (26)     |
| NPY (II)            | = 20             | 32     | 15                    | 11               | 0      | 22          |
| [Pro²⁸]NPY          | = 20             | 20     | 17                    | 0                | 16     | 97          |
| [Pro²⁸]NPY          | = 0              | 15     | 26                    | 0                | 23     | 36          |
Tertiary Structure and Binding of NPY

in which the amphiphilic helix is stabilized through intramolecular, hydrophilic interactions. Thus, for the final test of the importance of the PP-fold we decided to apply the classical approach of Kaiser and Keszdy in a slightly modified form. The structural element to be probed, the PP-fold of NPY, was exchanged with the corresponding segment of the homologous peptide, pancreatic polypeptide. In other words we used a similar peptide segment which is very different in sequence (see Fig. 1) but which has been structurally designed through the evolutionary refinement of nature, not man. The hybrid peptide bound equally well as NPY to NPY-Y2 receptors (Fig. 6), which strongly indicates that the PP-fold is an important but purely structural element in the interaction of NPY with the Y2 receptor. In fact, peptide PYY (7), which also binds with full potency to NPY receptors (15, 16, 32), is similar to the hybrid analog, since 12 of the 31 amino acid residues in the PP-fold area differ between NPY and PYY.

The receptors for PP-fold peptides appear to recognize the combined C-terminal and N-terminal segments of the molecules brought together by the inter-exchangeable PP-fold
structure (Fig. 7) (5). This conjecture has recently been supported by two studies in which the terminals of NPY were joined in a biologically functional way by different artificial constructions (39, 40). A major element of the discriminatory specificity among receptors for PP-fold peptides is determined by the way they recognize the C-terminal segment of the ligands, and here residue 34 appears to be specially important (5). The chemical properties of these residues determine not only whether a given PP-fold peptide will bind to either a PP or NPY receptor. Substitutions in the C-terminal end of NPY have also led to the development of an analog, [Leu3',Pro34'] NPY, which is a high affinity ligand for Y1 receptors but does not bind to Y2 receptors (41), in contrast to most of the analogs tested in the present study.

It is not yet clear whether the PP-fold motif is involved in the structure and function of PP-fold peptides in more than just combining the C- and N-terminal segments of the molecule (Fig. 7). Although most of the hydrophobic face of the amphiphilic a-helix is used for intramolecular interactions (4), the PP-fold motif, as a whole, still presents a considerable hydrophobic patch along the combined axis of the fold. It is therefore possible that the PP-fold functions as a stabilized, amphiphilic structure in analogy with the amphiphilic but relatively unstable motifs of Kaiser and Kizdy. Furthermore, it should be noticed that the electrostatic dipolar moment of the stabilized a-helix (42) could be instrumental in positioning, e.g. the important guanidino functions localized at the C terminus of the molecule (40).

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