Neuropeptide Y (NPY) is a 36-amino-acid peptide amide with numerous biological activities. These functions are mediated through several pharmacologically distinct receptors. To date five receptor subtypes have been cloned. Here we report the isolation, by low stringency homology cloning from a hypothalamic library, of a cDNA encoding the human homolog of the murine neuropeptide Y receptor subsequently reported (1). Translation of the human Y1-like receptor clone suggested that it encoded a receptor which is truncated in the third extracellular loop. Comparison of the human Y1-like sequence to that of the human Y1 receptor suggested that the truncated receptor could have resulted from a frameshift due to a single nucleotide deletion in the sixth transmembrane domain. Southern blot analysis suggested that the gene is single copy in the human genome. The gene is located on chromosome 5q. To test the hypothesis that allelic variation of nucleic acid length within the sixth transmembrane domain of the Y1-like receptor may exist to produce a functional receptor, genomic DNA from 192 individuals of various ages, ethnic backgrounds, and degrees of obesity were analyzed electrophoretically and by direct sequencing. No variation was detected in any of the subjects, indicating that this receptor subtype may be a transcribed pseudogene in humans.

Neuropeptide Y (NPY) is a 36-amino-acid peptide amide that is widely distributed in the central nervous system, where its effects include blood pressure regulation, memory enhancement, anxiety/sedation and increased food intake, and in the periphery, where it affects vascular and other smooth muscle activity, intestinal electrolyte secretion, and urinary sodium excretion (2–3). These functions are mediated through several pharmacologically distinct receptors (4). Until recently, based on the rank order of potency of NPY and related peptides to compete $^{125}$I-labeled NPY binding, it was believed that there were three NPY receptor subtypes (4). Both the Y1 and Y2 subtypes had high affinity for NPY and PYY. They were differentiated by the high affinity of the Y1 subtype for the NPY analog $^{31}$Leu,$^{34}$Pro-NPY and its low affinity for NPY$_{13-36}$ compared to the low affinity of the Y2 receptor for $^{31}$Leu,$^{34}$Pro-NPY and its high affinity for NPY$_{13-36}$. Both these receptors have now been cloned (5–9). The Y3 subtype has high affinity for NPY but low affinity for PYY. The cloning of Y3 has not yet been reported. Nevertheless, molecular cloning efforts have resulted in the isolation of three additional NPY receptor subtypes. The Y4 or PP receptor (10–11) has high affinity for pancreatic polypeptide, a member of the NPY family, and lower affinity for NPY and PYY. The (rat) Y5 receptor (12) has a pharmacological profile similar to Y1 in that it has higher affinity for $^{31}$Leu,$^{34}$Pro-NPY than for NPY$_{13-36}$. The profile differs from that of Y1 in that Y5 has more than 10-fold higher affinity for NPY$_{1-36}$, NPY$_{13-36}$, [D-32Trp]NPY, and pancreatic polypeptide than Y1.

Weinberg et al. (1) recently reported the isolation of another novel NPY receptor from a mouse genomic library. While they designated this receptor “Y5”, its sequence is clearly different from the rat Y5 receptor discussed above (12). The receptor described by Weinberg et al. has nanomolar affinities for NPY, PYY, NPY$_{1-36}$, and $^{31}$Leu,$^{34}$Pro-NPY, lower affinity for NPY$_{13-36}$, and very low affinity (> 1 μM) for pancreatic polypeptide.

We had independently isolated a homolog of this mouse “Y5” receptor from a human hypothalamic cDNA library using low stringency homology cloning techniques. The human cDNA sequence suggested a single nucleotide deletion in the sixth transmembrane region that would predict truncation (at 290 amino acids) of the receptor. Inability to identify a variant without the nucleotide deletion in the sixth transmembrane region in approximately 200 human subjects of diverse ethnicity and degrees of adiposity suggests that this gene might not be functional in humans.

**EXPERIMENTAL PROCEDURES**

Cloning of a Human NPY Y1-like cDNA and Gene—A random primed cDNA library was prepared from human hypothalamic poly(A)$^+$ RNA (Clontech) in λ gt10 and screened using standard low stringency homology cloning techniques (13). Hybridization was overnight in NC buffer (4 × SSC, 7 mM Tris-Cl, pH 7.4, 1 × Denhardt’s solution, 40% formamide, 10% dextran sulfate, 100 μg/ml sheared herring sperm DNA) at 37°C. Y1 and Y2 DNAs, $^{32}$P-labeled using random primer techniques (14), were used as probes. Filters were washed at room temperature in 2 × SSC/0.1% SDS and then at 37°C in 0.1 × SSC/0.1% SDS. During purification of positive plaques, four filters were prepared and probed with $^{32}$P-labeled Y1 or Y2 DNA under high (washes at 65°C) or low (washes at 37°C) stringency conditions. Those plaques that hybridized probe under high stringency conditions and proven by sequence analysis to be Y1 or Y2 were discarded. Those that hybridized probe under low but not high stringency conditions were investigated further. The λ inserts were subcloned into the pGEM-T plasmid vector and sequenced. One clone had sequence homology to the...
human Y1 GPCR. Using a 32P-labeled fragment of this clone as a probe, the human hypothalamic cDNA library was re-screened using high stringency conditions; two plaques were isolated, purified, and subcloned into pcDNA3, and sequenced. The same probe was used to screen a human genomic library in Lambda Fix II (Stratagene) using high stringency conditions; positive plaques were isolated and purified. λ DNA was prepared using the Qiagen Lambda kit according to the manufacturer’s specifications.

**Nucleotide Sequence Determination—**All sequencing was performed on an Applied Biosystems model 373A automated sequencer using the dideoxy-termination method (14). Sequences were analyzed using the GCG sequence analysis software package (15).

**Southern Hybridization—**Approximately 15 μg of human and murine genomic DNA were digested with restriction enzymes, and duplicate Southern blots were prepared as described previously (8). The blots were probed with 32P-labeled DNA that contained the open reading frame of the putative Y1-like receptor (nt 1–1110, Fig. 1). Hybridization was overnight at 37°C in NC buffer. The membranes were first washed at room temperature in 1× SSC/0.1% SDS. One was then washed in 0.1× SSC/0.1% SDS at 65°C (high stringency) while the other was washed in 0.1× SSC/0.1% SDS at 50°C (low stringency). A commercially prepared zool blot of genomic DNA (Clontech) was processed similarly, with the exception that it was washed at 57°C.

**Chromosomal Localization—**Purified λ DNA containing the human Y1-like gene was labeled with digoxigenin-dUTP using nick translation technique (13). The labeled DNA was combined with sheared human genomic DNA and hybridized to normal metaphase chromosomes derived from phytohemagglutinin-stimulated peripheral blood lymphocytes in buffer containing 50% formamide, 10% dextran sulfate, and 2× SSC. Specific hybridization signals were detected by incubating the hybridized samples in fluoresceinated anti-digoxigenin antibodies followed by counterstaining with DAPI (16). A total of 80 metaphase cells were analyzed; 42 exhibited a specific chromosomal labeling.

**PCR—**PCR was used to amplify the putative coding region of the Y1-like DNA from human genomic DNA as well as from the human genomic λ clones described above. The forward oligonucleotide encompassed the start site (GGTT GAATTC ATG GAA GTT TCC CTA AAC CAC CGC sequence analysis software package (15). Sequences were analyzed using the GCG sequence analysis software package (15).

**Analysis of Sixth Transmembrane Region—**Since the sequencing data from both the cDNA and genomic clones suggested a problem in the putative sixth transmembrane region of the Y1-like DNA, experiments designed to detect sequence differences were conducted. A forward (5′-CCGCAGGAGAAATGCAAAGG-3′) and reverse primer (5′-GTCGTGGTGGCAGC-3′) (nt 570–727 and nt 878–894, respectively, indicated by arrowheads in Fig. 1), were synthesized and end-labeled with [γ-32P]ATP in polynucleotide kinase buffer containing 20 units of enzyme for 30 min at 37°C. PCR reactions were performed, each using 75 ng of genomic DNA and 100 ng of each labeled oligo. Cycling conditions consisted of denaturation at 94°C for 1 min, annealing at 55°C for 2 min, and extension at 72°C for 2 min for 35 cycles. The PCR products were electrophoresed on a 43-cm non-denaturing 5% polyacrylamide gel and visualized by autoradiography. Samples for sequencing were prepared similarly using unlabeled oligonucleotides and ethidium bromide visualization. Bands were excised from the gel, spun through a cotton plug, and spun through a Qiaquick column according to the manufacturer’s protocol. These PCR products were sequenced as described above.

**RESULTS**

**Cloning of a Novel Human NPY Y1-like cDNA and Gene—**With the goal of cloning additional NPY receptor subtypes, a human hypothalamic cDNA library was screened using low stringency homology cloning techniques and a mixture of 32P-labeled Y1 and Y2 DNAs as a probe. One clone, n10–3, contained a fragment of a putative GPCR that had 56% nucleic acid identity to the human NPY Y1 receptor and 49% identity at the amino acid level. Hydrophobicity plots and comparison to the human Y1 sequence indicated that the fragment extended from the N terminus to the beginning of the fifth transmembrane region. Using a 32P-labeled fragment of clone n10–3 (nt 114–625, Fig. 1) as a probe, the human hypothalamic cDNA library was re-screened using high stringency conditions. Two clones were isolated and purified.

Sequencing revealed that one clone encoded a partial protein lacking the first 90 nucleotides of the open reading frame present in n10–3. The second, n25–1, appeared capable of encoding a full length receptor (Fig. 1). Comparison of its nu-
cleic acid sequence to that of human Y1 showed that the two were 59.7% identical over the entire Y1 open reading frame. However, when the nucleic acid sequence of n25–1 was translated, the encoded protein appeared to be only 290 amino acids in length (Fig. 1). A stop codon was encountered at the beginning of what would have been the third extracellular loop. Comparison of this amino acid sequence to that of Y1 indicated a 53% identity through amino acid 276 (Fig. 2), whereas there was essentially no similarity between the two amino acid sequences beyond that point.

Close examination of the comparison between the nucleic acid sequences n25–1 and Y1 revealed that if a deletion occurred around nucleotide 830 (amino acid 275), the resulting shift in the open reading frame of n25–1 predicts an amino acid sequence for n25–1 different from that of Y1. Insertion of a nucleotide (for example, thymidine) in that region would yield an open reading frame for n25–1 that was 370 amino acids in length (Fig. 1) and restore the overall amino acid similarity between n25–1 and Y1 to 52% (Fig. 2).

In addition to its overall sequence similarity to Y1, the putative protein encoded by clone n25–1 is similar to the murine homolog in containing many motifs characteristic of GPCRs in general and Y1 in particular. The nucleotide sequence surrounding the initiation codon (AnnATGG) agrees well with Kozak's consensus sequences (17). While n25–1 lacks the consensus sequences for N-linked glycosylation in the N terminus that are present in Y1, n25–1 resembles Y1 in that it contains such a sequence in the second extracellular loop (EC2) (6). Interestingly, the murine Y1-like receptor has the glycosylation sites in the N terminus but not in EC2 (1). Like Y1, both n25–1 and the murine homolog have four extracellular cysteines, one in the N terminus and one in each extracellular loop. Both contain an aspartate in transmembrane region 2 that is highly conserved in GPCRs (18) and have an “ERY” motif at the beginning of the second intracellular loop. This is most commonly a “DRY” motif (19) but in Y1 and Y4 it is “ERH” and in Y2 it is “DHR.” Both also have the “FXXC/SWLP” motif in transmembrane region 6 that is conserved in most GPCRs (19). Finally, in the seventh transmembrane region of the “restored” amino acid sequence of n25–1 protein as well as in the murine homolog, there is the conserved “NPXXY” motif (19) and in the C terminus there is a cysteine residue that is generally considered to be a site for receptor palmitoylation (20) as well as several serine and threonine residues that could be involved in regulatory phosphorylation (21).

Comparison of the nucleic acid and amino acid sequences of this Y1-like receptor to those of the human Y2, Y4, and Y5 receptors also supports the hypothesis that this sequence predicts a protein that is a member of the NPY receptor family (Table I). On the nucleotide level, the coding regions of the Y2, Y4, and Y5 receptors are 45, 53, and 45% identical to the Y1-like clone respectively; on the amino acid level they are 30, 40, and 34% identical, respectively.

To test whether the truncated form was capable of binding ligand, the n25–1 insert was subcloned into the mammalian expression vector pcDNA3, and the recombinant plasmid was transiently transfected into COS-7 cells. Specific binding of 125I-PYY to these cells was not observed (data not shown).

Hypothesizing that we might have isolated a mutant receptor clone and being interested in studying the gene associated with this cDNA, a human genomic library was screened at high stringency with the radiolabeled fragment of n10–3 (described above) as a probe. Two of the clones isolated, hg29 and hg40, were used to prepare λ DNA. These DNAs were used as templates in PCR reactions with oligonucleotides that bracketed the receptor open reading frame. The PCR products were the same size as the open reading frame of the cDNA, suggesting that the coding region for this receptor was not interrupted by any introns. In addition, the sequences of the genomic PCR products prepared from the genomic clones were identical to that of n25–1. Identical sequence was also observed from a PCR product prepared directly from human genomic DNA with these same primers.

**Southern Blot Analysis of Human Genomic DNA** — In an ef-
Receptor of obesity (body mass index range, 16.8–86.7 kg/m²). PCR

fort to determine whether there were additional genes related to this Y1-like gene and to see if this gene was present in rats, we prepared duplicate Southern blots of human and rat genomic DNA cut with EcoRI or BamHI. The blots were probed with 32P-labeled DNA encompassing only the coding region of n25–1 and were washed using low or high stringency wash conditions (Fig. 3, A and B). Since none of the restriction enzymes were predicted to cut within the open reading frame, multiple bands would be expected only if there were more than one cognate sequence for n25–1 in the genome. Single bands were observed in the lanes containing genomic restriction fragments of both enzymes probed at both high and low stringency. These results support the hypothesis that the n25–1 Y1-like gene is single copy, with no closely related homologs detectable by hybridization. N25–1 was subsequently localized to chromosome 5q31 as determined by fluorescent in situ hybridization by Genome Systems. No bands were observed in the lanes containing rat genomic DNA, suggesting that the gene is not present in rats.

Electrophoretic and Sequence Analysis of 192 Human Genomic DNA Samples—In experiments designed to detect allelic variation for the Y1-like receptor, we examined genomic DNA from 192 individuals of various ages (range, 2.4–89.9 years; mean, 28.9 years), ethnic backgrounds (135 Caucasians, 16 African Americans, and 2 Asians) and degrees of obesity (body mass index range, 16.8–86.7 kg/m²). PCR reactions, using 32P-labeled oligonucleotides and the genomic DNA as a template, were performed to generate a small (approximately 185 base pairs) DNA fragment that included the predicted amino acid 277 (Fig. 1). Electrophoresis of these fragments on a nondenaturing polyacrylamide gel demonstrated similar electrophoretic mobility, suggesting that there were no differences in sequence length (Fig. 4). To confirm that this was the case, 38 samples were sequenced. There were 18 females and 20 males; 27 were Caucasian, 7 were Hispanic, 3 were African American, and 1 was Asian. The ages of these subjects ranged from 7.5 to 89.7 years (mean 30.1, standard deviation 19.3) and their body mass indexes ranged from 16.8 to 77.2 kg/m² (mean 30.8, standard deviation 12.3). The genomic DNAs from all these individuals were identical to the original cDNA, n25–1 (Fig. 5). Thus, no supportive evidence for an alternative allele was detected in this heterogeneous group of individuals.

Southern Blot Analysis of Genomic DNA from Various Mammalian Species—Hybridization of 32P-labeled DNA encompassing the coding region of the Y1-like receptor to a Southern blot containing genomic DNA from monkey, rat, mouse, cow, dog, and rabbit revealed that the gene was clearly present in monkey and mouse (Fig. 6).

**DISCUSSION**

We report identification of a human hypothalamic cDNA clone, n25–1, encoding an NPY Y1-like receptor that is truncated in the third extracellular loop. Comparison of the nucleic acid sequence of this clone to that of the human Y1 receptor suggested that the insertion of a single nucleotide in the sixth transmembrane region (immediately after nucleotide 830 in Fig. 1) would restore an open reading frame, resulting in a full length GPCR with 52% amino acid identity to the human Y1 receptor. The mouse homolog of this human Y1-like receptor was recently cloned (1). Its nucleotide sequence is 82% identical to the human receptor, and the deletion of a single nucleotide around nucleotide 830 in the human is indicated in a computer alignment of mouse Y1-like receptor with the human Y1-like receptor (n25–1). If that nucleotide were added to the human sequence, the human and mouse exhibit 80% amino acid identity (Fig. 2). This homology is somewhat less than those for the murine and human Y1 and Y2 receptors, which have 97 and 94% amino acid identity, respectively. Nevertheless, it is greater than the 74% amino acid identity observed when the human and rat Y4 receptors are compared (22). The murine Y4 sequence has not yet been reported. Comparisons of the 5’ and 3’ untranslated regions of the human Y1-like cDNA to those of the mouse show 75% and 69% identity, respectively.

The literature generally recognizes two major categories of pseudogenes, those arising by gene duplication and those arising from incorporation of an mRNA reverse transcript into the genome (known as a processed pseudogene) (23–24). In general, pseudogenes have multiple deleterious alterations, the number of which is proportional to the duration of the sequence’s existence as a pseudogene. Alterations include base substitutions, additions and deletions that introduce nonsense codons, stop codons, and frameshifts precluding the formation of a full length peptide. Pseudogenes that have arisen by gene duplica-

**Table I**

| Receptor subtype | Y1-like | Y1 | Y2 | Y4 | Y5 |
|------------------|---------|----|----|----|----|
| Y1-like          | 100     |    |    |    |    |
| Y1               | 59/52   | 100|    |    |    |
| Y2               | 45/30   | 47/32| 100|    |    |
| Y4               | 53/40   | 58/46| 57/32| 100|    |
| Y5               | 45/34   | 44/33| 41/30| 42/29| 100|

*Ref. 12.*

![Fig. 3. Southern blot of human genomic DNA. Human and rat genomic DNA were digested with BamHI or EcoRI, separated on an agarose gel, and transferred to nitrocellulose. The blot was probed with 32P-labeled Y1-like receptor DNA that encompassed only the coding region of the cDNA. The blot was washed using low (A) or high (B) stringency wash conditions.](image)

![Fig. 4. PCR analysis of human genomic DNA. 32P-labeled primers were used in PCR reactions to generate fragments from nucleotide 708 to 894 (Fig. 1) of the Y1-like receptor. The products were electrophoresed on a 5% polyacrylamide gel and visualized by autoradiography. Lane 1, PCR product from the native cDNA clone (n25–1); lane 2, from the “restored” clone with the single nucleotide added as indicated in Fig. 1; lanes 3 and 4, from human genomic DNAs.](image)
tion are usually present on the same chromosome as the parental gene (although they could of course be transferred to other chromosomes by a subsequent translocation event), retain the parental pattern of introns, and are usually not transcribed. Processed pseudogenes, which may be dispersed throughout the genome, are characterized by a lack of introns. They are often colinear with the functional mRNA, having a 5' cap site, 5' and 3' untranslated sequences that correspond to those of the parental transcript, and poly(A) tracts at their 3' ends. They are also often flanked by short direct repeats. Processed pseudogenes are also usually not transcribed.

Analysis of the genomic DNA from 192 human subjects revealed that all harbored the same truncated Y1-like receptor sequence as our original cDNA clone. This finding suggests that this Y1-like receptor is most likely a pseudogene in humans. However, the genetic structure of the Y1-like receptor gene is not typical of either a processed pseudogene or one that arose by gene duplication. First, the sequence appears to harbor only one deleterious alteration. That the Y1-like gene is 52% identical to Y1 suggests that the two diverged more than 70,000,000 years ago (25). If the Y1-like gene had become nonfunctional at that time, one would expect that it should contain many additional nucleotide changes rendering it incapable of encoding a full length receptor. In addition, the gene was isolated from a cDNA library and was thus transcribed.

The coding region of the Y1-like receptor is not interrupted by an intron and thus is unlikely to have arisen from duplication of the Y1 gene. In addition, it is located on chromosome 5, whereas Y1, Y2, and Y5 are on chromosome 4, and Y4 is on chromosome 10. Although we did not see a poly(A) tail on our cDNA, we did observe a potential polyadenylation signal approximately 1.4 kilobases downstream of the stop codon (data not shown). These observations suggest the possibility that the Y1-like receptor gene arose from the Y1 receptor gene via incorporation of a product of reverse transcription.

We observed that the gene appears to be present in the monkey and mouse genomes but absent in those of rat, cow, dog, and rabbit. Considering the close genetic relationship between rat and mouse, these results are puzzling. It would be interesting to determine whether or not the monkey Y1-like gene is functional. It would also be interesting to determine chromosomal location and the physiological function of the gene in mouse. Perhaps the NPY function mediated through this receptor is important for murine physiology but not for human, thereby relieving evolutionary pressure on the gene.

In summary, we have isolated a human Y1-like receptor pseudogene.
cDNA and gene that encode a defective (truncated) GPCR. Analysis of 192 individuals suggests that this allele is widespread in the human population and may be a transcribed pseudogene. Nevertheless, since the human Y1-like clone bears 80% identity to the functional murine Y1-like receptor, it would be likely that the human receptor became a pseudogene relatively recently. Alternatively, there may be another as yet undetected functional allele, this receptor may oligomerize with other NPY receptors to form a functional protein (26), or it may undergo post-transcriptional modification, such as RNA editing or translational frameshifting, to generate a functional receptor (27–28).

It is also important to note that the simultaneous publication of two clearly different NPY receptor subtypes (1, 12) has led to a conflict of nomenclature as they were both identified as “Y5”. We would propose that the murine “Y5” receptor reported in this journal (1) and the human homolog reported here henceforth be known as Y6.

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