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A TSH-HCG-BETA CARBOXY TERMINUS EXTENSION PEPTIDE (CTEP) CHIMERA IS FULLY BIOLOGICALLY ACTIVE AND PROLONGS THE PLASMA HALF-LIFE OF TSH.

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Heterodimeric TSH is a member of a family of glycoprotein hormones which includes FSH, LH and hCG that share a common α- and a unique, hormone specific β-subunit. Both subunits are glycosylated and contain two asparagine-linked (N-linked) oligosaccharide chains on the β- and either one (TSH, LH) or two (FSH, hCG) on the β-subunit. Additionally, hCGβ has four serine-linked (O-linked) oligosaccharide chains on the carboxy terminal extension peptide (CTEP) that is absent from the other β-subunits. The increased *in vivo* bioactivity and longer plasma half-life demonstrated by hCG, compared to the other glycoprotein hormones, has been attributed, in past, to this extension peptide. More recently, with the advent of more refined genetic engineering techniques it was possible to construct a hybrid of FSHβ and CTEP of hCGβ that prolongs the half-life of FSH and increases its *in vivo* potency several fold. Although not unequivocally proven, previous studies have suggested that carboxy terminus of hCGβ may attenuate its inherent thyrotropic activity and this inhibition could be relieved by the removal of last four amino acids (isoleucine, leucine ,proline, and glutamine). These studies raised an interesting possibility that addition of CTEP hCGβ onto TSHβ may reduce its thyrotropin activity. In the present study we have constructed a chimera of hTSHβ-subunit with the CTEP of hCGβ-subunit. Using the polymerase chain reaction (PCR), an hTSHβ minigene and a CTEP hCGβ DNA fragment were synthesized and a fusion gene was constructed by sequential cloning in pGEM-7Z vector. The wild type hTSHβ and hTSHβ.CTEP hCGβ excised from pGEM-7Z were subcloned into transient expression vector, pLBCMV, at Xba I-Bam HI sites. Human embryonic kidney (293) and monkey kidney (Cos-7) cells were cotransfected with either pLBCMV.TSHβ (WT) or pLBCMV.TSHβ.CTEP.hCGβ (chimera) with pAV2.hCGαcDNA by calcium phosphate precipitation method. Both, WT and chimeric TSH were expressed to the same extent as judged by immunoradiometric assay (IRMA), suggesting that similar to FSH, CTEP hCGβ had no adverse effect on αβ subunit assembly and/or secretion of TSH heterodimer. The bioactivities of the WT and chimeric TSH were determined by their ability to stimulate cAMP production in rat thyroid FRTL5 cells. Our results show that the presence of CTEP of hCGβ did not attenuate the biological activity of the chimera which was identical to that displayed by WT TSH. The metabolic clearance rate (MCR) of chimeric TSH was significantly reduced (~4 fold). Since the *in vivo* bioactivity of glycoprotein hormones depends largely on MCR, presumably chimeric TSH will show increased *in vivo* potency. Currently studies are underway to examine this possibility .

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