C.79-Hepatitis C virus and type 2 diabetes: Molecular homology between HCV E2 envelope and glucagon

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Background

200 millions people were infected with HCV in the world. Prevalence of type 2 diabetes in chronic HCV ranges 24-50%, a frequency 5 times greater than the rest of hepatic cirrhosis. Prevalence of hepatitis C among diabetes is 5 to 12%, versus 0.1 to 2% in the general population (Mehta SH, 2001). A direct involvement of HCV core has been hypothetized inducing a high level of Tumor Necrosis Factor-alpha and suppression of tyrosine phosphorylation of insulin receptor substrate-1 (Shintani Y, 2004).

We analyse the mechanism of action of HCV in diabetes/insulino-resistence production.

Methods

Basic **L**ocal **A**lignment **S**earch **T**ool **P**rotein (BLASTP) comparison between human glucagon and HCV proteins [followed by visual examination of 2073 HCV (genotypes 1, 2, 3, 4, 5 and 6) E2 envelopes from the European database of Pr Gilbert Deleage (Lyon) (
euhcvdb.ibcp.fr
)], and analysis of glucagon structure-function relationship and three
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imensional (3D) structure (Koth CM, 2012).

Results

We found a homology between human glucagon, especially miniglucagon (19-29),

and HCV E2 protein chimera; the glucagon motif H……RR..DFVQ W LM

was conserved in HCV E2 motif H… … …….RR..DF .QGW.PI,

including the complete receptor binding motif located at the COOH-terminus and containing the residues D15, A19, F22, W25, L26, M27, T29 (M27 replaced by I; and *linearly* D15 is missing, A19 replaced by V):

Receptor binding residues * * * * * * *

Numbering 15 19 22 25262729

Glucagon 15-**DSRRAQDFVQ**-**W**-**LMNT**-29

HCV E2 chimera 459-**CRRVE DFVQ**G**W**G**L I N**-473

HCV E2 variant **T**-474

17-**RR**-18 is a protease cleavage site.

The 2 gaps for glycines G (=Gly) are also encountered in a phylogenetically related glucagon in insects, the Adipokinetic Hormone pQVNFTPGWGTG (Gade G, 1997; Tran GMK, 2011), an 11 residues long peptide, which possesses the GWG motif of HCV E2.

Adipokinetic Hormone	pQVNFTPGWGT	(pQ = pyroGlu)
HCV 2b E2	E- DFRI GWGT	

Mini-glucagon (19-29) AQDFVQWLMNT is 1000 fold more powerful than glucagon itself (Dalle S, 2002). It is a very potent (ID50 close to 0.1 pmol/l) inhibitor of insulin release from beta-cell.

The glucagon (1-21) and des-(22-26) glucagon have potencies of