ARAŞTIRMA RESEARCH ARTICLE

AMINO ACID SIMILARITY, BETWEEN STATIN BINDING SITE OF HMG CoA REDUCTASE AND TASTE PERCEPTION-RELATED PROTEINS: A POSSIBLE MECHANISM FOR STATIN-INDUCED TASTE DISORDERS

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ABSTRACT

Objective: *Statins are widely prescribed worldwide and used by millions of people to decrease blood cholesterol level. Taste disorders are among many documented side effects of statins and reported in less than 2% of the patients who use a statin. The molecular mechanism of statin-induced taste disorders is not known. In this study, a bioinformatics approach was used for the elucidation of this mechanism.*

Material and Method: *In order to gain insight into the mechanism of statin-induced taste disorders, we searched human protein database by using Basic Local Alignment Search Tool (BLAST) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) as query.*

Results: *Our search revealed two proteins: Polycystic kidney disease 1 like 1 (PKD1L1) and transcription factor AP-2 beta (TFAP2B) both of which are involved in taste perception. Our results suggest a possible partial interaction between statins and PKD1L1 and TFAP2B.*

Conclusion: *Further studies such as molecular docking and identification of statin binding proteins by affinity column chromatography using statins as substrate can clarify the contribution of such an interaction to the mechanisms of statin induced taste disorders.*

Key Words: *Statins, taste disorder, polycystic kidney disease 1 like 1 protein (PKD1L1), transcription factor AP-2 beta protein (TFAP2B)* ***Nobel Med 2012; 8(3): 105-107***

HMG CoA REDÜKTAZIN STATİN BAĞLANMA BÖLGESİ İLE TAT ALGILAMAYLA İLİŞKİLİ PROTEİNLER ARASINDAKİ AMİNO ASİT BENZERLİĞİ: STATİNE BAĞLI TAT BOZUKLUKLARI İÇİN OLASI BİR MEKANİZMA

ÖZET

Amaç: Statinler dünya genelinde sık reçetelenmekte ve milyonlarca insan tarafından kan kolesterol seviyesini düşürmek için kullanılmaktadır. Tat bozukluğu statinlerin bilinen yan etkilerinden biridir ve statin kullanan hastaların % 2'sinden azında görülür. Statine bağlı tat bozukluklarının moleküler mekanizması bilinmemektedir. Bu çalışmada, bu mekanizmanın aydınlatılması için biyoinformatik bir yaklaşım kullanıldı.

Materyal ve Metod: Statine bağlı tat bozukluğunun mekanizmasını aydınlatmak için 3-hidroksi-3-metilglutaril-koenzim A redüktaz (HMGCR) sorgu kabul edilerek insan protein veri tabanında BLAST yöntemiyle araştırma yapılmıştır.

Bulgular: Bu araştırmada tat ile ilişkili iki protein bulunmuştur: Polikistik böbrek hastalığı 1 benzeri 1 (PKD1L1) ve transkripsiyon faktör AP-2 beta (TFAP2B). Bu sonuçlar statinlerle bu iki tat duyusu proteininin kısmi etkileşime girebileceğini düşündürmüştür.

Sonuçlar: Moleküler kenetlenme ve statinlerin substrat olarak kullanıldığı afinite kolon kromatografi yöntemiyle kolona bağlanan proteinlerin tanımlanması gibi analizler bu etkileşimlerin statine bağlı tat bozukluğunun mekanizmasına olan katkısını açığa çıkarabilecektir.

Anahtar Kelimeler: Statinler, tat bozukluğu, polikistik böbrek hastalığı 1 benzeri 1 protein (PKD1L1), transkripsiyon faktörü AP-2 beta protein (TFAP2B) **Nobel Med 2012; 8(3): 105-107**

INTRODUCTION

Statins are the most widely used antihyperlipidemic agents. They selectively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) which is involved in the biosynthesis of not only cholesterol but also coenzyme Q10, dolichol etc. The decrease of these vital compounds other than cholesterol likely results in many statin related side effects including myopathy, hepatotoxicity, peripheral neuropathy, impaired myocardial contractility, autoimmune diseases etc.[1] Taste disorders are also among the side effects of statins affecting less than 2% of patients.[2] Although the percentage of the patients using statins experiencing taste disorders is low, this might still account thousands of people worldwide.[2-5] Therefore the elucidation of the mechanisms of statin induced taste disorders can affect thousands of patients worldwide.

During our preparation for an experimental study aiming to test the pleiotropic effects of atorvastatin by using *Caenorhabditis elegans (C.elegans)* as a model organism, we searched for *C. elegans* orthologs of human HMGCR in Wormbase.[6] Our search revealed, as already known, the gene F08F8.2 (WBGene00017268) and its corresponding protein WP:CE30649 as *C. elegans* HMGCR (*Ce*HMGCR). We then searched the homologs of *Ce*HMGCR by BLAST (Search parameters: "blastp", "e-value threshold: 1e+0", "filter:+") in Wormbase by using the amino acid sequence of *Ce*HMGCR as query.[6] Our reason was to determine other *C. elegans* proteins that might have the potential to interact with atorvastatin. Our BLAST analysis revealed the gene F35H10.10 (WBGene00018073) and its corresponding protein WP:CE24945. Interestingly this protein has a "7 transmembrane sweet-taste receptor of 3 GCPR" domain.[7] This similarity led us consider a possible interaction between statins and the proteins involved in taste perception as a potential mechanism of statin-induced taste disorders. Although the exact mechanism of statin-induced taste disorder has not been elucidated yet; the changes in bile acid formation, fatty acid profile and vitamin A metabolism were proposed as likely mechanisms.[8] The binding of statins to the homologs of HMGCR's statin binding site has not been proposed so far as a mechanism involved in statin-induced taste disorders. In this study we aimed to discover the human proteins that have a role in taste perception and, at the same time, have similarity to statin binding site of HMGCR.

MATERIAL and METHOD

In order to find the proteins that are both involved in taste perception and have similarity to statin binding site (562-L, 565-S, 568-R, 590-R, 683-V, 684-S, 690-D, 691-K, 692-K, 735-K, 752-H, 755-N, 853-L, 856-A, 857-L) of HMGCR.[9] We searched human protein database by using BLAST algorithm and the amino acid sequence from 451 to 880 of HMGCR isoform 1 as query.[10] This queried region of the protein covers HMG-CoA reductase superfamily putated conserved domain and statin binding sites. Search parameters were as follows: database; non-redundant protein sequences, organism; Homo sapiens, algorithm; blastp (protein-protein BLAST), default algorithm parameters except; maximum target sequences 20000, expect threshold 1000, word size 2.

RESULTS

Of the hits found by our BLAST analysis, only two proteins were found to be involved in taste perception and additionally had similarity to statin binding amino acid sites of HMGCR. These two proteins are polycystic kidney disease 1 like 1 isoform CRA_b (PKD1L1, GENE ID: 168507) and transcription factor AP-2 beta (activating enhancer binding protein 2 beta) (TFAP2B, GENE ID: 7021)[10] (Figures 1 and 2). PKD1L1 has two identical amino acids (Figure 1) and TFAP2B one identical amino acid (Figure 2) with HMGCR's statin binding site.

DISCUSSION

Our results suggest a possible interaction between statins and PKD1L1 and TFAP2B which were involved in taste perception. The fact that PKD1L1 has two identical amino acids (Figure 1) and TFAP2B one identical amino acid (Figure 2) with HMGCR's statin binding site suggests only partial interaction of statins with these proteins.

PKD1 proteins are required for the functional expression of PKD2 isoforms at the cell surface. The PKD2 family are transient receptor potential (TRP) signalling molecules that mediate sensing of fluid flow, taste, and pH. The PKD1 family (PKD1, PKD1 like 1 to 3 [PKD1L1 to 3]) are 11-transmembrane signalling molecules and they heterodimerise with PKD2.[11,12] Genetic ablation of PD2L1 expressing cells was reported to eliminate gustatory nerve response to sour stimuli, indicating that these cells function as sour taste detectors.[13]

TFAP2B was reported to have a role in the development of the midbrain through the differentiation of sensory neurons for taste, olfaction and palpation.[14] Therefore, being a transcription factor, it might also be playing a role in the expression of some taste perception related proteins in adults. The interaction of statins with PKD1L1 and TFAP2B can be tested experimentally by →

in silico and *in vitro* tests. *In silico* analysis by molecular docking studies can be performed to increase the likelihood of interaction. *In vitro* studies such as affinity column chromatography by using statins as substrate will be the definite experiments. Total protein extracts from the tissues such as tongue, soft palate etc. that are expressing taste receptors; and brain tissues containing taste sensory neurons are the suitable test materials. This can also allow the discovery of unknown interacting proteins.

We believe that our findings and hypothesis can be helpful in the elucidation of the mechanisms of statin induced taste disorders affecting a significant number of patients among millions of people using statins worldwide.[15] Further studies can also help the production of new statin molecules devoid of these side effects.

Additionally, we believe that the strategy used in this study can be used in gaining insight into the molecular mechanisms of other drug-induced side effects.

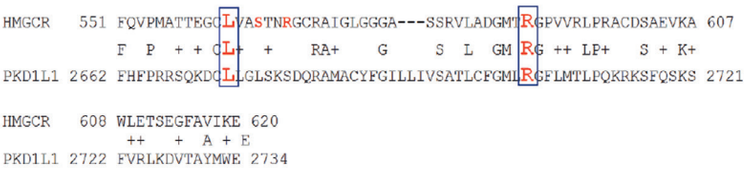

Figure 1. Similarity between HMGCR and PKD1L1. Statin binding amino acids were shown in red. The identities in the statin binding amino acids were highlighted in blue rectangles. [Algorithm parameters and scores: Score = 25.8 bits (55), Expect = 302, Method: Compositional matrix adjust., Identities = 19/73 (26%), Positives = 33/73 (45%), Gaps = 3/73 (4%)]

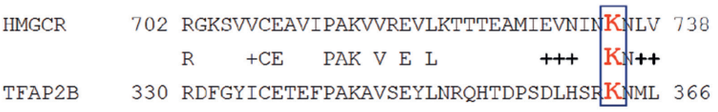

Figure 2. Similarity between HMGCR and TFAP2B. Statin binding amino acid was shown in red. The identity in the statin binding amino acid was highlighted in blue rectangle. [Algorithm parameters and scores: Score = 24.6 bits (52), Expect = 738, Method: Compositional matrix adjust., Identities = 11/37 (29%), Positives = 17/37 (45%), Gaps = 0/37 (0%)]

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