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Heart Disease, Longevity, and Cholesteryl Ester Transfer Protein

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Introduction

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein and thus the gene product is expressed in high levels in the liver, heart, placenta, and lymphnodes (Genomics Institute of the Novartis Research Foundation, 2008). The function of CETP is to transport cholesteryl esters and triglycerides between very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL) (Bauerfeind et al., 2003). This is a metabolic function which is important for delivering neutral fat and cholesterol from the liver and GI tract to the periphery. CETP also delivers excess fat from the periphery to the liver (Bauerfeind et al., 2003).

Homozygotes for with the I405V V/V genotype, with reduced levels of CETP, have a decreased risk of atherosclerosis due to modified levels of HDL and LDL particles (Boekholdt et al., 2004). Furthermore since lipid metabolism is involved in conservation of cognitive function I405V V/V homozygotes also tend to have a reduced risk and onset of dementia as they age (Barzilai, 2006). Data from studies show that a large proportion of centenarians are homozygous for the I405V polymorphism (Barzilai, 2006). Since a reduction in the amount of CETP has been found to play a role in the reduced risk of heart disease and the conservation of cognitive function, researchers and pharmaceutical companies have been looking into the development of CETP inhibitors as drugs for the treatment of arterial diseases.

Background Physiology

Cholesterol is a steroid metabolite, responsible for maintaining functional animal cell membrane permeability and structure. It is vital in the production of steroid hormones, bile acids, and some lipid-soluble vitamins (Leah, 2009). While the right amount of cholesterol is beneficial to the body, research has shown that an excess is pathogenic (Barter, 2000).

Cholesterol is mainly produced in the liver, intestines, adrenal glands, and reproductive organs. Since cholesterol is hydrophobic, it requires the assistance of lipoproteins to travel in water-based blood plasma (Thompson, 2004). Thus, in the liver cholesterol is combined with apolipoproteins to form VLDL, which is released into the blood stream and subsequently converted to LDL. LDL's function is to transport cholesterol from the liver to other parts of the body via the circulatory system (Thompson, 2004). Since LDL-cholesterol can be retained in arteries by arterial proteoglycans and begin the formation of atherosclerotic plaque, which causes peripheral vascular disease, strokes, and myocardial infarctions, LDL-cholesterol is nicknamed 'bad cholesterol' (Barter, 2000). On the other hand, HDL-cholesterol is nicknamed 'good cholesterol', because HDL is believed to remove cholesterol from arteries and transport it back to the liver for excretion or reuse (Barter, 2000). This process is known as reverse cholesterol transport. Epidemiological studies have shown LDL-cholesterol levels correlate with incidence of vascular diseases, while HDL-cholesterol levels inversely correlate with incidence of vascular diseases (Tanne, 2005).

Cholesterol metabolism is controlled by enzymes, membrane receptors, and transfer proteins in the gastrointestinal system and blood plasma. One particular cholesterol-regulating transfer protein, the aforementioned CETP, has been extensively studied (Tanne, 2005). CETP is a plasma protein which is involved in the transfer of lipid proteins between lipoproteins, and its net effect is a reduction in the content and size of HDL particles (Barter, 2000). Consequently,

inhibition of CETP raises HDL-cholesterol levels and lowers LDL-cholesterol levels in the body. Since higher concentrations of HDL-cholesterol and lower concentrations of LDL-cholesterol are believed to be preventative against cardiovascular disease, drugs which inhibit CETP are being tested (Barter, 2000); however, there is some evidence that CETP inhibition is a double-edged sword – the increased particle size and cholesterol content of HDL as a result of CETP inhibition may preclude the HDL from efficiently transporting cholesterol out of arteries (Barter, 2000). In support of this, laboratory studies have shown partial CETP inhibition to be protective against atherosclerosis, while the complete absence of CETP activity results in dysfunctional HDL (Barter, 2000).

CETP Alleles and Polymorphisms

The CETP gene is located on chromosome 16 and contains a large variety of mutations and is highly polymorphic. Many of the mutations in the gene can be separated into three major groups including missense, nonsense and silent mutations (Boekholdt et al., 2004). Missense mutations result in the production of single amino acid substitutions. The effects of these mutations are often milder, but some (such as the D442G and I405V variants) can have a significant effect on protein function. Nonsense mutations are mutations which produce premature stop codons. During mRNA translation, this causes the protein product to become truncated, and depending on the gene location this can lead to either partial or complete CETP deficiency. Silent mutations are common and they do not produce an amino acid substitution due to the redundant nature of the genetic code. As a result they are thought to play only a minor role in CETP function (Boekholdt et al., 2004).

An interesting and common mutation is the D442G variant, which is known to cause partial CETP deficiency. Homozygotes for this allele retain 25-50% of normal function, whereas heterozygotes retain 60-85% (Boekholdt & Thompson, 2003). The mutation causes the conversion of the aspartic acid at position 442 to a glycine in exon 15 of the gene (Chen, 2008). The D442G polymorphism has been associated with Alzheimer's disease risk, as studies showed that the D442G heterozygote genotype occurred more often in healthier patients than in those with Alzheimer's disease (Chen, 2008). Although the study, after correcting for multiple testing showed a lack of statistical significance for this conclusion, further adjustment of the data for sex and age showed that the G allele might be protective against the development of Alzheimer's disease (Chen, 2008). The reasoning for this conclusion is supported by the observation that the variants have altered CETP structure and function leading not only to reduced CETP levels but lowered CETP activity in comparison to the wild type (Chen, 2008). Studies on heterozygotes showed that plasma CETP activity was only 60%-85% and HDL levels were elevated by 10%-80% in comparison to the wild type. Since CETP is synthesized and secreted in brain tissue and there are higher levels of CETP-positive astrocytes (a type of glial cell) in Alzheimer's patients than in controls, there is a possibility of the G alleles playing a role in reduced local synthesis of CETP and increased HDL levels in the brain (Chen, 2008).

The I405V variant is the second most common variant and is found in over 25% of studied populations. Studies indicate that it is three times greater in populations with an average age of 100 than in a group with a median age of 70 (Barzilai, 2006). It is believed that individuals with the heterozygous genotype tend to produce both versions of CETP as the alleles are co-dominant to one another (Bruce et al., 1998). While both homozygous I/I and the heterozygous individuals produce almost identical amounts of CETP, the V/V homozygotes tend

to have a 9-23% CETP deficiency (Bruce et al., 1998) & (Boekholdt et al., 2004). A decrease in CETP function increases HDL (high density lipoproteins) levels in the body, and decreases LDL (low density lipoprotein). The result of this is that HDL-c levels are approximately equal in individuals with the I/I or I/V genotypes, while they are ten percent higher in V/V individuals (Bruce et al., 1998).

Not only do I405V V/V homozygotes tend to have higher HDL levels and low LDL levels, they produce larger HDL and LDL particles which are less likely to get trapped in vessels. This consequently results in a decreased risk of CAD (coronary artery disease) or atherosclerosis (Boekholdt et al., 2004). Furthermore, it is believed that lipid metabolism partially mediates the conservation of cognitive function in the brain, and as a result I405V variants tend to have reduced risk and onset of dementia as they age (Barzilai, 2006). After 158 Ashkenazi Jews between 95 and 107 years of age were evaluated for cognitive function and tested for the CETP I405V variant, it was found that those with the CETP I405V genotype were twice as likely to have good cognitive function (a score greater than 25 on the Mini-Mental State Examination) (Barzilai, 2006).

Pharmacological implications

Recognizing the therapeutic potential of CETP inhibition, pharmaceutical companies have engineered and tested CETP inhibitors in clinical trials. Two prominent CETP inhibitors developed over the past decade are torcetrapib (engineered by Pfizer) and anacetrapib (engineered by Merck).

Based on a 2004 study in the New England Journal of Medicine including 19 patients with low HDL-cholesterol levels, torcetrapib was initially a promising candidate for improving lipoprotein profiles. The study showed that torcetrapib significantly increased HDL-cholesterol and decreased LDL-cholesterol levels, and this effect was even greater when the drug was combined with statin (atorvastatin) therapy (Brewer, 2004). However ILLUMINATE, a subsequent study including 15,000 patients, indicated that while torcetrapib plus statin therapy raised HDL-cholesterol levels, compared to statin monotherapy this combination therapy caused an excess number of adverse events such as death and myocardial infarction (Tall, 2007). A further study, the ILLUSTRATE study, showed no difference in atherosclerotic plaque levels in the torcetrapib-statin combination therapy and the statin monotherapy groups (Tall, 2007). This indicates that torcetrapib causes adverse cardiovascular events by mechanisms other than atherosclerosis, such as vasospasm or potential interaction with the renin-angiotensin-aldosterone system. Due to its harmful effects, torcetrapib is no longer in development.

Anacetrapib on the other hand is still under development, and recent studies reported in The Lancet indicate that this drug has great potential. In healthy patients and patients with dyslipidemia it was shown to increase HDL-cholesterol and decrease LDL-cholesterol levels, and unlike torcetrapib it did not exhibit any off-target effects such as hypertension (Duriez, 2007). Importantly, it also did not increase the incidence of adverse events (Duriez, 2007). However these phase 1 trials were small, and long-term safety and efficacy data for anacetrapib have not been reported.

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