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Studies on PCSK9 in the regulation of cholesterol metabolism

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ABSTRACT

Elevated levels of plasma cholesterol, mainly in low density lipoproteins (LDL), are a major risk factor for coronary heart disease. The level of plasma LDL cholesterol (LDL-C) is largely dependent on the number of hepatic LDL receptors (LDLRs). Increased number of LDLRs leads to higher uptake of LDL particles and lower concentration of plasma LDL-C. Proprotein convertase subtilisin Kexin Type 9 (PCSK9) is a novel key regulator in cholesterol metabolism. PCSK9 reduces the number of available hepatic LDLRs leading to increased plasma levels of LDL-C. Inhibition of PCSK9 has a great potential as a cholesterol-lowering agent. However, the physiological role of PCSK9 is largely unknown.

In this study we investigated the regulation of PCSK9 in rats and humans, by hormones and diets and during the diurnal phases. We can show that:

- I) Reduced bile acid synthesis, but not changes in PCSK9, likely contributes to the age-dependent hypercholesterolemia in rats. Treatment with growth hormone (GH) restores bile acid synthesis to juvenile levels and upregulates the gene transcription of PCSK9.
- II) Hormonal and dietary regulation of hepatic LDLRs in the rat is frequently mediated by PCSK9. Treatment with estrogen, glucagon and a cholesterol-enriched diet reduces PCSK9 expression, while it is increased by insulin. The transcription factor SREBP-2 is partly involved in the hormonal and dietary regulation of PCSK9, although our results suggest that the glucagon-mediated suppression of PCSK9 may involve other mechanisms.
- III) Circulating PCSK9 has a pronounced diurnal variation and is strongly reduced during fasting in humans. These changes are presumably related to oscillations in hepatic intracellular cholesterol levels mediated by SREBP-2. GH treatment reduces circulating PCSK9 in men, whereas a ketogenic diet does not alter circulating PCSK9 levels.
- IV) Endogenous estrogen exerts rapid and distinct effects on cholesterol metabolism in females, with reduced levels of circulating PCSK9, plasma total and LDL-C, whereas the levels of HDL- and LDL- triglycerides (TGs) and apoAI increase. Some of the effects of estrogen on cholesterol metabolism may be mediated by a rapid induction of GH secretion.

The hormonal regulation of PCSK9 can partly explain the cholesterol-lowering effects of GH, estrogen, glucagon and thyroid hormone. Our results further indicate that such hormonal regulation may involve SREBP-2 independent mechanisms. The regulation of PCSK9 during the diurnal phases and fasting may explain why plasma LDL-C levels remain stable during these situations. We have also shown that PCSK9 can be dietary regulated, partly explaining the pronounced resistance to development of hypercholesterolemia following a cholesterol-enriched diet in the rat. Neither a ketogenic nor a vegan diet alters circulating PCSK9 in humans.

Hormonal, dietary and diurnal regulation of PCSK9 may influence serum LDL-C levels, a fact that should be considered in the use of current and novel anti-PCSK9 agents.

Keywords: aging, bile acids, cholesterol, coronary heart disease, diets, diurnal rhythm, estrogen, fasting, glucagon, growth hormone, HMG CoA reductase, hormones, hypercholesterolemia, lipoproteins, LDL cholesterol, LDL receptor, lathosterol, PCSK9, regulation, statins