GENETICALLY DIVERSE PIG MODELS IN NUTRITION RESEARCH RELATED TO LIPOPROTEIN AND CHOLESTEROL METABOLISM

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1. ABSTRACT

The pig is a widely accepted animal model for nutrition research related to growth and development, atherogenesis, obesity, and lipoprotein and cholesterol metabolism. We review current knowledge of lipoprotein metabolism in pigs and describe research in populations of genetically diverse swine. Specifically, we report the results of experiments showing that dietary cholesterol during neonatal life affects atherogenesis and indices of central nervous system development and lipid metabolism differentially in genetically obese and lean pigs and in pigs selected genetically for low or high plasma total cholesterol.

2. INTRODUCTION

The pig has been used for approximately 40 yr as a model organism for research into cholesterol and lipoprotein metabolism with application to atherogenesis. In addition to developing spontaneous atherogenic lesions, young prepubertal pigs develop fatty streaks and early atherosclerotic lesions within several wk when fed diets high in fat and cholesterol. There were reviews of much of this work about a decade ago, whereas, an excellent summarization of the history of the use of pig atherogenic models was presented 6 yr ago. In addition to use as an atherogenesis model, the pig continues to be a model for other aspects of cardiovascular research because of a number of similarities to the human. The anatomy

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of the coronary arteries and the pattern for development of collateral circulation after permanent ischemic episodes are 2 important similarities. Many aspects of various pig cardiovascular models were reviewed a decade ago. We do not attempt a comprehensive review of porcine cholesterol and lipoprotein metabolism but will briefly survey general aspects including a few references to indicate current endeavors in the field; the major emphasis is on results obtained in our laboratory with genetically obese and lean pigs, and pigs genetically selected for high and low plasma cholesterol.

3. CHOLESTEROL AND LIPOPROTEIN METABOLISM

In humans, cholesterol is obtained partially from animal products in the diet and synthesized partially de novo. Synthesis is from the 2 carbon moiety, acetate, to yield the 6 carbon moiety, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). After decarboxylation, the remaining 5 carbon moieties are assembled into a 30 carbon moiety and formed into the cholesterol ring structure with 4 rings and 27 carbons. Cholesterol synthesis is regulated primarily by the enzyme HMG-CoA reductase that catalyzes an early (6 carbon molecule) committed step toward cholesterol synthesis; the reductase is regulated highly and activity is decreased in the presence of cholesterol, to achieve a balance between endogenous synthesis and dietary intake. In most mammals, liver is a major site of cholesterol synthesis, with considerable activity in intestinal mucosa and in organs that synthesize steroid hormones, such as adrenal cortex and gonads. The central nervous system (CNS) has the capacity to synthesize cholesterol as well. The cholesterol molecule is essential for homeostasis of mammals; cholesterol is the precursor for synthesis of steroid hormones and for bile acids, it is a major component of several lipoproteins and it is an integral part of biological membranes. Sources of cholesterol are endogenous synthesis plus a dietary contribution ranging from zero in strict herbivores to considerable amounts in carnivores and some omnivorous humans.

Whole body cholesterol input (synthesis + diet + reuptake from the gut) equals output (endogenous products + deposition + excretion). Approximations of input and output of cholesterol metabolism in an adult omnivorous human follow (adapted from Fig. 5 of Bietz and Knight and Fig. 4-1 of Marinetti). There are 100 g cholesterol in the total body. Diet provides 400 mg (300 to 500 mg); whereas, 900 mg is synthesized endogenously. Cholesterol removal from the body is great via secretion into the gut lumen, mostly as bile acids and sterols; fecal sterols are to a large extent reabsorbed, so net excretion is approximately 1100 mg/da, balanced by accretion rate. Some 200 mg/da enters various body pools such as skin, steroid hormones and cell membranes. Thus, the 5 major facets of cholesterol metabolism are dietary intake, endogenous synthesis, production of various products such as hormones and membranes, bile acid synthesis and fecal sterol reabsorption.

Cholesterol is transported in plasma as a component of various lipoprotein molecules. Dietary cholesterol is absorbed, then exits the intestinal cell mostly as chylomicron particles. These large particles contain primarily triglyceride, but are also the carrier for entrance of dietary cholesterol, as cholesterol esters, into the lipoprotein transformation mechanisms. Chylomicrons are reduced to chylomicron remnants after removal of triglycerides; remnants reenter the liver. Liver synthesizes and secretes a smaller triglyceride and cholesterol ester rich particle, the very low density lipoprotein (VLDL), that gives rise to intermediate and low density lipoproteins (LDL) after removal of triglyceride. Apolipoprotein B-100 (apo B-100) is present on the surface of LDL particles which allows them to bind to the LDL receptor, present in various peripheral tissues, including liver. Uptake of LDL allows cholesterol to be transferred to tissues for use in biosynthetic mechanisms and as structural components of cell membranes. The high density lipoprotein (HDL) particle is synthesized primarily in liver; it has a major role