

Psychosocial and reproductive influences on plasma lipids, lipoproteins, and atherosclerosis in nonhuman primates

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Abstract Until recently, research in experimental atherosclerosis focused primarily on nutritional influences on plasma lipids, lipoproteins, and atherosclerosis. We review here the results of recent studies of independent and interactive influences of psychosocial and reproductive influences on atherosclerosis in nonhuman primates. These studies have produced evidence that, as in human beings, individuals with certain personality characteristics who are frequently faced with stressful or challenging situations are at increased risk of coronary artery disease. Preliminary evidence suggests that this relationship may be mediated, in part, by heightened sympathetic arousal, i.e., cardiovascular hyperresponsiveness, to the environmental challenge. Also, as in human beings, evidence has been produced that certain negative behavioral and psychosocial variables can have a significant independent influence on plasma lipids. As regards reproductive influences, the cynomolgus macaque seems to share with premenopausal white women a relative protection against coronary artery atherosclerosis. This "female protection" against diet-induced atherosclerosis is abolished by ovariectomy, which also results in increased total plasma and low density lipoprotein (LDL) cholesterol concentrations. Subordinate social status also seems to abolish female protection in some individuals. Preliminary evidence suggests that subordinate females most liable to this loss of protection are those with apparent stress-induced chronic ovarian endocrine dysfunction, which, in turn, is associated with increased plasma LDL cholesterol and decreased plasma high density lipoprotein (HDL) cholesterol concentrations.—Clarkson, T. B., M. R. Adams, J. R. Kaplan, and D. R. Koritnik. Psychosocial and reproductive influences on plasma lipids, lipoproteins, and atherosclerosis in nonhuman primates. *J. Lipid Res.* 1984. **25**: 1629–1634.

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INTRODUCTION

Since the early 1900's, nutritional influences on plasma lipids, lipoproteins, and atherosclerosis have dominated

research in experimental atherosclerosis. Until recently, there have been only a few efforts to document the influence of some other factors with important influences on plasma lipid concentrations and on atherosclerosis extensiveness such as psychosocial and reproductive factors. Lack of research progress in those areas has related primarily to the lack of suitable animal models. Over the past several years it has become apparent that nonhuman primates, particularly the cynomolgus macaques, are extremely useful for studies of psychosocial influences and psychosocial/reproductive interactions on coronary artery atherosclerosis. The rapid advances being made in this area of comparative atherosclerosis have prompted us to summarize these observations in this minireview. Psychosocial and reproductive studies are presented jointly because this recent evidence has suggested that gender and menopausal status affect plasma lipids, lipoproteins, and atherogenesis by way of interactions between psychological/social events and reproductive function.

PSYCHOSOCIAL PHENOMENA

Overview

The Type A or "coronary prone" behavior phenomenon is perhaps the best known psychosocial factor with regard to atherosclerosis and CHD in human beings. The Type A individual responds to a stressful or demanding environment with a sense of time urgency, intense competitiveness, and poorly controlled hostility. The relative absence of these attributes denotes a contrasting Type B pattern. Results of both retrospective and prospective studies indicate that Type A's (or indi-

Abbreviations: CHD, coronary heart disease; LDL, low density lipoprotein; HDL, high density lipoprotein.

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viduals possessing many of the component characteristics) develop CHD more frequently and are more likely to die of myocardial infarction than Type B's (1-6). These effects are largely independent of the actions of the major risk factors such as plasma cholesterol concentration, blood pressure, and smoking (3). The importance of Type A status is not as a personality type per se, but rather as it relates to a complex of emotional and physiologic responses to a stressful or challenging environment. In addition to the Type A pattern and its component characteristics, factors such as anxiety, depression, socioeconomic status disadvantage, and work overload have also been related to CHD or atherosclerosis (6-9). Like the Type A, the importance of these characteristics relates to individual emotional and physiologic responses to environmental challenges or stresses.

While behavioral factors, especially Type A, have been shown to affect atherosclerosis independently of serum lipids and lipoproteins, there exists a large literature (10) showing that psychosocial phenomena can have acute as well as chronic effects on serum lipids and lipoproteins. Studies of individuals' responses to stressful or challenging situations, such as medical student examinations, viewing of emotion-evoking films, public speaking, race car driving, and studies of life events profiles suggest that negative psychosocial experiences can result in increased plasma triglyceride, free fatty acid, and cholesterol concentrations. These findings indicate that, whatever the independent effect of behavior on atherosclerosis, behavioral factors also influence serum lipids and through such a mechanism may affect atherogenesis additionally.

Effects on atherosclerosis

One of the earliest studies of psychosocial influences on nonhuman primate atherosclerosis was reported by Lang (11). He found that squirrel monkeys (*Saimiri sciureus*) fed a cholesterol-containing diet and subjected to either cage restraint or shock avoidance were affected more frequently with coronary artery atherosclerosis than were animals living under control conditions. More recently, Hamm et al. (12) reported that competitive male and female cynomolgus macaques (*Macaca fascicularis*) fed a cholesterol-containing diet and living in social groups had less coronary artery atherosclerosis than did noncompetitive animals. Kaplan et al. (13) reported that among male cynomolgus macaques consuming a cholesterol-containing diet, socially dominant and competitive animals living in stable (unstressed) social groupings were relatively less affected with coronary artery atherosclerosis than were dominant and competitive animals living in unstable, reorganized (stressed) social groups. Subordinate, noncompetitive individuals also were less

affected regardless of whether they lived in stable or unstable conditions. This finding seems to be consistent with the hypothesis that among human beings individual behavioral characteristics (such as Type A or potential for hostility) interact with the social environment to increase CHD risk. Finally, Kaplan et al. (14) showed that an atherogenic diet was not necessary for significant psychosocial effects on coronary artery atherosclerosis to be produced. In that study, animals living in unstable, reorganized social groupings had more coronary artery atherosclerosis in comparison to their stable, unmanipulated counterparts.

As among human beings, it has been speculated that, aside from plasma lipid alterations, one of the possible mechanisms underlying the association between behavioral phenomena and atherosclerosis involves the hemodynamic and hormonal responses frequently accompanying behavioral arousal ("stress"). It has been suggested that certain individuals (e.g., Type A's) may be cardiovascularly hyperresponsive to stressful situations and experience damage to their arteries through frequent and marked increases in heart rate and blood pressure associated with arousal. This hypothesis was tested by Manuck, Kaplan, and Clarkson (15) and Kaplan, Clarkson, and Manuck (16) who examined the extent of atherosclerosis in cholesterol-fed cynomolgus macaques that responded to a standard psychological challenge with high heart rates. It was found that the high responders had significantly greater extent of coronary artery, thoracic aorta, and carotid bifurcation atherosclerosis than did their low responder counterparts (15, 16). Such a finding is initial evidence in favor of the hypothesis that an inherent cardiovascular hyperresponsiveness to stress may explain, in part, the association between behavioral factors and coronary artery atherosclerosis. More recently, Glagov (17) demonstrated that cynomolgus macaques having low heart rates (either naturally or through ablation of the sinoatrial node) had reduced coronary artery atherosclerosis in comparison to animals with high heart rates.

In summary, these studies seem to indicate that psychosocial influences on atherogenesis can result from the interaction of personality type and social environment, as is thought to occur in human beings. Further, there is preliminary evidence that heightened sympathetic arousal (as indicated by increased heart rate or high heart rate responsiveness) may represent a mechanism by which acceleration of atherogenesis is mediated.

Effects on plasma lipid concentrations

There are few studies of psychosocial influences on plasma lipid concentrations in nonhuman primates. However, the studies reported are generally consistent

with the studies of human beings which show negative psychosocial experiences to be associated with elevated plasma lipid concentrations. Squirrel monkeys appear to be particularly liable to changes in plasma lipid concentrations associated with psychosocial and/or environmental changes. Workers at our Center investigated the changes in plasma cholesterol concentrations during capture and relocation of squirrel monkeys from their natural habitat in South America to the laboratory in Winston-Salem, North Carolina (18). Shortly after entering a trap in South America, squirrel monkeys had total plasma cholesterol concentrations of about 100 mg/dl. During a two to three week confinement in the laboratory in South America and while they were consuming a diet of fruit and vegetables, the total plasma cholesterol concentrations increased to about 180 mg/dl; after travel by air to Winston-Salem, plasma cholesterol concentrations were about 200 mg/dl. After arrival at Winston-Salem, the animals were fed monkey chow, and after a few months plasma cholesterol concentrations returned to about 100 mg/dl. The increases noted in total plasma cholesterol concentration during capture and relocation were shown to be accounted for by changes in the low density lipoprotein (LDL) cholesterol concentrations (18). In a study involving squirrel monkeys fed a cholesterol-containing diet, Lang (11) found that monkeys subjected to cage restraint or shock avoidance had significant, acute increases in plasma cholesterol concentration immediately following the manipulation when compared to unmanipulated animals. As noted in a previous section, the manipulated animals were found to have an increased prevalence of coronary artery atherosclerosis.

In addition to studies with squirrel monkeys, several experiments with Old World monkeys have been reported. In some of these the effects on plasma lipid concentrations of individual behavioral characteristics (aggressiveness, competitiveness versus submissiveness) have been examined. Bramblett, Coelho, and Mott (19) found that among African green monkeys (*Cercopithecus aethiops*) submissive behavior was associated with elevated concentrations of total plasma cholesterol among both males and females. More recently, Hamm et al. (12) reported that submissive, noncompetitive male and female cynomolgus macaques (*Macaca fascicularis*) had decreased HDL cholesterol concentrations and increased ratios of total plasma to high density lipoprotein (HDL) cholesterol concentrations in comparison to their competitive counterparts. As noted in a previous section, the submissive males and females also had more extensive coronary artery atherosclerosis.

Rather than attempting to induce "stress" through behavioral or psychological manipulations, some investigators have attempted to mimic the physiological effects

of stress through administration of exogenous "stress" hormones. Dimsdale, Herd, and Hartley (20) found that exogenous doses of epinephrine resulted in significant increases in total plasma cholesterol concentrations of animals fed a diet very low in cholesterol (monkey chow).

Not all experiments have shown associations between psychosocial factors and elevated plasma lipid concentrations or between exogenous hormones and plasma lipid concentrations. For example, Kaplan et al. (13, 14, 21) found no significant associations between plasma lipid concentrations and either individual behavioral characteristics (competitiveness, submissiveness) or altered social environments (unstable social groups). Also, with regard to exogenous hormones, Sprague et al. (22) found no effect on plasma lipids when cortisol was added in quantities sufficient to prevent diurnal variation in cortisol concentrations. Despite these negative findings, the data, on balance, indicate the likelihood that in monkeys, as well as human beings, certain behavioral and psychosocial conditions (and the physiological states likely to accompany these conditions) can have a significant impact on serum lipid concentrations and through this mechanism may affect atherosclerosis.

GENDER AND REPRODUCTIVE STATUS

Overview

Pre-menopausal white women are relatively protected against coronary artery atherosclerosis and are at lower risk of CHD when compared to white men of similar age. The mechanism(s) involved in this "female protection" are understood poorly. Differences in exposure to "traditional" risk factors for ischemic heart disease account for some of the male-female differences but much remains to be explained. The evidence regarding the influence of menopause is somewhat contradictory, but most human population studies have found evidence for increased severity of coronary artery atherosclerosis (23, 24) and increased risk of CHD (25–32) in women experiencing natural or surgical menopause. Other studies have found no relationship (33–36). Based on these observations it has been speculated widely that estrogen is responsible for the protection of premenopausal white women, and the estrogen-deficiency state accompanying menopause is responsible for increased risk of CHD in postmenopausal women. This speculation is based, at least in part, on the well-known association between exogenous administration of estrogens and alterations in plasma lipid and lipoprotein profiles in a direction associated with diminished risk of ischemic heart disease, i.e., decreased LDL, increased HDL.

Male-female differences in plasma lipids and lipoproteins and atherosclerosis

The results of a recent series of studies have shown that female cynomolgus macaques are relatively protected against coronary artery atherosclerosis when compared to males, and that there are male-female differences in plasma lipids and lipoproteins (12, 21, 37).

Rudel and Pitts (37) described male-female differences in plasma lipids and lipoproteins in 40 cynomolgus monkeys with diet-induced hyperlipoproteinemia. Plasma lipoproteins from individual monkeys were separated by agarose column chromatography and characterized biochemically. In both males and females LDL was the fraction that showed the greatest increase. LDL mass concentrations were not different between males and females, but males responded to increased dietary cholesterol with an increase in LDL molecular weight, while females responded with an increase in the number of LDL particles, i.e., increased micromolar concentration. This size difference was found to be due principally to the presence of more cholesteryl ester in the LDL particles of the males. Also, the females showed a tendency to have higher HDL concentrations and different HDL composition than the males. Females had a higher percentage of protein and lower percentages of cholesterol and cholesteryl ester in HDL.

Hamm et al. (12) described male-female differences in severity of atherosclerosis in 16 male and 16 female cynomolgus macaques fed an atherogenic diet for 16 months. At necropsy, males were found to have significantly greater atherosclerotic stenosis of coronary and iliac arteries than did females, and this effect was independent of male-female differences in plasma lipids and lipoproteins. Severity of coronary artery atherosclerosis was found to be inversely correlated with the HDL cholesterol concentration in both males and females.

Kaplan et al. (21) described male-female differences in plasma lipids and atherosclerosis of 15 male and 23 female cynomolgus macaques fed a moderately atherogenic diet for 30 months. Males were found to have more extensive atherosclerosis in the coronary arteries and carotid bifurcations. In this experiment males had significantly lower plasma HDL cholesterol concentrations (33 mg/dl versus 39 mg/dl) and significantly higher systolic blood pressure (105 mm Hg versus 96 mm Hg). As in Hamm's study, dominant females were protected against diet-induced atherosclerosis when compared to subordinate females. In contrast to previous studies of males, this protection was independent of the social environment, i.e., it occurred in both stable and unstable groupings. These authors postulate that psychosocial stress associated with low social status accelerated atherogenesis by its influence on ovarian endocrine

function, i.e., many socially subordinate individuals were affected with chronic ovarian dysfunction.

The studies of Hamm et al. (12) and Kaplan et al. (21) indicate that female cynomolgus monkeys share with white women a relative protection against coronary artery atherosclerosis when compared to white men of the same age and suggest that social factors are capable of abolishing this relative protection.

Ovarian influences on plasma lipids, lipoproteins and atherosclerosis

Two studies have dealt with the influence of ovarian function on plasma lipids and atherosclerosis. One of these offered preliminary evidence for a mechanism by which negative psychosocial factors induce ovarian endocrine dysfunction, thereby altering plasma lipid concentrations and abolishing female protection.

McGill et al. (38) compared plasma lipids, lipoproteins, and atherosclerosis in hysterectomized and ovariectomized baboons fed an atherogenic diet. In this study there was no effect of ovariectomy on concentrations of cholesterol, triglyceride, and phospholipid in whole plasma, LDL, or HDL, or in extent of atherosclerosis of coronary, aorta, carotid, brachial, or iliac-femoral arteries. Also, there was no effect of estrogen replacement therapy on extent of atherosclerosis in ovariectomized baboons.

A subsequent study by our group (39) addressed the influences of ovariectomy and social status on extent of atherosclerosis in the cynomolgus macaque. In this study ovariectomy resulted in a more atherogenic plasma lipid pattern (increased total plasma and LDL cholesterol concentration) and two- to tenfold increases in extent of coronary artery, carotid artery, and iliac-femoral artery atherosclerosis. Findings from this study also suggest that alterations in hypothalamo-pituitary or adrenocortical function, associated with the stressful effect of low social status, influence atherogenesis in females of this species through influences on ovarian endocrine function. Among females with intact ovaries, low social status was associated with abnormal ovarian endocrine function (high frequencies of anovulatory cycles and cycles with progesterone-deficient luteal phases). Females with a particularly high rate of ovarian dysfunction (mean = 70% of cycles) could not be distinguished from ovariectomized females as regards plasma lipids (increased total plasma and LDL cholesterol concentrations) and increased extent of coronary artery atherosclerosis. Normal ovarian function was associated with high social status, a less atherogenic plasma lipid pattern, and protection against advanced coronary artery atherosclerosis. These findings offered preliminary evidence that stress-induced chronic ovarian endocrine dysfunction associated with low social status may approximate the

endocrine deficiencies associated with ovariectomy and therefore result in alterations in plasma lipid profiles and increased extent of atherosclerosis similar to those observed in ovariectomized females.

In summary, female cynomolgus monkeys seem to share with premenopausal white women a relative protection against coronary artery atherosclerosis when compared to males of the same age. Also, evidence exists that psychosocial factors can abolish this relative protection, and that this effect may be mediated by chronic suppression of ovarian endocrine function. Ovarian function appears to be an important factor because, as in human females, premature loss of ovarian function due to ovariectomy also seems to abolish this relative protection. The atherogenic effect of impaired or absent ovarian function can be explained, in part, by increases in total plasma cholesterol and LDL cholesterol concentrations. In this species, ovarian endocrine function seems to play an important role in regulation of plasma lipids and lipoproteins and in the atherosclerotic process. ■

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