Social Status, Social Stress and Fat Distribution in Primates

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INTRODUCTION

The relationship between the stress associated with low social status and disease susceptibility is apparent in human and non-human primates. In human beings, low socioeconomic status is associated with increased mortality from all causes, increased coronary heart disease (CHD) morbidity and mortality, increased rates of depression, the prevalence of the metabolic syndrome, and central obesity (1). We have studied these relationships in female cynomolgus monkeys for many years. Like human beings, low social status (subordinate) female monkeys are more susceptible than their dominant counterparts to a number of pathological processes that result in disease, including depression and coronary artery atherosclerosis. This chapter will focus on the relationship between social status, fat distribution patterns, and two disease endpoints in adult female cynomolgus monkeys, coronary heart disease risk and depression.

A NONHUMAN PRIMATE MODEL OF CORONARY ARTERY ATHEROSCLEROSIS AND CHD RISK

Atherosclerosis (an accumulation of fatty, connective, and necrotic tissue) of the coronary arteries is the principal pathological process which causes CHD. Cynomolgus monkeys (Macaca fascicularis) are currently the only animal model of sex differences in susceptibility to diet-induced atherogenesis. Among Caucasians in Western society, men have about twice the incidence of CHD and twice as extensive coronary artery atherosclerosis as women (2–4). The male to female ratio of coronary artery atherosclerosis extent in cynomolgus monkeys is also about 2:1. Like women, female cynomolgus monkeys are protected against atherosclerosis relative to their male counterparts (5).

Female cynomolgus monkeys have menstrual cycles that are similar to those of women in terms of length and cyclic hormone fluctuations (6,7). Following bilateral ovariectomy, extensive coronary artery atherosclerosis develops in females in amounts that are indistinguishable from those of males (8). CHD risk is also increased in oophorectomized and postmenopausal women (9). Subcutaneous replacement of estradiol, or estradiol and progesterone in physiological doses protects against atherosclerosis in female monkeys (10), and hormone replacement therapy (HRT) is associated with decreased CHD risk in postmenopausal women (11). Thus, ovarian function, and in particular estradiol, is implicated in the phenomenon of female protection, both in women and in female cynomolgus macaques.
PSYCHOSOCIAL FACTORS THAT INFLUENCE CORONARY ARTERY ATHEROSCLEROSIS AND CHD RISK IN FEMALE MONKEYS

Social Status

Cynomolgus monkeys typically live in large social groups that are characterized by complex social relationships. Complex social living includes the possibility of social stress effects on health. A major social organizing mechanism of monkey society is the social status hierarchy (12). Female monkeys with low social status, or subordinates, are behaviorally and physiologically different from dominants.

The distinguishing behavioral characteristics of subordinates are depicted in Figure 15.1. Subordinate females are the recipients of about three times the hostility or aggression of their dominant counterparts. They are groomed less, i.e., they spend less time in positive affiliative behavior. They spend more time vigilantly scanning their social group than dominants. The purpose of this vigilant scanning appears to be to track and avoid dominants in order to avoid aggressive interactions. Subordinates also spend significantly more time alone than dominant females (13–15). Primates typically communicate non-verbally by touch, facial expressions and body language or postures. Although human primates are able to communicate with language, they still rely heavily on non-verbal communication. When a female monkey spends time alone, it means that the monkey is not in physical contact or within touching distance of another monkey. Rather, the monkey is socially isolated. This is intriguing given the observations in human beings that suggest that social support is associated with reduced CHD risk, and observations in monkeys suggesting that social isolation increased coronary artery atherosclerosis and heart rate (16–18). Thus, it seems that subordinates are subject to hostility and have very little social support.

Physiological characteristics of subordinates that distinguish them from dominants include differences in measurements of adrenal function. Following dexamethasone suppression, the adrenal glands of subordinate females hypersecrete cortisol in response to an adrenocorticotropic hormone challenge, and are also relatively insensitive to cortisol negative feedback (15). Since the hypersecretion of cortisol is typically viewed as indicative of a stressed individual, these findings imply that, in general, subordinate females are stressed females.

Subordinate females also have a greater number of abnormal menstrual cycles than dominant females (8). Progesterone concentrations are lower during the luteal phase, and estradiol concentrations are lower in the follicular phase of the menstrual cycles of subordinate females. Moderately low luteal phase progesterone concentrations indicate that although ovulation may have occurred, the luteal phase was hormonally deficient. Very low luteal phase progesterone concentrations indicate an anovulatory cycle (19,20). Thus, stressed, subordinate females have poor ovarian function compared to dominants. Subordinate females with poor ovarian function have more coronary artery atherosclerosis than their dominant counterparts (Figure 15.2). Indeed, the coronary artery atherosclerosis extent in these subordinate, stressed females is comparable to that found in both ovariectomized females and males (5,8).

The effects of stress on ovarian function in women are difficult to evaluate because of the difficulties in characterizing menstrual cycle quality over long periods of time. However, the results of several studies are consistent with the hypothesis that stress can have a deleterious effect on ovarian function in women (21–23). Furthermore, mechan-
istic pathways relating stress to impaired reproductive function in female primates have been identified, suggesting that the stress–ovarian function impairment hypothesis is plausible from a physiological perspective. Activation of the hypothalamic-pituitary-adrenal axis, endogenous opioid pathways, increased prolactin release, and changes in sensitivity to gonadal steroid hormone feedback have all been proposed to mediate the effects of behavioral stress on the reproductive system (24–30). Intriguingly, women with hypothalamic amenorrhea also have increased hypothalamic-pituitary-adrenal activity similar to that observed in subordinate female cynomolgus monkeys (31). The relationship between poor ovarian function during the premenopausal years and CHD risk is also difficult to ascertain in women due to the double challenge of characterizing ovarian function, and detecting an adequate number of clinical CHD events. However, La Vecchia reported that women with a history of irregular menstrual cycles are at increased risk for CHD (32).

Ovarian hormones (particularly estradiol) are also associated with the function of the coronary arteries. In response to neuroendocrine signals, coronary arteries either dilate or constrict to modulate the flow of blood to the heart. Inappropriate coronary artery constriction, or vasospasm, early in life may change flow dynamics, injuring the epithelium and exacerbating atherosclerosis. Coronary vasospasm later in life in the presence of exacerbated atherosclerosis may increase the likelihood of myocardial infarction. In cynomolgus monkeys, the coronary arteries of normal cycling females dilate in response to acetylcholine infused directly into the coronary artery, whereas those of ovariectomized females constrict. The dilation response can be restored in ovariectomized females by administering estradiol, i.e. estrogen replacement therapy (33,34). The coronary arteries of dominant females with good ovarian function dilate in response to an infusion of acetylcholine, whereas those of subordinate females with poor ovarian function constrict in response to acetylcholine (35). Thus, female primates with poor ovarian function may be at increased CHD risk for two reasons: (1) impaired coronary artery function, and (2) increased atherogenesis.

Ovarian function declines at menopause, particularly the production of estradiol and progesterone. Importantly, clinically detectable events occur most frequently during and after the menopausal decline in ovarian function. Thus, the impact of premenopausal ovarian function on CHD risk may be temporally separate from the clinical manifestation of CHD. However, atherogenesis is a dynamic process that occurs over a lifetime. We hypothesize that atherogenesis during young and middle adulthood may be accelerated among socially stressed women. These women enter the menopausal years with exacerbated atherosclerosis. During the estrogen-deficient menopausal years, exacerbated atherosclerosis, combined with a more atherogenic lipid profile and increased likelihood of coronary vasospasm, result in increased CHD among women who experienced excessive premenopausal social stress.

Social Status, Social Stress, and Depression

Social stress is believed to precipitate depression (36–40) Unfortunately, depressive disorders are prevalent and the rate of occurrence is increasing (41). The results of several studies suggest that low social status is associated with increased risk of depression, although the nature of the relationship is unclear (42,43). In one prospective study in which low social status predicted first onset of major depressive disorder, a lack of social support (social isolation) appeared to mediate this relationship, at least in part (44). Thus, social support may reduce risk of depression following stressful life events (45,46).
Figure 15.3 The effects of low social status on the prevalence of behavioral depression in female monkeys. (Based on data from Shively et al. (47))

The hypothesis that social subordination is stressful, and results in a depressive response in some individuals, was examined in the following experiment. Forty-eight adult female monkeys were fed an atherogenic diet, housed in small social groups, and social status was altered in half of the animals such that half of the subordinates became dominant, and half of the dominants became subordinate (Figure 15.3).

Current subordinates hypersecreted cortisol, were insensitive to negative feedback, and had suppressed reproductive function. Current subordinates received more aggression, engaged in less affiliation, and spent more time alone than dominants. Furthermore, they spent more time fearfully scanning the social environment and displayed more behavioral depression than dominants. Current subordinates with a history of social subordination were preferentially susceptible to a behavioral depression response. The results of this experiment confirm that the stress of social subordination causes hypothalamic-pituitary- adrenal and ovarian dysfunction, and support the hypothesis that chronic, low-intensity social stress may result in depression in susceptible individuals (15,47).

**Interim Summary**

Low social status in female primates is associated with worsened coronary artery atherosclerosis. These females are the recipients of hostility/aggression, and they are also relatively socially isolated. Females with low social status are also preferentially susceptible to a depressive response to social stress, particularly if they have a history of social subordination.

Social stress increases the risk of CHD and precipitates bouts of depression in human beings. Low socioeconomic status is associated with increased risk of depression and CHD. The relationship between socioeconomic status and health in human beings is linear; there is no apparent threshold. The upper class has better health than the upper middle class, and so on down the hierarchy. Risk of disease is increased even among relatively low social status employed individuals with adequate health care, nutrition, and shelter. Thus, the health gradient does not appear to be due to poverty, per se (48). Perhaps the reason low social status is associated with increased risk of disease in human beings is because low social status is stressful. Like the monkeys, human primates with low social status have relatively little control over their lives, and low control is a source of chronic stress that could engender physiological responses that are deleterious to health.

**REGIONAL ADIPOSITY AND CORONARY ARTERY ATHEROSCLEROSIS IN FEMALES**

We examined the relationship between social status, social stress, and central obesity in a series of studies of social group-living cynomolgus monkeys. In all of the experiments discussed below, adult monkeys were fed a moderately atherogenic diet that contained between 0.25 and 0.39 mg cholesterol/calorie and 40% of calories from fat (primarily saturated fat). These monkeys were housed in small social groups of four to six animals of the same gender.

The initial investigation of regional adiposity and coronary artery atherosclerosis was a retrospective necropsy study of 36 adult female cynomolgus monkeys (49). Whole body and regional adiposity were determined using anthropometric measurements. Whole body adiposity did not predict the extent of coronary artery atherosclerosis. However, the relative amount of subcutaneous fat deposited on the
trunk (estimated by the ratio of subscapular:triceps skinfold thickness) versus the periphery was associated with coronary artery atherosclerosis extent. Females in the top half of the distribution of subscapular:triceps skinfold ratio had more than three times as much coronary artery atherosclerosis than females in the lower half of the distribution (49).

**REGIONAL ADIPOSY AND METABOLIC ABERRATIONS**

Female cynomolgus monkeys with high central fat have higher glucose and insulin concentrations in an intravenous glucose tolerance test than females with relatively low central fat. They also have higher blood pressure and total plasma cholesterol concentrations, and lower HDL cholesterol concentrations compared to low central fat females (50). In women, central obesity has been linked with a metabolic syndrome consisting of impaired glucose tolerance, raised serum triglycerides and low levels of HDL cholesterol (51).

**SOCIAL SUBORDINATION AND REGIONAL ADIPOSY**

To determine characteristics of subordinate females which increase their risk of coronary artery atherosclerosis, whole body and regional adiposity were evaluated using anthropometric measurements in 75 adult female cynomolgus monkeys (52,53). Subordinate females were more likely than dominants to be in the top half of the distribution of the subscapular:triceps skinfold ratio. This suggested the possibility of a relationship between stress and patterns of fat distribution that is associated with increased coronary artery atherosclerosis in monkeys and increased risk of coronary heart disease in women. Since that observation, we have attempted to further our understanding of the potential relationship between stress and fat distribution.

**SOCIAL STRESS AND REGIONAL ADIPOSY IN MALES**

Since truncal fat patterns are associated with androgenic hormone profiles, it is possible that the androgenic fat distribution pattern observed more frequently in social subordinates is due to ovarian dysfunction. To begin to address this possibility, the relationship between stress and fat distribution patterns was studied in male monkeys. Coronary artery atherosclerosis is exacerbated in male cynomolgus monkeys when their social groups are repeatedly disrupted. Social disruption has been achieved in several experiments by altering the constituency of social groups frequently (e.g. every 4 weeks) for a 2-year period. Generally, the monkeys respond to alterations in group membership by increased aggression and decreased affiliation (54). Thus, repeated social reorganization was used as the stressor in the following study of males.

The monkeys were assigned to treatment groups using a method of stratified randomization that matched the groups for pretreatment plasma cholesterol concentrations. Pretreatment anthropometric measures were used to control for small (non-significant) differences in adiposity that were present prior to treatment. Computed tomography was used to measure intra-abdominal and subcutaneous abdominal fat in forty monkeys and regional skinfold thicknesses were also measured (55). Males that lived in the stress condition produced by repeated social reorganization had significantly higher ratios of intra-abdominal:subcutaneous (IA:SQ) abdominal fat (56).

This experiment provides important evidence supporting the hypothesis that social stress can alter regional fat deposition. The stressor was manipulated by the experimenter rather than resulting from social group living, as in the previous observation of an association between social status and regional fat deposition. These findings also indicate that stress can alter fat distribution patterns independent of ovarian function; however, the mechanism(s) that might relate these two factors remains to be determined.

**MECHANISMS MEDIATING THE RELATIONSHIP BETWEEN SOCIAL STRESS AND REGIONAL ADIPOSY**

To identify potential mechanisms through which social stress might alter fat deposition patterns, a study was recently completed in which behavior, the function of the hypothalamic-pituitary-adrenal
Table 15.1  Associations between abdominal fat distribution and behavioral characteristics of female monkeys

<table>
<thead>
<tr>
<th>IS: SQ</th>
<th>Low</th>
<th>High</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% time being groomed</td>
<td>12(1.3)</td>
<td>8(1.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>% time grooming</td>
<td>13(1.8)</td>
<td>7.5(0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>% time alone vigilant scan</td>
<td>36(2.2)</td>
<td>43(2.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>% time alone</td>
<td>45(2.6)</td>
<td>54(3.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>% mild aggression—attacker</td>
<td>31(6.3)</td>
<td>13(4.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>% mild aggression—victim</td>
<td>12(3.6)</td>
<td>46(9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>% severe aggression—attacker</td>
<td>19(3.5)</td>
<td>17(5.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>% severe aggression—victim</td>
<td>11(3.8)</td>
<td>31(9.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Social status (0 = Subordinate, 1 = Dominant)</td>
<td>0.6(0.1)</td>
<td>0.3(0.1)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

IA: SQ, Intra-abdominal to subcutaneous abdominal fat ratio as measured using computed tomography.

axis, and the sympathetic nervous system were characterized in female cynomolgus monkeys. Abdominal fat mass was characterized by computed tomography as previously described (49,55). The monkeys lived in their social groups for 2.5 years, and social behavior was recorded throughout this time period. Females above the mean of the ratio of IA:SQ abdominal fat mass were compared to females below the mean.

Females with high IA:SQ abdominal fat ratios spent less time in affiliative social interaction, were more frequently the victims of aggression, and were socially subordinate compared to females with low IA:SQ abdominal fat ratios (Table 15.1).

There was also a modest correlation between behavioral depression and the IA:SQ ratio (Spearman’s rho = 0.26, P = 0.05, 1-tailed test), suggesting that females with relatively greater amounts of intra-abdominal fat were more likely to display behavioral depression. Heart rate, a non-invasive indicator of sympathetic nervous system activity, was measured while the animals were in their social groups, using a telemetry system, from 15:00 h to 8:00 h the following day for three consecutive days. Heart rates of these animals are generally lowest at night, increase during the time of day when there is the most activity in their building, and decrease in the afternoon after the activity level in the building declines. Two months following the formation of social groups, there were no differences in high versus low IA:SQ females. However, by 24 months, differences between these groups had emerged. The heart rates of all females were similarly elevated during the day; however, in the afternoon and night, heart rates of the females in the high IA:SQ abdominal fat group were higher than those in the low group (P = ≤ 0.05; Figure 15.4).

Hypothalamic-pituitary-adrenal (HPA) function was assessed using a dexamethasone suppression test. Suppression of serum cortisol in response to dexamethasone was greater in females in the lower...
half of the distribution of IA:SQ abdominal fat mass ($P < 0.05$; Figure 15.5). This observation suggests that the central regulatory areas of the HPA axis of females with a relatively low IA:SQ ratio are more sensitive to circulatory cortisol concentrations than those with relatively high IA:SQ. Taken together, these data suggest that females with relatively greater amounts of visceral fat are also characterized by behavioral and physiological attributes indicative of chronic stress. Furthermore, the sympathetic nervous system and the HPA axis may mediate the relationship between social stress and regional adiposity. Our findings in cynomolgus monkeys support the hypothesis proposed by some that stress and a hypersensitive HPA axis are central abnormalities in abdominal obesity of human beings (51).

**SUMMARY**

In primates, abdominal obesity is associated with low social status, the metabolic syndrome, and increased risk of morbidity and mortality due to depression and cardiovascular disease. Data from studies of monkeys suggest that social stress may be an underlying cause. We hypothesize that the stress of social subordination or social instability causes increased sympathetic nervous and HPA function. The chronic stimulation of these two systems leads to increased blood pressure and heart rate, and imbalances in sex steroid production which result in injury to the artery wall, and deposition of fat in the viscera. Visceral fat depots in turn exacerbate the metabolic effects of stress. Some of these physiological stress responses affect the function of the brain, resulting in depression.

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**REFERENCES**


