Effects of Excess NaCl Intake on Blood Pressure and Cholesterol-Induced Atherosclerosis in the Monkey

BY MOTOOMI NAKAMURA, M.D., HIROAKI MURAKAMI, M.D., AND UMPEI SHIGEMI, M.D.

Abstract: Effects of Excess NaCl Intake on Blood Pressure and Cholesterol-Induced Atherosclerosis in the Monkey

- The *Macaca irus* is a monkey species that is highly susceptible to experimental cholesterol atherosclerosis of the aorta, coronary and cerebral arteries and cutaneous xanthomatosis-like lesions induced by feeding a diet high in cholesterol and/or coconut oil for 14 months.

The monkeys fed an atherogenic diet were divided into two groups: monkeys receiving excess sodium and controls. The excess sodium group showed a significantly higher systolic blood pressure as compared with the control group; however, elevation of blood pressure was mild and was not considered as significant hypertension.

The loading of excess sodium chloride in monkeys fed an atherogenic diet did not enhance severity of atherosclerosis of the aorta, coronary and cerebral arteries.

Additional Key Words

- *Macaca irus* (monkey)
- cerebral arteries
- predilection site
- xanthomatosis

...There is a considerable number of papers reporting on the lesser incidence and severity of coronary atherosclerosis as well as aortic atherosclerosis in the Japanese as evidenced by pathological, epidemiological and clinical findings. However, it became clear from a prospective population study that cerebral thrombosis is much higher in incidence than that of cerebral hemorrhage, even in the Japanese. It has been demonstrated also that there is a possible ethnic difference in severity of cerebral atherosclerosis between the Japanese and Americans in the direction of greater involvement in the Japanese cases. Angiographical and pathological studies revealed that the prevalent sites of advanced severe atherosclerotic changes of the Japanese differed from those in Americans. An epidemiological study demonstrated that the incidence of stroke in the Japanese was higher in the area where intake of salt was high. As far as we are aware, no detailed studies have been reported about the effects of feeding excess NaCl on blood pressure and an experimental atheromatosis, especially of the cerebral arteries in subhuman, primate species. It was hoped that data obtained from monkeys may be more directly related to understanding atherosclerosis, especially of the cerebral arteries of humans, than those obtained from lower animals, because of similarities between the monkey and man, including anatomy of the body and vascular system especially in brain, blood type, relative duration of periods of life, period of gestation and pregnancy, requirements for nutritional factors and susceptibility to many biological diseases. The present study was designed to study the effect of salt overloading on experimental atherosclerosis and blood pressure in primates.

Methods

EXPERIMENTAL ANIMALS

Twenty crab-eating monkeys (*Macaca irus*) from 4 to 14 years of age were housed in individual metal cages kept at a temperature of 25°C. They were fed laboratory monkey chow crackers (Oriental) with an addition of 125 mg vitamin C twice a week for approximately two months in the pretreatment period. During this observation period, clinical examinations, such as tuberculin test, chest x-ray, chemical analysis of plasma and bacteriological examinations of urine and feces, were performed and found to be normal clinically. All animals were in splendid condition with a fine coat and good musculature. They were well accustomed to laboratory chow during this period.

EXPERIMENTAL DIET AND SALT

After the two-month observation period, the monkeys were fed Purina monkey chow crackers (Oriental: 5% fat), approximately 30 gm per kilogram of body weight, and cholesterol for two months, and then fed a diet containing 100 gm of monkey chow crackers, 30 gm of coconut oil and cholesterol for an additional 12 months. Crackers were saturated with coconut oil overnight below 60°C. An amount of 0.5 gm cholesterol and 0.3 gm sugar per kilogram of body weight was given throughout the entire 14-month experiment. Cholesterol and sugar were mixed with a small amount of water and given as a knop once a day for six days a week. Vitamin C was given twice weekly throughout the...
experimental period. In this way, cholesterol and saturated fatty acids were given in a form that all monkeys regard as palatable. Twenty monkeys, who were fed a cholesterol-containing diet, were divided into two groups from the beginning of the experiment: namely, ten monkeys were given ordinary city tap water as a control group and the remaining ten monkeys were given 0.9% sodium chloride solution for drinking water (excess NaCl group). In the preliminary stage, we forced monkeys to drink more salty water; however, they refused it. At the end of the experimental period all 20 monkeys remained alive and active. The daily consumption of food and/or salt of all monkeys was measured.

MEASUREMENT OF BLOOD PRESSURE
The monkeys were trained to permit, in the cage, measurement of blood pressure over the brachial artery by use of a sphygmomanometer cuff for children without anesthesia. Blood pressure was determined usually at monthly intervals. Many animals eventually became tame after the initial period. We could measure only systolic blood pressure by palpation of pulse. At the end of the experiment, the animals were anesthetized with pentobarbital sodium and arterial pressure was measured directly through a catheter with a pressure transducer, and an ECG also was recorded.

PLASMA ChOLESTEROL LEVEL
Blood was withdrawn usually at monthly intervals from a vein of a lower extremity and plasma was obtained. Total cholesterol concentration was determined by the method of Zak.6

BODY WEIGHT
The body weight of each monkey was measured every month.

PATHOHISTOLOGICAL EXAMINATIONS
At the end of the fourteenth month of the feeding experiment, the monkeys were anesthetized and killed, and complete autopsies performed. The brain, heart, kidney, lungs, liver, spleen, pancreas, stomach, intestine, xanthoma-like skin lesion, and adrenals were removed and fixed with 10% formalin for routine histological study. The aorta and proximal portion (2 to 3 cm from the orifice) of the coronary arteries were stained with brilliant blue according to the method described by Insull,7 and surface area of involvement (SI) of lipid deposition was determined as percent of total surface area. Atheromatosis (lipid deposition) of the intracranial arteries was readily visible under dissection microscope, even in the earliest stage of its development, without brilliant blue staining. SI of the coronary and the presence of lesions in the cerebral arteries were examined under dissection microscope. Frozen sections of the liver, skin and arterial tissues were made for lipid staining. Also, the proximal portion of the aorta, the left anterior descending coronary artery, the myocardium supplied by the left anterior descending coronary artery and the portions of Y-shaped or T-shaped bifurcations of the cerebral arteries were fixed with formalin for routine histological examination. The functional portion of the basilar arteries to the posterior cerebral artery, and the inoculated portion of the anterior communicating artery to the right anterior cerebral artery, were chosen for routine histological examination. The remaining part of the aorta which includes the aortic arch, the thoracic and abdominal aortas, and a part of the liver were minced in 20 volumes of Folch mixture (chloroform/methanol = 2:1) and used for measurement of total cholesterol by the Zak method.6 Four monkeys (Nos. 8, 10, 17, and 18; table 1) were used for a study on incorporation of H3-cholesterol into various tissues, which will be published separately.

Results

WEIGHT
All monkeys except Nos. 7, 8, and 9 in the control group and Nos. 17 and 18 in the excess NaCl group gained weight on the atherogenic diet throughout the experiment, as shown in tables 1 and 2. No differences in weight changes were observed between the control and excess NaCl groups.

PLASMA CHOLESTEROL CONCENTRATION
As shown in figure 1, plasma total cholesterol of the animals increased slightly after using a diet containing cholesterol and low fat; there was a considerable rise in plasma cholesterol levels after the diet with cholesterol and coconut oil was begun as compared with before. Plasma cholesterol levels increased throughout the entire experimental period, reaching a mean of 800 mg/dl by the twelfth month. The only exceptions were monkeys 2, 3, 16 and 18, who never had

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<td>Mean</td>
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TABLE 2

Summary of Experimental Data of Monkeys on High Cholesterol

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Average* plasma cholesterol (mg/dl)</th>
<th>Systolic BP Average* BP (indirect)</th>
<th>Direct BP</th>
<th>Gain wt. (kg)</th>
<th>Aorta Lesions</th>
<th>Coron. Lesions</th>
<th>Cerebral Xanthomatosis</th>
<th>Cholesterol cone. (mg/gm Aorta)</th>
<th>Liver</th>
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*Mathematical average of values of plasma cholesterol or indirect systolic blood pressure determined 14 times during the entire experimental period was calculated.

†Presence (+) or absence (—) of microscopic lesions.

‡Examination was not performed.

FIGURE 1

Effect of cholesterol and coconut oil ingestion on plasma cholesterol of control and excess NaCl monkeys.

- - - - - Monkeys taking 0.9% NaCl solution (NaCl excess); o-----o Monkeys taking city tap water (control).

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plasma cholesterol levels above 350 mg/dl. Plasma cholesterol concentration was not statistically different between the control and excess NaCl groups, when the data were analyzed without regard to sex or age. A mathematical average of plasma cholesterol of each animal during the entire experimental period was calculated as an average plasma cholesterol, and its value was listed in table 2.

BLOOD PRESSURE

The average systolic blood pressure was 87 mm Hg in both groups when the experiment was started. The individual variation of blood pressure levels was considerable at the beginning but decreased at the later stage as shown in figure 2. A statistically significant increase of systolic blood pressure was found in the excess NaCl group after eight months until the end of the experiment. Also, a significant difference between the two groups was found in the systolic blood pressure recorded under anesthesia before sacrifice. However, there was only one monkey (No. 11) whose blood pressure rose above 150 mm Hg. One monkey (No. 17) in the excess NaCl group had an increase of blood pressure only at the end of the experiment. The average difference of systolic blood pressures between the control and excess NaCl groups was only 13 mm Hg. Therefore, an elevation of blood pressure in monkeys with excess salt was not considered as significant hypertension. A mathematical average of systolic blood pressure of each animal during the entire experimental period and direct systolic blood pressure are listed in table 2.

The uptake amount of 0.9% NaCl solution of the excess NaCl group was larger than that of tap water in the control group. The average amount of NaCl taken in animals of the excess NaCl group during the entire period was approximately 5 gm per day.

MACROSCOPIC LIPID DEPOSITION AND LIPID CONCENTRATION OF THE ARTERIES, SKIN AND OTHER ORGANS

In seven of 20 monkeys fed an atherogenic diet, many yellowish infiltrates were found in the skin, beginning over the limbs, hip, abdominal skin and face, but not on the fingers, hand or foot. The skin infiltrates (xanthomatosis) were dull yellow, 1 to 3 mm in diameter, and irregular in outline. There was no inflammation around the lesion. No tender subcutaneous nodules were seen. The development of skin xanthomatosis became marked when plasma cholesterol concentration reached around 1,000 mg/dl. The monkeys appeared robust when autopsy was performed.

As shown in table 2, macroscopic lipid deposition of the aorta was found in 18 of 20 monkeys, of the coronary arteries in 9 of 20, and of the cerebral arteries in 4 of 20 monkeys. When the average plasma cholesterol was above 300 mg/dl, the animals usually showed a macroscopic aortic lipid deposition. In two
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animals (Nos. 14 and 19), some fatty plaque formations were observed in the aorta. As shown in table 2, total cholesterol concentration of the aorta showing macroscopic lesions was above 11 mg per gram of unfat dried tissue. There was a significant correlation between SI and total cholesterol concentration of the aorta ($r = 0.72$, $P < 0.01$). There was a significant correlation between an average plasma cholesterol and SI of the aorta ($P < 0.05$, $r = 0.50$). There was no significant correlation between SI of the aorta or coronary or cerebral arteries and the average level of systolic blood pressure. In the aorta, lipid deposition was usually remarkable in the ascending aorta and aortic arch, especially around the orifice of the branching large arteries, and was lesser in thoracic or abdominal portion. No significant difference in degree of macroscopic lipid deposition of the arteries and liver was found between the control and excess NaCl groups.

In four monkeys showing a significant macroscopic lipid deposition in the cerebral arteries, lesions were found at the basilar artery in four animals, at the anterior communicating arteries in two animals, and at the vertebral artery in one animal.

HISTOLOGICAL EXAMINATION

Cerebral Arteries

Among 20 monkeys, four monkeys (Nos. 8, 10, 17 and 18) were not used for histological examination because of radioisotope studies. In the remaining 16 monkeys, six of eight monkeys of the excess NaCl group and four of eight control animals demonstrated a focal accumulation of foam cells associated with a slight reduplication of the internal elastic lamina in the intracranial cerebral arteries (fig. 3). However, prominent fragmentation of the internal elastic lamina or fibrosis of the intima was not observed in the cerebral arteries. Lesions were localized only in the intima and never extended to the media.

There was no apparent difference in the incidence of histological lesions in the cerebral arteries between the control and excess NaCl groups. The average blood pressure of monkeys showing histological lesions was $101 \pm 8$ mm Hg (mean $\pm$ SD [N = 10]), which was not significantly higher than that of monkeys showing no histological lesions, being $93 \pm 4$ mm Hg (N = 6). Average plasma cholesterol concentration of animals showing histological lesions was $650 \pm 194$ mg/dl (mean $\pm$ SD), which was not significantly higher than that of animals showing no lesion ($462 \pm 245$ mg/dl).

Coronary Artery

The proximal part of the left anterior descending coronary artery of 16 monkeys was used for histological examination as in the case of the cerebral arteries. Foam cell accumulation in the intima was found in 10 of 16 monkeys as shown in table 2. Fibrosis of the intimal lesions was not prominent. In the animals showing severe foam cell accumulation, lesions were extended into media and fragmentation of elastic membrane was found as shown in figure 4.

Lesions were found in animals whose plasma cholesterol level was remarkably elevated; however, no statistically significant difference of average plasma cholesterol was found between the animals showing histological lesions ($623 \pm 178$; mean $\pm$ SD [N = 10]) and the animals showing no lesions ($507 \pm 327$ [N = 6]), probably because of individual variability. Also, there was no significant difference in average systolic blood pressure between the animals having lesions and those with no lesions.

FIGURE

Section of the basilar artery showing an accumulation of foam cells in the intima. Internal elastic lamina shows a slight reduplication in part (Monkey No. 19). Hematoxylin-toxin stain. X 73.

FIGURE

Section of the left anterior descending coronary artery showing a narrowing by an accumulation of foam cells extending into media and fragmentation of elastic fibers (Monkey No. 5). Hematoxylin-eosin stain, X 33.
The most extensive lesions were found in the aorta and its immediate branches. The intimal fatty plaques consisted of a collagenous matrix interspersed with clumps of foam cells. Occasionally in the deeper portions of the intimal lesions, extracellular accumulation of lipids was seen. These were usually associated with focal disruption of the internal elastic membrane (fig. 5).

Fragmentation of the elastic lamina and foam cell accumulation invading into media were found in 14 of 16 monkeys examined histologically. Vascularization of the media, ulceration and thrombus formation were not observed in the present study.

Other Organs
Liver cells in the central and intermediate areas of the lobules showed a remarkable fat deposition; however, liver cells in the peripheral areas showed a slight degree of lipid deposition.

Figure 6 shows histological findings of xanthomatous lesions of the skin. The earliest change of the skin was the appearance of new capillaries mantled with foam cells within the dermal papillae. Larger, older-appearing lesions occurred at deeper levels and consisted of granulomatous masses of foam cells with increasing collagen deposition. These foam cells are similar to those in the arterial intimal lesions.

There was no evidence of infarction in the myocardium and brain. ECG showed no significant changes. The average heart weight to body weight ratio (tissue gram per kilogram of body weight) of each animal was 3.5 ± 0.3 in the control group and 3.7 ± 0.7 in the excess NaCl group, respectively (mean ± SD). There was no statistical difference of all tissue weight-body weight ratio, including the heart, between the control and the excess NaCl groups. Lipid accumulation was negligible in the spleen and kidney, except for the liver.

Discussion
It is apparent from the present experiment that a disease which resembled human xanthomatosis and atherosclerosis of the aorta and coronary and cerebral arteries developed in crab-eating monkeys by feeding them a diet containing high cholesterol for 14 months. There appeared to be no difference in response to dietary regimen between older and younger animals, although statistical analysis was not performed because of small group size and magnitude of variability. There is a study performed by Kramsch and Hollander on the experimental atherosclerosis of crab-eating monkeys (Macaca irus). They reported that the consistent predominance of coronary atherosclerosis over lesions in other arteries was an unusual feature of this monkey species and no cerebral atherosclerosis was found. However, we could not confirm such species specificity. In the present study, monkeys in whom plasma cholesterol level remained below 300 mg/dl showed no macroscopic atherosclerotic lesions in the aorta, coronary and cerebral arteries. In monkeys in whom plasma cholesterol was
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maintained above 300 mg/dl, arterial macroscopic lesions were found predominantly in the aorta, less frequently in the coronary arteries and rarely in the cerebral arteries. The prevalent site of aortic atherosclerosis in the monkeys in this study was ascending, arch and thoracic aortas, which differed from the site of advanced atherosclerosis in older humans whose lesions were predominantly in the abdominal aorta, but was similar to the site of fatty streaks in young humans, especially of xanthomatosis.

Cutaneous xanthomatosis was found after several months of the high cholesterol and coconut oil feeding regimen; the plasma cholesterol concentration reached approximately 800 mg/dl or more. However, we did not find large cutaneous nodules sized about 1 to 2 cm raised which was reported by Mann and Andrus in a rhesus monkey. All animals in whom macroscopic lipid deposition was found in the aorta and coronary and cerebral arteries had a significant increase of plasma cholesterol, being more than 400 mg/dl for more than ten months. The relationship between macroscopic surface involvement or cholesterol content of the aorta and plasma cholesterol concentration was highly significant statistically. From the above considerations, it appeared that arterial and skinn lesions observed in the present study resulted from the experimentally induced hypercholesterolemia. We could not confirm the predominant involvement of coronary artery over other arteries as an unusual feature of this monkey species.

Many studies on experimental atherosclerosis in primates were reported, but surprisingly, examinations of spontaneous or experimental atherosclerosis of the intracranial arteries have been less detailed than that of the larger elastic and muscular arteries and coronary vessels. Chawla et al. and Clarkson found no spontaneous lipid deposition in the cerebral arteries of either rhesus or squirrel monkeys. Only in a rhesus monkey in whom plasma cholesterol was raised by feeding excess dietary cholesterol and maintained above 600 or 1,000 mg/dl for three or four years, was a significant cerebral atheromatosis found. However, Bullock et al. and Kramsch and Holland reported that no unequivocal atherosclerosis was found in the cerebral arteries, though severe aortic and coronary atherosclerosis was found. Andrus et al. reported that cerebral atherosclerosis in the chimpanzee was not related at all to plasma cholesterol concentration with or without an addition of dietary cholesterol.

In the present study the lipid deposition of the intracranial cerebral arteries was found macroscopically in four and microscopically in ten monkeys whose plasma cholesterol was above 400 mg/dl; however, there was no statistically significant difference in plasma cholesterol concentration, blood pressure, age and with or without excess dietary salt between monkeys with cerebral atheromatosis and those without cerebral atheromatosis. The prevalent site of experimental cholesterol atherosclerosis in the intracranial arteries was the basilar arteries in the present study, which was consonant with other studies in primates.

We found no lesions in the middle cerebral arteries or internal carotid arteries where early lesions were frequently found in humans.

Surface involvement of the aorta was not related to the level of systolic blood pressure, probably because the changes of blood pressure by loading salt did not exceed 20 mm Hg. Also, excess sodium chloride alone was not shown to accelerate development of cerebral atherosclerosis in primates during one year or so. Experimental hypertension has been induced by feeding excess sodium chloride in rats, rabbits and chickens. In these studies, relatively higher amounts of salt were given than in the present study.

Further study will be required in order to elucidate effects of salt for longer periods of time. It would be of interest to study the effect of salt on cerebral atherosclerosis in primates who have significant hypertension and moderate hypercholesterolemia.

Summary
Experimental cholesterol atherosclerosis of the aorta and coronary and cerebral arteries was induced in Macaca irus monkeys by feeding them a diet high in cholesterol and/or coconut oil for 14 months.

An excess level of sodium chloride was associated with mild elevation of blood pressure but no increase in severity of the atherosclerosis.

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