Experimental Production of Syndrome of Obesity, Hyperinsulinemia and Hyperlipidemia in Monkeys[1] (36599)

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(Introduced by F. P. Brooks)

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Elevated serum lipid levels and/or abnormal carbohydrate–insulin mechanisms have been observed with increasing frequency in obese persons (13). In addition, abnormalities in lipid/carbohydrate metabolism have also been demonstrated in atherosclerotic and atherosclerotic prone individuals (6, 8, 9, 12, 14). Similar metabolic abnormalities have been produced in rats made obese by lesions of the hypothalamus (3). In this paper we report the development of hyperbeta- and hyperprebeta-lipoproteinemia, decreased glucose tolerance and abnormal serum insulin levels in association with obesity in a subhuman primate.

Methods. Subjects. Data are reported on 19 male and 2 female monkeys (*Macaca mulatta*) obtained commercially. The animals were classified arbitrarily as obese if their body weights exceeded 15 kg. Two groups of obese animals were studied: in one obesity was obtained by placement of lesions in the hypothalamus; in the other, obesity occurred spontaneously when the animals reached "middle age" (12–14 years old). Brain lesions were aimed at the ventromedial area of the hypothalamus, using the procedures of Hamilton and Brobeck (5). When properly placed, these lesions were followed by hyperphagia and obesity. Two of the spontaneously obese animals developed overt diabetes. No insulin was given for treatment of hyperglycemia and glycosuria. Throughout the study all animals were housed in individual cages and fed Purina Monkey Chow (15% protein) *ad libitum*. Supplemental nourishment included one multiple vitamin tablet three times a week. Water was available *ad libitum*.

Procedure. Glucose tolerance tests were administered to all animals after overnight fasts. The tests were conducted under sodium amytal anesthesia by iv injection of 20 ml of 50% glucose solution. Serial blood samples were taken just before the injection and 5, 10, 20, 40, and 60 min after injection and analyzed for glucose (glucose oxidase method) and immunoreactive insulin (IRI). Serum IRI was measured in triplicate by a modified, double antibody method of Hales and Randle (4) using ^{125}I and insulin binding reagent obtained pure from Amersham/Searle Co. The IRI results are expressed in microunit equivalents of human crystalline insulin per milliliter of serum. The "IRI response" of each animal is the sum of the IRI increments above fasting levels in the 5 blood samples. Blood glucose diminution rate is expressed as percentage per minute fall from peak postinjection values [K-glucose (11)].

Plasma cholesterol, triglycerides, free fatty acids (FFA), lipoproteins and blood glucose were determined in unanesthesized animals after an overnight fast. Plasma cholesterol and triglyceride were determined by established methods (1, 15), lipoprotein by electrophoresis according to the method of Lees and Hatch as modified by Masket (10) and FFA by the method of Dole and Meinertz (2).

Results. Figure 1 shows examples of hypothalamic obese, middle-aged spontaneously obese and middle-aged lean monkeys. The data in Table I show that animals with spon-

[1] Supported in part by Grant HE 08805, National Heart and Lung Institute, MH 10179, National Institute of Mental Health and by a grant from the Heart Association of Southeastern Pennsylvania. The technical assistance of David Lewis is greatly appreciated.

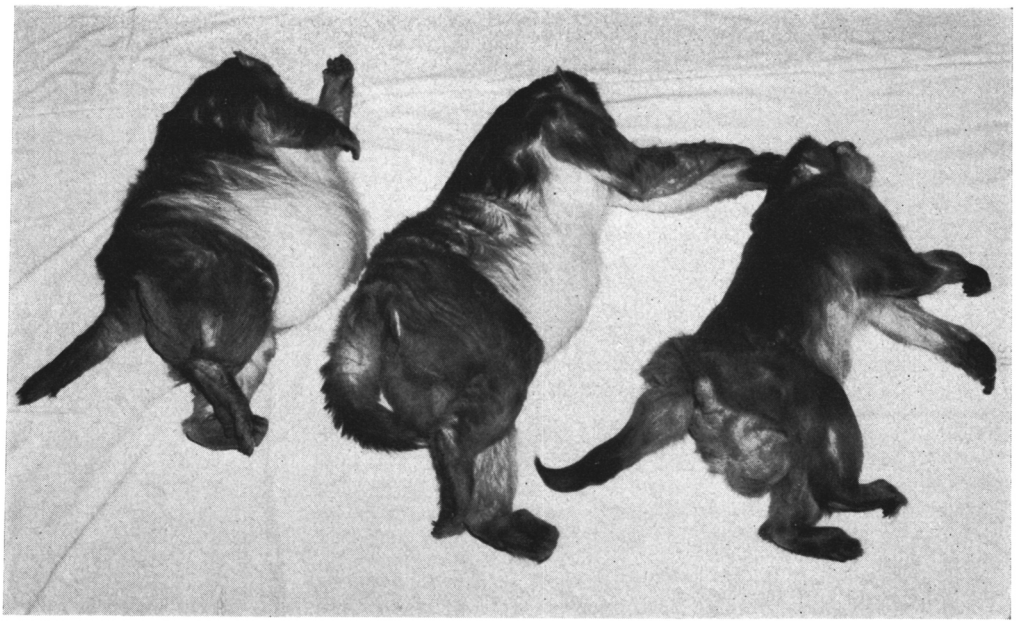

FIG. 1. Obesity and leaness in mature rhesus monkeys. Left to right: Animal with hypothalamic obesity (22.7 kg), animal with spontaneous obesity (21.0 kg) and lean animal (9.7 kg). All animals are male, approximately 12 years old and have been tranquilized.

taneous and with hypothalamic obesity maintained normal fasting blood glucose levels, but had a reduced IRI response to glucose loading. The K-glucose values of the obese animals were significantly lower than those of the lean monkeys. The two animals with overt diabetes showed essentially no IRI response. Serum IRI levels of these animals supposedly are maintained at their maxima in the fasting state and show little or no response to the glucose challenge.

The plasma lipid and liproprotein data are presented in Table II. The mean fasting FFA level of the spontaneously obese group was significantly higher than that of the lean animals without metabolic abnormality. Abnormally high fasting FFA levels were consistently demonstrable in the two diabetic monkeys. The development of hyperbeta- and hyperprebeta-lipoproteinemia in both groups of obese animals (Fig. 2b and c) was reflected in significant elevations of their serum cholesterol and triglyceride levels. The hyperlipidemia and hyperlipoproteinemia were

TABLE I. Carbohydrate Metabolism and Serum Insulin (IRI) Activity of Monkeys with and without Metabolic Abnormality.

Animal groups (no.)	Fasting blood glucose (mg/100 ml; mean ± SE)	K-glucose (% diminution/min; mean ± SE)	IRI (μU/ml; mean ± SE)	
			Basal	Response
No metabolic abnormality (7)	87.9 ± 5.2	3.80 ± 0.11	92.0 ± 13.4	2,571.4 ± 273.2
Obesity, spontaneous (7)	78.5 ± 2.4	2.46 ± 0.24[a]	594.9 ± 70.4[a]	1,348.1 ± 151.9[a]
Obesity, hypothalamic (5)	70.4 ± 2.9	2.05 ± 0.14[a]	619.8 ± 55.5[a]	1,004.6 ± 254.5[a]
Diabetic (2)	(254–320)[b]	(0.70–0.87)[b]	(35–94)[b]	(37–97)[b]

[a] t test, obese animals vs those with no metabolic abnormality, $p < .01$.

[b] Numbers in parentheses represent range of 4–5 measurements made in each animal.

TABLE II. Plasma Lipids and Lipoproteins of Monkeys With and Without Metabolic Abnormality.

Animal groups (no.)	Free fatty acid (mEq/liter; mean ± SE)	Triglycerides (mg/100 ml; mean ± SE)	Cholesterol (mg/100 ml; mean ± SE)	Lipoproteins[a]	
				Prebeta	Beta
No metabolic abnormality (7)	0.45 ± 0.04	45.2 ± 5.3	133.1 ± 3.8	—	—
Obesity, spontaneous (7)	0.61 ± 0.03[b]	165.5 ± 6.3	183.1 ± 5.5[b]	+	+
Obesity, hypothalamic (5)	0.57 ± 0.05	175.6 ± 6.1[b]	194.8 ±11.4[b]	+	+
Diabetic (2)	1.13 (1.05–1.20)[c]	600.5 (274–927)[c]	317.0 (267–367)[c]	++	++

[a] (—) Normal; (+) moderate increase; (++) marked increase.

[b] t test, obese animals vs those with no metabolic abnormality, $p < .01$.

[c] Numbers in parentheses represent range of 4–5 measurements made in each animal.

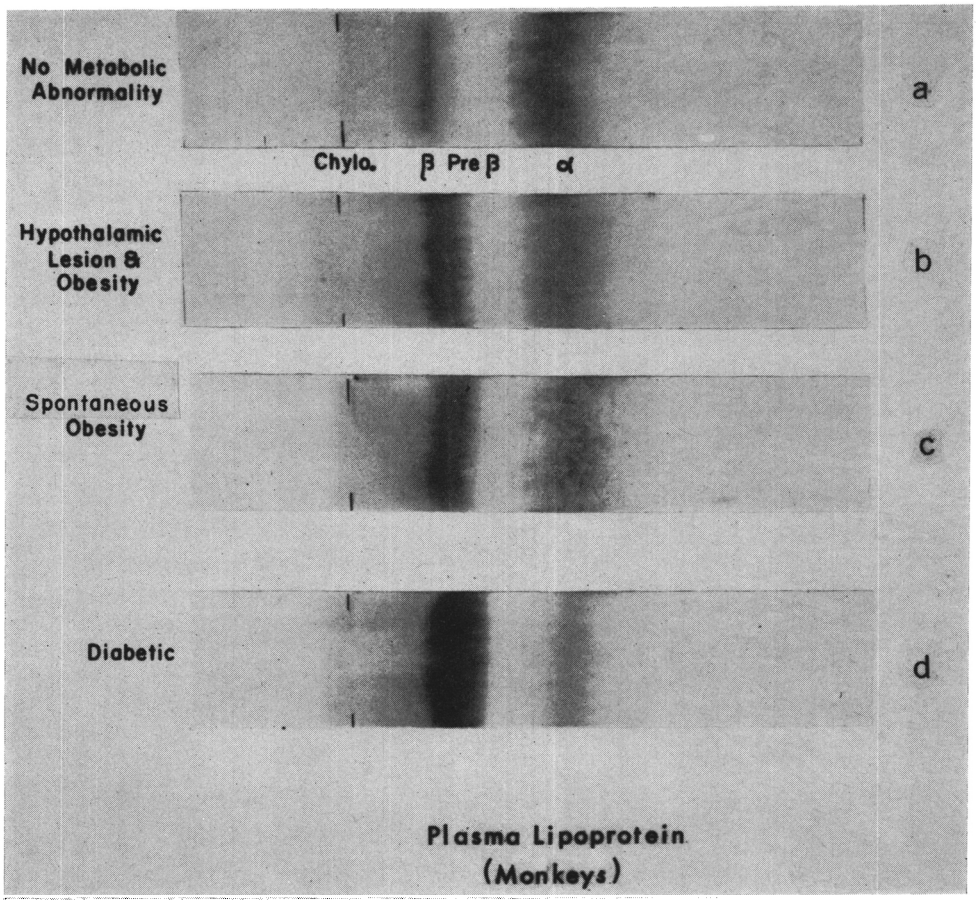

FIG. 2. Plasma lipoprotein electrophoretogram of: (a) lean animals with no metabolic abnormality: beta band is narrow and lightly stained; (b) animals with hypothalamic obesity: beta band stains more heavily than that of (a), a prebeta band has appeared; (c) animals with spontaneous obesity: pattern is similar to (b); (d) diabetic animals: alpha band is reduced, while the increase in beta and prebeta fractions is exaggerated.

greatly exaggerated in the untreated diabetic animals (Fig. 2d).

Discussion. Some middle-aged monkeys are apparently predisposed to the development of spontaneous obesity, abnormal insulin production, hyperlipidemia, decreased K-glucose and overt diabetes. Essentially the same series of metabolic consequences can be induced hastily in practically all animals by the production of hypothalamic obesity. This primate model should be adaptable for investigation of the interrelationship between abnormalities in carbohydrate and lipid metabolism. In addition, the preparation can be utilized for longitudinal studies, difficult to accomplish in man, of the events involved in the development of obesity, hyperlipidemia, diabetes and atherosclerosis (7).

Summary. A syndrome of obesity, high basal serum immunoreactive insulin, blunted insulin response to glucose loading, decreased K-glucose, hyperbeta- and hyperprebeta-lipoproteinemia progressing, in some animals, to overt diabetes mellitus has been observed in monkeys. The syndrome develops spontaneously in "middle-age" animals, or earlier in animals with obesity resulting from hypothalamic lesions.

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Received Feb. 24, 1972. P.S.E.B.M., 1972, Vol. 140.