Metabolic Abnormalities Linked to Obesity: Effects of Dexfenfluramine in the Corpulent Rat

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The JCR:LA-corpulent rat is a useful experimental model for the obese-diabetic-dyslipidemic syndrome that mimics the human condition and exhibits spontaneous development of atherosclerosis and myocardial lesions. A 30-day treatment of 6-month-old rats with dexfenfluramine 1, 2.5, and 5 mg per kilogram decreased body weight through loss of adipose tissue mass. The effect is caused primarily by the ability of dexfenfluramine to reduce food intake. The maximum depression of food intake and greatest weight loss is seen during the first 10 days of treatment in this experimental model; thereafter, body weight stabilizes. However, during this period, there is a marked decrease in serum concentrations of triglycerides, cholesterol, and insulin. Corpulent male rats were also treated from 6 to 37 weeks of age with dexfenfluramine 2.5 mg/kg. This also produces a sustained decrease in body weight and a decrease in circulating insulin concentrations. Preliminary evidence demonstrates a substantial decrease in the incidence of necrotic myocardial lesions produced by ischemic events. This study establishes that dexfenfluramine treatment can decrease the severity of associated risk factors for cardiovascular disease, namely obesity, diabetes, and dyslipidemias. Furthermore, we report the first evidence that long-term treatment with dexfenfluramine can largely prevent the occurrence of myocardial lesions and end-stage cardiovascular disease in this animal model prone to atherosclerosis.

THE ANORECTIC AGENT DL-fenfluramine was introduced as a nonstimulatory treatment of obesity.[1] Subsequently, this led to the development of dexfenfluramine, which is the therapeutically active isomer of DL-fenfluramine. This compound reduces food intake and exhibits beneficial modifications of metabolism, which include improvements in insulin sensitivity and hypolipidemic effects.[2-6]

The treatment of obesity has two major objectives. The first is reduction of excess fat and a consequent decrease in body weight. This can be achieved by the ability of dexfenfluramine to reduce food intake, with perhaps an additional positive effect on energy expenditure.

The second objective is improvement of metabolic imbalance. It has become clear from studies reported by Vague,[7] Bjorntorp,[8] and Després et al[9] that obese people can be divided into two broad categories, namely those exhibiting gynoid obesity (femoral obesity) and those exhibiting android obesity (abdominal obesity). Associated with this latter condition are a variety of pathologic states, which include insulin resistance and type II diabetes, hypertension, and dyslipidemias. This combined syndrome is often referred to as syndrome X,[10] and these dysfunctions represent powerful risk factors for the development of premature atherosclerosis, ischemic heart disease, and stroke (Fig 1). Consequently, the treatment of upper-body obesity has now focused not only on weight loss but also on the metabolic disturbances that can predispose one to premature cardiovascular disease.

In assessing the efficacy of drugs such as dexfenfluramine in the treatment of obesity, it is now necessary to establish the medical outcomes that are to be achieved and how success will be determined. Hitherto, this has relied mainly on the measurement of body weight. Obesity per se is not necessarily a predisposing factor for cardiovascular disease, as seen in the case of gynoid obesity. Treatment with dexfenfluramine normally produces an initial rapid loss of body weight that often diminishes unless some other intervention or change in life-style is accepted by the patient. However, it has become evident that even when body weight has stabilized to a new lower level, there are beneficial changes in metabolic parameters, which include improvements in insulin sensitivity and decreases in circulating glucose and blood lipids.[2-6]

If these latter improvements in the associated risk factors for cardiovascular disease are achieved, then treatment with dexfenfluramine can be considered a success independently of whether further weight loss occurs. These metabolic parameters may be even more important than weight loss in assessing the therapeutic benefits of dexfenfluramine. It can therefore be argued that treatment should be continued beyond the point where major weight loss has ceased. The reason for such a decision is that an improvement in insulin sensitivity and control of glucose and lipid metabolism will produce long-term benefits in health, including a decrease in cardiovascular disease. As in the case of many therapies used in these conditions, outcomes in terms of incidence of heart disease and stroke have not yet been established in the human population. The rationale for the treatment therefore relies on the predicted detrimental effects of diabetes and dyslipidemias with respect to cardiovascular disease.

One way to address these problems is to use animal models that mimic the combined syndrome of upper-body obesity, diabetes, and dyslipidemias seen in the human population. Such studies can provide well-controlled experimental evidence for metabolic effects of agents such as dexfenfluramine, and their efficacy in decreasing the risk factors for cardiovascular disease and the incidence of atherosclerosis and myocardial lesions.

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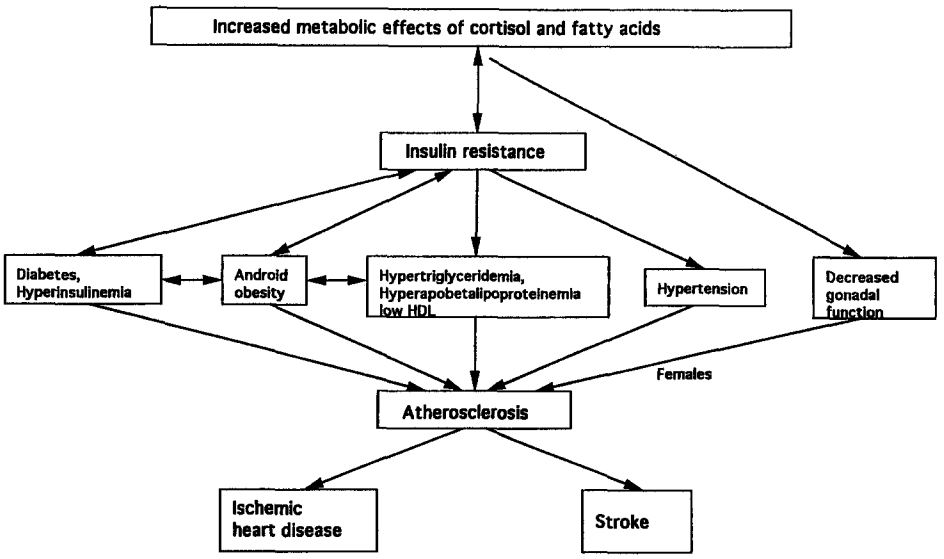

Fig 1. Schematic representation of mechanisms that could link an increased control of metabolism by cortisol and fatty acids to obesity, diabetes, dyslipidemias, hypertension, and increased cardiovascular disease. HDL, high-density lipoprotein.

THE JCR:LA-CORPULENT RAT AS AN EXPERIMENTAL MODEL

The JCR:LA-corpulent rat, when homozygous for the cp gene, is markedly obese, hyperlipidemic, and insulin-resistant.[6,11] Most importantly, corpulent male rats develop atherosclerosis and ischemic myocardial lesions. Of the five major strains that incorporate the cp gene, the JCR:LA-corpulent rat is the only strain to exhibit cardiovascular disease.[11-15] This emphasizes the multifactorial origin of cardiovascular lesions and the importance of background genotype. The JCR:LA-corpulent rat therefore provides an important experimental model with which to determine the efficacy of drugs used to treat obesity in terms of body weight loss, improvements in metabolism, and decreases in cardiovascular disease.

EFFECTS OF TREATING JCR:LA-CORPULENT RATS WITH DEXFENFLURAMINE

Female JCR:LA-corpulent rats were treated for 30 days with dexfenfluramine in daily doses of 1, 2.5, or 5 mg per kilogram.[6] This treatment produced a sustained loss of body weight that was mainly due to a decrease in the mass of adipose tissue. The weight loss was maximum during the first 10 days of treatment, and thereafter plateaued. By contrast, control rats continued to gain weight (Fig 2). The loss of body weight was accompanied by a decrease in food intake that was maximal during the initial treatment period but was sustained throughout the 30 days.

Treatment of rats with dexfenfluramine decreased circulating concentrations of glucose, triacylglycerol, free cholesterol, phospholipids, and insulin (Table 1). Changes in these metabolic parameters appeared to be related mainly to the anorectic action of dexfenfluramine, since similar effects were obtained by food restriction in male and female corpulent rats.[6] However, in other experimental models and in human studies, dexfenfluramine has been shown to improve insulin sensitivity and to have antihyperglycemic and hypolipidemic effects that are independent of food intake and weight loss.[2-5] It was also demonstrated that addition of dexfenfluramine to drinking water at a dose as low as 0.25 mg/kg daily produced a sustained decrease in body weight and food intake of male and female rats over a 9-week period.[6] This type of experimental approach was therefore adopted for long-term studies of the effects of dexfenfluramine treatment.

Corpulent male rats were treated from 6 to 37 weeks of age with dexfenfluramine at a dose of approximately 2.5 mg/kg administered in the food. This resulted in a decrease in body weight of approximately 16% at the end of treatment. However, the rats still remain relatively obese. There was a sustained decrease in food consumption and an approximately 50% decrease in circulating insulin concentrations in dexfenfluramine-treated rats. The older male rats did not show any significant decrease in triacylglycerol concentrations in the serum.

The main purpose of these studies was to determine whether dexfenfluramine treatment can decrease the number of myocardial lesions and the extent of atherosclerosis. So far, preliminary results demonstrate that dexfenfluramine produces an approximately 95% decrease in the incidence of scarred (stage 4) lesions that are characterized by the presence of mature collagen deposits.[11-15] These lesions appear to arise through ischemic events in the myocardium that probably result from thrombotic or vasospastic episodes. Studies are in progress to evaluate the extent of arterial atherosclerosis in dexfenfluramine-treated rats.

CONCLUSIONS AND IMPLICATIONS FOR THE TREATMENT OF OBESITY

The principle effect of dexfenfluramine treatment after 37 weeks in male corpulent rats was a marked decrease in plasma insulin concentrations. This indicated an improvement in insulin sensitivity, but was not accompanied by a long-term decrease in hypertriglyceridemia. Previous stud-

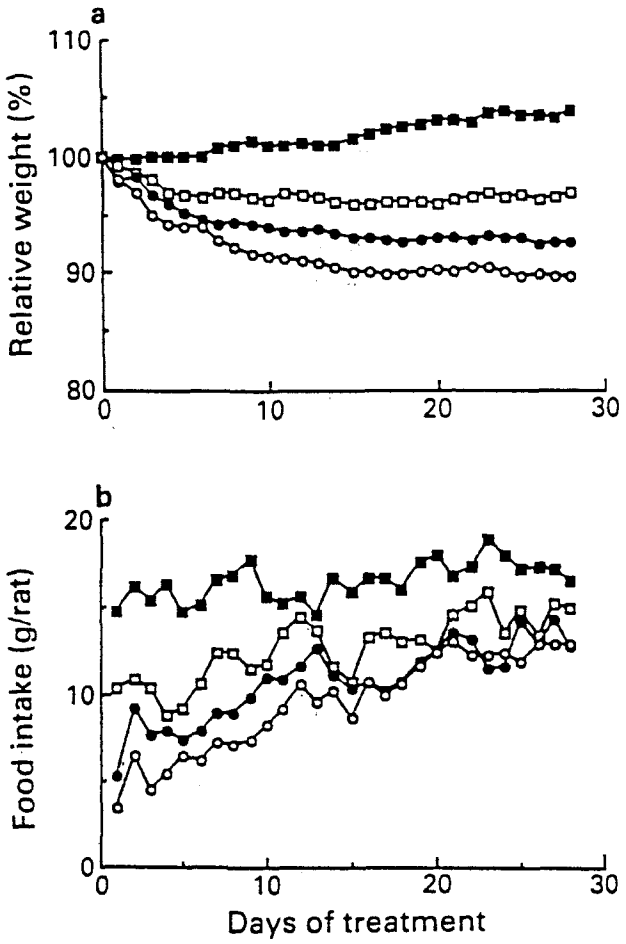

Fig 2. Effect of different doses of dexfenfluramine on body weights and food intakes of female JCR:LA-corpulent rats. Female corpulent rats were fed ad libitum and injected daily for 30 days with 0.16 mol/L NaCl alone (controls, ■) or 0.16 mol/L NaCl containing a dose of 1 (□), 2.5 (●), or 5 (○) mg D-fenfluramine per kilogram. (a) Mean weight change relative to the weight of each group of rats at the beginning of treatment (Table 1). (b) Mean daily food consumption for three cages of rats. SD values have been omitted from the figure for the sake of clarity. (Reprinted with permission.[6])

ies showed that even major decreases in serum lipid concentrations do not in themselves reduce the incidence of myocardial lesions in male corpulent rats.[16,17] By contrast, treatments that decrease plasma insulin concentrations inhibit the processes that lead to myocardial lesions in male corpulent rats.[18-20]

Dexfenfluramine reduces food intake through the serotonergic system of the hypothalamus.[1,21] This compound also has profound effects on hormonal balance that are probably mediated through the hypothalamic-pituitary-adrenal axis. Long-term treatment with dexfenfluramine can decrease the release of glucocorticoids and fatty acids in response to stress stimuli.[3] Both cortisol[22-26] and fatty acids[22,27-29] in turn produce insulin resistance in tissues and can lead to diabetic symptoms.[8,9,22,25] Such an increased regulation of metabolism by cortisol and fatty acids relative to insulin will increase gluconeogenesis and very–low-density lipoprotein secretion, and will decrease the uptake of intermediate- and low-density lipoproteins by the liver. This can lead to hypertriglyceridemia and hypercholesterolemia[9,22,25,30,31] Consequently, the decreased potential for counterregulation by cortisol and fatty acids (Fig 1) could contribute to the improved insulin sensitivity produced by dexfenfluramine and its effects in decreasing the concentrations of glucose and triglycerides in the blood.

It also appears likely that an excessive action of glucocorticoids relative to corticotropin-releasing factor is involved in the development of upper-body obesity.[8,22,25,32-34] This explains why adrenalectomy,[35] by decreasing the effects of glucocorticoids,[36-38] arrests the progress of obesity that is observed in many animal models.

An increased production of cortisol and fatty acids after stress reactions, and the associated insulin resistance (Fig 1), has also been implicated as a risk factor that leads to increased circulating triglyceride and cholesterol with decreases in high-density lipoprotein cholesterol.[25,31] This lipoprotein profile and/or a stress-type metabolism (including insulin resistance) contribute to the development of premature cardiovascular disease.[25,31,39-41] It is therefore predicted that diminishing stress responses and improving insulin sensitivity should decrease circulating triacylglycer-

Table 1. Treatment of JCR:LA-Corpulent Female Rats for 30 Days With Dexfenfluramine

		Doses of Dexfenfluramine (mg/kg)		
	Control (n = 9)	1.0 (n = 9)	2.5 (n = 8)	5.0 (n = 9)
Weight at day 0 (g)	464 ± 17	462 ± 30	456 ± 31	474 ± 18
Weight at day 30 (g)	482 ± 26	448 ± 36	422 ± 29	425 ± 18
Food (g/d per rat, days 24-30)	17.6 ± 2.4	14.8 ± 1.9*	12.9 ± 2.3*	12.6 ± 1.5*
Glucose (mmol/L)	6.90 ± 0.53	6.40 ± 0.53§	6.27 ± 0.48‡	6.56 ± 0.77
Triacylglycerol (mmol/L)	8.28 ± 3.36	6.60 ± 2.82	4.99 ± 2.72‡	5.10 ± 2.84‡
Free cholesterol (mmol/L)	1.88 ± 0.81	1.60 ± 0.64	1.07 ± 0.39‡	1.28 ± 0.50
Phospholipids (mmol/L)	4.40 ± 1.06	3.94 ± 0.92	3.16 ± 0.66†	3.56 ± 0.64§
Insulin (mU/L)	260 ± 161	139 ± 90§	131 ± 57‡	104 ± 50†

NOTE. Results are the mean ± SD. *P* values are for differences between the treated group and controls.
*$P < .005$.
†$P < .01$.
‡$P < .025$.
§$P < .05$.

ols and cholesterol. This should diminish the development of atherosclerosis and the ensuing myocardial lesions. The study of corpulent rats provides the first experimental confirmation that the incidence of myocardial lesions can be diminished through long-term dexfenfluramine treatment. It also emphasizes that such effects can be produced in the absence of a complete normalization of body weight. It is therefore proposed that more emphasis should be placed on measurement of associated risk factors for atherosclerosis as end points in the therapeutic application of dexfenfluramine. Hopefully, such improvements in risk factors will also be matched by decreases in the incidence of atherosclerosis, ischemic heart disease, and stroke in the human population.

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