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OVERVIEW OF SKELETAL MUSCLE ADAPTATION TO DIET-INDUCED WEIGHT CONTROL

Buhao ZOU[1], Masataka SUWA[2], Shuzo KUMAGAI[2,3]

Abstract

Skeletal muscle plays an important role in energy metabolism. Therefore, its characteristics have been studied in numerous experiments on obesity as well as diabetes to investigate their contribution. According to the clinical and experimental data mainly obtained from cross-sectional studies, fiber composition, capillarization, enzyme activities, glucose transporter (GLUT) 4 and uncoupling protein (UCP) 3 levels in the muscle were considered to be involved in the possible pathogenesis of obesity. In this review, we summarize these characteristics of skeletal muscle in diet-induced weight control and suggest that these characteristics are the consequences of obesity-related metabolic alteration rather than the predeterminate factors of obesity.

Key Words: Obesity, High-fat diet, Weight loss, Skeletal muscle

1. Introduction

1) Obesity is a worldwide epidemic

In industrialized countries, obesity has reached epidemic proportions and it has recently been declared a major public health problem. Obesity and overweight are highly prevalent at every age in both sexes. In the United States (U.S.), data derived from 1999 National Health and Nutrition Examination Survey suggest that 61% of U.S. adults are either overweight (body mass index (BMI)≧25) or obese (BMI≧30). It is estimated that about 300,000 deaths a year are caused directly or indirectly by obesity there. In the last 10 years, the incidence of obesity in the U.S. has increased by about 8%. According to the data from the Japanese Ministry of Health and Welfare Survey in 1998, Japan's obese (BMI≧25) population older than 15 years old was reported to be more than 23 million. The numbers of obese young men have increased by about twofold in the past 20 years. Similarly, the obese population has been forecast to reach 200 million in the next 10 years in China.

2) The health risks of obesity

Obesity is roughly classified into Simple Obesity and Symptom Obesity. Here, we will only focus on the former, which is an important part of life-style related diseases. Although clinical problems usually occur when overweight exceeds 20%, being overweight by more than 10% of standard body weight is defined as "Obese".

Obesity is not just a matter of being overweight. It is also hazardous to health, although some near-normal weight subjects may also suffer the same clinical complications as obese individuals. The most important of these disorders that obesity appears to play a role in precipitating or at least aggravating are non-insulin dependent diabetes mellitus (NIDDM), hypertension, atherosclerosis, coronary heart disease and

1) 九州大学人間環境学府
Graduate School of Human-Environment Studies, Kyushu University, Kasuga, Fukuoka 816-8580, Japan
2) 九州大学健康科学センター
3) 九州大学人間環境学研究院

cerebral hemorrhage. In particular, visceral obesity, among several obese indices, has been more closely associated with these chronic diseases[1,2] and syndromes[3] such as "insulin resistance syndrome" or "Syndrome X" than subcutaneous obesity[4,5,6,7]. In addition to these metabolic disorders, it can't be ignored that in today's body-conscious society, overweight individuals are also subjected to diverse degrees of subjective and objective discrimination. This causes social adjustment disorders that range from moderate to severe.

The term "Obesity" is derived from the Greek expression "ob-edere", which literally means over-eating. Along with the industrialization process, a decrease in physical activity and other pathogenesis have arisen from a sedentary life-style. That is to say, whenever the intake of calories exceeds calories consumed, the body becomes obese. Skeletal muscle accounts for about 40% in the resting status, and more during exercises, of total energy consumption. Since it was reported that the percent of type I fibers was negatively correlated with the percentage of body fat (%fat), skeletal muscle characteristics have been investigated in many obesity-related studies. As for intervention methods, there have been two basic research approaches: weight control by intake administration or by exercise training. In this article we overview only the former.

3) Skeletal muscle characteristics

Due to its utilization of glucose and fatty acids, skeletal muscle plays an important role in energy metabolism as well as the liver. Thus, it has been used to study the mechanism of the development of obesity in many studies. The main characteristics of skeletal muscle found in studies are muscle fiber composition, muscle capillarization, enzyme activity, glucose transporter 4 (GLUT4) and uncoupling protein 3 (UCP3) level, etc.

Skeletal muscle fibers are categorized as slow-twitch (type I) and fast-twitch (type II) fibers according to their contraction velocity. This contractive difference is due to the ATPase activity of the contractive protein, myosin heavy chain. Recently, type II fibers have been further subclassified by myosin ATPase staining into type IIA, type IIX and type IIB fibers in the rat muscle and type IIA and type IIX in the human muscle[8]. The indices of capillaries around fibers were seldom investigated. Muscular capillary density is an important factor in insulin resistance and glucose uptake since it affects not only the absorption of nutrients but also insulin function. Utriainen et al.[9] found that the ratio of capillaries per fiber was positively correlated with both basal and insulin- stimulated blood flow. The nutritive extent of a single capillary of type IIB fibers is 20~30% larger than that of type I fibers. This is compatible with the insulin-insensitivity rank of muscle fibers and is considered to explain the difference in insulin sensitivity between different fibers[10]. Generally, it is believed that type II fibers have more capillaries around them[11]. Andersen et al.[12] reported a rank order of this index in man as type I=type IIA>type IIX and a similar mean fiber area of types I and IIX.

As for oxidative capacity, the resting oxygen uptake adjusted for muscle size was found to correlate positively with the proportion of type II fibers and inversely with the proportion of type I fibers[13]. Muscle oxidative enzyme activity followed in rank order by type I>type IIA>type IIX in human[14], while type IIA>type IIX>type I>type IIB in rat[15]. The rank order for glycolytic enzyme activity in both humans[14] and rats[15] is type IIB>type IIX>type A>type I.

The Randle cycle theory indicates the interaction between fatty acid and glucose metabolism[16]. Skeletal muscle is quantitatively the most important tissue involved in maintaining glucose homeostasis, and accounts for ~80% of glucose disposal following a glucose infusion or ingestion[17,18,19]. Insulin-mediated glucose uptake occurs principally in the skeletal muscle, which is thus the major determinant of insulin sensitivity[17,20]. Type I fibers have a higher insulin sensitivity and a higher glucose uptake at rest and during hyperinsulinemic euglycemic clamp than type II fibers. This is compatible with the observation that NIDDM subjects whose insulin sensitivity is diminished have a low percentage of type I fibers[21] and a high percentage of type IIX fibers[21,22]. Type IIB muscle fibers are the most insulin-insensitive and are not adapted to oxidation of fat during muscle work. This characteristic most probably reflects or contributes to the further development of insulin resistance and

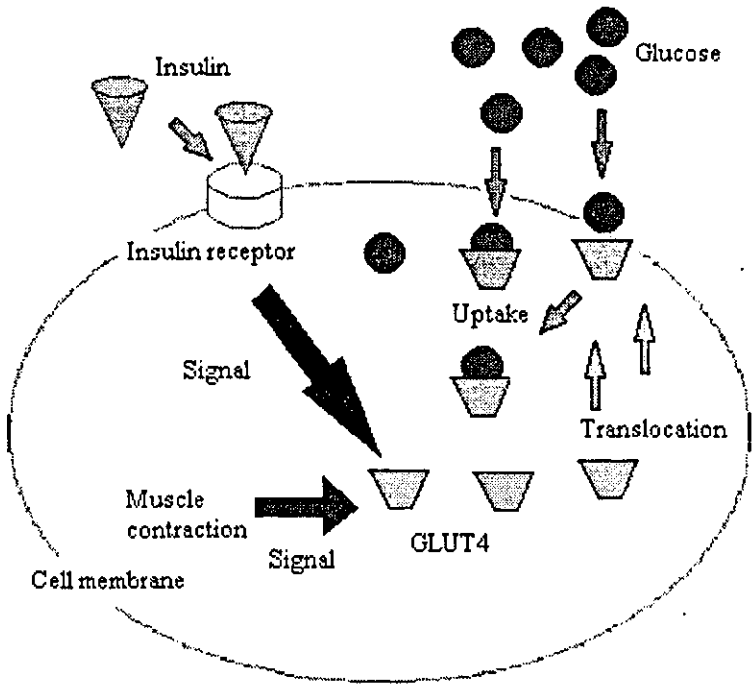
thus to the further perpetuation of obesity[23]. Glucose transport across the cell membrane is mediated by a family of structurally related carrier proteins GLUTs. GLUT4 is one of these and has been proposed to be the predominant glucose transporter isoform expressed in insulin-sensitive tissues such as skeletal muscle and adipose tissue[24,25] (Fig. 1). Its expression correlates with the metabolic nature (oxidative vs. glycolytic) of skeletal muscle fibers, rather than with their contractile properties (slow twitch vs. fast twitch)[26]. In humans, the GLUT4 concentration in oxidative muscle fibers (type I and type IIA) is higher than that in glycolytic fibers (type IIX). In rats, GLUT4 is expressed higher in red compared with white muscle[26,27,28,29]. Furthermore, GLUT4 has been regarded as being of particular importance for maintaining whole body glucose homeostasis, because it has been thought to catalyse the rate-limiting step for glucose uptake and metabolism. Glucose transport in the skeletal muscle is mediated by a process involving the translocation of GLUT4 from an intracellular site to the plasma membrane and t-tubules[30]. Red muscle contains a higher amount of GLUT4 transporters at the plasma membrane than white muscle in the basal and insulin-stimulated states but GLUT4 translocation does not differ between muscle types[26].

UCPs are mitochondrial carrier proteins that catalyse a regulated protein leak across the inner mitochondrial membrane, diverting free energy from ATP synthesis to the production of heat, making them important for thermogenesis (Fig. 2). The uncoupling protein homologues UCP2 and UCP3 could account for this adaptive thermogenesis in a wide variety of animal species[31,32,33,34,35]. UCP3 is a particularly good candidate as a regulator of adaptive thermogenesis, because it is expressed predominantly in brown adipose tissue in rodents and in skeletal muscle[34], a tissue that makes an important contribution to net energy balance[36,37], in both rodents and humans. The expression of UCP3 at the protein level is fiber-type specific, following a rank order of type IIX>type IIA>type I[38]. The abundant expression of UCP3 in type IIB fibers does not fit with a role of UCP3 in fatty acid handling.

2. Discrepancies in cross-sectional studies on the relationship between muscle characteristics and obesity

Lillioja et al.[39] observed a significant correlation between the %fat and the muscle fiber composition (r=-0.32 for percent type I and r=0.32 for percent type IIX). This observation was consistent with those in other human studies in that the proportion of type I fibers was negatively correlated with the percentage of body fat[40,41,42] or BMI[43]. Moreover, women with a

Fig. 1. Glucose transporter (GLUT) 4



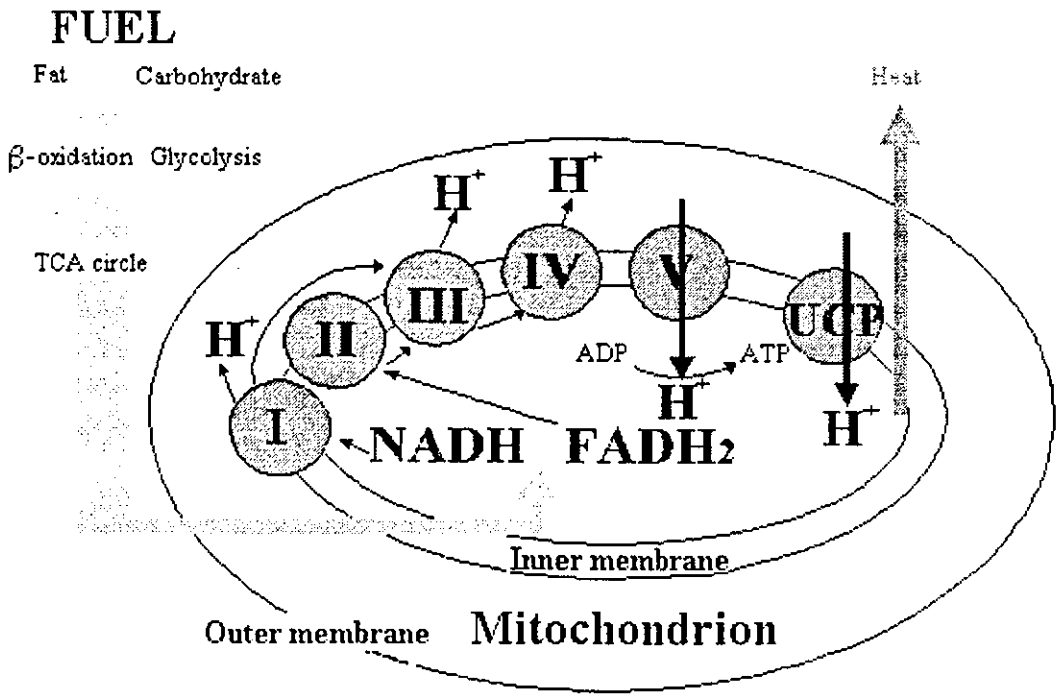
higher waist-hip ratio had less type I muscle fibers and were more insulin-resistant when evaluated by hyperinsulinemic glucose clamp measurements[44]. Abdominally obese subjects with insulin resistance, as well as patients with NIDDM, showed a low percentage of type I fibers and elevated type II (particularly type IIB) fibers[21]. In obese Zucker rats, the proportion of type II fibers was larger in the vastus lateralis and rectus abdominis muscles[45]. The muscle fiber composition was then considered to be a predeterminate factor for obesity. However, according to the different rank orders of muscle oxidative enzyme activity in humans and rats, it is highly unlikely that humans and rats have the same muscle fiber composition in obese subjects.

A different opinion was raised by Simoneau and Bouchard[46] who found no relationship between skeletal muscle fiber type proportion and relative subcutaneous fat distribution. From their data, which showed significant and negative correlations in both genders between the sum of six skinfold thicknesses and aerobic-oxidative capacity of skeletal muscle, a low oxidative capacity of skeletal muscle was suggested to be associated with obesity. In another study reported by Simoneau et al.[47], both obese and NIDDM subjects exhibited a higher glycolytic-to-oxidative ratio than lean controls did. This hypothesis was supported later by the observation of a lower oxidative enzyme activity in obese subjects[48,49,50,51] or a negative correlation between oxidative capacity of muscle and percentage of body fat[41] or visceral adiposity[52]. However, different results also arose, which negated the difference in absolute oxidative enzyme activity between obese participants and non-obese controls[53,54] or even suggested the opposite opinion[55,56].

Capillarization was also suggested to be a determinant of obesity. Several studies indicated an inverse correlation between obesity and the capillary to fiber ratio[39,57] or capillary density[23,39] although there were some contradictory reports from other groups. Lithell et al.[58] studied muscle samples from 48 glucose-tolerant middle-aged men. They found that the lipoprotein lipase activity was correlated with capillary density. The serum insulin concentration, which is closely associated with obesity, correlated positively with the mean fiber area per capillary. In the study by Märin et al.[21], control subjects with abdominal obesity and insulin resistance, as well as patients with NIDDM, exhibited a low capillary density suggesting a possible regulatory effect of insulin on myosin synthesis in muscles.

In rats, the difference in skeletal muscle fiber types

Fig. 2. Uncoupling protein



was accompanied with different insulin receptor[59] and GLUT4 levels but not the intrinsic activity of GLUT4[29,59]. Megeney et al.[60] found a significantly high correlation between the proportion of oxidative fibers and GLUT4 content. The GLUT4 protein level is not decreased in obese subjects[61,62]. However, in the skeletal muscle of obese[63] or obese diabetic[64] subjects, GLUT4 translocation was found to be impaired.

Compared to lean controls, obese Zucker fa/fa rats have a 41% decrease in UCP3 mRNA concentration in the soleus muscle[65]. In human obesity, the muscle UCP3 mRNA concentration had no correlation with BMI[66,67]. In NIDDM patients, a positive correlation between UCP3 expression and whole-body insulin-mediated glucose utilization rate, that is, an inverse correlation with insulin resistance was noted[68].

Unfortunately, without interventions, all of these cross-sectional studies were inadequate to clarify any of these discrepancies.

3. Studies of diet-induced obesity

1) Muscle fiber composition

Abou Mrad et al.[69] carried out a high-fat-diet (HFD) trial using rats to determine whether a significant relationship exists between susceptibility to HFD-induced obesity and skeletal muscle fiber type or not. They observed a significantly higher proportion of type I muscle fibers in obesity-resistant rats' medial head of the gastrocnemius muscle than obesity-prone rats both before and after the HFD feeding period. Together with the cross-sectional data of Wade et al.[40], they considered the preexisting differences in muscle fiber composition to be a determining factor of susceptibility to dietary obesity. This hypothesis was widely accepted in view of the higher oxidative capacity of type I fibers. However, the hypothesis could not explain the different rank order of oxidative capacity in muscle fibers between humans and rats. To clarify this, Suwa et al.[70] employed genetically fast-twitch fiber dominant rats (FFDR) and fed them HFD as well as control rats. Interestingly, the FFDR were more obesity-resistant than the control rats. This observation precluded the skeletal muscle fiber composition as a determinant of obesity. Less type I fibers in obese subjects may be a consequence rather than a predeterminate factor of obesity. The significant difference in oxidative enzyme activity and its increase between the FFDR and control rats suggest muscle oxidative capacity and its adaptation to be possible candidates.

2) Muscle capillarization

There have been few studies on the relationship between the obese process and capillarization. Increased circulating insulin concentration has a capillary proliferative effect, perhaps to compensate for reduced capillary insulin diffusion and metabolic capacity of the muscle[71]. Holmäng et al.[72] demonstrated that the number of capillaries per unit muscle surface area was significantly increased after insulin exposure. In the later stage, obesity causes insulin resistance of the skeletal muscle and then, more seriously, hyperinsulinemia. This is why the process of obesity is usually accompanied with an increase in the serum insulin concentration. So, exposure to insulin, which was used by Holmang et al.[72], can be considered as a simulation of the obese process by this means. It is then difficult to explain the inverse correlation between obesity and the capillary to fiber ratio[39,57] or capillary density[23,39] found in cross-sectional studies. Further studies are needed.

3) Enzyme activity

Accompanying the accumulation of adipose, a high-fat diet (HFD) brought about an increase in the muscle oxidative enzyme activities[54,73,74,75,76,77] and the ability to endure exercise. The improved aerobic capacity was considered to be the result of the oxidative enzymatic adaptation in the muscles[73,78]. However, Iossa et al.[79] did not find an increase in activity of succinic dehydrogenase (SDH) and citrate synthase (CS) in HFD-fed rats, although the whole body lipid oxidation was enhanced through an increased mitochondrial capacity to use lipids as metabolic fuels. Similarly, Gayles et al.[54] reported that no significant difference in absolute enzyme activities was observed between obesity-prone rats and obesity-resistant rats after a 5-week HFD period. HFD did not produce an adaptation in those muscle enzyme systems. By the correlations between enzyme ratios (phosphofructokinase (PFK)/ β-hydroxyacyl coenzyme A dehydrogenase (β-HAD) and β-HAD/CS) and body weight gain, they suggested that rats most susceptible to weight gain on a HFD

were characterized by an early tissue enzymatic profile that favors carbohydrate over fat use[54]. It worth noting that metabolic differences among HFD rats tended to occur early (1-2 week) and disappear by week 5 in this study. Reestablishing a normal weight gain profile at the expense of an elevated body weight might occur due to the prolonged diet intervention, in which case both the difference in the percentage of diet fat and the diet period may contribute to the different results.

4) GLUT4

Wilkes et al.[80] fed male Sprague-Dawley rats a modified HFD for 3 weeks and found that feeding a HFD induced a reduction in insulin-stimulated glucose uptake in rat skeletal muscle. This was consistent with other studies in rats[81,82,83,84,85]. HFD reduces glucose tolerance, insulin-stimulated glucose disposal and glucose uptake in the skeletal muscles[86]. The insulin resistance[86,87,88] in the skeletal muscles of animals subjected to the HFD appeared to be due to a reduced GLUT-4 protein concentration[84,86,89,90] and the impaired translocation of GLUT4 to the plasma membrane [84,90].

5) UCP3

Although having an important contribution to thermogenesis, UCP3 was not modulated by changes in environmental temperature[65] or acute exercise[91] but by food intake[65] or the fatty acid flux[91]. The skeletal muscle UCP3 mRNA[92,93,94] or UCP3 protein levels[95] are upregulated by a HFD. However, Surwit et al.[96] negated the effect of HFD on UCP3 in mice. Clapham et al.[97] reported that transgenic mice which overexpress human UCP3 in the skeletal muscle weighed less than their wild-type littermates even though they were hyperphagic and had a striking reduction in adipose tissue mass. Weigle et al.[93] measured the muscle UCP3/actin mRNA ratio in moderate fat high-energy diet-fed rats. The obesity-resistant rats had a 3-fold higher UCP3/actin mRNA ratio than obesity-prone rats. It seemed that these rats might initially resist weight gain through a greater induction of muscle UCP3. Elevation of the circulating free fatty acid levels in animals fed by intralipid plus heparin infusion caused significant increases in the UCP3/actin mRNA ratio compared with saline-infused fed controls in both the extensor digitorum longus and soleus muscles. Brun et al.[98] have shown that the muscle UCP3 levels are increased during postnatal development in mice using diets that elevate the circulating free fatty acid levels. The gastrocnemius muscle UCP3 levels were increased in previously fasted rats when they were re-fed a HFD which increased the circulating free fatty acid (FFA) levels[99]. Muscle UCP3 did not change when these rats were re-fed a low-fat diet which did not increase FFA. It seems that muscle UCP3 functions more to aid in the disposition of FFA than to defend body fat stores against chronic changes in energy intake[93].

4. Studies of diet-induced weight loss

1) Muscle fiber composition

Yamaguchi et al.[100] reported the absence of a difference in muscle fiber composition of the soleus and extensor digitorum longus muscles between food-restricted and control rats. Niskanen et al.[101] investigated the influence of an improvement in insulin resistance by weight loss on skeletal muscle fiber composition. They took skeletal muscle biopsies before and after a 12-week very low calorie diet from 7 obese non-diabetic subjects. No significant change in the proportion of type II fibers occurred during the study. Similarly, Kempen et al. [102] reported the absence of a change in fiber type distribution after 8 weeks' energy restriction. Energy restriction was also used to study the age-associated fiber loss and fiber type changes of the vastus lateralis muscle in rats. The data indicated that calorie restriction begun in late middle age could retard this kind of degeneration in the skeletal muscle [103]. Instead of food restriction, a fructose-rich diet was used in other studies[104,105]. The body weight of rats in the diet group was significantly lower compared to the rats in the control group. The percentage of type I fibers decreased and type IIA fibers increased significantly in the diet-fed rats. Fructose-rich diet-induced insulin resistance was suggested to contribute to these changes.

2) Muscle capillarization

Niskanen et al.[101] demonstrated that the skeletal muscle capillary density did not change with the

improvement in insulin sensitivity induced by weight loss. Lindgarde et al.[106] used a 6-month diet-exchange protocol to study middle-aged men with impaired glucose tolerance. The number of capillaries per fiber was normal throughout, but as the muscle fiber size was reduced in relation to the decreased body weight, the capillary density increased during the dieting period.

3) Enzyme activity

Simoneau et al.[49] found that the activities of some muscular oxidative enzymes (cytochrome c oxidase (COX) and β-HAD but not CS) in women but not in men decreased after a 4-month weight loss program which combined a very low calorie diet and an intensive program of behavioral intervention. The glycolytic enzyme (glyceraldehyphosphate dehydrogenase (GAPDH) for both genders but phosphofructokinase (PFK) for men only) activities decreased in both men and women. Enzymes reflecting β-oxidation (β-HAD) in obese women did not change after the 8 weeks' energy restriction[102]. Similarly, Steinberg et al.[107] found that two weeks of 66% food restriction compared to ad libitum-fed controls had no effect on rats' β-HAD or CS activities, although the mean body weight decreased by more than 10%. Lindgarde et al.[106] studied middle-aged men with impaired glucose tolerance. Enzyme activities in the gastrocnemius muscle were subnormal and uninfluenced by changed dietary habits, although the body weight was reduced significantly.

4) GLUT4

Morbidly obese patients have been studied before and 6 months after biliopancreatic diversion, an operation that induces predominant lipid malabsorption[108]. Glut4 expression was restored and insulin resistance was fully reversed in parallel with significant weight loss. However, in the gastric bypass surgery study by Friedman et al., muscle biopsies obtained from the vastus lateralis before and after weight loss revealed no significant change in the levels of GLUT4 glucose transporter protein, although maximal insulin-stimulated glucose transport activity in incubated muscle fibers was increased twofold to 88% of normal[109]. Seraphim et al.[110] observed the same phenomenon in their study. Weight loss did not change the skeletal muscle GLUT4 content in rats. The study of Cartee et al.[111] in adult, middle-aged, and old rats duplicated this result. A similar result was obtained in a 30% calorie restrictive survey for 6 years in monkeys. Whole body insulin sensitivity was significantly increased while the expression of GLUT4 was not altered[112]. It seems that the mechanism for the improvement in insulin sensitivity due to energy restriction results from enhanced transporter translocation and/or activation rather than GLUT4 concentration.

5) UCP3

The muscle UCP3 expression levels are increased acutely with fasting[35,65,91,98,113,114,115,116] but decreased by 50% food restriction for 1 week[65]. A much longer intervention such as in a study with 10 weeks of dietary restriction, which led to a 10% weight loss, did not result in any significant changes in the muscle UCP3 mRNA levels in either obesity-prone or obesity-resistant animals[93]. The upregulation of UCP3 mRNA concentrations during the fasting period seems to be transient, maybe in response to acute metabolic and hormonal changes. The long-term downregulation is consistent with the increased feeding efficiency that contributes to the increased weight gain observed after cessation of energy restriction. Weigle et al.[113] supposed the free fatty acids to be a potential mediator of the increase in muscle UCP3 expression that occurs during fasting. This was supported by the data of Schrauwen et al.[91], which showed that regulation of UCP3 was a fat metabolism-mediated effect.

5. Conclusions and perspectives

Longitudinal studies provided the possibility to reveal the causality between skeletal muscle characteristics and obesity. Except for a few differing opinions, which might be due to the difference in methodology, muscle fiber composition, capillarization and enzyme activity, the GLUT4 and UCP3 levels seem to be the consequences of an obesity-related metabolic alteration rather than the predeterminate factors of obesity. They are affected by the adipose accumulation/consumption-induced change in glucose, insulin, FFA, etc. The difference in adaptation to these changes may lead to the difference in obesity/lean sus-

ceptibility.

The different results in this review might result from some limitations in the study protocols. Muscle oxidative enzyme activities are different in various muscles or muscle portions. Compared to the precise open biopsy method used in animal studies, it is difficult to obtain muscle tissue from the same portion using a needle muscle biopsy method in human studies. Physical activity is another important confounding factor that should be taken into account since it greatly regulates the muscle enzyme activities. Generally speaking, cage-raised animals are much easier to control in terms of their physical activities than humans. A similar energy intake is also important for comparability. In view of the above, we are carrying out studies based on a more precise study protocol. In these studies, skeletal muscle adaptation to diet-induced weight control is being investigated in rats. Visceral adipose was chosen to be the classificatory criterion. Energy intake is not significantly different. Muscle samples are collected from the same portion of the same muscle before and after the diet periods. Results which may contribute to the knowledge of obesity/lean-susceptibility are expected.

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食によるウェイトコントロールに対する骨格筋の適応

鄒　歩浩

要　約

骨格筋はエネルギー代謝の重要な役割を担い、肥満と糖尿病に関する多くの研究において、対象とされている。主に横断研究の成績から、骨格筋特性（筋線維組成、毛細血管分布、酵素活性、糖輸送担体（GLUT）4、脱共役蛋白（UCP）3など）の個体差は肥満発症の原因と考えられてきた。この総説は食事によるウェイトコントロールが骨格筋特性に及ぼす影響について総括した。その結果、これらの骨格筋特性の個体差は肥満の原因だけでなく、脂肪増減に伴う代謝適応であることが示唆された。

Ⅳ. 高脂血症

4. 身体活動と脂質代謝－運動疫学およびmetabolic fitnessとの観点から－

熊谷秋三・長野真弓

はじめに

高脂血症および脂質代謝障害は，冠動脈疾患の有力な危険因子の一つである．本稿では，心疾患の予防に関する運動疫学的研究の成果をまず概説するとともに，近年注目を集めているmetabolic fitnessの概念を紹介し，インスリン抵抗性(あるいは，その代償機構としての高インスリン血症)を基盤とした種々の病態の集積であるインスリン抵抗性症候群への身体運動の効果とその背景(メカニズム)を，特に脂質代謝改善の観点から解説する．

運動の疫学からみたエビデンス

●心疾患発症との関連から

Powellら[1]は，疫学的研究デザインがしっかりした研究論文(新規発症例と有病者例の区別，発症率，相対危険度，オッズ比，死亡率の計算が可能なことなど)を検討した結果，研究デザインが優れている論文ほど，身体活動(運動)と冠動脈硬化性心疾患(CHD)発症率との間に有意な負の関連があるとした．すなわち，身体不活動のCHD発症率の相対危険度は，1.9～2.4の範囲にあり，この数値は高血圧，高脂血症，喫煙の相対危険度にも匹敵する．また，相対危険度と身体活動量との間には量-反応関係が認められた．これらは，いずれも観察疫学的な研究手法での成績であるが，原因と結果の関連性の強さ，量-反応関係の存在，結果の一致性から判断して，身体活動量の増加がCHDの発生に対して一次予防的な効果を有することを意味している．

アメリカ人を対象にした種々の危険因子別に予測されたCHDの寄与危険度は，高コレステロール血症に続き，身体的不活動の貢献度が高いことが明らかとなっている[2,3](表-1)．また，費用便益分析の結果から，CHD予防における身体活動を高めることの健康的・経済学的意義を評価すれば，生活の質で補正された生存年数(QALY)に対する運動のコストは，その他のCHDの危険因子に対する療法のなかで一番安価であることが明らかとされた．すなわち，米国の疾患管理予防センター(CDC)[2]は高脂血症との関連から，CHDの予防にとって身体活動を増やすことが，最も安価な方法であるとの試算を出している．

●高脂血症との関連から

高脂血症と身体活動(運動)に関する疫学研究は，そのほとんどが横断的研究および無作為化比較対照研究を含んだ短期間の介入研究である．その結果を要約すれば，身体トレーニングに伴い，良好な脂質代謝の改善を認めるが，その成績は体重によって変化する．すなわち，体重低下群では一層の脂質代謝の改善を認め，体重増加群では逆の成績を認める．今後の課題としては，長期コホート研究でも類似した成績が観察されるかどうかの検証が必要となろう．

表-1　CHDに対する代表的危険因子の有病率，寄与危険度，費用便益(米国)[2,3]

危険因子	有病率(%)	寄与危険度(%)	費用便益
身体活動度低下	58.0	34.6	11,313ドル/QALY
高血圧症	18.0	28.9	25,000ドル/QALY
喫煙	25.5	25.0	21,947ドル喫煙による生涯利得
肥満	23.0	32.1	不明
高コレステロール血症(200mg/dl以上)	37.0	42.7	28,000/QALY

・寄与危険度の%はおのおのリスクごとに計算したため，単純に合計できない．
・QALY：生活の質で調整された生存年数．
・身体活動低下，高血圧症に関する費用便益分析の結果は以下の文献を参照した．
Hatziandrue, E. I., Koplan, J. P., Weinstein, M. C. et al. : A cost-effectiveness analysis of exercise as a health-promotion activity. Am J Pubulic Health 78 : 1417-1421, 1988.
・喫煙に関する費用便益分析の結果は以下の文献を参照した．
Weinstein, M. C., Stanson, W. B. : Cost-effectiveness of interventions to prevent or treat coronary heart disease. Annu. Rev. Public Health 6 : 41-63, 1985.
・高コレステロール血症に関する費用便益分析の結果は以下の文献を参照した．
Oster, G., Colditz, G. A., Kelly, N. L. : The economic costs of smoking and benefits of quitting for individual smokers. Prev. Med. 13 : 377-389, 1984.
(CDC : Public health focus : Physical activity and the prevention of coronary heart disease. Morb. Mortal Wkly Rep. 42 : 669-672, 1993より改変引用)

metabolic fitnessと身体運動

● metabolic fitnessとは[4]

身体活動に伴う脂質代謝の改善には，ある特定の体力要素というよりも，身体活動量の増加それ自体が脂質代謝の改善に貢献しているとの報告がある．この現象を最も的確に表現する概念として，Despresら[5]は，"metabolic fitness"の用語を提唱した．つまり，彼らは，"metabolic fitness"を，「心疾患の発現に関与している糖・脂質代謝の諸変量が総合的に安定・機能した状態」と定義した．そして，このfitnessは，有酸素的作業能によってではなく身体活動量の相違によって変化しうるとしている．

近年，インスリン感受性の低下(インスリン抵抗性および高インスリン血症)に基づく一連の病態群を総称してインスリン抵抗性症候群と呼んでいる[6]．以前より，虚血性心疾患あるいは動脈硬化性疾患における危険因子としての肥満，高血圧，耐糖能異常，高脂血症の存在はよく知られていた．一方，肥満者の多くは高血圧，耐糖能異常，高脂血症などを合併しやすいこと，逆に耐糖能異常者には肥満，高血圧や脂質代謝異常の合併が高率であることなどもよく知られた事実である．すなわち，これらの危険因子が同一個体に集積(cluster)しやすいこと，またこれらの危険因子が相互に強く結びついていることが注目されるようになってきた．

DeFronzoら[6]はインスリン抵抗性症候群と呼称し，肥満，NIDDM(2型糖尿病)，高血圧，冠動脈疾患の重積を述べている．また，松沢ら[7]は内臓脂肪蓄積を重視し，「内臓脂肪症候群」を提唱し，この内臓脂肪蓄積を介して耐糖能異常，高脂血症，高血圧などが助長されることを強調している．Haffnerら[8]は疫学的前向き調査を行い，ベースラインでの高インスリン血症を認めた群では，肥満度や脂肪分布の影響を除去しても，有意に高血圧，高中性脂肪(TG)血症，低高比重リポ蛋白コレステロール(HDL-c)血症，およびNIDDMの発症頻度が高率であることを報告し，高インスリン血症の存在がこれらの冠動脈危険因子の重積に先行することを明らかにし，DeFron-

zo ら[6]が表現したインスリン抵抗性症候群と呼ぶのが妥当であると結論した．すなわち，Despres らが提唱した metabolic fitness とは「インスリン抵抗性症候群と類似した病態を包含する概念であると同時に，その代謝機能が統合的に正常機能している状態の程度」を意味する概念とも受け取れよう．

●身体運動の効果

現在までに，インスリン抵抗性症候群に含まれるそれぞれの病態の改善に及ぼす運動効果に関する多くの研究成果がそれぞれの専門領域において報告されてきた[9~11]．これらの成績から判断して，運動の長期継続がインスリン抵抗性症候群の改善，すなわち metabolic fitness の改善に好ましい効果を有することが期待できる．おそらく，これらの変化に関与する重要な因子としては，持久性競技者や有酸素トレーニング後に観察されるインスリン感受性の改善が考えられる[5]．この点に関しては後述する．

身体トレーニングに伴う脂質代謝と有酸素的作業能の改善は，必ずしもパラレルに変化しないことから，身体活動量の増加それ自体が脂質代謝の改善に貢献していると考えられている[5]．一方，横断的研究であるが，二重標識水法で評価された身体活動量（エネルギー消費量測定のゴールデンスタンダード）よりも有酸素的作業能（最大酸素摂取量）の方が高齢者の糖・脂質代謝指標との関連性が強いことが報告されている[12]．したがって，metabolic fitness の決定要因としての体力および身体活動量の貢献度に関しては，介入を含むコホート研究によるさらなる検討が望まれる．

身体運動による脂質代謝改善メカニズム

ここでは，脂質代謝の改善に寄与するメカニズムを，骨格筋特性，脂質代謝調節関連酵素，インスリン感受性，および遺伝子多型の観点から解説する．

●骨格筋線維組成

Thickened ら[13]は，骨格筋の線維組成と脂質代謝との関連性を初めて明らかにした．すなわち，特定の筋における遅筋線維の割合（% ST）線維と HDL-c およびアポ蛋白 A1（ApoA1）との間には有意な正相関を，一方 TG との間には有意な負の相関を認めた．おそらくこの背景としては，ST 線維における高いリポ蛋白リパーゼ（LPL）活性が TG-rich なリポ蛋白の異化作用を促進させ，HDL 前駆物質の増加をもたらすためと考えられる．これを裏づける証拠として，骨格筋の LPL 活性と HDL-c との間に有意な正相関が報告されている．LPL は，毛細血管の内皮表面でその作用を発現するが，ST 線維の酸化的代謝は骨格筋への酸素と脂肪酸を供給する筋周囲に存在する毛細血管によって支援されている．通常，筋線維組成別にみた毛細血管数は，ST 線維が多いことが知られている．つまり，持久性トレーニング後に生じる高い LPL 活性は，豊富な毛細血管床の増加が一部には貢献しているのかもしれない．これらの成績を示した Thickened ら[13]は，遺伝的に規定された筋線維の分布は，骨格筋内の毛細血管床で TG-rich リポ蛋白の末梢におけるクリアランスを変化させ，おそらく HDL-c 代謝に影響する重要な要因の一つではないかと指摘している．また，Keens と Lithell[14]は，トレーニングによる HDL-c 改善への骨格筋適応の重要性を，片脚でのトレーニング実験で明らかにした．すなわち，トレーニング脚における超低比重リポ蛋白（VLDL）-TG の異化や HDL2-c の産生は，非トレーニング脚に比べ有意に亢進していることを認めた．**図-1**に，血清 HDL-c 水準と代謝に及ぼす骨格筋線維分布の影響を表現したモデルを示している[15]．

●脂質代謝調節関連酵素[16]

(1) コレステロールエステル転送蛋白（CETP）

CETP は，末梢組織由来のコレステロールエステルを HDL からアポ蛋白 B 含有リポ蛋白に転送している蛋白である．この蛋白を欠損している症例では，著明な高 HDL 血症を認めることから，

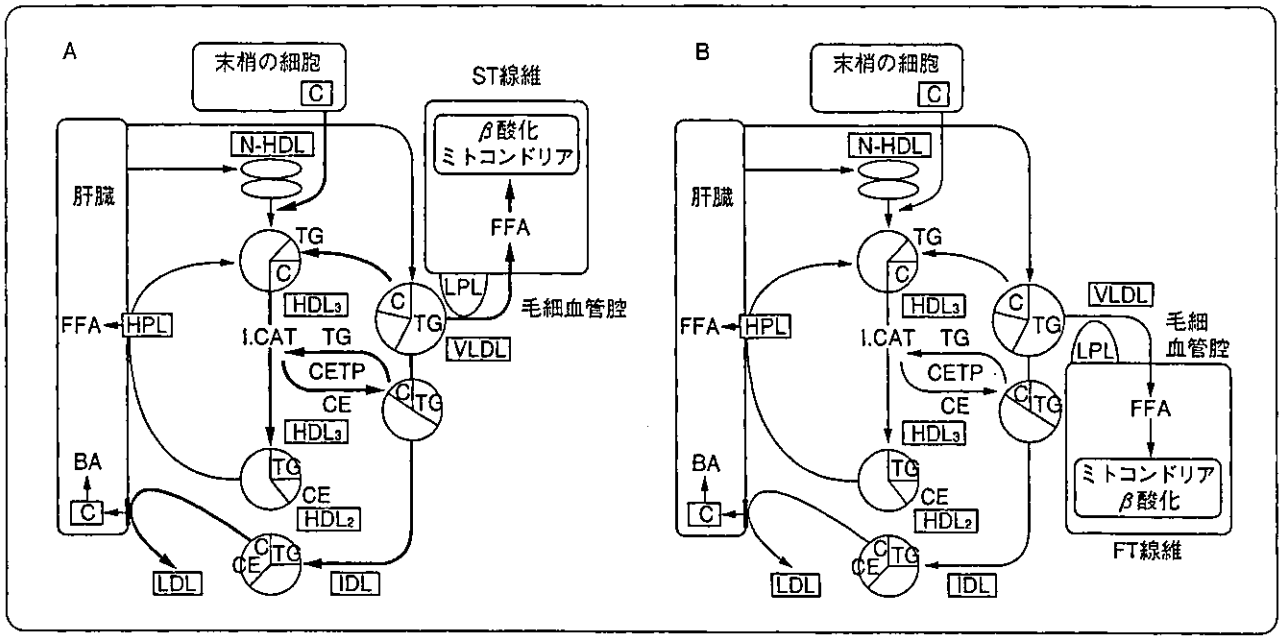

図-1　高比重リポ蛋白コレステロール(HDL-c)水準と代謝に及ぼす異なる二つの筋線維組成の影響を示したモデル[15]　高い比率のST線維(% ST)を有する個人は，少ない比率の人に比べ，筋中のLPL活性が高く，中性脂肪(TG)から多くの脂肪酸を得ることができる．TGを豊富に含んだリポ蛋白であるVLDLは，HDL-c (HDL2)産生の重要な要因である．

A：脂質代謝に及ぼすST線維の影響．太い線の矢印は，流量の増加を表現しており，HDL2粒子の周りの太い線は数の増加，つまりHDL2粒子の濃度増加を意味している．ミトコンドリアの周囲の太い線はミトコンドリア密度の増加とβ酸化の促進を意味している．

B：脂質代謝に及ぼすFT線維の影響．N-HDL：幼若HDL，LCAT：レシチンコレステロールアシルトランスフェラーゼ，HPL：肝性リパーゼ，CETP：コレステロールエステル輸送蛋白，C：コレステロール，CE：コレステロールエステル，TG：中性脂肪，FFA：遊離脂肪酸，IDL：中間型リポ蛋白コレステロール，LDL：低比重リポ蛋白コレステロール．

CEPTはHDL代謝の調節因子の一つと考えられている．血清のCETP活性は，一過性および長期の有酸素運動によって抑制されるとする成績がある．すなわち，マラソンランナー(MR)群と非運動群との比較研究において，MR群のCEPT活性が有意に低値である．また，一過性の運動後(230km自転車競技)にも，CETP活性およびその蛋白量は，競技終了後1週間まで有意な低下が継続する．さらに，30分間の有酸素運動を2回/週，9～12ヵ月実施した結果，血清CEPT量が有意に低下し，同時にHDL-cの有意な増加，および運動開始前の血清CEPT量とHDL-cおよびLDL-c/HDL-c比の変化量との間に有意な関連性を認められる．

(2)　レシチンコレステロールアシル転換酵素(LCAT)活性

LCATは，血中で遊離コレステロールをエステル化する酵素であり，主としてHDL_3を基質としている．HDL_3が末梢より得られた遊離コレステロールをコレステロールエステルに転換し，HDL_3をHDL_2に変換する酵素である．LCATは，生理的条件下ではCEPTと有意な正相関を示し，運動群では非運動群に比べ，LCAT活性は高く，さらに有酸素運動によってLCATは有意に増加する．また，運動の急性影響に関しては，成績の一致がみられない．後述するが，持久性競技者の高いLPL活性やトレーニングによる増加は，HDL前駆物質の産生を高め，高いLCAT活性は，HDL2-c水準の増加と密接に関係

している．

(3) LPL 活性

LPL は，主として筋組織，脂肪組織に存在し，TG を豊富に含む外因性および内因性(カイロミクロンや超低比重リポ蛋白；VLDL)を水解し，末梢組織に遊離脂肪酸(FFA)を供給する役割を担っている．男性の筋組織中の LPL 活性は，長距離ランナーは短距離ランナーと対照群に比べ有意に高値であるが，ボディビルダーの筋および脂肪組織での LPL 活性は，体重でマッチされたコントロールとの間に有意差を認めない．これらの事実は，筋の LPL 活性にはトレーニング特異性があり，有酸素運動によって筋の LPL 活性は促進されることを示唆している．事実，有酸素トレーニングに伴う筋の LPL 活性の増加，および脂肪組織の LPL 活性と HDL-c 水準との間には有意な正相関が観察されている．身体活動および体力水準からみた，脂肪組織の LPL 活性の基礎値とインスリンに対する脂肪組織の LPL 活性の反応性の違いを図-2に示す[17]．例えば，肥満者では，LPL 活性の基礎値は高いが，反応性が低い．トレーニングに伴い，前者は低下し，後者は増加する．一方，高度にトレーニングされた痩せ型の競技者では，脂肪組織の LPL 活性の基礎値は肥満者と同程度に高いが，インスリンへの LPL 活性の反応性も高い．持久性競技者の低 TG 血症は，脂肪組織や骨格筋の血管内皮表面に位置する LPL 活性の増加による TG-rich リポ蛋白のより効率的な分解の結果であるものと考えられている．

(4) 肝性トリグリセライドリパーゼ(HTGL)活性

HTGL は，VLDL レムナントを IDL (中間型リポ蛋白)に変化するとともに，ホスフォリパーゼ作用により HDL_2 が HDL_3 に変換する役割を有すると考えられている．HTGL 活性は，日常生活が非活動群に比べ活動的な群で有意に低く，ヘパリン静注後の血中 HTGL と体力および HDL-c との間には，有意な負の相関が認められる．また，15週間にわたる持久性トレーニング後に HTGL 活性は低下するとの成績があるが，HTGL の変

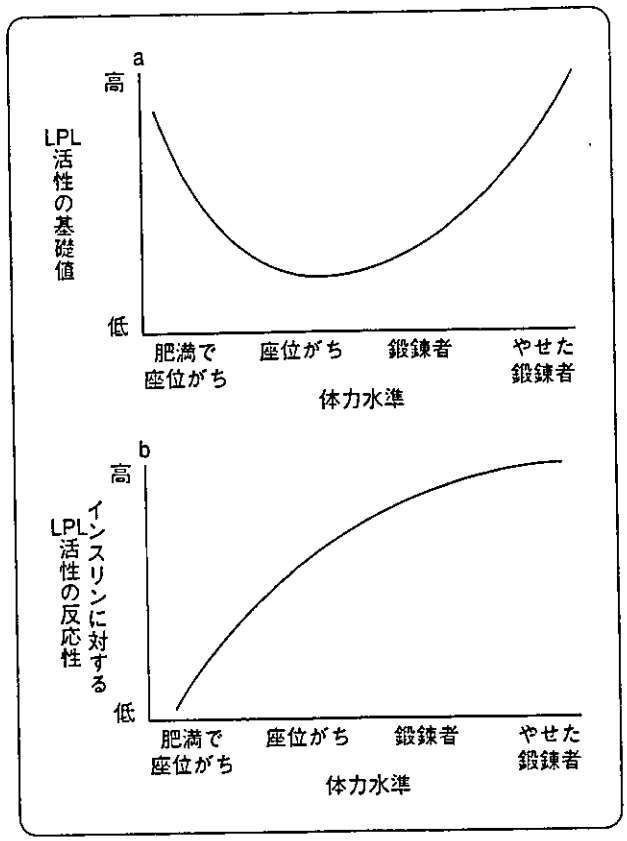

図-2 体力水準別にみた脂肪組織の LDL (AT-LPL)活性の基礎値(a)とイスンリンに対する AT-LPL 活性の反応性(b)[17]

動と HDL-c の増加との間に有意な関連性は認められていない．さらに，運動とダイエットを用いた体重減量によっても，HTGL 活性の低下が生じる．一方，トレーニング状態，食事および形態学的特性に差を認めない持久性ランナーで，HDL-c 水準のみが異なる 2 群を対象に，血中 LPL と HTGL 活性と HDL-c との関連性を検討した結果，HDL-c は LPL 活性と正相関し，一方 HTGL 活性とは負の相関が報告されている．長期の座位状態で認められる高 HTGL 活性は，TG-rich リポ蛋白の分解低下の結果として，HDL2-c 産生低下をもたらすが，身体的に活動的な状態では，HDL2-c の産生増加に貢献している LPL 活性は高く，HTGL 活性は低いことから，座位がちな人よりも高い HDL2-c 濃度をもたらすと考えられる．

以上を要約すると，主として持久性運動は脂肪酸の利用率を高め，LPL 活性を増加し，さらに

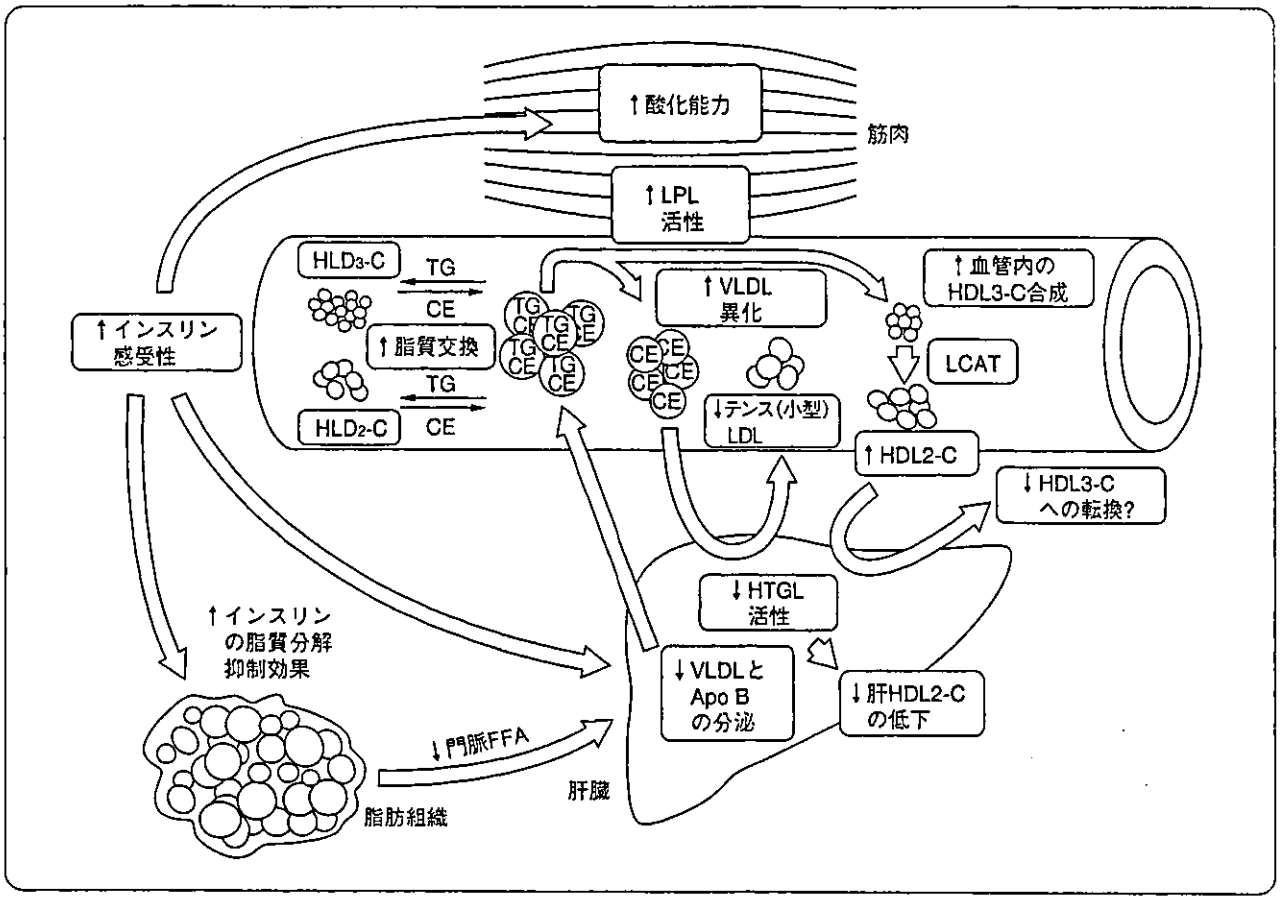

図-3　有酸素性トレーニングに伴う脂質およびアポリポ蛋白代謝適応の要約[5)]

LCAT活性の増加，HTGL活性低下およびCETP活性の低下をもたらし，TG-richリポ蛋白の異化亢進を活性化することで，血中TGや低比重リポ蛋白(LDL-c)の低下を生じさせ，HDL2-cの増加をもたらすものと考えられる．

●インスリン感受性

現在までに，インスリン抵抗性症候群を構成する諸病態の改善に及ぼす運動効果に関する多くの研究成果が報告されている[9~11)]．これらの成績から判断して，運動の長期継続がインスリン抵抗性症候群の改善，すなわちmetabolic fitnessの改善に好ましい効果を有することが期待できる．最近，Wallaceら[18)]は高インスリン血症を有する座位傾向にある男性への有酸素性トレーニングにレジスタンストレーニングを加えたクロストレーニングを実施した結果，糖・脂質代謝状態や血圧の改善率は有酸素性トレーニングのみのグループに比較し有意に良好であることや，これらの改善が同一個体に同時に出現することを明らかにした．おそらく，これらの変化に関与する重要な因子としては，持久性競技者や有酸素トレーニング後に観察されるインスリン感受性の改善が考えられる[4,5,19)]（図-3）．この適応は，インスリンによる筋への糖の取り込みを増加させ，インスリンによるantilipolitic effectを改善させる．門脈系を介しての遊離脂肪酸輸送の低下や血中のインスリン水準の低下で，肝でのVLDLおよびApo B分泌の低下をもたらし，HDL前駆物質の産生を高めている可能性が示唆されている．

●遺伝子多型

一過性および身体トレーニングの諸効果には，個人差を認めることから，この背景には遺伝子多型の影響が想定されている．遺伝子多型とは，同一集団内に特定の遺伝子座の対立遺伝子の種類が