Effects of energy restriction and exercise on the sympathetic nervous system

WHM Saris
Nutrition Research Centre (NUTRIM), University of Limburg, Maastricht, The Netherlands

Thermogenesis or facultative heat production is a fundamental process of the human body to respond to overnutrition and undernutrition in an attempt to maintain a constant lean body mass. In this process the sympathetic nervous system (SNS) is an important regulator of metabolic processes. Variations in energy intake and energy expenditure through exercise cause changes in SNS aimed to maintain energy homeostasis. Studies have shown that acute energy restriction leads to a reduction of the sympathoadrenal drive, resulting in a reduced thermogenic response. Overfeeding increases SNS activity, expanding the surplus energy by accelerating metabolism. When the SNS is stimulated, all types of adrenoreceptors are activated, but thermogenesis is primarily mediated by both β1-adrenoreceptors and β2-adrenoreceptors. Response to energy restriction also results in modulation of the adrenergic receptor number and sensitivity. Comparing lean and obese individuals there is increasing evidence that in the obese the adaptive responsiveness of the SNS to changing energy status is blunted.

The increased activation of SNS to respond adequately on the altered substrate demands during acute and prolonged physical exercise (training) is accompanied with an increase of resting metabolic rate (RMR) and lipid oxidation. The higher level of lipid oxidation at the same relative intensity of exercise is probably fueled by increased lipolysis of muscle triglycerides. Therefore, exercise may play an important role to overcome the impaired lipid oxidation in muscle of obese individuals, as was demonstrated in a number of studies.

Keywords: energy restriction; exercise; sympathetic nervous system; obesity; thermogenesis

Introduction

Thermogenesis or facultative heat production is a fundamental process of the human body to respond to overnutrition and undernutrition, in an attempt to maintain vital body functions, which are mainly related to the lean body mass. From an evolutionary point of view, powerful, adaptive mechanisms to protect lean body mass against seasonal food shortage and famine have been selected. As a result, the body is capable of activating a number of energy saving mechanisms to protect the vital functions for as long as possible. Based on this so-called ‘survival of energy shortage’ principle, it cannot be disputed that, in periods of food abundance the body is able to gain rapidly fat tissue as a buffer for future periods of starvation. Unfortunately, in developed societies we have to implement frequently these energy restriction periods artificially in order to keep body weight within acceptable margins. This powerful drive to maintain vital body functions activating a number of energy-saving mechanisms is at least partly responsible for the failure in long-term weight maintenance. The sympathetic nervous system (SNS) plays a vital role in this adaptive metabolic process.

Metabolic response to energy restriction

Keys and colleagues in their classic Minnesota semi-starvation study, in the late 1940s, clearly demonstrated the adaptive metabolic effects of artificially imposed starvation. Thirty-two volunteers underwent a 24 week energy restriction regimen of 2.7 MJ/day. During this period, they lost 23% of their initial body weight (Table 1). Simultaneously, resting metabolic rate (RMR) decreased absolutely by 36%, especially muscle mass which decreased by about 40%, while vital organs were relatively unaffected. Overall lean body mass (LBM) decreased by 26%. The relative decrease in RMR per unit of LBM (a decline of 14%) is important for the discussion about adaptive mechanisms. This response is considered to be an indication of an increased metabolic efficiency of the residual LBM. Grande et al. regarded the actual decrease in metabolic activity of the LBM to be the main factor responsible for the reduced

<table>
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<th>0</th>
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<th>Change (%)</th>
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<td>146.3</td>
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Adapted from Keys et al., 1950.

Correspondence: WHM Saris, Nutrition Research Centre (NUTRIM), Department of Human Biology. University of Limburg, PO Box 816, NL-6200 MD Maastricht, The Netherlands
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RMR. Their analysis of data from a series of experimental semi-starvation studies were based on relatively short-term experiments (<4 weeks). In contrast, Keys et al., in the Minnesota starvation study reached the conclusion that about two-thirds of the decrease on RMR was originated in the reduction of LBM. These differences indicate a change in adaptive mechanisms over time. An important component in the total energy expenditure (TEE), which was not measured in the Minnesota experiment, was the change in physical activity. But the evidence from indirect measurements, such as tiredness and apathy, showed clearly that this expenditure component was also affected.

Recently, Prentice and colleagues published meta-analysis data of 29 studies about the physiological responses to slimming. These studies were mostly based on energy restriction regimens in obese subjects, in contrast to the Minnesota study and other early semi-starvation studies. It is reasonable to question whether under such circumstances, when there is an abundance of fat mass, is the metabolic adaptation the same? Even in the more severe energy restriction studies, it became clear that the decrease in metabolic rate seemed to plateau between 20% and 25%. This is substantially lower than the changes observed in the lean volunteers of the Minnesota experiment. Most of the differences can be explained by the fact that the ratio of fat to active tissue loss is related to the initial fat mass. To fill the gap between energy intake and expenditure, obese subjects rely much more on their fat stores and lose a lower proportion of active tissue than lean subjects. From this meta-analysis it became clear that the maximal adaptive effect of RMR per unit of LBM is less than 15%.

Another important question related to the adaptive response to energy restriction is the time course. James and Shetty were able to show that the metabolic adaptation (i.e. enhanced metabolic efficiency), is seen in the first two weeks of energy restriction. In the well controlled study of De Boer et al., it was shown that a substantial part of this initial rapid phase of metabolic adaptation occurs during the first day of energy restriction. After 24 h on a 4.2 MJ/day diet, the TEE decreased by 5%. This adaptation, which must be independent from changes in body composition, is reversible because at the end of the eight week diet period and after one day of re-feeding on a normal maintenance diet, TEE increased by 6%. This direct response can be partly attributed to the change in diet induced thermogenesis (DIT), as a consequence of the diminished food intake. The facilitative component of DIT is partly mediated by the SNS.

The second adaptive response is related to the decrease in body weight and especially LBM. In the De Boer et al. study this component was calculated at a rate of about 5% per month of energy restriction. It seems reasonable therefore, to assume that the reduction in RMR during energy reduction occurs in two different phases. The initial phase is partly attributable to the increase in metabolic efficiency. With continued energy restriction, the further decline in RMR is mainly accounted for the loss of LBM. This also raises the question whether the severity of the energy restriction influences the decline of RMR. Prentice et al. have addressed this issue by combining the data of 22 studies and using a range of energy restriction regimens for a duration of 4–6 weeks. They found a highly significant difference between the 15% suppression of RMR, elicited by diets with an energy content of less than 3 MJ/day compared to the 5% reduction in RMR on diets, providing about 5 MJ/day. They concluded that there is a threshold at about 5 MJ/day, below which a more pronounced physiological defence against weight loss occurs. The rate of weight loss was about 2% body weight per week for the very low energy diets (VLED) (1.7–3 MJ/day) vs 1.3% for the moderate energy restricted diets (5 MJ/day). These differences indicate a higher than proportional loss of LBM to fat mass on a VLED. In general, a loss of body mass, at a ratio of LBM to fat mass of 1 : 3, is accepted as normal for obese individuals, since fat mass is supported by a certain amount of LBM which will be redundant if fat mass is lost. The greater than optimal loss of LBM during severe energy restriction, can partly be explained by the relative short length of the observation period. Especially during the first weeks of a VLED, the loss of LBM is higher due to the larger energy gap and the relatively slow start before maximal lipolysis and fat oxidation is reached. Data of a number of VLED studies over three months did not reveal a larger than proportional loss of LBM than about 25%. This supports the idea that if the observation period is long enough, the observed differences in the first phase of the weight loss period will disappear in the total adaptive process during energy restriction.

It has been known for many years that catecholamines have an important impact on thermogenesis. The increased rate of cellular metabolism induced by catecholamines manifests itself in an elevation of thermogenesis and fuel utilization, while its stimulatory effect on the breakdown of complex fuels supplies the energy required for the increased cellular metabolism. Therefore, it is conceivable that changes in SNS activity may play an important role in the reduction of metabolic rate during energy restriction.

One of the major problems concerning the alteration in SNS activity during energy restriction, is the reliability of the techniques available for assessing sympathetic activity and function. Changes in catecholamine circulation do not necessarily reflect receptor or post-receptor activity levels. Therefore, it is very important to assess the functional consequences of changes in SNS activity since several compensatory mechanisms may be activated to minimize a change in endogenous SNS activity. Thus, measurement of the thermogenic function and substrate mobilization will be of value in the interpretation of the results.

Plasma noradrenaline appearance rate, using a labelled tracer, may be a better physiological index of the functional status of SNS than plasma noradrenaline.
levels, although the interpretation can be difficult if the relationship between noradrenaline release and spill-over is changed. Young and Landsberg\(^9\) were the first to demonstrate a close link between SNS activity and fasting, using the noradrenaline turnover technique. They reported a significant decrease in the noradrenaline turnover in cardiac tissue of 48 h fasted rats. The decrease of noradrenaline turnover during fasting was completely reversed by one day of re-feeding.

A number of studies of obese subjects have confirmed this reduced catecholaminergic drive during energy restriction. In the study by Shetty et al.,\(^10\) energy restriction was associated with a decrease in circulating levels of noradrenaline and lower urinary excretion of hydroxy-3-methoxy mandelic acid (HMXMA), an end-product of catecholamines. Bessard et al.,\(^11\) studied young obese women and found a decrease in noradrenaline levels in the urine after a weight loss of 12 kg on a 1 week VLED. In this study, the noradrenaline excretion was still low after one week of re-feeding, which is in contrast to the study by Jung et al.,\(^12\) who showed a rise in urinary HMMA excretion and plasma noradrenaline levels within three days after re-feeding in previously energy-restricted individuals.

Perhaps the best set of data to show the adaptive response of the SNS to energy restriction and energy overfeeding was published by O'Dea et al.,\(^13\) using a constant infusion of tracer noradrenaline. The effects of undereating for 10 days, (VLED, 2 MJ/day), a weight maintenance diet or a hyper energetic diet (+4.2 MJ/m\(^2\) body surface area), on noradrenaline turnover was studied in six individuals of normal body weight. Noradrenaline turnover rate increased significantly with increasing energy intake and was a more sensitive indice than plasma noradrenaline levels, which rose, but not significantly (Table 2). The study clearly demonstrated that SNS activity varied in response to short-term changes in energy intake in normal weight subjects. There were marked differences between individuals which may partly explain why energy can be constantly maintained despite large differences in habitual energy intake. The follow-up paper of the same group was important, reporting the response in six very obese individuals, tested for the same period.\(^14\) Despite significant gains or losses in body weight, as was observed in the lean groups, noradrenaline turnover failed to change significantly in response to the changes in energy intake in obese subjects, in contrast to lean subjects (Table 2). This absence of any reduction in noradrenaline metabolism with undereating and at most a very small rise with overeating, perhaps indicate that SNS responsiveness to energy state is blunted in obese individuals.

Differences in the SNS-induced activity to increase facultative thermogenesis seem to have sufficient quantitative importance to be involved in the propensity to obesity in humans. In a group of 30 men with a wide range of body fat, the SNS activity was evaluated.\(^15\) The functional thermogenic response was assessed by stepwise infusion of the β-agonist isoproterenol. The β-adrenergically mediated thermogenesis was blunted in the obese subjects as reflected by a significant positive correlation between percentage of body fat and the plasma isoproterenol concentration to increase RMR by 15% (Figure 1). Weight reduction resulted in an increase in thermogenic response.

In the study of Bazelmans et al.,\(^16\) the observed blunting of the SNS activity did not result in an increased weight gain and decreased loss. A period of 10 days is probably too short to clear effects of a low response in metabolic drive of the SNS. However, over a few years such levels of impairment could be responsible for differences in weight gain between individuals under the same environmental conditions.

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**Figure 1** Simple (unadjusted) correlation between percentage body fat and plasma concentration isoproterenol to increase RMR with 15%. Adapted from Blaak et al., 1995.

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<table>
<thead>
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<th>Table 2</th>
<th>Noradrenaline turnover during undereating, weight maintenance and overeating in normal weight and obese subjects</th>
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<tbody>
<tr>
<td></td>
<td><strong>Hypo</strong> (2 MJ/day)</td>
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<tr>
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<td>Lean</td>
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<tr>
<td>Plasma noradrenaline (μg/ml)</td>
<td>154</td>
</tr>
<tr>
<td>Noradrenaline appearance rate (μg/min/m(^2))</td>
<td>0.21</td>
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Adapted from O'Dea et al., 1982 and Bazelman et al., 1985.
Another important piece of evidence for the regulatory role of SNS in the RMR changes seen during semistarvation, came from drug studies with an experimental manipulation of the SNS activity. For instance, L-3,4-dihydroxyphenylalanine (L-dopa) which acts as a sympathomimetic, results in an increased level of noradrenaline. In a study of obese subjects on a severe energy restriction diet, administration of L-dopa prevented the expected drop in RMR.\textsuperscript{10} The effects of β-adrenergic blockade have also been studied extensively. As a result of β-blockade by propranolol, a small (3%), but significant decrease in RMR was found.\textsuperscript{16} This indicates the involvement of the β-adrenergic system in RMR. In literature, both an unchanged or decreased RMR have been reported as a result of β-blockade. On weight maintenance diets the RMR of obese subjects diminished by nearly 9% after propranolol administration.\textsuperscript{17} After one week of energy restriction, the effect of a similar dose of propranolol only produced a non-significant drop in RMR. It was concluded that the blocking effect on RMR was mediated by inhibition of the SNS activity stimulation rather than by its effects on thyroid metabolism.\textsuperscript{17} In a study on fed, fasted and re-fed rats Rothwell et al.\textsuperscript{18} provided evidence for catecholamine-induced changes in thyroid hormone metabolism and for a sympathetic involvement in thyroid dependent responses to the nutritional manipulation.

The major physiological role of SNS is to exert the efferent control of cardiovascular homeostasis via the arterial blood pressure. Therefore, changes in electrolyte status that coincide with energy restriction are a potentially confounding factor in the response of the SNS. Leiter et al.\textsuperscript{19} suggested that low sodium intake with a VLED primarily caused an increase in noradrenaline and can therefore explain some of the differences observed in the literature. The sodium restriction can override the reduction in noradrenaline activity that might have occurred otherwise. Therefore, these effects on SNS activity should be considered during energy restriction. Although, in the study of Mansell et al.\textsuperscript{20} sodium and potassium intake was controlled in order to minimize the confounding effects of fluid deprivation and intravascular volume depletion, an effect on the outcome of the acute effects of starvation (48 h) on SNS activity cannot be excluded. It might be expected that an effect of starvation would also be a reduction in sensitivity to catecholamine-induced thermogenesis. Mansell et al. found an enhanced thermogenic response to adrenaline during the first 48 h which disappeared after 7 days of prolonged undernutrition. It was suggested that the functional result of a fall in SNS activity with underfeeding is offset by an increase in the physiological effects of catecholamines. This increased responsiveness to circulating catecholamine levels reflects post-synaptic events, which might also be modified by alteration in nutritional status. Adrenergic receptor numbers and their sensitivity have been shown to undergo modulation in response to changes in circulating catecholamine levels. In response to altered agonist levels up-regulation as well as down-regulation of α-receptors and β-receptors have been known to occur.

The effect of energy restriction on adrenoreceptor regulation in obese subjects has not been extensively studied and the results are conflicting. In addition to unchanged lymphocyte β\textsubscript{2}-adrenergoreceptor density, increased numbers of β\textsubscript{2}-adrenergoreceptors have been shown on femoral adipocytes. Platelets, α\textsubscript{2}-adrenergoreceptors and lymphocyte β\textsubscript{2}-adrenergoreceptors were studied in obese female subjects before and after a four week VLED, leading to a 7.8 kg weight loss.\textsuperscript{21} Basal venous noradrenaline levels decreased. Energy restriction did not alter basal β\textsubscript{2}-adrenergoreceptor density, whereas α\textsubscript{2}-adrenergoreceptor density significantly increased, this was also reported in two other studies. This increased α\textsubscript{2}-adrenergoreceptor density may represent an up-regulation in response to decreased circulating noradrenaline values, since receptor number and/or affinity may vary inversely with the ambient concentration of agonist. Thus, as a consequence of a low noradrenaline level due to energy restriction, an increase in receptor activity is expected. So far, the results are contradictory since adequate validation studies are lacking.

In summary, by reviewing the available literature it can be concluded that acute energy restriction leads to a reduction in the sympathoadrenal drive, resulting in a reduced thermogenic response. Overfeeding increases SNS activity, expending the surplus energy by accelerating metabolism.

When the SNS is stimulated, all types of adrenoceptors are activated, but thermogenesis is primarily mediated by both β\textsubscript{1}-adrenergoreceptors and β\textsubscript{2}-adrenergoreceptors. Response to energy restriction also results in modulation of adrenergic receptor number and sensitivity which makes the physiological response in terms of thermogenesis difficult to predict. Comparing lean and obese individuals there is increasing evidence that in obese subjects the adaptive responsiveness of the SNS to changing energy status is blunted.

### Substrate mobilization during energy restriction and sympathetic nervous system activity

The changes in substrate utilization during energy restriction aim to:

- maintain glucose production by glycogenolysis and gluconeogenesis for the glucose consuming tissues, in particular the brain
- reduce the breakdown of vitally needed body protein
- maximize lipolysis and fat oxidation to cover the energy needs as much as possible.

The drop in SNS activity during fasting with consequent decrease in RMR helps to economize on energy utilization.
Substrate mobilization and especially lipolysis, cannot completely be attributed to the SNS. Lipolysis is very sensitive to changes in plasma adrenaline levels and in conjunction with the suppressed insulin levels during energy restriction, hepatic glucose output and lipolysis will be enhanced.

The relative small increase in adrenaline is unlikely to affect thermogenesis. Therefore, the combination of SNS suppression and adrenal medullary stimulation results in an adequate substrate mobilization with no effect on the RMR. It is clear that these metabolic alterations are an integrated response of the SNS activity, catecholamines, thyroid hormone and insulin. It is beyond the scope of this review to discuss the role of these hormones in regulating the metabolic rate. In the Danforth paper, a model is proposed to uncouple the changes in SNS activity and RMR from diet induced alterations in thyroid and insulin action.

Exercise and thermogenesis

The idea of stimulating metabolic rate to facilitate weight loss or to increase the success of weight maintenance is not new. For instance, crude thyroid extracts were already used at the turn of the century as a thermogenic drug. However, like most proposed compounds, thyroid hormones have undesirable side-effects at levels high enough to increase metabolic rate.

Another well-known example of a common addictive drug which stimulates metabolic rate, is nicotine. Smoking a packet of cigarettes a day, raises the metabolic rate by 10%. About 50% of the weight gain after cessation can be explained by the reduction of RMR.

Recently the role of exercise as a maintenance strategy in weight control, has received renewed attention. There are a number of reasons which make exercise an attractive alternative for artificial stimulation of the metabolic rate. Perhaps the most important argument is the physiological increase of energy expenditure and the concomitant activation of several metabolic pathways for the mobilization of substrates. There is evidence of increased sensitivity of the SNS which is of interest in relation to the reduction in sympathetic drive during energy restriction.

Exercise and resting metabolic rate

A large number of studies have addressed the question whether regular exercise has any effect on RMR. Poehlman hypothesized that RMR could be increased when the energy turnover rate is highly concurrent with the maintenance of an energy balance. Supporting this view is the observation of Tremblay et al., showing a 6.5% drop in RMR in highly trained athletes following three days of detraining. To date, the literature on the relationship of RMR and level of physical activity is not very consistent. The important drawback of this type of study is the lack of precision in measuring the level of physical activity which may obscure such a relationship.

It is encouraging that in the study of Westerterp et al., using the doubly labelled water method to measure daily physical activity in sedentary and moderately active subjects, a positive relationship between total energy expenditure (TEE) and RMR was found ($r^2 = 0.72$). The observed group in this study was not involved in any kind of training. Nevertheless, based on the valid doubly labelled water technique, a significant relationship between level of exercise and RMR was shown. In endurance-trained individuals or previously in active individuals after exercise training, often higher RMR values were found. Consistent observations have been made that lipid oxidation is proportionally higher at the same absolute levels of exercise. The relationship between the rise in free fatty acids (FFA) and the increase in oxygen consumption appeared to be physiological, showing a tendency to a linear relationship when plasma FFA rise is relatively high ($>800 \mu\text{mol}/\text{litre}^{-1}$), as can be observed during exercise or during the first week of energy restriction. Bahr et al. have suggested that an increase in FFA mobilization-oxidation and cycling may explain a substantial part of the enhanced post-exercise RMR. This implies that the increase in RMR and lipid utilization observed in trained subjects, are closely linked.

Another important question related to the topic of this paper is: to what extent does exercise prevent the fall in RMR? Several studies have addressed this issue, usually by a direct comparison of a group treated with a diet alone and a group treated with a diet plus exercise. In a review of 13 studies, Saris came to the conclusion that the positive effect in favour of exercise is deficient. There is evidence that incorporating exercise results in a favourable ratio between loss in LBM and fat mass. This is especially true in those studies with a high level of compliance to the exercise programme. It demonstrates that exercise can partly prevent the secondary fall in RMR which is directly related to the changes in body composition. However, a comparison of exercise intervention on the basis of RMR per unit of LBM does not reveal any positive effect. Most of the studies with no effect on RMR per unit of LBM used a VLED as dietary intervention. Therefore, it was suggested that in a situation of severe energy restriction, the adaptive response of a lower RMR against weight loss counteracts the possible stimulating effects of exercise on RMR. Exercise itself increases the energy deficit. The interaction of exercise and energy restriction is best seen at levels of moderate energy restriction and seems to disappear with severe energy restriction.

Exercise and the sympathetic nervous system

Most studies that have examined the effect of training on the SNS activity, have been performed in young lean
individuals. Only a few studies have addressed this issue in obese subjects. Furthermore, SNS activity was often evaluated based on plasma concentration of the catecholamines alone. As mentioned before, this gives limited information and may be misleading. Both higher or lower noradrenaline levels, or no effect after training have been found. A limited number of studies have used the noradrenaline turnover technique. Poehlman and Danforth reported that the increase in RMR induced by an eight week training programme in older persons, was associated with a higher noradrenaline turnover rate. Schwartz et al. studied the effect of a three month dietary weight loss or exercise training programme on SNS activity in moderately obese subjects. Resting plasma noradrenaline and adrenaline did not differ significantly before and after treatment in either group. Noradrenaline turnover rate declined significantly by 17% in the diet group, but was not significantly changed in the exercise group. This suggests an effective counteraction of the well-established diet-induced reduction of SNS activity by a training programme.

In a four week daily endurance training programme, Jennings et al. found no systematic increase in noradrenaline turnover rates. The variation between individuals was relatively high. Besides these noradrenaline turnover studies, several other studies have shown some evidence that the increase in RMR is mediated by an increased sensitivity of the SNS. For example, in the hindquarter muscle of rats, Richter et al. demonstrated a clear increase in oxygen consumption during adrenaline perfusion in trained vs untrained animals (Table 3).

Tremblay et al. showed in trained and sedentary males that administration of propranolol, a non-specific β-blocker, resulted in a significant decrease in RMR and lipid oxidation in the trained subjects, whereas no change was observed in the sedentary group. It was concluded that the β-adrenergic system is involved in the increase in RMR and lipid oxidation in trained individuals.

The increased activation of SNS in response to exercise is accompanied by a rapid elevation of β2-adrenoreceptor density in the muscle of individuals of normal weight. In fat cells, physical training increases sensitivity to noradrenaline and adrenaline of β-receptor-mediated lipolysis. Both male and female athletes in training, show a decrease in α-adrenergic, and increase β-adrenergic pathway efficiency. This favours an increased utilization of fatty acids related to carbohydrates as fuel. However, the plasma FFA oxidation is lower in the trained than in the untrained state. This greater utilization of fatty acids in the trained state is most probably fueled by increased lipolysis of muscle triglyceride. To what extent this can be considered as negative in relation to adipose tissue lipolysis needs further research. The increased RMR and lipid utilization as found in an increasing number of studies, might reflect a stimulation of the skeletal muscle metabolism mediated by β-adrenergic stimulation. The effects of exercise and energy restriction on β-adrenoreceptor activity in obese subjects was recently studied. As a result of the VLED, there was a 7.8 kg weight loss, RMR per kg LBM did not change. Basal plasma insulin and noradrenaline levels significantly decreased. After the diet, the lymphocyte β2-adrenoreceptor density significantly increased during a 60 min exercise bout which was not the case before the diet. Energy restriction, but not exercise resulted in an increased basal platelet α2-adrenoreceptor density. This observed increase, as was also reported in two other studies with moderate energy restriction, may represent an up-regulation in response to decreased circulating noradrenaline levels. The exercise induced up-regulation of β2-adrenoreceptors might play a role in the increased exercise-induced lipolysis during energy restriction.

In the last few years, substantial interest has emerged in treating obesity by drugs which promote lipid mobilization and energy expenditure. The pharmacological strategy is based on the utilization of β-adrenergic agonists. Exercise seems to fit very well in this concept, though much more research is needed to quantify the effects in relation to weight balance. Also the duration and intensity of the exercise required to produce the beneficial SNS effects is unknown. Further research is warranted.

**References**


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*Adapted from Richter et al., 1984.*
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