Brown Adipose Tissue Participate in Lactate Utilization during Muscular Work

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Abstract: In an experiment involving five healthy volunteers studied the dynamics of the skin temperature of the back and neck, combined with the dynamics of blood glucose and lactate during treadmill ramp test and 10 minutes of the recovery period. Skin temperature decreases in all cases at the beginning of the ramp test, but after reaching the anaerobic threshold temperature increases rapidly and reaches a maximum at the time of the refusal of work or shortly thereafter. Since the moment of reaching the anaerobic threshold and to the end of the observation period strong positive correlation between the maximum temperature of the selected area of the body surface and lactate content in the peripheral blood is observed. Blood glucose levels do not correlate with the skin temperature. The data obtained can be used as some evidence in favor of the hypothesis of the participation of brown adipose tissue in lactate utilization.

1 INTRODUCTION

Brown adipose tissue (BAT) today is one of the most thoroughly studied objects in the human body. As it has recently been shown, it is widely distributed in adults (Virtanen et al., 2013) and at the same time this tissue is associated with the possibility of normalization of carbohydrate and fat metabolism and the ability to prevent the development of obesity and the metabolic syndrome effects (Cypess et al., 2009). The studies of molecular, cellular and physiological mechanisms of BAT especially intensified after discovering muscle peptide “irisin” (Boström et al., 2012), which is produced during exercise and has hormonal effects on fat cells, contributing to their transformation into mitochondria-rich structures similar to BAT cells (Spiegelman, 2013). Soon after that an experiment with the rat showed that physical exercise significantly activates specific membrane transporter lactate (De Matteis et al., 2013), not long before detected in mice BAT cells (Iwanaga et al., 2009). Thus, new evidence has been obtained for previously expressed hypothesis that BAT is involved in the homeostatic reactions not only in the case of exposure to cold, or high-calorie foods, but also in the case of strenuous exercise, contributing to the rapid utilization of lactate (Son'kin et al., 2010).

Meanwhile, to obtain direct evidence for the involvement of human BAT in lactate utilization during physical work is not easy, because the main method of in vivo study of BAT activity is positron emission tomography (PET), unsafe with repeated use over a short time. Infrared thermography is a good alternative to this method. It is totally harmless method that gives reliable results in the case of registration of the dynamic changes in temperature. This method allows to register the projection zone of thermal radiation thermogenic subcutaneous structures on the skin (Lee et al., 2011).

The principle of BAT cells operation is that they contain a large amount of mitochondria - specific uncoupling protein UCP1, which is embedded in the mitochondrial membrane. Its activity leads to termination of the ATP synthesis together with high intensity of mitochondrial oxidation (Cypess et al., 2009). Free energy formed in this reaction is released as heat. It is the base for "warming" (thermoregulatory) BAT effect (so-called "non-shivering thermogenesis"). This type of metabolism is useful not only to maintain temperature homeostasis, but also for "burning" excess amounts of certain substrates, in particular - the nutrient that allows the body possessing BAT, maintain homeostasis substrate and prevent excessive fat accumulation (Harms and Seale, 2013). The removal of heat from the source - BAT - occurs in all possible ways, including infrared radiation, which is

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projected onto the surface of the skin. Modern thermal imaging matrix technology allows completely harmless and non-invasive study of the distribution of thermal fields on the surface of the human body, and this kind of dynamic thermogram can be used successfully to identify the active brown fat in humans (Lee et al., 2011; Sacks and Symonds, 2013), which, as shown by PET studies in combination with histochemical study biopsies, is most often located in adults' neck and supraclavicular depots (Sacks and Symonds, 2013; Cypess et al., 2009; Virtanen, 2009).

The purpose of this study was to investigate the dynamic changes of maximum surface temperature in the upper half of the back and dorsal surface of the neck in conjunction with the content of blood lactate during exhaustive physical work and recovery hoping to find signs of lactate utilization by BAT.

2 ORGANIZATION AND METHODS

The investigation was conducted at the Moscow State Centre for athletes testing. Treadmill ramp test was used as a model of strenuous exercise. The standard initial belt speed was 7 km / h, it was increased every 10 s at 0.1 km / h. 5 healthy physically active men volunteers aged 20-35 participated in the experiment. Before the load test, all the participants were granted access - conclusion of a cardiologist, and gave written informed consent to participate in the research. The research program was approved by the Ethics Committee RSUPE.

Morphological and functional characteristics of the subjects are shown in table 1.

At rest, during the test, and within 10 minutes of recovery some physiological parameters of the subjects were recorded: heart rate (HR), ventilation, and gas exchange. At rest, before the beginning of the test and then every 2-3 minutes during work and recovery blood samples were collected from the distal phalanx of the finger, for the determination of glucose and lactate. The anaerobic threshold value was determined individually by the dynamics of blood lactate level under the control of pulmonary ventilation (PV) and CO_2 emission.

Used equipment: treadmill HP Cosmos, gas analyzer Metamax 3B, heart rate monitor Polar RX 800, glucose and lactate analyzer Biosen C-line, infra-red video camera NEC TH 9100SL.

Dynamic registration of thermogram was produced in video mode with a frequency of 4 frames / s, while the imager was located at a height of 1.4 m above ground level at a distance of 3 m from the subject, being on a treadmill. While processing the thermogram with the help of the specialized software Image Processor ® current maximum temperature at selected area of the skin (Fig. 1) reflecting the thermal radiation projection of most heated subcutaneous structures was fixed. Room temperature was maintained at 21-22 °C. Thermogram registration started after 10-15 minutes of adaptation to the test room temperature.

Statistical analysis of the results was performed by means of MS Excel.

3 RESULTS

Fig. 1 shows examples of infrared thermal images, on the basis of which the maximum temperature on the selected area of the skin surface of the back and neck was calculated. Dotted line at the thermogramms allocates surface area of the back, including the back of the neck, where the maximum temperature was automatically recorded throughout the experiment in the video at 4 frames per second. As seen from the thermograms the hottest areas of the skin at all stages of the experiment are found at the back of the neck.

Before performing the test, most of the selected surface of the back and neck has a temperature in the range 32,5-33,0°C. During work at speeds below the anaerobic (lactic) threshold skin surface cools back through perspiration, and only in the neck keeps the temperature above 32°C. When the work is completed, the back surface thermogram represents a mosaic picture, which contains some parts of a fairly high temperature, interspersed with the areas that remain cold. The hottest areas in this case are on the skin of the neck, under which, as is known, loci BAT depots are located.

Dynamic changes in temperature of each of our subjects in conjunction with the dynamics of lactate and glucose in the peripheral blood are shown in Fig. 2. It is clearly seen that all five subjects show the same pattern: the temperature of the skin during the period of adaptation to the experimental conditions is either declining slightly or does not change, then it is gradually decreasing during the execution of ramp test, reaching a minimum at a speed of 11-13 km / hour, and then begins to increase rapidly and reaches a maximum at the time of the refusal of work or a bit later. During the

Table 1: Morpho-functional characteristics of subjects.

Subject	A.I.	G.A.	Sh.D.	Ya.A.	Z.A.
Age, years	20	35	23	28	24
Body mass, kg	78	95,5	62	70	71,5
Body height, sm	175	192	170	176	174
Body mass index	25,5	25,9	21,5	22,6	23,6
VO2max, l/min	4,9	5,8	4,5	3,9	5,5
Anaerobic threshold, km/h	14,0	14,6	14,8	12,6	14,6
Duration of test, min:s	15:25	14:40	18:30	14:05	18:30
Heart rate max., 1/min.	197	186	197	193	192
Lactate max., mM/l	10,06	8,92	12,58	15,03	10,78
Glucose min/max, mM/l	4,34/5,44	3,65/5,20	4,11/6,88	3,53/5,69	3,78/7,04

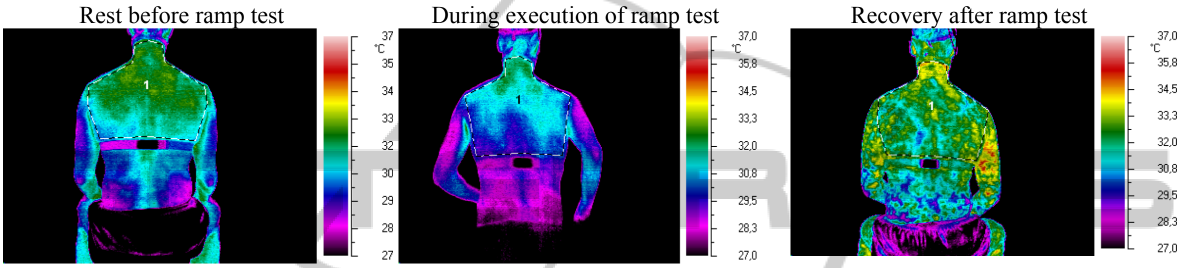

Figure 1: Examples of infrared thermal images obtained at different stages of testing. Subject – Ya.A.

recovery period, the temperature is gradually going down, but by the end of 10 minutes still does not reach the level recorded before the ramp test.

Noteworthy is the fact that the curve of temperature variation is very unstable and the graph looks like a broad band due to the large scatter of the data. This is due, firstly, to a rather complex picture of the functional manifestations of skin temperature - in fact plural functions are involved in the process: nervous control, and skin blood flow, and sweating, all of these factors interact in a complex manner, which leads to a large scatter in the data.

Also in this case the temperature profile was made in the course of movement, and though the test body was relatively motionless in a horizontal plane, it nevertheless constantly fluctuated in the vertical plane, thus creating an additional disturbance for measuring temperature in dynamic observations. However, the general trend of the temperature dynamics is not only evident for each subject , but practically identical for all 5 participants.

Superimposed on the line of temperature dynamics markers, reflecting changes of lactate and glucose in the peripheral blood, allow to notice some interesting facts.

Firstly, there is a large apparent difference in the dynamics of changes of lactate and glucose during the ramp test: Lactate increases exponentially throughout the test time, while the glucose in most cases varies little during work, and rises to a relatively high level only with the start of recovery. The range of variation of lactate is much broader than the relatively narrow range of variation of glucose.

Secondly, no connection between the dynamics of glucose and skin temperature is visible. But there is a demonstrative interaction between temperature and lactate: while the load is below the anaerobic threshold, skin temperature depends on the lactate level in moderately negative manner, and if the load goes above the anaerobic threshold we see strongly positive correlation (Fig. 3).

We obtained a very high coefficient of correlation between the two indicators (R2> 0.94). This can testify in favor of the assumption of a causal relationship between lactate levels and the level of skin temperature after reaching the anaerobic threshold. Careful consideration of individual curves ensures that in all 5 cases, increase in lactate level precedes raise of the temperature. The question of what is a direct trigger for the activation of structures, thermal radiation of which is projected onto the skin and is fixed by infrared device, requires further detailed study.

4 DISCUSSION

The fact that skin temperature initially decreases during intense muscular work, and then may rise in some of the subjects, and the beginning of this increase is linked to the achievement of anaerobic

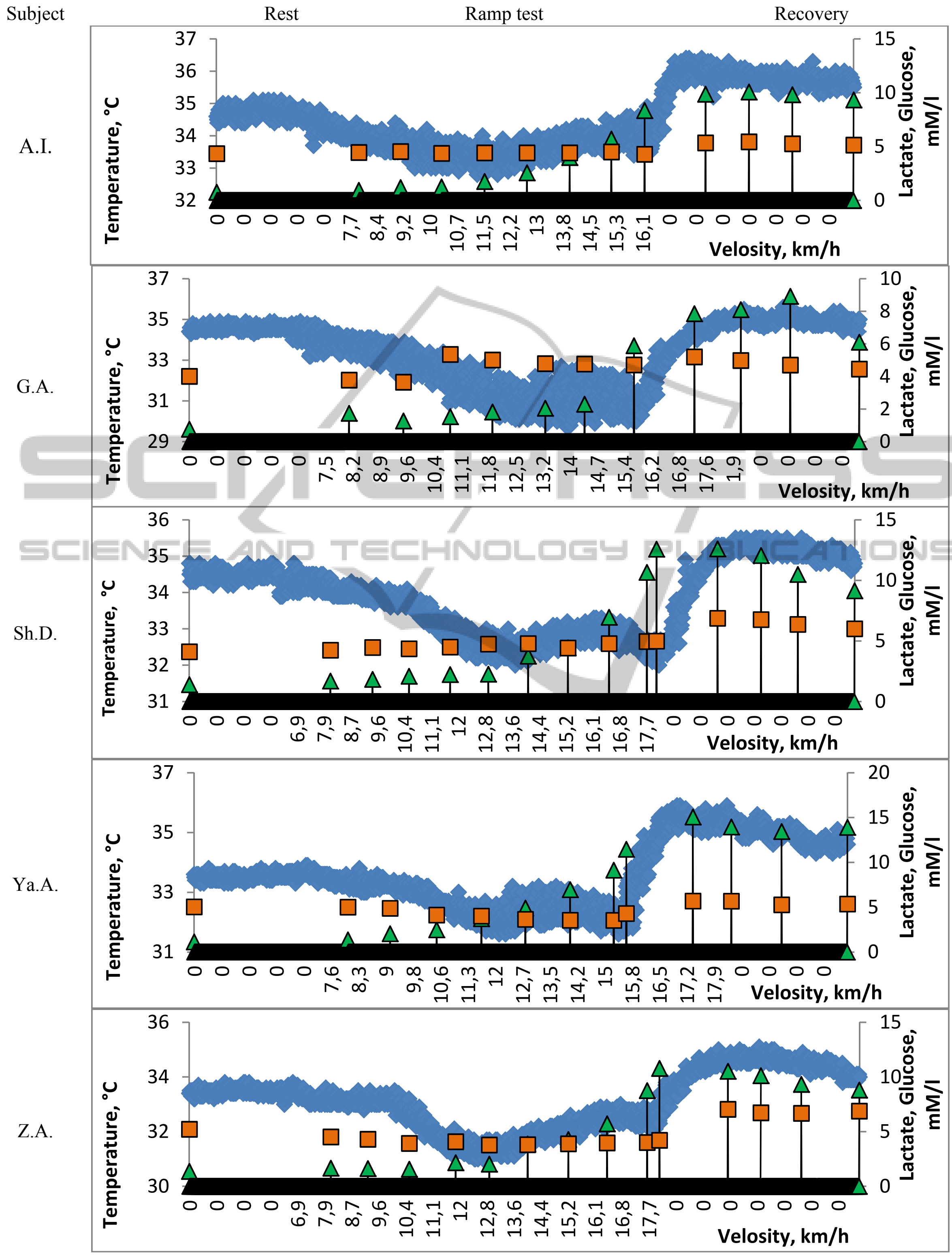

Figure 2: Individual dynamics of maximal skin temperature, blood lactate (triangles) and glucose (squares) during ramp test and recovery.

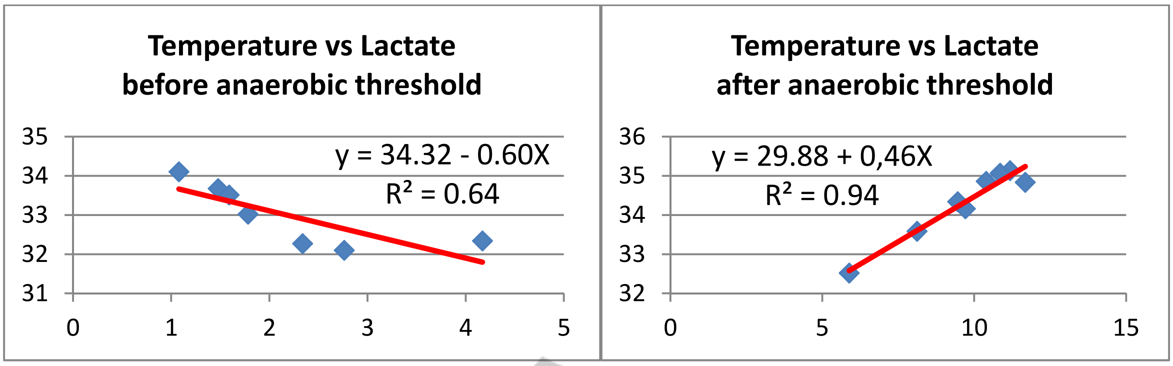

Figure 3: The relationship between the maximum surface temperature of the skin of the back and neck and lactate content in peripheral blood before the anaerobic threshold (left) and after it (right).

threshold, was previously reported through forehead thermographing (Akimov, Son'kin, 2011). In this paper it was shown that such a reaction is typical for 2/3 of the subjects, whereas 1/3 shows no increase in temperature at loads above the forehead anaerobic threshold. However, it is impossible to unambiguously correlate these events with the activity of BAT, as this tissue under the skin of the forehead is missing. We should rather speak about the change in the overall thermal state of the body.

An entirely different matter is the maximum surface temperature of the back, and especially the neck, where according to PET and biopsy studies the most significant fragments of BAT or analogues thereof are located (Sacks and Symonds, 2013; Virtanen et al., 2009), having a powerful metabolism. Maximum temperature in these areas of the skin increases very fast right before the refusal of work. High level of the temperature is also observed during the recovery (at least 10 minutes), and this level closely correlates with the dynamics of blood lactate. In this case we have to emphasize that there is no correlation of the level of blood glucose with this temperature curve. These results are difficult to interpret differently than to associate BAT obviously increased activity with targeted utilization of lactate.

Brown adipose tissue in the last 2-3 years has become well known among physiologists as an active participant of the metabolic processes in the human body (Harms M., Seale P., 2013; Spiegelman, B., 2013; Virtanen, K.A. et al., 2013). Due to its uncoupled mitochondria, brown adipose tissue is involved in maintaining temperature homeostasis and glucose homeostasis (Cypess A.M. et al., 2009; Lee Y.-H. et al., 2014; Sacks H. and Symonds M., 2013). The latest research suggests BAT also participate in maintaining lactate homeostasis (De Matteis et al., 2013; Son'kin V. et al., 2010).

First to describe the thermal effect of BAT under cyclic physical work were Japanese authors (Shibata and Nagasaka, 1987), who used a thermocouple to measure the temperature in BAT in rats while running on a treadmill, and it was about 0.5 degrees higher than the rectal one. However, this does not imply that the activation of BAT is somehow related to the metabolism of lactate. Relatively recently, it was shown that in mice BAT cells have specific transmembrane lactate transporter MST1. Through the activity of this molecule lactate penetrates inside the mitochondria and becomes available for oxidation (Iwanaga et al., 2009). And finally, a group of Italian researchers recently showed that running training leads to a twofold increase in the content and activity of MST1 in rat BAT (De Matteis et al., 2013).

5 CONCLUSIONS

Given the fact that the muscles can produce hormone irisin during contractile function, and this hormone stimulates the conversion of white fat cells into "beige" cells, which are similar by the metabolic activity with BAT (Boström et al., 2012; Harms and Seale, 2013; Lee at el., 2014; Spiegelman, 2013), begs the question of the biological sense of the phenomenon. If BAT or its metabolic analogs are able to utilize lactate produced during muscular work, and thereby fulfill another kind of homeostatic activity - the question of the biological sense gets a clear and unequivocal answer. But in this case there rise a plurality of application issues related to the ability to use the newly opened physiological phenomena in the labor process and the sport, not just a series of measures in prophylactics of obesity pandemic.

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