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REVIEW ARTICLE

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Exercise starts and ends in the brain

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Abstract Classically the limit to endurance of exercise is explained in terms of metabolic capacity. Cardio-respiratory capacity and muscle fatigue are thought to set the limit and the majority of studies on factors limiting endurance exercise discuss issues such as maximal oxygen uptake ($\dot{V}O_2$max), aerobic enzyme capacity, cardiac output, glycogen stores, etc. However, this paradigm does not explain the limitation to endurance exercise with large muscle groups at altitude, when at exhaustion exercise is ended without limb locomotor muscle fatigue and with sub-maximal cardiac output. A simple fact provides a basis for an explanation. Voluntary exercise starts and ends in the brain. It starts with spatial and temporal recruitment of motor units and ends with their de-recruitment. A conscious decision precedes a voluntary effort. The end of effort is again volitional and a forced conscious decision to stop precedes it, but it is unknown what forces the off-switch of recruitment at exhaustion although sensation of exertion certainly plays a role. An alternative model explaining the limitation of exercise endurance thus proposes that the central nervous system integrates input from various sources all related to the exercise and limits the intensity and duration of recruitment of limb skeletal muscle to prevent jeopardizing the integrity of the organism. This model acknowledges the cardio-respiratory and muscle metabolic capacities as prime actors on the performance scene, while crediting the central nervous system for its pivotal role as the ultimate site where exercise starts and ends.

Keywords Brain · Endurance · Exercise · Fatigue · Limitation

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Introduction

Classically the limit to endurance of exercise is explained in terms of metabolic capacity. When substrate availability decreases, when oxygen transport capacity is reached, when muscle metabolic capacity is fully used, muscle fatigue occurs and the effort cannot be maintained anymore. Cardio-respiratory capacity and muscle fatigue are thought to set the limit. Indeed, the majority of studies on factors limiting endurance exercise discuss issues such as maximal oxygen uptake ($\dot{V}O_2$max), aerobic enzyme capacity, cardiac output, muscle glycogen stores, etc. In order words, in the classic paradigm the limits to endurance are explained by arguments of metabolic nature. However, there are experimental situations, discussed hereunder, where it is not possible to explain the limitation to endurance using this paradigm, and it is therefore necessary to look for an alternative (Jones and Killian 2000; Noakes 2000; Noakes et al. 2001; Walsh 2000).

A simple fact provides a basis for such an alternative. Any voluntary exercise starts and ends in the brain. Exercise involves the contraction of muscle tissue through an increase in spatial and temporal recruitment of motor units. Similarly the exercise ends with a de-recruitment of motor units. Both are the result of modulation of descending motor command. A conscious decision is necessary to start a voluntary effort and even though it is not clear what forces the de-recruitment of motor units, the end of effort is again volitional and a (forced) conscious decision precedes it. Central command in the motor cortex is perceived as a sense of effort, and exercise is volitionally terminated when the sense of effort and other sensations such as muscle pain become more intense than is tolerable. Thus, the perception of effort is an important factor that limits exercise. However, the sensory aspects of exercise are not widely appreciated, at least in part because of a reluctance to accept subjective data (Jones and Killian 2000). A simple example is an incremental

exercise test on a cycle ergometer when a subject pedals at increasing power outputs and, at a certain maximum output, cannot maintain the effort anymore and ultimately decides to stop cycling. The majority of subjects will tell you that they "simply had to stop". This is usually referred to in the literature as "volitional exhaustion" and this point is generally believed to coincide with "true" maximum metabolic and cardiovascular capacity.

The CNS as limiting factor

The obligatory decision to stop or reduce the effort is conscious, and thus likely occurs at cortical levels, probably forced by sub-cortical brain circuitry. But what provides the input to the central nervous system (CNS) leading to the forced decision to end an exercise? Noakes recently proposed the existence of a functional entity dubbed a "central governor", which would limit exercise performance (for reviews see Noakes 2000; Noakes et al. 2001). Such a governor would prevent the recruitment of muscle mass beyond levels of intensity and duration where potential damage could occur to the heart or other vital parts of the organism. The notion of such a governor is not new. In fact AV Hill and colleagues in 1924 proposed a governor limiting exercise performance (Hill et al. 1924), but until recently their original idea was not developed further. For extensive discussion of the Hill model the reader is referred to the papers of Noakes (2000) and Noakes et al. (2001). Even though the CNS as the ultimate limiting factor would appear obvious, the notion of a central governor that limits exercise to protect the integrity of the organism remains hypothetical.

Interestingly, in contrast to endurance exercise with large muscle groups, the concept of the CNS sometimes limiting exercise performance with small muscle groups is quite well established and accepted. Over the last 75 years much data have been obtained from the study of human muscle contraction, on small muscle groups and during isometric exercise. On numerous occasions it was found that maximum voluntary contraction does not always lead to full activation of the muscle and an increase in force can be obtained by superimposing an electrical stimulus (interpolated twitch technique). This observation led to the concept of central fatigue (or an exercise-induced decrease of muscle force due to a reduction in recruitment) as opposed to peripheral fatigue (a decrease in force due to a decrease in muscle fibre contractility following metabolic events in the muscle). It is beyond this paper to describe in detail the supraspinal, spinal and sub-spinal aspects of fatigue and the reader is referred to the excellent reviews of Fitts (1994) and Gandevia (2001). When studying exercise performance with small muscle groups it has become clear that exercise capacity is not simply determined at the muscle level, and that central command plays a very important role too. Indeed, depending on the exercise paradigm voluntary full activation of muscle is not always achieved.

By contrast, the notion of the CNS limiting performance during dynamic exercise with large muscle groups has not had much attention. Indeed, the last 75 years also yielded an enormous amount of data on dynamic exercise such as running, cycling or other exercise modes involving large muscle groups, but these studies on dynamic exercise with large muscle groups generally focused on the metabolic determinants of exercise capacity. Recently Noakes reviewed many of these studies and provided strong arguments that the classic paradigm of limitation by metabolic capacity is not sufficient, especially when looking at data obtained in hypoxia and hyperoxia (Noakes 2000; Noakes et al. 2001).

Interpreting data from Operation Everest II, a simulated climb of Mt. Everest in a hypobaric chamber, Bigland-Ritchie and Vollestadt (1988) proposed a hypothesis of CNS limitation of exercise performance at high altitude. They postulated that "*there is an upper limit to the total CNS motor drive that can be sent to the various limb muscles. Either the limited oxygen delivery capacity can be used to drive a small muscle mass to work at maximum intensity or the work can be spread between larger muscle masses, provided the total metabolic demands do not exceed those that can be supplied by the restricted oxygen available.*" A posteriori this hypothesis allowed one to account for several unexplained findings of Operation Everest II, including sub-maximal cardiac output and the absence of metabolic muscle fatigue at maximum cycling exercise at altitude, but further evidence was needed.

In an effort to further explain factors limiting exercise performance at high altitude, Kayser et al. (1994) provided additional data supporting the notion of central limitation of dynamic exercise with large muscle groups. Indeed, at high altitude small muscle mass exercise capacity remained unchanged. In contrast, the exercise capacity of large muscle groups was greatly reduced, but terminated with sub-maximal cardiac output and without signs of muscle fatigue (see Exercise at high altitude for further details). The recently proposed central governor hypothesis would allow one to account for the limitation of exercise capacity at altitude (Noakes 2000; Noakes et al. 2001). This central governor would not necessarily have an anatomical locus, but may just be of functional nature. It would receive inputs from various systems, all related to the exercise at hand, and integrate these inputs to provide an output towards the cortex forcing the decision to stop the effort if the total input to the governor went beyond a given threshold. For example, during heavy exercise, signals from the legs, from ventilation, from the heart and from the brain, etc. would all provide input to the central governor, eventually leading to the cessation of effort.

Exercise in sedentary subjects

At the university hospital of Geneva there is a policlinic devoted to patient care for muscle-related health problems. Over the course of several years a collection of data was made from 21 patients (7 male, 14 female, mean age 41 years, range 13–68 years) having unexplained vague complaints of fatigue and exercise intolerance. Underlying disease, including muscle disease, fibro-myalgia, etc. was extensively looked for, but none could be found and apart from the complaints the subjects were apparently in good health. As part of the investigation the subjects did a classic incremental exercise test on a cycle ergometer until voluntary exhaustion. Generally the results of such tests are interpreted as maximal and reflecting the metabolic capacity of the individual. However, in this series of presumably healthy subjects this was clearly not the case, as can be seen in Figs. 1 and 2. Figure 1 shows the relationship between maximum age- and sex-specific predicted heart rate and maximum heart rate reached, the dotted line being the identity line. Accepting the premise that the prediction of maximum heart rate holds for these subjects, it can be clearly seen that none of the subjects reached "maximum" exercise levels. Figure 2 shows the levels of arterial blood lactate reached. The subjects reached only relatively low levels of maximum power output and low levels of blood lactate, the dotted line indicating a 10 mM concentration level, normally easily reached by the majority of subjects in good health. What was the reason for the cessation of exercise in these subjects? They were asked to exercise as hard as possible and the endpoint of the exercise was voluntary exhaustion. It thus follows that a conscious but apparently obligatory decision was taken to end the effort. Less clear is what forced this conscious decision. Since in these subjects maximal metabolic capacity was probably not reached (below maximum cardio-vascular capacity and no indirect evidence of muscular fatigue) other reasons must be proposed. Although I do not have the answer I suspect that an unusually strong perceived exertion by these sedentary subjects led to the cessation of exercise. These subjects were not used to heavy exertion and the sensation related to the exercise may have led their CNS to impose an "early" switch-off. One could simply call this "lack of motivation" to drive full muscle recruitment but this would not be taking the subjects who certainly gave "their best" seriously. In fact the latter reasoning is precisely the same as used by numerous studies in the literature reporting maximum exercise data, although the fact that subjects decide consciously to stop the effort is generally only briefly alluded to, or not at all. The above findings on sedentary subjects are corroborated by the fact that untrained subjects often do not show the so-called plateau phenomenon for $\dot{V}O_2$ at the end of an incremental exercise test, the finding of the plateau being proposed as proof of attaining "true" $\dot{V}O_2$max (Fielding et al. 1997). Taken together it seems that maximum exercise capacity in untrained subjects measured in laboratory conditions may be limited by the CNS imposing "early" exhaustion before signs of attaining maximum metabolic capacity.

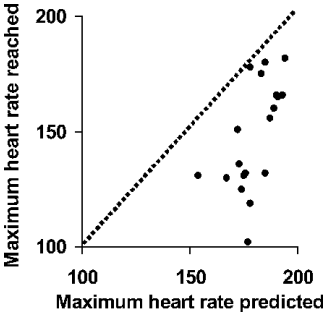

Fig. 1 Measured versus predicted maximum heart rate in a cohort of sedentary subjects not used to strenuous exercise. In spite of the maximum subjective sensation of exertion, the predicted maximum heart rate was not reached

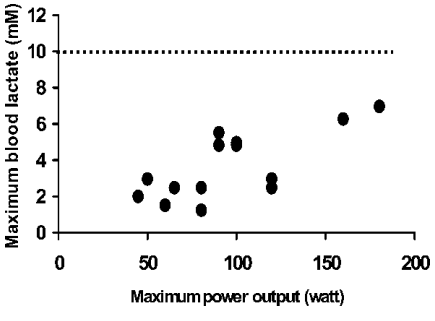

Fig. 2 Maximum blood lactate versus maximum power output in sedentary subjects not used to strenuous exercise. Power output and maximum blood lactate levels are low

An additional strong argument in favour of this reasoning comes from recent experiments in trained subjects comparing exercise after administration of naloxone or placebo. Naloxone, an opiate antagonist, leads to significant reductions in $\dot{V}O_2$max and exercise performance when compared to control (Sgherza et al. 2002). The authors of the paper concluded "*that in a laboratory setting peak working capacity was limited by the individual's perceived exertion – which can be attenuated by endogenous opioids – rather than by physiologic fatigue*". Pointing out the importance of sensation with regard to exercise endurance, Jones and Killian (2000) also proposed that it is time to move away from simplistic explanations of limitation based on limited capacities of oxygen-delivery mechanisms and to accept a more complex picture of the mechanisms that support muscle motor function and eventually lead to the symptoms that force us to stop exercising, also in clinical conditions where breathing, cardiac or skeletal muscle activity is limited. The recent attempts to better describe the conscious perception of the sensation of fatigue, the search for its physical correlates in the CNS, and its role in exercise performance are therefore to be commended since they may provide us with insight in the complex

relationship between sensation and performance (St Clair Gibson 2003).

Exercise at high altitude

In a recent review Wagner (2000) stated that even if it has been known since time immemorial that exercise capacity is reduced at altitude, the physiological underpinning of this impairment is not fully understood. Wagner looked at the literature concerning the reduced cardiac output during maximal exercise performance at high altitude. Based on model predictions he made the interesting point that an increase of cardiac output to sea level values would make little difference with regard to oxygen transport and hence to exercise capacity at altitudes equivalent to the summit of Mt. Everest. Wagner's model predicts that an increase in convective transport would be offset by a decrease in diffusive transport in the lung and the muscle due a decreased blood transit time. It now appears that increased parasympathetic neural activity fully accounts for the lowering of exercise heart rate at high altitude although the reason why maximum cardiac output is reduced at high altitude remains unclear (Boushel et al. 2001).

At exhaustion from heavy exercise at high altitude there are only a few or no signs of metabolic fatigue in the muscles used. Since during heavy exercise at high altitude maximum cardiac output is not reached and maximal exercise is stopped without evidence of muscle fatigue, the reason for cessation of exercise at high altitude must therefore be sought elsewhere.

In 1994 Kayser et al. published data providing evidence for central limitation to exercise performance at high altitude (Kayser et al. 1994). Healthy subjects did two types of dynamic exercise. The first consisted of cycling at 75% of VO_2max until exhaustion, whereas the second consisted of repeatedly lifting a weight over a pulley using the forearm muscles at a load corresponding to 75% of aerobic capacity of the muscles involved. The exercise paradigm was constructed in such a way as to obtain exhaustion times that were similar at low and high altitude. The difference between low and high altitude exercise was that cycling exercise was performed at 75% of local VO_2max (i.e. power output at altitude was 24% lower than at sea level) whereas arm exercise was performed at the same absolute power output in both environmental conditions. At low and high altitude arm exercise had the same exhaustion times and the same myo-graphical signs of muscle fatigue (Fig. 3). By contrast, cycling exercise, engaging large muscle groups, led to myo-graphical signs of muscle fatigue at sea level but not at altitude (Fig. 3) while the exhaustion time was similar. More interestingly, when at altitude the subjects indicated that they were unable to continue cycling and that the point of voluntary exhaustion was reached, instead of allowing the subjects to stop cycling the load was increased and at the same time the subjects were given extra inspiratory oxygen, normalizing arterial saturation (SaO_2). After a few breaths the subjects were able to continue cycling, at the higher load, and only then did myo-graphical signs of muscle fatigue appear. The muscle at altitude is thus perfectly capable of performing heavy intensity exercise and can develop signs of metabolic fatigue but only does so if the volume of muscle at work is small, or, for exercise with large muscle groups, if supplemental oxygen is given.

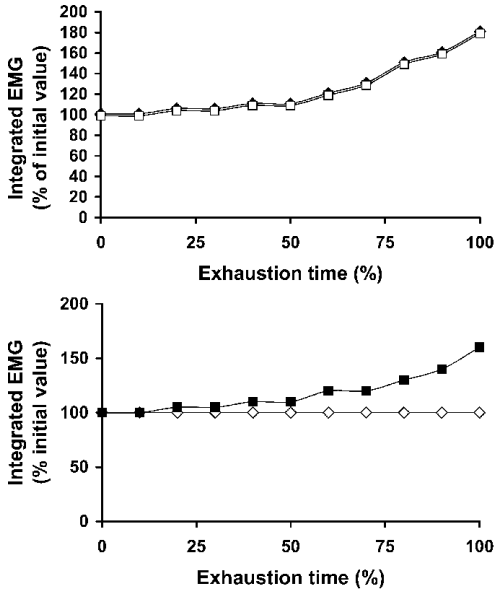

Fig. 3 *Top panel* shows integrated EMG as a function of exhaustion time during dynamic exercise with one fore-arm at high altitude (*open symbols*) and sea level (*closed symbols*). The *curves* are superimposed suggesting similar muscle metabolic fatigue in the two conditions. *Bottom panel* shows integrated vastus lateralis EMG as a function of exhaustion time during dynamic exercise on a cycle ergometer, at high altitude (*open symbols*) and sea level (*closed symbols*). At sea level iEMG increased suggesting muscle metabolic fatigue, whereas at altitude, at an exercise intensity of 75% of that at sea level, exhaustion time was the same but attained without changes in iEMG (adapted from Kayser et al. 1994)

CNS limitation of exercise with large muscle groups would explain these findings, but the nature of the input to the CNS leading to the cessation of exercise remains unknown. Vital organs may be involved: the brain and the heart because they are critically dependent on sufficient oxygenation, and the respiratory system, because it is working at greatly increased rates possibly leading to respiratory muscle fatigue. With regard to the latter it was shown that endurance exercise at 5050 m at 75% of local peak oxygen uptake does not allow steady-state ventilation to be attained, and that a steep increase in ventilation eventually leads to the cessation of exercise with indirect signs of diaphragm muscle fatigue (Cibella et al.1996). At high altitude during heavy exercise an increase in alveolar ventilation has such an additional energetic cost of ventilation that the increase in oxygen uptake only serves the increase in oxygen cost of the increase in ventilation. Consequently the net result in terms of oxygen supply to the locomotor muscles would be nil (Cibella et al. 1999). It thus would make sense if

the respiratory system provided input to the CNS limiting the exercise in order to protect its vital function for the organism as a whole, especially if increases in breathing efforts are useless with regard to extra oxygen uptake.

Two recent studies on exercise at high altitude provide further evidence for the hypothesis of a CNS limitation to exercise performance in hypoxia (Calbet et al. 2002, 2003). These studies report extensive data on maximum exercise capacity in subjects in hypoxia equivalent to an altitude of 5300 m, before and after acclimatization. Measurements included gas exchange at the mouth and in the leg, blood gases, cardiac functioning and several metabolic parameters. The findings were similar to those reported before: a decrease in maximum oxygen consumption and exercise performance, accompanied by a decrease in maximum cardiac output and sub-maximal use of muscle metabolic potential. The authors state that "*The reduction in cardiac output experienced with severe acute hypoxia could be envisaged as a regulatory mechanism aimed at protecting either the heart itself or, more importantly, the CNS from hypoxic damage due to the risk of increased desaturation at very high cardiac output … The down regulation of maximal cardiac output was likely mediated by PaO_2 and presumably CaO_2- and SaO_2-sensing mechanisms that adjust the output drive from cardiovascular nuclei in the CNS*". The authors then discuss two other mechanisms possibly involved, which are reduced contractility of the myocardium and reduced venous return. For the former there are no data in the literature supporting decreased contractility, even in more severe conditions of hypoxia. But since venous return is related to exercise intensity it is conceivable that cardiac filling through decreased muscle pump action would have been attenuated. Then the authors state that "*the fact that it was possible to continue the incremental exercise test with reoxygenation* [FiO_2 of 0.55] *argues against a peripheral (muscular or metabolic) mechanism as the main cause of fatigue in severe acute hypoxia*". This indicates again the central role of the CNS in limiting motor unit recruitment through motor command. A reduction in the intensity and duration of maximal activation of large muscle groups takes place in hypoxia, but exactly what limits the recruitment of motor units remains unknown. The CNS plays a central role but the input and mechanisms of this regulatory system remain to be identified.

Exercise with an expiratory resistance

In an effort to better understand the mechanics of breathing with expiratory flow limitation during exercise, the research group of Peter Macklem developed a model mimicking obstructive pulmonary disease in healthy human subjects by having subjects breathe against a Starling resistor during expiration, limiting flow at ~1 l/s (Kayser et al. 1997). During expiratory flow-limited exercise the subjects recruit expiratory muscles, develop high expiratory pulmonary pressures impeding venous return, hyperinflate the lungs burdening the inspiratory muscles, and develop a severe sensation of dyspnoea (Kayser et al. 1997; Iandelli et al. 2002; Aliverti et al. 2002). We used this model to study the effects of such an expiratory resistance on exercise performance in healthy subjects (Kayser et al.1997). Subjects exercised twice, once with and once without the resistance. Exhaustion time was greatly reduced during expiratory flow-limited exercise and was accompanied by increased expiratory and inspiratory muscle recruitment and an increase in the sensation of difficulty of breathing. Since exercise with expiratory flow limitation was stopped earlier than exercise in control conditions, and with sub-maximal heart rates and fewer signs of leg fatigue (Fig. 4), reasons other than maximum cardiac output or muscle fatigue must account for the cessation of exercise. Breathing sensation was near-maximal (almost 10 on a Borg scale of 0–10), and was highly correlated to respiratory pressure swing amplitude (Kayser et al. 1997). Even though it may appear obvious that the resistor impeded exhaustion time, this experiment is in full agreement with the hypothesis that changing the amplitude of an input to the CNS may lead to an earlier conscious decision to stop the exercise, in this case on the basis of an important load on the respiratory

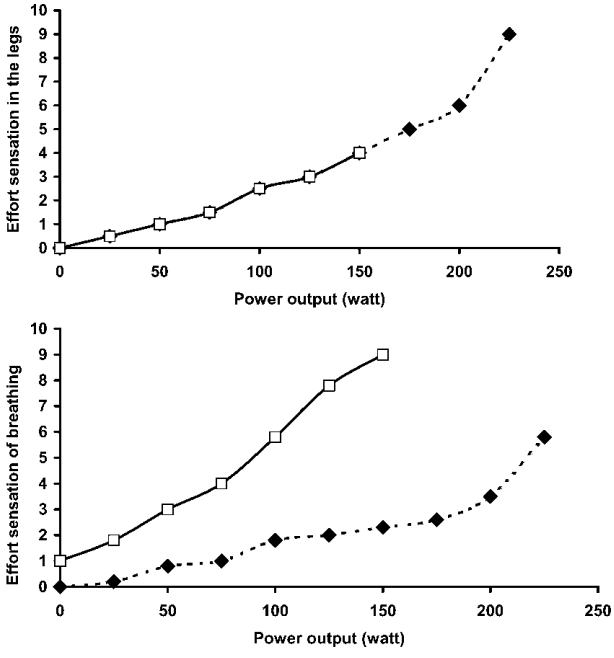

Fig. 4 *Top panel* shows effort sensation in the legs as a function of power output during cycle exercise while breathing through an expiratory resistance. (*Closed symbols* Control, *open symbols* resistive exercise.) The *curves* overlap, but exercise while breathing through the resistance is stopped earlier. *Lower panel* shows effort sensation of breathing as a function of power output during cycling exercise while breathing through an expiratory resistance. (*Closed symbols* Control, *open symbols* resistive exercise.) Exercise against the resistance is stopped earlier, suggesting limitation of endurance from strong respiratory effort sensation (adapted from Kayser et al. 1997)

muscles and a maximal sensation of respiratory effort. Further support for this contention comes from experiments where subjects exercised at 90% of $\dot{V}O_2$max in control conditions while the work of breathing was either loaded or un-loaded (Harms et al. 2000). Time to exhaustion was prolonged with unloaded breathing and reduced with loaded breathing. The change in exercise performance was significantly correlated with the changes in perceived leg and respiratory effort and it was subsequently shown that unloading would prevent diaphragm fatigue (Babcock et al. 2002).

Endurance versus intensity

The relationship between endurance and exercise intensity is hyperbolic, a relationship already described by AV Hill in 1925 (Hill 1925). At high intensities exhaustion times are short whereas at low intensities exercise can be maintained for longer, and at a given low intensity the hyperbole approaches an asymptote, an intensity that would be maintained ''indefinitely'', a level also known as critical power (CP). This relationship is determined by the maximal use of energy sources available to the organism: alactic anaerobic (PC and ATP), lactic anaerobic (anaerobic glycolysis) and aerobic (sugar and fat oxidation). For short duration exercises the first two metabolic pathways allow high power outputs, whereas for lower power outputs aerobic metabolism becomes the main energy source, and maximum glucose and fat oxidation rates set the limits (Monod and Scherrer 1965; Wilkie 1981). In the same issue of this journal DiPrampero convincingly shows that it is possible to use this relationship to accurately predict the performance of athletes, provided that the athletes indeed reach what DiPrampero (2003) describes as the ''energetic bottleneck'', or perhaps the ''true'' maximal metabolic power of the organism while engaged in physical activity.

There is no question that the contention of maximum sustainable metabolic power determining a given exercise performance is correct. But exercise performance depends directly on the CNS motor command which sets the level of metabolic demand. The question is therefore how metabolic power output relates to sensation and fatigue accompanying exercise performance. Interestingly enough the intensity–duration relation has rarely been used to describe and study fatigue (Walsh 2000).

As discussed before, at high altitude exhaustion from maximum cycling exercise is reached without many signs of metabolic stress of the limb locomotor muscles and with sub-maximal cardiac output. By contrast, the load on the ventilatory system is high, and for a given mechanical power output ventilation is increased with regard to normoxic control conditions (Cibella et al. 1999). Walsh proposes an interesting way to apply the concept of critical power in these conditions (Walsh 2000). The power duration relationships are generally perceived as applying to limb locomotor muscle. But during maximal exercise the respiratory and cardiac muscles also perform at intensities many times their resting levels. Furthermore, these organs must be able to continue to service the organism after reaching exhaustion from the exercise, and their integrity must therefore be protected. Walsh proposes that both the cardiac muscle and the respiratory muscles also have their respective power–duration relationships, but that these would be characterized by a higher CP as compared to the limb locomotor muscles. In other words, when the body is engaged in a maximum exhaustive exercise challenge the leg muscles would exhaust before the respiratory or cardiac muscles. However, even with a higher CP creating greater fatigue protection for homeostatic bodily systems, there are conditions when these systems may approach exhaustion. In such cases, central mechanisms would express themselves more fully and inhibit activation of limb musculature (Noakes 2000; Walsh 2000).

For example, at an altitude equivalent to the summit of Mt. Everest, maximum exercise performance is only one-fifth of that at sea level, and accompanied by a greatly reduced cardiac output. At the start of exercise SaO_2 is already low, and at peak exercise SaO_2 will even drop to 40%, a level indeed approaching dangerously low levels for the brain and other critically oxygen-dependent organs such as the heart. If exercise intensity is increased, SaO_2 would drop even more and could lead to unconsciousness from insufficient oxygen for the brain or myocardial failure. It would thus make a lot of sense if the organism, one way or the other, could limit the recruitment of muscle to a level commensurate with what the system can supply in terms of oxygen without jeopardizing its integrity. In this regard it is noteworthy that heavy exercise never puts the heart into danger, at altitude or at sea level, at least in healthy subjects without pre-existing cardiac problems. Even when exercising maximally at simulated altitudes close to the summit of Mt. Everest catheterization studies showed that the heart is doing fine and is not maximally taxed, even though working at greatly reduced rates (Reeves et al. 1987). Although it does not imply a causal relationship a drop in brain tissue oxygen saturation at maximal exercise in hypoxia was recently reported (Imray et al. 2003) and is potentially involved in the process leading to the eventual inescapable decision to stop exercising.

It is also noteworthy that, with the exception of some particular situations such as heat stroke or other clearly pathological conditions, exercise is always ended before the advent of serious organ or systemic damage. Consequently the hyperbolic relationship between power and endurance during large muscle group exercise not only adequately relates to maximum metabolic power but de facto also represents a safety margin imposed by the organism in order to protect its integrity and survival. The CNS, integrating input from various sources related to the exercise, limits the extent to which the organism is being pushed close to the edge beyond which life-threatening damage would occur. For obvious

reasons it would be unethical to push subjects beyond their limits although it is possible that some fatalities in sports competitions can be explained in this way, for example, Tom Simpson who had taken amphetamines and collapsed from hyperthermia while climbing Mont Ventoux on a hot day during the 1967 Tour de France.

In this regard it is interesting to note that for the effects of exercise on small muscles a protection exists in the sense that even under maximum electrical stimulation muscle ATP cannot be decreased below ~60% of resting values, and rigor-mortis from lack of ATP is impossible to achieve from exercise due to local control mechanisms. Before severe damage can be done regulatory mechanisms within the muscle reduce the rate of ATP hydrolysis and thus prevent catastrophe from failing ATP stores. Again the organism is apparently equipped with a system protecting its integrity, but here on a peripheral level.

The exercising brain

Physical activity leads to increased metabolic rate in the active tissues, foremost in the active limb locomotor muscles, but obviously also in the heart and in the respiratory muscles. What is often overseen is that the increased motor command also necessarily leads to increased metabolic rates in the activated brain structures associated with a given physical activity, which are commensurate with exercise intensity. At high exercise intensity and hence intense regional neuronal activity, energy demand may exceed energy supply, and an imbalance may occur in brain regions activated during exhaustive exercise. Dalsgaard and colleagues (2002) developed a human exercise model in which they compared brain metabolic ratios (arterial–internal jugular vein differences) during heavy exercise in control conditions to that during partial neuro-muscular blockade (with curare). In the latter condition, for a given power output, a greater effort or central command is necessary. They found that the metabolic ratio (O_2:glucose + 1:2lactate) decreases during and after high-intensity exercise or, under partial neuro-muscular blockade, when the will to exercise is intense. They speculate that intense activity in cerebral regions causes energy demand to exceed production, in turn draining energy reserves and they suggest that local depletion of brain glycogen could play a role in central fatigue (Dalsgaard et al. 2002). Interestingly, during exercise with partial neuromuscular blockade the subjects did not perceive a maximal sensation of exertion although they were unable to increase the work rate. The authors suspected that this could be due to the fact that the subjects did not experience the muscle pain usually associated with intense exercise. In a follow-up study they subsequently showed that when the afferent sensory input to the CNS is increased by doing exercise in conditions of ischemia (thigh cuff) this also leads to a decrease in the brain metabolic ratio. The authors proposed that the more pronounced metabolic response of the CNS to maximal exercise is caused by cerebral integration of afferent input from fatiguing skeletal muscle, as opposed to exercise under partial neuro-muscular blockade where the load on the limb muscle, and thereby also sensory input to the brain, is sub-maximal (Dalsgaard et al. 2002, 2003).

Another exercise paradigm in which the role of the CNS as a prime limiting factor of exercise endurance is becoming clear is sub-maximal exercise endurance in the heat (Nielsen and Nybo 2003). Nielsen and colleagues have looked at the effects of hyperthermia during exercise on performance and found that a core temperature of ~40°C is an independent cause of fatigue. Cardiovascular alterations and metabolic changes in the exercising muscles do not seem to be the main factors underlying fatigue during prolonged exercise in the heat. By means of the twitch interpolation technique they found that hyperthermia reduces central motor command leading to a decrease in sustained muscle contraction. A high core temperature thus impairs the ability to maintain maximal muscle activation and the reduced force seems to relate to a failure of the CNS in producing an adequate drive to the muscles. Hyperthermia is accompanied by hyperventilation which, through the consequent decrease in $PaCO_2$, leads to cerebral vasoconstriction. Nielsen and colleagues also found that exercise in hyperthermia is accompanied by a decrease in cerebral blood flow. They speculated that the pre-syncope symptoms sometimes experienced during exercise in the heat may be related to the reduction in cerebral blood flow. The same authors also showed that hyperthermia during sub-maximal exercise is accompanied by a gradual slowing of the EEG which is correlated with the subjects' sensation of exertion as well as with the changes in cerebral blood flow. However, it remains unknown if these relationships are in any way causally related.

Another interesting situation in which the CNS was shown to be involved as a limiting factor for recruitment of motor units is maximal voluntary contraction of the knee extensors after 3 h of cycling without glucose supplementation as compared to adequate glucose intake. In the latter euglycaemia was maintained but in the former arterialized blood glucose had dropped from 4.5 mM to 3.0 mM and muscle activation during a 2-min maximal voluntary contraction was reduced as evaluated with the twitch interpolation force (Nybo 2003).

Changes in neurotransmitters have also been suggested to be involved in central fatigue. Good evidence exists suggesting that increases and decreases in brain 5-hydroxytryptamine (5-HT) activity during prolonged exercise may hasten and delay fatigue respectively (Davis and Bailey 1997). The precursor of 5-HT is tryptophan and the synthesis of 5-HT is thought to be driven by the blood supply of free tryptophan in relation to large neutral amino acids such as the branched chain amino acids (BCAA). The ratio of BCAA/tryptophan

has indeed been shown to be related to exhaustion from sustained heavy exercise (Blomstrand 2001). Neurotransmitter concentration changes may thus alter the cognitive response to, or be involved in, the subconscious fatigue-generating mechanisms (St Clair Gibson et al. 2003).

The above cited and other findings of CNS involvement in fatigue clearly ask for more research on the role of the CNS during physical activity. Modern imaging techniques, non-invasive techniques, but probably also invasive techniques like those used by Dalsgaard and colleagues (2002) applied in innovative experimental setups will help us better understand the highly complex way in which our brain controls and limits our physical activity and how this relates to exercise-induced sensation (St Clair Gibson et al. 2003).

Conclusions

The notion of the CNS limiting endurance of effort is useful for explaining numerous experimental findings as well as observations in the field which cannot otherwise be explained by prevailing theories. Theoretically the body is only pushed to its maximum during whole-body exercise, when it then drops down unconscious. But with the exception of certain pathological conditions such as heat stroke during long distance running, exercise is stopped by a forced but conscious decision not to go on well before catastrophe occurs, and the hypothesis of the CNS as the ultimate limiting factor appears to be a serious candidate as a useful alternative paradigm to explain the limits to exercise performance in humans (see Fig. 5).

When interpreting research data, for example obtained in conditions of hypoxia, it is thus useful to use this conceptual framework of limitation by the CNS. In the quest for ever-increasing performance in sports, it is also useful to use the proposed paradigm. This paradigm does not refute the fact that cardio-respiratory and muscle metabolic capacities are of prime importance with regard to exercise performance. It remains clear that a combination of genetic talent and a lot of training leads to a high $\dot{V}O_2$max, but in competition the difference between a winner and a loser may indeed be not so much in differences in $\dot{V}O_2$max but rather in how big a safety margin the CNS imposes in order for the organism to stay clear of serious damage. Perhaps Kenyan long distance runners do so well because they are able to push the limits imposed by the CNS closer to the danger zone, which would explain their edge over other long distance runners who have otherwise quite similar physiological characteristics. This notion is corroborated by the recent finding that these runners are capable of running distances such as 10 km at extraordinary high fractions of their $\dot{V}O_2$max of more than 90% (Billat et al. 2003).

In summary, cardio-respiratory and metabolic capacity remain of prime importance in setting the stage for the level of performance that can be sustained for a given time. But exercise starts and ends in the brain, and there is an increasing amount of experimental evidence that the CNS is ultimately the limiting factor of exercise performance.

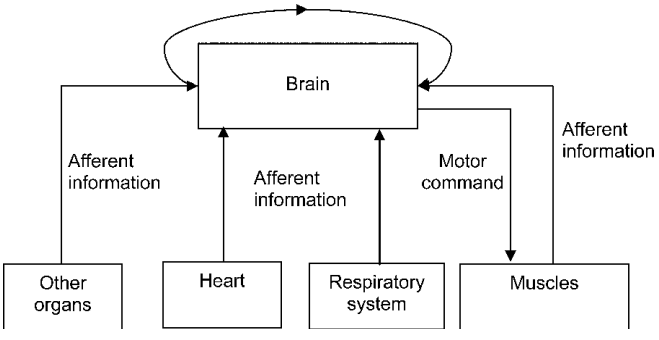

Fig. 5 Hypothetical model of the CNS as prime limiting factor of exercise performance. In the model, the CNS receives input from various sources including the brain itself, the heart, the respiratory system, the tendons, the muscles, etc., integrates all these signals and provides limitation to exercise intensity and duration by modulating motor command in order to protect the integrity of the organism

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