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**Professor Bengt Saltin Symposium - Environmental
Challenges to Human Performance**

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**Professor Bengt Saltin Symposium - Environmental Challenges to Human
Performance**

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Invited Symposium Review

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Abstract

This short review is from a presentation made at the Bengt Saltin Symposium, October 15-17, at the 2015 CSEP conference, Hamilton, Canada. The review provides context of the important work of the late Dr. Saltin's contributions to environmental physiology. In addition to well-controlled laboratory experiments to better understand the influence of hypoxia or temperature, or both, Dr. Saltin also led several field expeditions to the North Greenland, Kenya, Himalayas and the Andes, where he studied several aspects of human adaptation to environment. The 1998 Danish High-Altitude Expedition to the Andes, in particular, resulted in many major contributions to the field of altitude physiology including, but not limited to; mechanisms of reductions in maximal oxygen uptake; the lactate paradox; acclimatization; muscle metabolism; gas exchange, cerebrovascular physiology, etc. Of note, many of these related studies were conducted in both Danish sojourners to altitude and Bolivian altitude natives of Aymara ancestry, thus providing some of the most mechanistic comparisons with high altitude natives to date. A framework of these physiological contributions in terrestrial extremes is provided in this review.

Key words: Bengt Saltin, Exercise, High Altitude Physiology, Temperature

Introduction

It is a great pleasure and privilege to provide an overview of the late Dr. Saltin's contributions to environmental physiology. Although Saltin's pioneering influence as a mentor and contributions to other areas of integrative physiology have been elegantly reviewed in a 157-page supplement published in the *Scandinavian Journal of Medicine and Science in Sports* in 2015, his impact in the broad field of environmental stress is equally as noteworthy. His early work conducted during his PhD studies (1959-64) while under the supervision of Per-Olof Astrand (Department of Physiology, University of Stockholm) is reported in detail in *Acta Physiologica Scandinavica* (Saltin, 1964). Upon reading this land-mark review paper (Saltin, 1964) - based on Saltin's PhD thesis which encompassed nine different experimental studies - in addition to the focus on how exercise and type of muscular work influenced maximal oxygen uptake, the importance of environmental stress in the context of muscular work and heat exposure with resultant dehydration were explored in characteristic detail and insight. Moreover, two sections in this review were based on field studies after prolonged 6-10 hour ski competitions. These field studies provided complementary information that would otherwise be impossible to duplicate in laboratory conditions. Perhaps it was this early experience of attempting to conduct sophisticated research in challenging conditions that motivated Saltin to continue the long-standing tradition of the earlier physiologists at the August Krogh Institute upon starting his

faculty position in Denmark in 1973. Here, in addition to well-controlled laboratory experiments to better understand the influence of hypoxia or temperature, or both, Dr. Saltin also led several field expeditions to the North Greenland (Helge et al., 2003), Kenya (Saltin et al., 1995), Himalayas (Savard et al. 1995) and the Andes (Calbet et al., 2003, 2004, 2009; Lundby et al., 2006; Van hall et al., 2009), where he studied several aspects of human adaptation to environment.

This review provides a selected framework to some of Dr. Saltin's contributions that have markedly progressed our biological understanding of mechanisms and integrative physiology of operating in terrestrial extremes. Due to space constraints, not everything can be covered; therefore, without meaning to be disingenuous, particular focus is provided on Saltin's published contributions to thermal regulation and physiological adaption to hypoxia. Finally, Saltin's early insights into the now 'new' concept of environmental 'cross-adaptation' are summarized in this review.

Thermal regulation.

As mentioned, a large part of Saltin's early career examined the importance of environmental stress in the context of muscular work and heat exposure with resultant dehydration (Saltin, 1964a; Saltin, 1964b). In several studies he established how heat stress might limit exercise capacity was a tenant focus of this work; the fundamental relationships between muscle and core temperatures,

metabolism, sweating rate, and dehydration were established (Saltin & Hermansen, 1966; Saltin et al., 1968; Saltin et al., 1970; Saltin et al., 1972; Nadel et al., 1972; Savard et al., 1988; Nielsen et al., 1990). Related mechanism(s) of acclimation to the heat were published (Nielsen et al., 1993; Nielsen et al., 1997) establishing that it is the high core temperature per se, and not circulatory failure that underpins exhaustion during heat stressed exercise (Nielsen et al., 1993). Follow up studies provided evidence that elevated heat release in contracting skeletal muscle appears to be tightly coupled with changes in heat liberation (González-Alonso et al., 2000). The latter heat liberation is mediated during ATP production via the metabolic reactions involved early in exercise (González-Alonso et al., 2000 & 2001). Together, these studies not only informed our fundamental understanding of how heat stress impacts integrated physiological responses and capacity, but also provided mechanistic insight into how heat stress alters ATP production. The role of ATP was further established as an O₂ sensor at the level of the erythrocyte in the regulation of skeletal muscle blood flow and O₂ delivery (González-Alonso et al., 2002).

Hypoxia.

It has been well established that maximal work capacity is reduced during acute exposure to high altitude. Saltin was one of the first to establish that the cause of the reduction in maximal oxygen uptake was, in part, due to a limitation of oxygen transport at the alveolar-capillary membrane (Blomqvist, et al. 1969),

and that the decrease in aerobic power can be offset by restoring a normal oxygen tension (Saltin et al. 1968). Related follow-up studies provided evidence that even moderate hyperoxia produced by increased ambient air pressure enhances the circulatory transport of oxygen in maximal exercise (Fagraeus et al. 1973), and that the working muscles have an aerobic potential exceeding what the circulation can normally offer (Fagraeus et al. 1973). Some of these early studies helped generated the notion that a combination of exercise training with an altitude (or hypoxic) condition may improve VO_2 max and performance more effectively than exercise alone (Adams et al 1975, Faulkner et al. 1967, Hostman et al. 1980, Saltin et al. 1966, Saltin et al. 1968). The impact of altitude on anaerobic capacity was also explored (Saltin et al. 1967), and revealed that altitude exposure may result in a detraining response. These early studies seemed to be paramount in a series of follow-up studies, both in the laboratory and field, which sought to successfully determine the mechanism(s) that explain the changes and reductions in VO_2 max during normobaric and hypobaric hypoxia (Calbet et al., 2003, 2004, 2009).

Acute hypoxia: As mentioned, it has been well established that, in acute normbaric hypoxia, maximal aerobic capacity is progressively reduced in close relationship to the reductions of inspired PO_2 and related reductions in arterial oxygen content (CaO_2). Land-mark research established that changes in CaO_2 induced by either breathing hypoxia, carbon monoxide, blood withdrawal or transfusion are compensated for by changes in cardiac output that ultimately

result in maintenance of systemic O_2 delivery during sub-maximal exercise (Asmussen & Nielsen, 1946; Ekblom et al., 1976). Specifically, at rest and during two-legged knee extension exercise, Saltin and his team employed isovolemic hemodilution to reduce CaO_2 (and Hb) via withdrawal of 1-1.5 liters of whole blood and concurrent replacement with albumin. This initial study revealed a low CaO_2 induces an elevation in submaximal muscle blood flow and that O_2 delivery to contracting muscles that is tightly regulated (Koskolou et al., 1997a, b). Elegant follow up studies demonstrated in humans that the regulation of cardiac output, leg blood flow, and O_2 delivery to contracting skeletal muscle is dependent on signaling primarily from CaO_2 , not PaO_2 (Roach et al., 1998). Over the next decade or so Saltin and his team further extended and explored the critical role – and related mechanisms – of O_2 bound to hemoglobin in increasing skeletal muscle vasodilatation during exercise in humans (e.g., González-Alonso et al. 2001, etc.). These findings, as discussed in the next section, were also extended at high altitude (Calbet et al., 2002).

In a series of elegant experiments under the guidance of Saltin three main mechanisms, each explaining about one-third, of why VO_2 max is reduced in hypoxia (10.5% O_2) was proposed (Calbet et al., 2003; Roach et al., 1998; Calbet et al., 2009). These mechanisms included: 1) reductions in inspired PO_2 ; 2) impairment in pulmonary gas exchange; and, 3) reductions of maximal cardiac output and peak leg blood flow (Calbet et al., 2003). It is relevant to note that these mechanisms are seemingly explicit to severe hypoxia (e.g., PaO_2 's 30-35)

and likely differ during more modest levels of hypoxemia (e.g., PaO_2 35-45 mmHg). For example, during severe acute hypoxia, but not moderate hypoxia, maximal cardiac output was reduced to a greater extent – reductions that were mediated via reductions in both maximal stroke volume and heart rate (Calbet et al., 2009). Together, these findings explain why reductions in VO_2 max are greater under conditions of severe acute hypoxia than could be explained by the fall in SaO_2 and CaO_2 (Fulco et al., 1998). Moreover, these studies stimulated and contributed to the controversial debate about the role of the CNS and the so-called 'Central Governor' model of fatigue (see: Noakes et al., 2004).

High altitude: As mentioned, Saltin led several field expeditions to study human adaptation to environmental stresses in to North Greenland (e.g., Helge et al., 2003), Kenya (e.g., Saltin et al., 1995), Himalayas (e.g., Savard et al. 1995) and the Andes (Saltin, 1967; Blomqvist et al. 1969; Savard et al. 1995). The pièce de résistance of these field studies was the 1998 Danish High-Altitude Expedition to the Andes. Here, the Danish researchers and volunteers conducted a series of experiments in Denmark before ascending to 5260m at Mt Chacaltaya in Bolivia. The volunteers then spent 9 weeks at this high elevation and conducted some of the most detailed mechanistic research at high altitude to date. Overall, these elegant experiments resulted in many major contributions to the high altitude physiology field. For example, new insights were established in the acclimatization process and on mechanisms of reductions in maximal oxygen

update (Calbet et al., 2003; Calbet et al., 2009), the lactate paradox (van Hall et al., 2001; van Hall et al., 2009), muscle metabolism (Lundby et al., 2006), gas exchange (Wagner et al., 2002), and cerebrovascular physiology (Iwasaki et al., 2011). Of note, many of these related studies were conducted at 4100m in both Danish sojourners to altitude and Bolivian altitude natives of Aymara ancestry, thus providing some of the most mechanistic comparisons with natives to date. These experiments contained the Danish trademark of invasive experiments (e.g., femoral arterial and venous cannulations for the determination of limb blood flow via thermodilution, indocyanine green for the assessment of cardiac output, blood volume manipulations, and various pharmacological blockades). To successfully conduct these extensive experiments in the field is an incredible achievement on many levels (Ainslie, 2004). A framework of these important physiological findings from the 1998 Danish High-Altitude Expedition to the Andes is provided next.

One of the fundamental questions that were addressed during the Chacaltaya expedition was why VO_2 max and cardiac output is reduced at high altitude. Using invasive approaches, Saltin and his team established that two circulatory factors, independent of O_2 transport to the muscle mitochondria, explain why VO_2 max fails to recover following acclimatization: they are 1) failure of cardiac output to normalize; and 2) preferential redistribution of Q to non-exercise tissues (Calbet et al. 2003). Related to the question of why VO_2 max is reduced, studies on the same expedition addressed why heart rate is lower during exercise at

altitude. Boushel and co-workers were able to show that the underlying mechanism is an enhanced parasympathetic neural activity (Boushel et al. 2001). This study was of great importance as it demonstrated that even when maximal heart rate at altitude is restored back to sea level values with a parasympathetic blockade, maximal cardiac output or stroke volume were not similarly enhanced. In other words, the reduction in maximal exercise heart rate at altitude is not the primary cause of the well-reported reductions in maximal cardiac output (Pugh et al., 1955; Saltin et al., 1968).

Concurrent studies on the Mt Chacaltaya expedition further explored that role of hemoglobin concentrations (Calbet et al., 2002) and plasma volume expansion on the regulation of cardiac output and O₂ delivery during submaximal and maximal exercise. The first experiment, under conditions when O₂ supply limits maximal exercise during large muscle mass exercise, established that elevations in hemoglobin do not improve exercise capacity, peak cardiac output or VO₂ max; however, compensatory changes in leg blood flow were evident in response to the reductions in hemoglobin. These compensatory changes in leg blood flow as a result of the experimental hemodilution lead to similar peak O₂ muscle delivery, such that there is an maintenance of maximal exercise capacity. These findings established that maximal cardiac output at altitude is not limited by a lower circulating volume or increased blood viscosity (Calbet et al., 2004).

So, what is the main mechanism(s) explaining the reduction in VO_2 max at altitude, especially when CaO_2 is normalized via acclimatization? As outlined earlier, the Chacaltaya expedition demonstrated that two circulatory factors, independent of O_2 transport to the muscle mitochondria, explain why VO_2 max fails to recover following acclimatization (Calbet et al., 2002): 1) failure of cardiac output to normalize (via mechanisms related to reductions in stroke volume rather than heart rate per se; reviewed in Stembridge et al 2015); and 2) preferential redistribution of cardiac output to non-exercising tissues. Finally, it is important to note that these two factors pertain to a large exercising muscle mass under such conditions where O_2 supply limits max exercise. When the exercise model allows preservation of O_2 supply for engagement of small muscle mass (e.g., one legged knee extension to fatigue), similar exercise capacities to sea level are reported (Calbet et al., 2009). These findings are explained by a) reducing the size of the active muscle mass leading to an improvement in pulmonary gas exchange; b) attenuation of the Bohr effect on O_2 unloading; and c) preservation of convection O_2 transport to the active muscle to sea level values.

Although it is not possible to cover all aspects of Saltin and his teams' contributions to high altitude physiology, one last area that is of topical relevance to touch on is that of the controversy and so-called 'lactate paradox'. This paradox has been aptly defined (Kayser 1996) as '*In acclimatized humans at high altitude the reduction, compared to acute hypoxia, of the blood lactate*

concentration at any absolute $\dot{V}O_2$, as well as the reduction of maximal lactate accumulation after exhaustive exercise, compared to both acute hypoxia or normoxia, have been considered paradoxical; these phenomena have therefore become known as the lactate paradox'. Based on earlier observations by the Danes (Lundby et al., 2000) that the 'lactate paradox' is a transient metabolic phenomenon that is reversed during a prolonged period of exposure to severe hypoxia (5400m) of more than 6 weeks, more detailed experiments were conducted as part of the prestigious Chacaltaya expedition (van Hall et al., 2009). Here, it was revealed that the net lactate release from the active leg was higher at 5260 m during chronic hypoxia compared to acute hypoxia at sea level. These findings imply an enhanced lactate utilization with prolonged acclimatization to altitude, and supports the absence of a lactate paradox in lowlanders sufficiently acclimatized to altitude.

Moreover, because of earlier reports that showed that high-altitude natives accumulate less lactate than normoxia lowlanders during incremental exhaustive exercise which was persistent after 6 weeks of de-acclimatization at sea level (termed 'the perpetual lactate paradox') (Hochachka, 1989), the Danes underwent follow up experiments in both lowlanders and high-altitude natives at sea level and after 2 and 8 weeks at 4100 m (El Alto, Bolivia). Again, the lactate paradox concept could not be demonstrated - and paradoxically - the high-altitude natives from the Andes actually exhibit a higher energy transfer, as evidenced by a greater muscle lactate accumulation, than lowlanders after 8

weeks of acclimatization (van Hall et al., 2009). Debates for and against the evidence of the lactate paradox has been outlined (Wagner & Lundby, 2007). As such controversy provides a catalyst for progression and this scientific debate is exemplary for moving science forward on this field.

Cross-adaption.

Physiological adaptation to environmental stressors is often studied in isolation, but these stressors are frequently combined outside of laboratory settings. Relevant examples include cold or heat and hypoxia. As recently highlighted (Lunt et al., 2010; Chauhan et al., 2015) especially in humans, there has been a paucity of research in this area. Thus, there is limited information about the effect that adaptation to one environment has on exposure to another thus forming a 'cross-adaptive' effect. It is relevant to note, however, that Saltin was exploring this 'new' concept of cross-adaptation as early as 1969 (Greenleaf et al., 1969). Moreover, the question of how environmental stress – whether it be heat, cold, hypoxia and/or prolonged exercise – impacted on integrative physiology and related metabolic adjustments was a long standing theme in Saltin's research. It is clear that he cherished conducting difficult and sophisticated research in challenging conditions.

In summary, the experimental complexities and related physiological integration of environmental challenges are clear. Few have made as great of an

experimental impact on this field as Saltin. It was a true highlight and privilege to participate in the CSEP Saltin Symposium and write this short review on some of his contributions to environmental physiology. In view that Saltin's interests in environmental physiology likely accounts for <5% of his better-known research contributions is a humbling statistic for many of us more junior researchers and provides perspective of the uniqueness of his career, talents and dedication.

Conflict of interest: None

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