Metabolic clues regarding the enhanced performance of elite endurance athletes from orchiectomy-induced hormonal changes

Craig S. Atwood [a,b,c,*], Richard L. Bowen [d]

[a] Section of Geriatrics and Gerontology, Department of Medicine, University of Wisconsin-Madison and Geriatric Research, Education and Clinical Center, Veterans Administration Hospital, Madison, WI 53705, USA
[b] Institute of Pathology, Case Western Reserve University, Cleveland, OH 44106, USA
[c] Centre for Aging and Alzheimer's Disease, School of Biomedical and Sports Science, Edith Cowan University, Joondalup, Australia
[d] OTB Research, Raleigh, NC 27615, USA

Summary This article examines the metabolic performance of an elite cyclist, Lance Armstrong, before and after his diagnosis with testicular cancer. Although a champion cyclist in 1-day events prior to his diagnosis of testicular cancer at age 25, he was not a contender in multi-day endurance cycle races such as the 3-week Tour de France. His genetic makeup and physiology (high $\dot{V}_{O_2max}$, long femur, strong heavy build) coupled with his ambition and motivation enabled him at an early age to become one of the best 1-day cyclists in the world. Following his cancer diagnosis, he underwent a unilateral orchiectomy, brain surgery and four cycles of chemotherapy. After recovering, he returned to cycling and surprisingly excelled in the Tour de France, winning this hardest of endurance events 7 years running. This dramatic transformation from a 1-day to a 3-week endurance champion has led many to query how this is possible, and under the current climate, has led to suggestions of doping as to the answer to this metamorphosis. Physiological tests following his recovery indicated that physiological parameters such as $\dot{V}_{O_2max}$ were not affected by the unilateral orchiectomy and chemotherapy. We propose that his dramatic improvement in recovery between stages, the most important factor in winning multi-day stage races, is due to his unilateral orchiectomy, a procedure that results in permanent changes in serum hormones. These hormonal changes, specifically an increase in gonadotropins (and prolactin) required to maintain serum testosterone levels, alter fuel metabolism; increasing hormone sensitive lipase expression and activity, promoting increased free fatty acid (FFA)

mobilization to, and utilization by, muscles, thereby decreasing the requirement to expend limiting glycogen stores before, during and after exercise. Such hormonal changes also have been associated with ketone body production, improvements in muscle repair and haematocrit levels and may facilitate the loss of body weight, thereby increasing power to weight ratio. Taken together, these hormonal changes act to limit glycogen utilization, delay fatigue and enhance recovery thereby allowing for optimal performances on a day-to-day basis. These insights provide the foundation for future studies on the endocrinology of exercise metabolism, and suggest that Lance Armstrong's athletic advantage was not due to drug use.

Introduction

Scientific explanations often arise from examining interventions, either deliberate or unintentional. This paper examines the performance of an elite cyclist, Lance Armstrong, before and after unilateral orchiectomy. Lance Armstrong is arguably the greatest cyclist who has ever ridden. Even prior to his diagnosis with testicular cancer, he was an elite athlete who had a sporting career that most would envy. Following his well-documented recovery from the metastatic testicular cancer that almost took his life, he recovered to win the Tour de France seven times and elevate himself into the kingdom of the worlds greatest athletes, some might say the greatest ever with regards to endurance sports. But, there is one question that continues to be raised with regard these exceptional performances: why this very good athlete, more adept at one day events (World Championship Road Race, 1993; San Sebastian Classic, 1995; Fleche Wallone, 1996) and not previously a contender in any of the long major tours (Tour de France, DNF 1993; DNF 1994; 36th 1995; DNF 1996), suddenly was able to win endurance events of 3 weeks duration (Tour de France, 1999–2005). The first glimpse of this transformation was in 1998, at the Tour of Spain, another 3-week endurance event, where he surprisingly finished fourth in an event that he had not even come close to placing in before. This was the beginning of his transformation from a winner of short (single day) races to winning the Tour de France (multi-day race that covers ∼3800 km, competed in 21–22 stages over a 3 week period in the month of July), the hardest endurance sport event in the world and which he has won every year from 1999 to 2005 (Fig. 1).

   Tests performed on Lance Armstrong at the University of Texas by Dr. Coyle between the age of 21 and 28 indicated an 8% improvement in muscular efficiency (i.e. increased power generated) at a given oxygen uptake ($\dot{V}_{O_2}$ [1]). While an 8% improvement in muscular efficiency might be obtainable in an untrained individual over time, such a large improvement in a trained elite athlete is rare to

Figure 1 Lance Armstrong climbing Alpe d'Huez in the stage 16 individual time trial of the 2004 Tour de France. Photo courtesy of Graham Watson.

say the least. Furthermore, in the months leading up to each Tour de France victory, he reduced his body weight and body fat by ∼7% (4–7 kg). Therefore, between 21 and his first Tour de France victory at almost 28 years of age, these changes contributed to an amazing 18% improvement in steady-state power per kilogram body weight when cycling at a given $\dot{V}_{O_2}$. This large improvement remains unexplained. This article is intended to provide a scientific explanation of the physiological factors leading to this improvement and his meta-

morphosis from a single day cycling champion into a 3-week cycling champion [2].

Many suggestions have been put forth to explain this transformation from a 1-day cyclist into the Tour legend of today. One obvious answer to this question is the fact that between the time of developing cancer (~25 years of age) and his return and fourth place in the Tour of Spain at 27 years of age, it is well recognized that strength and endurance increase to a peak, a peak that can be maintained for around 5 years. Indeed, the vast majority of winners of major tours are between the ages of 27–32. Interestingly, of the other great tour riders, all but Miguel Indurain won a tour before the age of 25. Armstrong did finish 36th in the Tour de France in 1995, and had it not been for his cancer, he might have improved on this in 1996, to the point where he may have been a contender in 1997/1998. And one could argue that coupled with his training, starting as a competitive swimmer (ages 12–15) and competitive running and triathlon racing (ages 14–18) coupled with subsequent cycling to age 27, that there was an upward and continual improvement that would explain this major change in endurance. However, Armstrong's improvement, during this 2–2.5 year period, when his training and racing were severely curtailed, was not so much a continual improvement as it was a major leap forward. Especially considering that for the first 12 months following diagnosis his exercise was inconsistent and reduced [3]. Then there is the fact that he won his seventh Tour at the age of almost 34. While riders have won the tour at 32 years of age, no 5-time Tour champion has done so.

It has been suggested that advances in training and conditioning are enabling athletes to extend their careers and perform at higher levels. Another simple explanation is his innate physical attributes, including a $\dot{V}_{O_2 max} = 83.8$ ml/kg, long femur length, resting heart rate of 32–34 bpm and lactate threshold = 178 bpm that could allow for these extraordinary performances (http://www.lancearmstrong.com and http://www.utexas.edu/). But these qualities do not necessarily translate into winning performances in long endurance races such as the great tours, as many who have similar qualities (for example, Oscar Freire Gomez, 3 time World Road Race Champion) would attest. In this respect, as indicated on the University of Texas, Department of Kinesiology and Health Education website, Lance Armstrong '⋯ is not a genetic freak. In testing hundreds of competitive cyclists during 20 years at the University of Texas, Dr. Coyle found two other individuals with the genetic potential comparable to Lance, as reflected in a $\dot{V}_{O_2 max}$ of approximately 6 l/min and 80 ml/kg/min, as well as a high lactate threshold and good cycling efficiency'. These results suggest another factor(s) is responsible for these exceptional performances.

Others have suggested the demon of sports enhancing drugs, supposedly rife amongst the professional and amateur cycling ranks, as responsible for this much publicized transformation. Indeed, the Tour federation had an open enquiry into this and a well publicized, if inappropriately timed and titled book [4] by David Walsh and Pierre Ballester, on the eve of his sixth Tour victory cast further aspersions on Armstrong's character. This enquiry has largely been driven by the lack of a good explanation for his transformation into an all-conquering Tour rider. No such aspersions were cast on another US rider, winner of three Tours in the late 80s and early 90s, namely Greg Lemond. It is unlikely that Armstrong has used drugs in achieving his victories. Indeed, he has never tested positive on any of the numerous drug tests that he was required to give during the year. So what then has allowed Armstrong to excel in this the hardest endurance sport event in the world?

Specifications for a tour winner

There are four major factors (besides good luck) that are required in order to win a Tour de France and that have led to Armstrong's dominance in this event. The first and most important is recovery, which as any Tour rider will attest is the key to winning a 3-week stage race. Armstrong's placing in the Tour of Spain was the turning point, a time when he realized that he could recover sufficiently from major daily exertions and to repeat these exertions day after day. The second factor, is that the Tour is usually won in the mountains, and in order to climb well, a rider has to have a high power to weight ratio, i.e. nearly all the great climbers are light. Armstrong's significant drop in weight (4–7 kg) during the racing season (after his bout with cancer), together with his intense training regime, lead to the development of a much higher power to weight ratio which allowed him for the first time to climb at the same rate as the best climbers in the world. The third required factor is related to the first two factors, recovery and power to weight ratio. The technical advance of developing a high cadence while training, racing and climbing is thought to limit muscle damage and the loss of muscle glycogen, allowing the same power output but with better recovery. Finally, Armstrong possesses the drive and mental toughness needed to train extremely hard. However, tremendous

recovery is required in order to train hard frequently enough to excel over others. His ability to recover, coupled with his scientific training schedules, intelligence and confidence in his abilities, provided him with a distinct advantage for the Tour de France every July.

The transformation

Clues as to what is responsible for his transformation from a 1-day to a 3-week endurance cyclist may be found in his encounter with cancer. To understand this transformation, we must first understand his treatment during his struggle with testicular cancer. Testicular cancer accounts for only about 1% of all cancers in males, but is the most common tumor in males between 15 and 34 years of age and afflicts ~7500 individuals per year in the US [5,6]. Lance Armstrong had an aggressive form of testicular cancer (non-seminomas) composed of 60% choriocarcinoma, 40% embryonal, and <1% teratoma (http://www.lancearmstrong.com/lance/online2.nsf/html/FAQ). Upon discovery of his testicular cancer in October of 1996, the therapeutic strategy decided upon was to remove the afflicted testicle (unilateral orchiectomy) and then undergo chemotherapy [3]. Following the first round of chemotherapy with BEP (bleomycin, etoposide, cisplatin), it was discovered that a second surgery would be required to remove brain metastases, and this was then followed up by three more rounds of a platinum-based chemotherapy (VIP; vinblastine, etoposide, ifosfamide, cisplatin) over the next 3 months to remove lung and other metastases [3]. The cancer and chemotherapy did not appear to have long term affects on his physiology [1]. Obviously it did not affect one of the more important physiological characteristics, long femur length, nor did it appear to affect his other physiological parameters that allow for high performance including his high $\dot{V}_{O_{2\,max}}$ [1]. In essence, the underlying components of his 'engine' were not affected.

Although chemotherapy can lead to long-term affects, the removal of a testicle (unilateral orchiectomy) results in permanent physiological changes. From an endocrinological perspective, it has been shown that unilateral orchiectomy leads to altered serum levels of certain hormones that are produced as part of the reproductive axis (known as the hypothalamic-pituitary-gonadal (HPG) axis). A feedback loop between sex steroid and inhibin production in the testes and LH and FSH production in the pituitary normally maintains an optimal balance of these hormones in the serum

(Fig. 2). Specifically, unilateral orchiectomy has been shown in many studies to lead to elevated levels of serum luteinizing hormone (LH; ~2-fold), follicle-stimulating hormone (FSH; ~2-fold), and prolactin (2.2-fold) while inhibin levels are decreased (~10%) (Table 1 [7−11]). Serum testosterone levels post-orchiectomy are almost the same as pre-cancer levels, indicating that the remaining testicle is able to respond to the increased gonadotropin stimulus to synthesize sufficient testosterone. This intriguing result suggests that other, unknown factors, determine the testosterone set-point in the bloodstream. However, like inhibin, 17β-estradiol levels also may be decreased [8], indicating that the remaining testicle is unable to maintain serum concentrations of these two hormones. The increased serum LH and FSH levels following orchiectomy are therefore likely due to the loss of negative feedback by inhibin (which normally suppresses FSH secretion), and estradiol (which appears to be the main regulator of LH secretion; [12]). These results suggest that in men, testosterone alone does not modulate LH/FSH secretion.

Serum concentrations of these hormones appear to remain constant post-surgery, at least for the first 10 years [11]. The degree of gonadotropin elevation also is significantly correlated with the cumulative platinum dose, i.e. the greater the dose the greater is the response to produce gonadotropins [13]. Interestingly, the median levels of LH and FSH are further elevated in those whose hCG levels are higher prior to orchiectomy (as in the case of Lance Armstrong [3]), but the relative levels are approximately the same as those individuals with no elevation in hCG. Specifically, for those men with increased pre-treatment serum hCG LH has been reported to increase from a median of 1.1 to 5.9 IU/L (5.4-fold), FSH from 0.1 to 8.7 IU/L (87-fold) and inhibin B from 56 to 75 pg/ml (1.3-fold) while testosterone decreased from 27 to 16 nM (1.7-fold [8]), as a response to the loss of hCG following orchiectomy.

That this axis should become dysregulated following orchiectomy is well established in the endocrinological literature (Table 1). In addition to the loss of a testicle, cisplatin-based chemotherapy (such as taken by Lance Armstrong) results in even greater elevations in serum FSH and LH levels and decreases in serum testosterone levels when compared with surgery-only and radiotherapy-only treatments [11,13,14]. This is likely a result of Sertoli (responsible for sperm production) and Leydig (responsible for testosterone production) cell atresia, an unfortunate side-effect of cisplatin chemotherapy. These increases in gonadotropins are similar to the increases observed as we go through
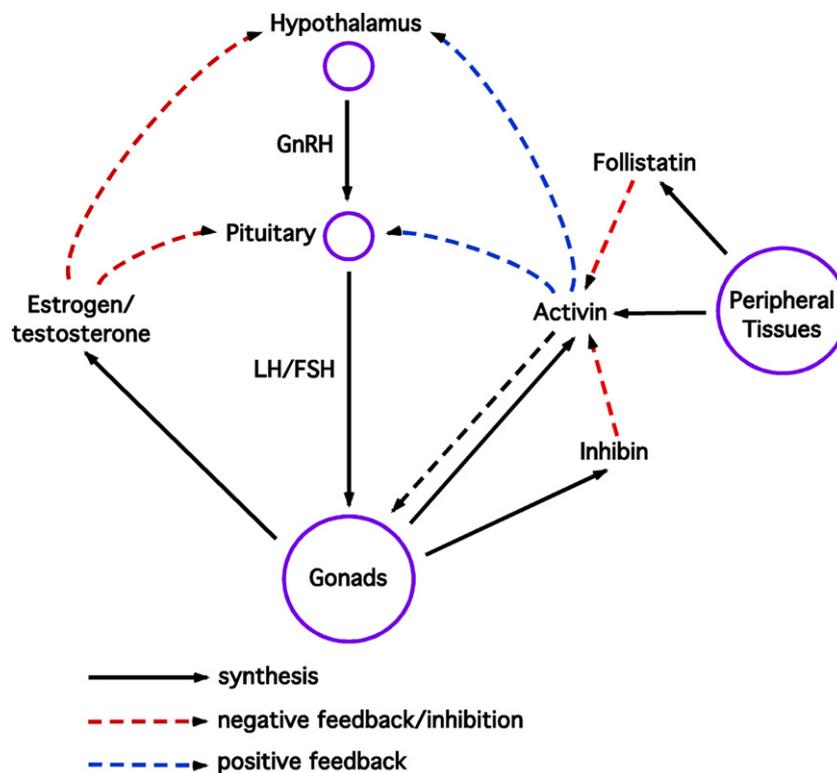
Figure 2 The hypothalamic-pituitary-gonadal axis. The concentration of each of the HPG axis hormones is regulated by complex feedback loops. The loop is initiated in the periphery by activins which stimulate the hypothalamus to release gonadotropin releasing hormone (GnRH). This in turn stimulates the anterior pituitary to secrete the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH). These then bind to receptors on the gonads and stimulate oogenesis/spermatogenesis, as well as sex steroid and inhibin production. The sex steroids feedback to the hypothalamus and pituitary, resulting in a decrease in gonadotropin secretion. Inhibin, produced primarily in the gonads in association with oogenesis/spermatogenesis, is known to bind to and inactivate activins. Activins stimulate GnRH and gonadotropin secretion. Inhibin therefore indirectly controls gonadotropin synthesis. Follistatin, expressed in many different tissues also inhibits activins.

'andropause', the male equivalent of menopause, where the function of the testes in producing testosterone and inhibin slowly declines with age. Therefore, in the case of Lance Armstrong, the HPG axis has almost certainly become unbalanced because of the unilateral orchiectomy and, addi-

Table 1   Serum hormone concentrations pre- and post-orchiectomy

Study	Chemo-therapy (cycles)	Post-surgery (years)	LH (IU/L) Before	After	FSH (IU/L) Before	After	Prolactin (ng/ml) Before	After	Inhibin B (pg/L) Before	After	Testosterone (nM) Before	After
1	3–4	3	9.5	10.3	7.7	11.1	—	—	—	—	7.0	5.1
2	?	0.42	3.1	5.2*	5.7	10.0*	—	—	108	95*	15	15
3[b]	None	0.25	5.6	22.6*	2.2	17.7*	8.6	9.8	—	—	5.7	16.6*
		1		9.9			8.4*	7.7				18.9*
4	2–3 (PVB, PEB or PE)	>1	3.2	6.4*	4.0	8.9*	10.7	23.8*	—	—	16.5	18.8
5	Cisplatin	>10	3.5	5.5*	—	—	—	—	—	—	17.1[a]	16.7

1 = Palmieri et al. [7]; 2 = Petersen et al. [8]; 3 = Zarrilli et al. [9]; 4 = Tomomasa et al. [10]; 5 = Nord et al. [11].

[a] Indicates control rather than pre-orchiectomy value.
[b] Patients had gynaecomastia-orchiectomy eliminated estrogen secretion and lead to elevations in gonadotropins as well as the large elevation in serum testosterone back to normal levels.
* Significantly different ($P \leqslant 0.05$). All studies were of unilateral orchiectomy.

tionally, chemotherapy of the remaining testicle would likely have led to further lowering of testes function with regard hormone production. How do such changes in serum sex hormones relate to Armstrong's improved recovery and perhaps his lower weight? The following section will first summarize how muscle cells utilize fuels for energy.

Fuel utilization and metabolism for exercise

There are three major sources of energy available to athletes: fat, carbohydrate and protein. The contribution of energy from protein is low (no more than 5% in marathon runners; [15,16]). Therefore, endurance athletes derive most of their energy needs from fat and carbohydrates. Muscle and liver store most of the body's carbohydrate, enough fuel ($\sim$400−600 g [17,18]) for approximately 90−120 min of high-intensity exercise [19]. Fat stores on the other hand could supply energy needs for 60−100 h [19,20] due to its higher energy content and abundance throughout the body compared with carbohydrates. Although fat can supply fuel for a number of days, the body utilizes a mixture of fat and carbohydrate in order to meet the ATP energy requirements of muscle cells during moderate to intense exercise for multiple reasons, including, (1) the generation of ATP per O_2 is greater for glucose (ATP:O_2 = 3.0) compared with fatty acids (ATP:O_2 = 2.8). Therefore, it is more advantageous to utilize glucose during periods of intense (anaerobic) exercise to meet energy (ATP) demands. Indeed, increases in glycolytic flux appear to decrease fat metabolism by decreasing the transport of FA into the sarcoplasma, lipolysis of intramuscular triacylglycerides by hormone-sensitive lipase (HSL), and transport of FA across the mitochondrial membrane (reviewed in [21]), (2) the rate of entry of free fatty acids (FFA) into muscle cells is dependent upon the concentration of unbound FFA in the plasma, (3) the contribution of unbound FFA in the plasma is restrained by solubility, (4) muscle extraction of plasma FFA may be limiting, (5) the contribution by intramuscular triglycerides to energy output while important, may become limiting during extended periods of exercise [20]. As a result, ß-oxidation of FFA alone cannot be mobilized rapidly enough to provide 100% of the ATP required by muscles at higher intensity levels for sustained periods of time. Therefore, endurance athletes like runners and cyclists use a mixture of these fuels to meet their immediate energy requirements. This is not a new concept; Randle proposed over 40 years ago that FFAs compete with glucose as the major energy substrate in (cardiac) muscle [22].

The contribution of carbohydrate will vary depending upon the intensity and duration of the event. The higher the intensity and the greater the ATP requirement the greater will be the requirement for carbohydrate oxidation to make up for the short fall of ATP production from ß-oxidation of fatty acids. Energy obtained from ß-oxidation will be dependent upon both intramuscular FFA stores [23,24] and FFA transported into myocytes from the plasma. Plasma FFA concentrations increase with exercise time, as does the level of unbound (to albumin) FFA, the fraction available for uptake by muscle cells [20,25,26]. Therefore, the greater the length of the exercise, the higher are the levels of total and thus unbound plasma FFA and the greater the contribution of ß-oxidation to the overall ATP requirement. Given the limited supply of body (primarily muscle and liver) glycogen, the limiting factor in how long an athlete can perform intense exercise is therefore going to be dependent upon the total amount and rate of utilization of carbohydrates. At high exercise intensity, dietary glucose is insufficient to maintain these stores. Therefore, the only way an athlete can accommodate the reduced availability of glucose is to increase FFA ß-oxidation, or to reduce speed. Interestingly, the utilization of carbohydrate is inversely correlated to that of FFA and falls throughout a marathon [20]. However, even the increase in FFA at this time cannot compensate for the loss of energy derived from glucose stores. Fatigue (or 'hitting the wall'), is characterized by a drop in speed which is a direct result of decreased carbohydrate utilization as a result of a fall in blood glucose levels due to depletion of muscle and liver glycogen stores and blood glucose stores [20]. Declines in blood glucose are not evident in non-fatigued athletes. Fatty acid utilization is unchanged during fatigue, indicating that lipid is the preferred fuel of muscles, but is rate limiting, and that carbohydrate utilization is required for optimal performance. Therefore, those athletes that can use a higher FFA/glucose ratio at any given speed (i.e. $\dot{V}_{O_2}$) for their overall energy needs will endure longer than those with a lower FFA/glucose ratio. Furthermore, athletes that do not utilize all their carbohydrate stores during an exercise period will have a greater chance of replenishing their carbohydrate stores to maximal levels compared to those that start with lower carbohydrate stores. This means exercise of a similar or greater intensity and duration can be achieved on subsequent days, and is perhaps the key to understanding the remarkable day-to-day endurance of Lance Armstrong compared with other cyclists.

Factors that promote triglyceride utilization will therefore have a marked impact upon the time to

exhaustion and recovery following intense exercise. The following sections will discuss factors that alter intramuscular utilization of triglycerides, as well as those that influence intramuscular glycogen stores.

The effects of hormones on fat and glycogen metabolism

Fat metabolism

The rate of FFA utilization by muscles is dependent upon the breakdown of intramyocellular fat stores and the mobilization of FFA from adipocytes and hepatocytes, although recent evidence suggests that utilization of intramyocellular stores of FFA may be as important for energy as mobilization of FFA from the blood [23,24]. Training/exercise itself increases lipolysis in muscles and plasma FFA and the reliance upon FFA for energy [27—33]. This also has been illustrated in trained versus untrained animals (rats) [34]. This is due in part to the increased enzymatic activity and expression of two lipases, HSL in skeletal muscle and heart [35—39] and lipoprotein lipase in skeletal muscle (and adipocytes [40]), and to increases in carnitine palmitoyl transferase in muscle [41], which promote increased intramuscular triglyceride lipolysis (e.g. [23,24]). HSL is expressed in all muscle fiber types, being higher in oxidative fibers than in glycolytic fibers [42,43]. HSL also is the rate-limiting enzyme for intracellular triglyceride hydrolysis in adipose tissue. HSL enzyme activities and expression are higher in adipose tissue after adrenaline treatment in trained compared with sedentary rats [44], suggesting training increases fatty acid mobilization and uptake for utilization by muscles. Whereas fatty acids liberated by adipocyte triglyceride hydrolysis are released into the bloodstream, the fatty acids produced from HSL-induced triglyceride hydrolysis in myocytes appear to be utilized by myocytes [45].

It has been suggested that HSL and LPL are activated by similar signals and act in a coordinated fashion to meet muscle energy demands: HSL hydrolyzes endogenous muscle triglycerides while LPL activity is increased in parenchymal cells in muscle and promotes triglyceride uptake (replenishment) by muscle [46]. Modulation of HSL expression and activity over the short-term and long-term is complex, but appears to be modulated by several interacting stimuli including muscle contraction and hormones (see below). With regard muscle contraction, HSL activity appears to be modulated by the frequency and duration of exercise as a result of changes in glycogen content (low glycogen induces HSL activity), free AMP, activation of AMP kinase and phosphorylation of inhibitory sites on

HSL [38,39]. It has been suggested that HSL also may be allosterically inhibited during prolonged exercise (or with rest) as a result of the accumulation of long-chain fatty acyl-CoA [38].

These changes indicate an adaptive response to endurance training [47] that decreases glycogenolysis in muscles and spares glycogen reserves. Conversely, detraining leads to an increased reliance on carbohydrate metabolism during exercise, as shown by a higher exercise respiratory exchange ratio, and lowered lipase activity, GLUT-4 content, glycogen level and lactate threshold [48]. Hence, well-trained individuals using a higher proportion of FFA for energy will spare more muscle and liver glycogen, and together with their higher basal glycogen reserves, can therefore maintain a similar level of intensity for a longer period of time compared with untrained individuals.

This shift from carbohydrate to fat utilization with training [27] also is observed with the hormonal changes associated with the menopause and andropause. As mentioned above these hormonal changes (decreased sex steroids and increased gonadotropins) are similar to those that occur following orchiectomy and lead to a more atherogenic lipid profile: increased triglycerides, LDL-cholesterol and its smaller dense subfractions and decreased HDL- and HDL2-cholesterol (reviewed in [49]). Interestingly, dysregulation of triglyceride-lipolysis such as occurs with menopause/andropause is linked to increased mobilization and elevations in the concentration of circulating FFA [50—53]. The increase in muscle lipolytic activity with aging [45] may explain age-related increases in endurance.

Experimental evidence indicates the hormonal changes associated with menopause/andropause are responsible for these changes in circulating FFA. For example, the fetal form of the gonadotropin LH is human chorionic gonadotropin (hCG), which promotes the expression of HSL [54], and therefore the lipolysis of triglycerides in muscle and fat stores. Furthermore, declines in testosterone or 17ß-estradiol increase HSL [55,56] in adipocytes and the synthesis and activity of hepatic lipase that regulates the rate of synthesis of structural apolipoproteins for VLDL and HDL [57—59]. Conversely, 17ß-estradiol decreases systemic FFA release in post-menopausal women [60]. Additionally, testosterone and dihydrotestosterone inhibit lipid uptake and lipoprotein-lipase (LDL) activity and expression in adipocytes, but only LPL expression appears to be mediated via the androgen receptor suggesting that other hormones such as LH might regulate HSL activity [55]. Recently, another lipase, adipose triglyceride lipase, has been

shown to be important in the mobilization of fat from adipose tissues [61]. The hormonal regulation of the expression/activity of this lipase has not been determined.

Another orchiectomy induced hormone-induced metabolic change that would promote increased ATP production and glycogen sparing may come from the increased HSL-induced hydrolysis of adipocyte triglycerides and the uptake of fatty acids by the liver and their conversion into ketone bodies. Production of ketone bodies has two major benefits: (1) they produce a large amount of ATP and it has been reported that LH and prolactin (also increased with orchiectomy; Table 1) promote the activity of a key enzyme (D-3-hydroxybutyrate dehydrogenase) involved in ketone synthesis [62], (2) many extrahepatic tissues utilize ketone bodies in the fasted state with the advantage that glucose is spared for more vital tissues like the brain [63]. The production of ketones by the liver increases both during prolonged exercise and during recovery from exercise [64], suggesting the body perceives starvation and exercise to be similar. Exercise also is known to increase ketone body utilization in skeletal muscle [65], although the contribution of hormonal changes to this increased production and utilization is unknown. It is interesting to speculate whether this increase in ketone production lessens lactate production, i.e. increases the lactate threshold as reported for Lance Armstrong [1].

Carbohydrate metabolism

Training increases muscle stores of glycogen [66]. Muscle contraction apart from increasing HSL also induces a parallel increase in glycogen phosphorylase [36] for glycogenolysis. In non-active postmenopausal women, reproductive hormonal changes are associated with reduced pancreatic insulin secretion, impaired insulin elimination leading to elevated insulin concentrations and a progressive increase in insulin resistance [67,68]. This can lead to impaired glucose tolerance and diabetes mellitus (found in nearly 20% of women aged 55–65 years [49]). It is less clear what affect the altered hormonal profile following unilateral orchiectomy has on serum insulin and carbohydrate metabolism in an athlete. However, an athlete that is rapidly utilizing, rather than storing fuels, is unlikely to have insulin resistance and suffer these problems. Indeed, exercise has been shown to prevent these hormone-related changes and almost completely reverse diabetes II. Since castration has been shown to decrease insulin expression and serum concentrations [69,70], but results in impaired insulin clearance on the other hand, it is possible that serum insulin concentrations also

are elevated following unilateral orchiectomy, as noted for bilateral orchiectomy [71]. If insulin levels were to be increased following unilateral orchiectomy, this would enhance glucose and FFA uptake by muscles.

Coupling orchiectomy-induced changes in serum hormones with fuel utilization, muscle repair and erythroid function

Benefits of orchiectomy-induced lipid changes to recovery

At times when the serum gonadotropin to estrogen ratio is high (pregnancy, neonatal life, orchiectomy and menopause/andropause), HSL expression is increased leading to increased fat mobilization from the liver and adipose tissues. This ratio is optimal during pregnancy and neonatal life in order to supply the developing fetus/baby with fatty acids. However, in older sedentary individuals, together with the other changes mentioned previously, this mobilized fat is not utilized but is laid down in intra-abdominal fat and muscle reserves resulting in the well-described increase in body weight with aging [72–76]. This increase in body weight is highly correlated with age-related diseases.

During exercise, the utilization of triglycerides is dependent upon lipolysis of myocellular and extra-myocellular stores of triglycerides. Therefore, while these hormone-induced atherogenic changes in the lipid profile may not be conducive to health in a sedentary individual, *in an athlete, increased gonadotropin-induced HSL expression would promote increased fatty acid utilization by, and mobilization to, muscles, and would decrease the requirement to expend limiting glycogen stores* (Fig. 3). Changes in the levels of other hormones affected by orchiectomy, such as prolactin, a hormone that promotes fat mobilization and utilization, also may enhance the FFA/glucose ratio. The capacity for an individual to endure during exercise will depend upon both the level of FFA to glycogen utilized at any given intensity ($\dot{V}_{O_2}$) together with the rate of increase in this ratio during exercise, and the rate of glucose uptake during exercise. In the case of Lance Armstrong, increased serum gonadotropin levels would result in a higher basal FFA serum concentration and muscle triglyceride utilization that would be elevated at rest and at any given exercise intensity compared with other athletes. And, as mentioned before, athletes capable of utilizing a higher ratio of fat to glycogen at any given exercise intensity will have greater endurance than those who must utilize a lower ratio of fat to glycogen. In this respect, although con-
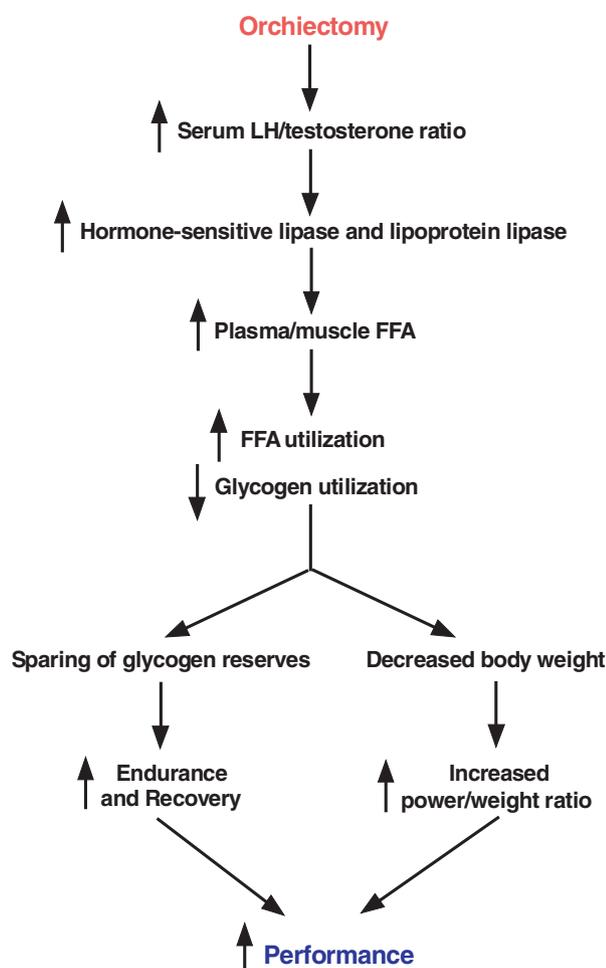
Figure 3 Schematic of biochemical changes following unilateral orchiectomy. Orchiectomy induces changes in the concentrations of serum HPG hormones that alter energy metabolism: increasing hormone-sensitive lipase and lipoprotein lipase expression and activity thereby promoting increased FFA mobilization to, and utilization by, muscles. This has two affects (1) to spare limiting glycogen stores and allowing for greater endurance and recovery, and (2) to decrease body weight which increases power to weight ratio, leading to increased performance.

tractions increase HSL activity, there appears to be an additive effect of hormones on contraction-induced increases in HSL activity [43]. Additionally, since HSL activity also is greater at rest, such athletes would have a higher utilization of FA to glucose, which would spare glucose and enhance glycogenesis during recovery. Finally, these altered hormone levels might act to promote fatty acid synthesis allowing replenishment of intramuscular triglyceride stores; there is some evidence indicating prolactin increases acetyl-CoA carboxylase activity and fatty acid synthesis in mammary epithelial cells [77,78], and fatty acid synthase, and lipoprotein lipase.

The advantages of increased fat utilization on performance are highlighted by the results of a chronic (4 week) eucaloric ketogenic diet (high fat) on submaximal exercise performance in trained cyclists. The mean ergometer endurance time for continuous exercise to exhaustion at 62–64% $\dot{V}_{O_{2\,max}}$ on this diet was 151 min compared to 147 min prior to the ketogenic diet [79]. Despite a drop in RQ (from 0.83 to 0.72), a 3-fold drop in glycogen oxidation and a 4-fold reduction in muscle glycogen, the endurance of these well-trained cyclists was slightly better. These results indicate that aerobic endurance exercise by well-trained cyclists is not compromised by 4 weeks of ketosis. Thus, physiological adaptations to a high fat diet conserve limited carbohydrate stores (glucose and muscle glycogen) and make fat the predominant muscle substrate at submaximal exercise. Therefore, enhanced HSL-induced FFA utilization by muscle during submaximal exercise would similarly be expected to spare body stores of glycogen and glucose.

Benefits of orchiectomy-induced muscle repair to recovery

Although less studied, another component of recovery, the ability of muscle fibers to repair between exercise bouts, also has been shown to be significantly impacted by HPG hormones. Alpha-actin expression has been shown to increase in luteal cells with hCG treatment [80] and HPG hormones affect fast fiber size and type IIb myosin heavy chain expression in the rat [81]. Furthermore, LH has been shown to increase junction and repair strength (above that of training alone) of collateral ligaments in rats whose ligaments had been surgically repaired [82].

Benefits of orchiectomy-induced erythroid function to performance

It has been demonstrated that the HPG hormone profile associated with orchiectomy and post-menopause leads to a statistically significant increase in the circulating concentrations of red blood cells and hemoglobin [83–85]. Such changes would have obvious effects for aerobic metabolism and lactate production, and the sparing of glycogen reserves.

Benefits of orchiectomy-induced recovery to performance

Recovery comprise refueling muscle glycogen and fat stores and repairing damage to muscle cells sustained as a result of the exertion. Therefore, in addition to the above sparing of glycogen reserves (i.e. until required later in a stage), preservation of glycogen reserves during stages will enable quicker recovery of glycogen reserves to maximal levels

from strenuous exercise, allowing for more complete recovery for the next days energy requirements. This more complete recovery (coupled with increased muscle repair) also affords the athlete with the ability to undertake longer and more intense exercise sessions, more often, which over the long term results in an individual who can train to a higher level. Indeed, most elite cyclists cannot handle the huge daily workloads of Lance Armstrong leading up to the Tour de France each year, i.e. what is perceived as training hard is relative to your ability to be able to recover. Armstrong's high cadence also may lessen muscle damage, helping aid recovery.

In summary, Lance Armstrong's high gonadotropin to sex steroid ratio will (1) increase serum FFA/ketone bodies and the utilization of FFA/ketone bodies by muscles, sparing glycogen reserves, (2) increase muscle repair and (3) increase haematocrit and hemoglobin concentrations, all of which will promote increased endurance and recovery.

Perhaps the most important benefit of these hormonal changes is the sparing of glycogen reserves, since this will allow for the most complete replenishment of carbohydrates stores (to maximal levels) each 24 h period prior to exercising again. This would ensure the athlete could perform at the same optimal level each and every day, and this day-to-day endurance is the key to winning races such as the Tour de France.

HPG hormones modulate body weight and composition

A major component to Lance Armstrong's success has been his ability to reduce body fat and therefore body weight during the racing season (4—7 kg), allowing a greater power to weight ratio, particularly useful in the mountains and time trials where time gained and lost determines who wins the Tour. The increased mobilization of fats for use in energy metabolism might also explain the decrease in body weight (fat) of Lance Armstrong following unilateral orchiectomy.

In sedentary individuals, decreasing serum testosterone and increased LH also promotes muscle catabolism leading to a decrease in muscle strength and lean mass (sacropenia) [73—75,86]. Lance Armstrong does not appear to have lost muscle mass, likely due to the fact that individuals who undergo unilateral orchiectomy have normal serum testosterone post-treatment, coupled with his intense exercise program. This is supported by the observation that four well trained men who pulled 130 kg sleds over 500 km across the inland glacier of Greenland in 1988 (retracing the route of the famous arctic explorer Fridtjof Nansen from 1888) over a period of 42 days [87] displayed an increased lean body mass despite the lowered serum testosterone and increased gonadotropin levels brought about by the intense physical effort and cold and energy deficits [87]. This suggested that exercise prevents sarcopenia despite changes in serum sex hormones. Irrespective of this, muscle mass does not necessarily equate with muscle strength (http://www.dolfzine.com/page216.htm). Moreover, exogenous testosterone does not improve performance in endurance events [88].

Muscle type and composition — effects of hormones

Intriguingly, hormonal changes associated with castration have been shown to increase the size, but not the number, of type II muscle fibers (usually of the A subtype) in humans after menopause/andropause and animals after castration, but these changes appear to be muscle specific, while type IIB appears to decrease in size [89—91]. Generally there is no change in type I fibers. Type I fibers contain myoglobin, numerous mitochondria, a rich capillary supply close to the periphery of the fiber that provides a rich supply of oxygen and nutrients and slow acting myosin ATPases. Type I fibers possess a high capacity for oxidative metabolism, utilize more FFA, are extremely fatigue resistant and specialized for the performance of repeated contractions over prolonged periods such as endurance cycling events. Type II muscle fibers contain little myoglobin, have fewer mitochondria, a poorer capillary supply, but greater glycogen and phosphocreatine stores and rapidly acting myosin ATPases. A high activity of glycogenolytic and glycolytic enzymes endows type II fibers with a high capacity for rapid (but relatively short-lived) ATP production in the absence of oxygen (anaerobic capacity). As a result lactic acid accumulates quickly in these fibers and they fatigue rapidly. Therefore, these fibers are suited for delivering rapid, powerful contractions for brief periods such as when climbing hills (http://www.medicdirectsport.com/exercisetheory/).

Type I fibers are required for long distance cycling events while riding at moderate speeds, however the requirement for type II fibers increases during times of more intense anaerobic exercise (i.e. like climbing mountains, time trials). The vastus lateralis muscle (part of the quadriceps muscle group) of successful marathon runners has been shown to have a high percentage (about 80%) of type I fibers, while that of elite sprinters contains a higher percentage (about 60%) of the type II

fast-twitch fibers. In this context, better endurance performance in horses is correlated with a higher percentage and relative areas of type I and type IIA fibers and lower percentages and relative areas of type IIB fibers than moderate performers [92]. As discussed above, type I fibers do not appear to change with castration, however, type IIA fibers increase in size. Interestingly, prolonged endurance training makes type II fibers more like type I fibers and is suggested to explain the higher pedaling cadence of Armstrong pre- and post-cancer (~85–95 rpm to 105–110 rpm [1]). Although the effects of these changes on athletic performance have yet to be fully elucidated it is possible that Lance Armstrong has not only optimized fuel utilization for type I fibers (increased FFA availability), but enhanced his anaerobic capacity as a result of an increase in the size of type II muscle fibers required during intense exercise.

Exercise-induced changes in serum hormones — impact on energy metabolism

Intense exercise regimes are well known to alter the concentration of serum hormones, particularly GnRH and LH pulsatility, leading to amenorrhea in some endurance trained women (e.g. [93–95]). Recent studies have suggested that it is not so much the 'stress' of exercise, but low energy availability that lowers serum gonadotropins and sex steroids [87,96,97]. In particular, insufficient fuel (glycogen/glucose and FFA) leads to a decrease in the release of LH from the pituitary (decreased LH pulsatility [97,98]). The body 'sensing' that it does not have enough food (i.e. starvation) is well known to suppress reproductive hormones (and increase longevity [99]). Exercise also has been shown to decrease serum leptin levels [100,101], an adipocyte-derived protein hormone that is a marker of fat accumulation. Therefore, decreased glucose/FFA availability such as following intense exercise or fasting/starvation may therefore act via decreased leptin secretion to decrease GnRH and LH pulsatility [102]. Put another way, high GnRH, LH and FSH is associated with increased glycogen and fat utilization since the reproductive environment is good. Thus, the increase in serum LH with age may be due not only to the decreased negative feedback of testosterone and increased activin levels that result from the decline in gondadal function but may be accentuated by the increased release of leptin from accumulating adipose tissue following menopause and andropause.

The high intensity exercise of the Tour de France might be expected to lead to a decrease in leptin, gonadotropin and sex steroid production, and therefore lower serum LH and testosterone levels. In this respect, the ability to consume and metabolize enough food by Tour riders who must consume 6000–6500 cal/day may limit recovery and suppress reproductive hormones. Indeed, plasma testosterone, LH and insulin, and muscle glycogen in liver, decline after exercise (1–7 h treadmill) and fasting (24–72 h) at least in male rats. Since hCG increased plasma testosterone levels in rats in the course of exercise and starvation, the decrease in plasma LH may be responsible for the decrease in plasma testosterone, which is time-related with the decrease in glycogen stores [98]. This suggests that glycogen stores regulate LH and testosterone secretion, and those individuals with higher glycogen (and fat) stores will have higher reproductive hormones. Additionally, the mixture of FFA to carbohydrates utilized is likely dependent upon the ratio of LH to sex steroids. In this respect, at any particular level of stress, Lance Armstrong would be expected to have a higher ratio. Indeed, such changes in the ratio compared to other cyclists of LH to testosterone might explain the increased endurance of male athletes as they age since the balance of sex steroids to gonadotropins begins to change in the mid-1920s. Younger athletes (i.e. 20 years of age) are generally not capable of matching the endurance of 30–40 year old athletes. Studies also have shown that training partially attenuates the decrease in serum testosterone associated with starvation (i.e. glucose utilization) in rats compared with untrained animals (40% compared to 300% decrease in testosterone [34]), indicating a training component to the regulation of sex hormone levels, that might be due to the increased utilization of FFA and sparing of glycogen, suggesting glycogen stores are the primary regulator of reproductive hormones. Thus, the level of LH to testosterone may modulate FFA to glycogen utilization in humans, and therefore sporting endurance.

Consequences of orchiectomy and chemotherapy

The cure rate for testicular cancer is high, and reoccurrence is highly curable. After 3 years without recurrence, the probability that a patient is cured is greater than 95% [103]. Recovery of spermatogenesis after treatment may be long, in some patients lasting more than 5 years [104]. Interestingly, elevated hCG is correlated with low sperm

concentration and quality parameters which improve following orchiectomy [10]. Sufficient androgen production is seen in the majority of the patients but some patients do suffer from testosterone deficiency. The effect of chemotherapy on Leydig cell function seems to be dose dependent [105]. In some patients with germ cell tumors, a compensated insufficiency of the function of the Leydig cells was still observed up to 60 months after chemotherapy. Of these patients 68% showed elevated FSH levels, which reflected a functional insufficiency of the Sertoli cells with impaired spermatogenesis [14]. Altered hormonal levels following unilateral orchiectomy, radiation and chemotherapy lead to impaired spermatogenesis and Leydig cell function and are persistently impaired in the majority of testicular cancer patients treated with radiotherapy or with more intensive (6 cycles) chemotherapy [7].

Fortunately, it would appear that Lance Armstrong is cured of testicular cancer. However, the dysregulation of the HPG axis, as a result of his treatment, can lead to many age-related diseases (e.g. heart disease, diabetes II, cancer, Alzheimer's disease, etc.). Alterations in serum hormones obviously induce altered energy metabolism as discussed above. But these hormones also regulate cell division, and in the dysregulated hormonal milieu following menopause/andropause or castration, we have proposed that these hormones control aging via cell cycle signaling; promoting growth and development early in life in order to achieve reproduction, later in life, in a futile attempt to maintain reproduction, they become dysregulated and drive senescence [99]. This increase in gonadotropin production would elevate the likelihood of future cancers, and would cause a general increase in the rate of aging. This typically occurs after menopause and later in andropause, as seen by the increase in cancers. However, unilateral orchiectomy exposes an individual to this altered hormonal signaling decades prior to others. Interestingly, the fetal form of LH, hCG, is a marker of cancer progression; the higher the serum concentration the greater the cancer burden. It is possible that this hormone is produced by the cancer to drive cell division and alter energy metabolism to allow for cancer growth.

How might an orchiectomy patient reduce the risk of these age-related diseases (including cancer reoccurrence)? Maintaining fitness to limit fat accumulation is an obvious strategy and should decrease risk of developing many age-related diseases. The re-establishment of the HPG hormones back to levels of a healthy reproductive male would be another important protective strategy.

This would involve giving back both testosterone and inhibin. Testosterone supplementation has been shown to improve the quality of life for men with testosterone deficiency.

The Armstrong advantage

While it is perceived that cancer, surgeries and chemotherapy might actually impede sports performance, the above evidence would suggest that unilateral orchiectomy promotes physiological maturation and athletic performance by enhancing fuel metabolism, muscle repair and erythroid function. Therefore, Armstrong's athletic advantage is most likely due to his unique genetic and physiological makeup coupled to the endocrinological changes induced by his unilateral orchiectomy, not drugs as suspected by certain reporters, cycling enthusiasts and French cycling authorities. Indeed, the use of drugs such as erythropoietin would be foolish given that there is evidence to suggest this mitogen can promote tumor growth [106,107].

Lance Armstrong's misfortune in developing testicular cancer has provided many clues as to the mechanisms that promote endurance, and suggest that the genetic makeup of an endurance champion may be mediated via signaling through hormones and hormone receptors of the HPG axis. Measurement of the serum ratio of gonadotropins (LH, hCG, FSH) and prolactin to sex steroids (androgens and estrogens) before, during and after exercise, together with fuel utilization parameters would determine if this is a common trait in elite endurance athletes as well as the endurance potential of athletes.

The question remains then, would you give your left testicle to win the Tour de France? Only the foolish would undergo orchiectomy or administer drugs to alter sex hormone levels to enhance performance in endurance sports given the long-term risks to health and longevity [99]. Likewise, the use of exogenous LH/hCG would be similarly problematic. Irrespective of this, artificially modulating these hormones for increasing human endurance performance is difficult due to the short half-life of LH in the blood. And while recombinant hCG has a longer half-life, it would be easily distinguishable from endogenous hCG. *We do not recommend unilateral orchiectomy or endogenous sources of these hormones as performance enhancing modalities.*

Competing interests

None

Authors' contributions

CSA and RLB conceptualized, researched and wrote this manuscript. All authors have read and approve the final manuscript.

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