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REVIEW

Drugs in sport: a scientist–athlete's perspective: from ambition to neurochemistry

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This article, by the United Kingdom's last Olympic Marathon Medal winner, Charlie Spedding, and his brother, the pharmacologist, Michael Spedding, covers the difficulties posed by the availability of powerful drugs to ameliorate athletic performance, from an athlete's perspective, particularly in view of the fact that performances are becoming highly optimised with less margin for further physiological improvement. The authors have had long athletic careers and argue that doping not only devalues performance but sport, and exercise, as a whole. Furthermore, the neurotrophic and metabolic changes involved in exercise and training, which can be modified by drugs, are central to health and reflect a part of the epidemic in obesity. *British Journal of Pharmacology* (2008) **154,** 496–501; doi:10.1038/bjp.2008.163

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Abbreviations: BDNF, brain-derived neurotrophic factor; EPO, erythropoietin; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator

Introduction

The aim of this article is to put the abuse of drugs in sport, doping, into a social and sporting perspective and also to point out how central to metabolism and exercise are erythropoietin (EPO) and haematocrit (see also Elliott, 2008). Exceptionally, we wish to contrast the scientific evidence with personal experience and in consequence this is a rather atypical article for the *British Journal of Pharmacology* and is at the interface of sports and science writing. Our qualifications in writing this article are that we combine 30 years of pharmacological drug discovery (MS) or pharmacy practice (CS); 40 years each of competition in athletics at club and national level (each of us have run between 90 000 to 100 000 km in training); from British Schools 1500 m champion to Olympic bronze medallist at marathon, with the English marathon record, still unbeaten (2 h 08 min, CS), to a club level career with a French 'national' level at marathon (2 h 36 min, MS).

Athletes attempt to extract the best possible results out of their bodies by repetitive but mixed and progressive training, which requires efforts, which appear surprising to the non-athlete. Ten miles run in horizontal sleet after a hard day's work does require motivation. The objectives of such training depend on the talent of the athlete and their degree of preparation, and range from casual keep-fit, to local and eventual world class competition. It is crucial, however, to maintain the honesty of a sport to allow children to have 'hero' figures to emulate, so that sufficient numbers participate to make the sport viable. Unfortunately, doping by a few may cause any excellent performance to be viewed as suspicious, devaluing the sport in general, with the risk that children are not encouraged to participate, with consequent major health risks for society (see below). The impact of sport on the main neurodevelopmental systems in the body is briefly covered at the end of the article.

Citius, fortius, altius?

Athletics is essentially a very simple sport, where effort is simply rewarded in a single figure—for example the time taken to run 5000 m. It is a luxury in modern life to be able to focus on a single figure, which is improved (within limits) by effort and application. This single figure places the athlete in a hierarchical triangle. In running, oxygen transport and use is limiting, so haematocrit and VO_{2max} are crucial and the limiting factors in middle and long distance events (CS has a 20% higher VO_{2max} than MS). But this is why doping is so insidious, as the crucial factors affecting performance can be modified. Non-athletes do not realise how fully trained athletes are fixing large quantities of air with a metabolic 'furnace' which is optimised by years of training.

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Absolute performance in sport is not the only reason why the vast majority of participants are involved. Athletics is an individual sport, but is also very social. MS has two friends who he raced regularly in the early 1970s and has run with ever since—bonds made by running together in horizontal sleet are strong. Few sports permit 30 years of performance at a reasonable level. Thus for most athletes, winning is only part of the reason for participating; doping arises as a problem when winning is the *only* reason for doing sport.

Sport can also reveal the unique effects of an outstanding talent. It is worth contrasting the relative benefits of talent and doping. We have lived through the full appreciation of what natural talent brings about. MS is 3 years older than CS and, as a 17 year old, was an established member of the school cross-country team when his 14-year-old brother proceeded to run away from the entire school in the annual cross country race, beating boys four years older. This talent allowed him to become a world class athlete, but only after 15 years of hard training. So could MS have achieved the same with more training? No, because when we were at peak of our athletic careers, training loads were broadly comparable (60–90 miles/week in 9–12 sessions)—higher training loads produced breakdown. Both optimised their performances, but started at different levels in the triangle of talent—and with different VO_{2max}. However, this demonstration underlines two issues.

First, any nation that wants to have a successful sports programme must screen the largest number of individuals possible to find highly talented individuals. This was done with great effect in the East German sports programme where all school children were screened. Unfortunately, the policy was tainted because selected athletes were then doped to further enhance performance. This approach produced athletic records, which are unbeaten 40 years on. Nevertheless it is a mission of schooling to detect and develop talent in individuals and the failure of schools to detect and foster talent in sport is not only damaging for sport, but contributes to the epidemic of obesity among school children.

Second, moderately or even well talented individuals may be really shocked and surprised when they come up against real talent (particularly as it may force them to re-evaluate their own futures), and it is very easy to say: that person must be doped, when it is just real talent. The problem is, when it is not.

Doping is an old problem. Doping (and suspicion of it) has always been present in sport. In 1903, in a landmark book on athletic training, Harry Andrews stated that: '…the use of drugs as stimulants. I have no words of condemnation of their use strong enough to express my mind on the subject'. Nevertheless, it is a very difficult problem, because of the scale of the effect. In the past, stimulants such as cocaine and strychnine, or sponge-cake soaked in champagne (Andrews, 1903) were not very effective. However, anabolic steroids in strength sports and EPO can change the nature of the performance completely. EPO can increase VO_{2max} by up to 20% (see Elliott, 2008), the difference between MS and CS, between a good club runner and a world class performer (although other factors may be in play (Spedding, 1985)). Furthermore, small doses, which may or may not be detectable, can yield prolonged changes in performance, haematocrit and plasma lactate levels (Russell *et al*., 2002), which could change a competition—and in such cases the entire basis of the sport is devalued.

There has been a revolution in the capacity to use oxygen. For example, in the 1970s, it was common to see a 400 m runner lying on the track, gasping like a stranded goldfish for long minutes, whereas now perfectly controlled interviews are given by champions within less than a minute. EPO completely changed cycling. Bjarne Riis won the Tour of France by using EPO (and admitted it and was subsequently disqualified years later); he so dominated the race that, in a defining moment he was able to climb past his opponents totally easily, looking each one in the eye as he passed them. The conclusions for his humbled opponents must have been very simple. At the time, there were very few instances of cyclists being 'caught' doping.

Contact sports are now filled with bulked up athletes—if a player weighs 80 kgs and is constantly tackling 120 kg players, at least some will look for chemical ways of equalising the equation. Fortunately there are almost no instances of professional rugby players being caught for doping with anabolic steroids, although several cases have been reported in American Football (see list of 'doping cases in sport', Wikipedia).

Individual athletes in such circumstances can be under terrible pressure to dope. It is now clear that the advent of EPO in cycling in the nineties forced athletes in a very hard but classic sport to systematically use the drug, which after a series of deaths, was then controlled at a team level by at least two teams. As athletes, we castigate the complacent and out of touch (or worse) officials who allowed the situation to develop, much more than the team managers who organised doping regimes, partly to ensure the safety of their athletes. Nevertheless, it was the individual athletes' choice and those (unknown and unappreciated) athletes who did not dope, at least have the satisfaction of having competed cleanly, but in a professional sport, this may not be much satisfaction for the athlete and his/her family.

However, a doped performance can still be an athletic performance. Ben Johnson was the first man to have run 100 m in under 9.8 s, even if the performance was aided by doping, and this is an achievement of sorts. One of the heroines of our early years was Marita Koch, still the world record holder at 400 m. She ran sublimely, but came out of the East Germany 'performance' system. Nevertheless, these athletes trained hard in difficult conditions and were dedicated to their sports—and had no choice but to submit to the system. But, they deprived other athletes of medals they might have won. A victim was Kathy Smallwood-Cook who perpetually ran second or third to these 'unbeatable' East German athletes and otherwise would have been recognised as one of the greatest UK athletes ever. This is why doping is so unjust and must be punished. Many people have heard of Ben Johnson, but only the cognoscenti remember Kathy Smallwood, who also ran sublimely. Generations of athletes have broken their careers in attempting to better these records.

The pressure to dope may also be increased because mathematical models indicate that world records are

reaching, or have reached, an asymptote, and the limits of human performance are being reached (Berthelot *et al*., 2008). Thus the ethos of the Olympic period of *citius*, *fortius*, *altius* needs to be rethought. Now, the presence of Ethiopian and Kenyan runners selected naturally from running at high altitude, and with haematocrits approaching 50%, the upper limit now accepted in cycling, dominate athletic events—even in local road races. It is very difficult for the young, sea-level, athletes to progress when they are being continuously well-beaten by athletes performing at a very different level, even in local races. Under these conditions of physiologically optimised performances, the effects of a sustained doping programme are more likely to make the difference between winning and losing first-class races.

So, as amateur athletes, what would *we* be prepared to do to win? First any amount of hard training, and sacrificing certain pleasures. Fortunately, it is not necessary to give up many pleasures and the hermit's existence proposed by H Andrews (1903) is not necessary. Andrews (1903) precautions to prevent the loss of vital fluids were original but fortunately have not been taken up in practice. Nevertheless, there is a fine line between doping and training to increase EPO levels, and other factors (Schwandt *et al*., 1991). Altitude training and sleeping in negative pressure tents to increase endogenous EPO, haematocrit and VO_{2max} are legal—injecting exogenous EPO is not. MS still spends his summer holidays running at 2000 m altitude to ameliorate his haematocrit, with a marked effect on performance which wanes in direct correlation with normalisation of haematocrit, but the goals are now only to beat his friends.

Most drugs used for doping have well defined therapeutic uses in helping the sick and the old. EPO is used to offset the decline in haematocrit in cancer. There is a progressive decline in VO_{2max}, particularly in elderly women, towards minimal values incompatible with any form of mobility. MS was once lodged, for a research meeting, in an old people's home and went out for a run before dinner. The corridors were 400 m long and an old lady in a walking frame puffed out of her door when he left. After four fast and easy miles he returned to find that the old lady had reached the end of the corridor. Both had probably been at the same percentage of VO2max for $\sim$20 min to achieve 4 miles and 400 m. Which was the most courageous and athletic performance?

However, athletic and strength training have been shown to have remarkable effects in aged people. Strength training in elderly long-term care residents with cognitive impairment improved the MMSE score by three points and the change in MMSE score was highly correlated with change in muscle function (Dorner *et al*., 2007). The use of drugs such as EPO, if it could be used safely (but see below), might be justified in the elderly, but not for winning veterans' athletics championships.

Regular exercise, even intense, can have major health benefits. In a 13-year prospective cohort study of 370 members of a runners' club (aged 50 and older) compared with 249 control subjects (initially aged 50–72 years), controls (93 deaths) had a 3.3 times higher death rate than runners' club members (26)—in every disease category. Compression of morbidity was not seen at the end of the study—with an average age of 72 years (Wang *et al*., 2002). In contrast, doping can take a physiological reaction to a training load, to non-physiological limits. It is now proven that many East German athletes had their lives ruined by the use of steroids. The German government set up a compensation fund of $2.5 million from which 311 athletes have claimed for a diverse series of side effects ranging from tumours to depression and sex changes. The start of the use of EPO can be defined by a change in death rates in athletes. Between 1987 and 1990, 20 Belgian and Dutch cyclists died from nocturnal heart attacks, leading to the situation of athletes exercising in the middle of the night. Between 1989 and 1992, seven Swedish orienteers died.

Mens sana in corpore sano

If oxygen use, and EPO, is so critical, what is happening metabolically and what links are there between body and brain? The metabolic changes following exercise are major and affect the principal energy systems in the body. The discovery that rats will voluntarily run several kilometres a night if provided with an exercise wheel has provided an important experimental tool. Exercising rats show marked changes in neurotrophins and brain electrophysiology.

Brain-derived neurotrophic factor (BDNF), the main activity-dependent neurotrophic factor (Black, 1998), increases following voluntary exercise in rats in both plasma and brain (Neeper *et al*., 1995; Widenfalk *et al*., 1999; Adlard *et al*., 2004, 2005; Klintsova *et al*., 2004; Berchtold *et al*., 2005; Huang *et al*., 2006; Rojas Vega *et al*., 2006; Vaynman *et al*., 2006a, b; Soya *et al*., 2007; Chen and Russo-Neustadt, 2007). BDNF evokes rapid excitation and transmitter release, and facilitates long-term potentiation (LTP) through TrkB receptors and MEK/MAP kinase activation (Kafitz *et al*., 1999; Xu *et al*., 2000). BDNF can induce rapid induction of LTP at dendritic spines and production of BDNF induces neurotrophic effects by increasing both excitatory and inhibitory synapses, even in adult neurones (Cohen-Cory, 1999). Thus the neurotrophin is increased both by neuronal activity and by physical exercise (Ferris *et al*., 2007) to increase the total number of connections in the brain, which has major implications for brain development. The exercise-induced changes in hippocampal BDNF are insulin growth factor-1 (IGF-1)-dependent (Chen and Russo-Neustadt, 2007) and IGF-1 and BDNF interface to modulate synaptic plasticity to change cognitive function (Ding *et al*., 2006).

Brain activity and energy metabolism are directly linked. We have shown that BDNF produced a concentration-dependent increase in the respiratory control index (RCI, a measure of the efficiency of respiratory coupling, ATP synthesis and organelle integrity) of mouse and rat brain mitochondria, coincubated with synaptosomes containing signal transduction pathways. This effect was mediated via a MEK/MAP kinase pathway and was specific for complex I (Markham *et al*., 2004); thus BDNF can increase the amount of ATP from a given quantity of oxygen, which is analogous to the requirements for increasing VO_{2max}. Metabolic changes were then reported in the hippocampus by BDNF (Vaynman *et al*., 2006a, b). Could this change in

mitochondrial efficiency be one of the mechanisms underlying the effects of training, but in the brain?

The temporal changes in BDNF production follow very closely the changes in running efficiency, which we empirically use for regulating training. Daily exercise and alternating days of exercise increased BDNF protein in rat brain, and the levels increased with running duration, even after 3 months of exercise. BDNF protein was elevated for several days after exercise. A second exercise exposure in trained animals (even after 2 weeks of inactivity) rapidly reinduced BDNF protein to levels requiring several weeks of exercise in previously untrained rats (Berchtold *et al.*, 2005). However, long-lasting cessation of running in spontaneously hypertensive rats (SHR, which can run up to 20 km each night) downregulates BDNF and its receptor, TrkB, in CA3 of the hippocampus. The effects of BDNF on energy metabolism are major because glucose induces BDNF and Trk B expression in the hypothalamus and site-specific knockdown of BDNF in the hypothalamus induces hyperphagia and obesity (Unger *et al.*, 2007). Mutations of the TrkB receptor or of BDNF in rodents or man induce hyperphagia and obesity, and in mice these can be reversed by hypothalamic administration of TrkB agonists (Tsao *et al.*, 2008). As BDNF and IGF-1 are induced by exercise in man (Ferris *et al.*, 2007; Tang *et al.*, 2008), these growth factors may have major effects on the epidemic of obesity and diabetes, especially as exercise is the most powerful antidote to type 2 diabetes.

Consider these figures: American children have 14 000 hours of education up to the age of 18, but by this age they will also have 16 000 hours of television during which time they will have witnessed 200 000 acts of violence (American Academy of Pediatrics, 2001). The 16 000 hours of television will substitute for time spent in play and exercise, which will change brain development, and also be responsible for the epidemic of obesity which threatens to erode the advances medical care made over the last hundred years. Thus it is crucial that children have access to sport and have role models, whom they can look up to. If they, and their families, think that success in sport can be achieved by injections rather than decades of effort then this is a major problem for society.

The other major players in insulin (and neurotrophin) sensitivity are modified by exercise (Holt and Sonksen, 2008). Peroxisome proliferator-activated receptor-gamma co-activator (PGC-1α) is a transcription co-activator, increased by exercise, with a central role in the regulation of cellular energy metabolism. Nuclear receptor co-activators and co-repressors impart tissue and situation selectivity to nuclear receptors (Germain *et al.*, 2006). PGC-1α stimulates mitochondrial biogenesis and promotes the remodelling of muscle tissue to slow–twitch composition that is metabolically more oxidative and less glycolytic, and a key component in endurance training (Russell, 2005; Liang and Ward, 2006; Liu *et al.*, 2007). Normal responses to a high-fat diet depend on the coordinated actions of peroxisome proliferator-activated receptors (PPARs) and PGC-1α. However, lipid-induced insulin resistance is associated with upregulation of PPAR-targeted genes, high rates of β-oxidation but no increase in tricarboxylic acid cycle activity. However, exercise enhances mitochondrial function, and restores insulin sensitivity in animals fed a high-fat diet (Muoio and Koves, 2007) with PGC-1α playing a key role. PGC-1α is deactylated and activated by sirtuins, which are NAD-dependent deacetylases and class III histone deacetylases: these molecules are critical for prolonging life-span of lower organisms, and modulating metabolism. Thus, small molecule activators of sirtuins prolong life span in yeast and have been proposed as novel agents for the treatment of type2 diabetes (Milne *et al.*, 2007). Sirtuin-1 is activated in the heart of aged rats by exercise, with anti-oxidant mechanisms (superoxide dismutase, catalase; Ferrara *et al.*, 2007). Thus, exercise stands at a critical point to modulate metabolism, increase mitochondrial synthesis and reverse or prevent obesity and diabetes mellitus. 16 000 hours of inactivity during childhood and adolescence, if not balanced by specific exercise programmes, will have a very deleterious effect on health.

Marked changes in electrophysiology in hippocampal and prefrontal circuits take place during running in rats and people. Hippocampal θ rhythm is induced by running, music or REM sleep: the frequency depends on running speed and links the increase in visual input to spatial memory as θ rhythm links cellular ensembles in the limbic system and links the particular hippocampal place cells involved in memory; θ rhythm, like BDNF, facilitates LTP (Buzsáki, 2005).

An issue for medication and care, rather than doping, is the interplay between the trophic effects of repetitive exercise and breakdown, particularly when inflammation, stressors, ageing and muscular damage (or overuse) are involved. Athletes plan to reach a training peak, prior to breakdown. Some athletes can manage greater training loads than others before breakdown. The reasons for this are very complex but the phenomenon has been recognised by serious coaches for a very long time (Andrews, 1903). The cumulative effects over many years can be very great and can even overshadow natural talent. What is happening? One possibility is that the balance between trophic and degenerative and stress and inflammatory responses varies between individuals and between different stages of life. Indeed injury- and infection-prone athletes show a greater increase in inflammatory cytokines after exercise (Cox *et al.*, 2007).

As every athlete knows, training effects are blocked by sickness and inflammation. Interestingly, the inflammatory cytokine, interleukin 1β blocks the effects of BDNF on respiratory coupling index in brain mitochondria (Markham *et al.*, 2008). MS considers that the reason why he is still running after a half century of competition is attention to running stride (eliminating mechanical strain on joints) and stopping training when ill or injured. Drugs, which would stop pathophysiological processes may have as much beneficial effects long-term, as current drugs used for doping, while being legal. However, current anti-inflammatory drugs merely mask damage and cannot be used long-term. Thus drugs which prevent the catabolic effects of stressors may have a use long term (Spedding and Gressens, 2008) and also may have beneficial effects in CNS disorders (Agid *et al.*, 2007).

Fahnestock (Garzon *et al.*, 2002; Peng *et al.*, 2005; Garzon and Fahnestock, 2007, see Spedding and Gressens, 2008) has

proposed that neurotrophin signalling is dysfunctional in Alzheimer's disease. BDNF mRNA and proBDNF and BDNF protein are reduced in the cholinergic target tissues of Alzheimer's disease patients compared with controls and are impaired in transgenic mice with mutations in APP. The finding that strength training can ameliorate the MMSE score by three points (Dorner *et al*., 2007) and these data listed above, indicate that physical fitness, may be favourable, but obviously not a prerequisite, for cognition. Indeed, *mens sana in corpore sano*.

What should we do about doping in sport?

- Obviously screen for cheats, and ban them when found, but detecting cheating is not easy. Longitudinal testing can measure changes in haematocrit, and if an athlete then trains at high altitude, increases can be put in perspective. We propose that for performances in endurance events at national level and above, simply cite the haematocrit (which is very easy to measure) with the performance, and then the future can judge the performance.
- What do we do with all the suspect records, which can possibly never be beaten without doping? Why not have a record for each century? Establish a list of new records from 2000. Alternatively asterisk suspicious records, but this will obviously cause controversy among the 'asterisked'.
- Much of the Western world, is faced with an obesity crisis. Children do not do much sport and talented individuals do not even get a chance to find their own talent, a crushing indictment of education. Life is difficult enough without depriving children of the knowledge of what they are good at. It is very easy for schools to ask their pupils to run 400 m (and 50 m for sprinters)—good performances should be encouraged and referred to local athletic clubs. Increasing the number of children participating will increase the pool of good athletes, increasing the profile of a sport, which in turn will increase interest in children.

Thus, doping devalues sport, and exercise. As humans are starting to reach the limits of 'normal' athletic performance, competition to reach the very top becomes more and more difficult. However, the old values, and health benefits, of doing sport for pleasure at a 'local' level remain valid. Schools and families need to reinforce the importance of exercise to children and young adults, because it is not only their physical health which is at risk (particularly because of obesity), but exercise and physical play appear to be critically important for brain development.

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