Review Article

ERGOGENIC AIDS: BOON OR BANE TO MANKIND?

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ABSTRACT

Ergogenics have revolutionized the field of sports and therapeutics. These mainly include mechanical, nutritional, physiological, psychological and pharmacological ergogenic methods. Nutritionally, ergogenic aids are utilized in an attempt to conserve energy during work performance in sports/cachectic conditions, either by providing an additional energy source, such as with glucose supplementation, or by favorably affecting metabolic processes that generate energy. Pharmacological ergogenic substances (e.g. anabolic steroids, psychostimulants) have been largely used and abused in therapeutics and sports. Therapeutic benefit of ergogens in the pipeline viz., phytoadaptogens and eugregorics is yet to be substantiated. This review is desired to provide the readers an idea of current status of ergogenic aids in therapy and the large scope which this entity provides for scientific research and validation in future.

Key words: ergogenics, anabolic steroids, phytoadaptogens, eugregorics

INTRODUCTION

Performance-enhancing substances have been used for thousands of years in traditional medicine by societies around the world, with the aim of promoting vitality and strength. Term 'Ergogenics' is derived from Greek word - *ergon* (tending to increase work power). Ergogenic aids means any potential means of improving energy production and utilization which produce enhancement in physical performance. As nutritional technology advanced, scientists have been able to synthesize and manufacture all known nutrients, and many of their metabolic by-products, essential to human physiology¹. Many of these substances are theorized to possess ergogenic potential when taken in quantities or forms normally not found in typical foods or diets. Research, although limited in most cases, supports the ergogenicity of some nutrients (e.g., creatine) when consumed in substantial amounts, suggesting such nutrients may function as drugs or nutraceuticals². Most nutritional ergogenic aids are utilized in an attempt to enhance energy metabolism during sport performance, either by providing an additional energy source, such as with glucose supplementation, or by favorably affecting metabolic processes that generate energy³. However, the means by which different nutritional supplements purportedly affect metabolism can vary greatly. For example, recent research suggests that antioxidant nutrients may offer protection to athletes from injury by free radicals, which are potentially damaging molecular species that are produced at an accelerated rate as metabolic rate is increased during physical activity³.

Formal drug doping testing by International Olympic Committee (IOC) was started in 1968 Olympics. The IOC doping legislation stipulates that any physiologic substance taken in abnormal quantity with an intention to artificially and unfairly increase the performance should be considered as doping and violation of ethics

of sport performance. Given this stipulation, the IOC and other athletic-governing organizations should consider the legality and ethics underlying the use of ergogenic nutraceuticals in sports^{4,5}. Early Olympics in 776 B.C athletes used hallucinogenic mushrooms, dried figs, and sesame seeds etc. as ergogenic aids. In 1920s, scientific & medical interest was developed towards diet & training of athletes. In 1940s, Testosterone came up as muscle mass & strength building drug. In late 1950s-1960s amphetamines & anabolic steroids got introduced in this field.

Romanian gymnast Andrea Raducan was stripped off her gold medal after failing the doping test for pseudoephedrine that was consumed in her cold remedy used as decongestant on the previous day of the event^{4,5}. In 1988, First time in the history of Olympics, a gold medalist sprinter – Ben Johnson was stripped off his medal in the track after being tested positive for anabolic steroids in doping tests. In 1992, NFL football player Lyle Alzado died from brain cancer, which he said was caused by his steroid use. Although steroids have been known to cause liver cancer there is no published evidence that anabolic steroids cause either brain cancer or the specific type of T-cell lymphoma that caused Alzado's death. However, Alzado also stated that he felt addicted to steroids and that he had become increasingly violent³⁻⁵.

TYPES OF ERGOGENIC AIDS

- I]. Mechanical
- II]. Psychological
- III]. Physiological
- IV]. Nutritional
- V]. Pharmacological

Mechanism of action of ergogens⁶

Ergogenic aids at “four places” in the scheme of energy formation (Figure 1-4):

1. Act as a supplementary source of energy E.g.: Carbohydrates and Fat
2. Reduce catabolism of fuel and hence increases rate of energy flux & work output.
E.g.: caffeine or amphetamines
3. Minimize the accumulation of by-products (lactic acid) of fuel catabolism.
E.g.: fluids, bicarbonate
4. Influence via nervous system: Promote recruitment of muscle fibers.

Figure 1

(Source – Internet:

http://www.lactate.com/triathlon/lactate_triathlon_anaerobic_energy.html)

Figure 2

(Source- Internet:

http://en.wikipedia.org/wiki/Catabolism#/media/File:Catabolism_schematic.svg)

Figure 3

(Source – Internet: <http://www.fitjog.com/fitness/mechanisms-of-muscle-energy-usage.php>)

Figure 4

(Source – Internet: <http://staff.jccc.net/pdecell/bio122/krebs.gif>)

ATP is the “energy-currency” for muscle contraction and generation of power or work-output. Anaerobic pathway leads to net 2 ATP generation, which is used in medium-term high performance (sprint-running). Aerobic pathway uses O_2 leads to net 34 ATP generation, which is used in long - term high performance (football, marathon, swimming).

Nutritional ergogenic aids may be theorized to improve performance in athletics in a variety of ways, primarily by enhancing energy efficiency, energy control or energy production. Athletes have utilized almost every nutrient possible, ranging from amino acids to zinc, as well as numerous purported nutritional substances, such as ginseng, in attempts to enhance physical performance^{5,7}. This review focuses primarily on nutritional ergogenic aids thought to enhance performance by favorably affecting energy metabolism. Although most purported nutritional ergogenic aids have not been shown to enhance physical performance in well trained, well-nourished athletes, some reliable scientific data support an ergogenic efficacy of several substances, including caffeine, creatine and sodium

bicarbonate, but additional research is needed to evaluate their potential for enhancing performance in specific athletics events. Chronic exercise training will induce beneficial changes in each energy system that is stressed. Many of these adaptations are specific to the muscle cells & the type of exercise task^{3,8}. For example, chronic aerobic endurance exercise training will improve functional capacity of the myocardium, increase blood volume and production of red blood cells, and increase quantitatively mitochondria and oxidative enzymes within exercised muscle groups, all adaptations that will facilitate the utilization of oxygen by the muscle tissues. Standardized aerobic exercise tasks will impose less stress to the muscle following these adaptations, thus helping to mitigate deviations from homeostasis. Many of these natural adaptations of the muscles to training are enhanced by various endogenous hormones, such as epinephrine, testosterone, human growth hormone (HGH) and erythropoietin (EPO), whose production and secretion may be enhanced during exercise⁶.

Deviations from homeostasis may contribute to developing fatigue. Stress of exercise leads to dehydration (hypovolemia), and hence hyper osmolarity with delayed peripheral vasodilatation & altered thermostat causing a rise in internal temperature (heat-injuries) reduce aerobic performance. In this case replacement of fluids alone leads to dilutional hyponatremia, so sodium replacement is also done more/equal to sweat loss (40 mEq/L = 0.5 -0.7 gms/L of fluid replaced) along with glucose replacement of 30-60 gms/hr. According to recommended guidelines (AASMFC) 250-500 ml of fluid 2 hours before exercise and continued every 15 min (500ml-2L/h) till 2 hours after exercise and the beverage temperature being

within 15-22°C range leads to increased exercise performance & rapid recovery from stress of exercise^{6,9}.

Doping is the administration of or the use by a competing athlete of any substance foreign to the body (drugs) or any physiological substance taken in abnormal quantity or by an abnormal route of entry into the body, with the intention of increasing in an artificial and unfair manner his performance in competition⁴.

Since the advent of athletic competition, athletes have utilized a variety of methods in attempts to enhance performance. Two of the earliest drugs used were alcohol and caffeine¹⁰, and their effectiveness as ergogens has been investigated since the latter part of the 19th century because they were commonly used by athletes in competition to help mask or prevent fatigue. As medical science progressed, advancing the understanding of human physiology, pharmaceutical research began to produce drugs or chemicals designed to mimic the action of endogenous hormones or compounds¹¹. For example, amphetamines and anabolic steroids were two of the first drugs to be used extensively in sport, being used indiscriminately during the 1950s and 1960s. Amphetamines were designed as sympathomimetics to the physiologic and psychologic effects of epinephrine, and anabolic steroids were designed to elicit effects associated with testosterone. Though amphetamines and anabolic steroids were developed with medically therapeutic applications in mind, their potential effectiveness to enhance physical performance eventually led to their use by athletes^{3,8,12}.

Various types of ergogenic aids have been exemplified with their therapeutic applications in Table 1.

Table 1

Types	Examples	Therapeutic applications
I] Mechanical	light-weight racing shoes, nasal breathing strips, artificial turf	sprint runners, short distance swimming and track events,
II] Psychological	hypnosis, stress management, imagery, short breaks at strenuous night shifts	Behavioral therapy of anxiety neuroses, depression, bipolar illness, post-traumatic stress disorders etc.
III] Physiological	blood doping, saline infusion, bicarbonate infusion, warm-up, warm clothing	Performance enhancer during dehydration, heat stroke, chill blains and endurance activities like (aerobic cycle- e.g: marathon race, mountain climbing, cycling, football)
IV] Nutritional	Anabolic-protein, chromium (potentiates insulin), vanadium, dichloroacetate, hydroxy-methyl-butyrate (HMB), caffeine, tri-methyl glycine (TMG), Omega-3 fatty acids (EPA/DHA), phosphatidic Acid (PA), Orotates, Taurine Energetic-carbohydrate, protein, pyruvate, lactate, fat, creatine-phosphate, carnitine branched chain amino acids, etc. Lipolytic-Polyphenols from Plants, EGCG from Green Tea, Fucosanthin from Brown Seaweed, Proanthocyanidins from Grape Seed, Chlorogenic Acid from Green Coffee Bean, Resveratrol from Grapes and Polygonum, Acetic Acid from Vinegar, Cyanidin-3-glucoside from Purple Corn Adaptogenic- Eleuthero coccus, Rhodiola rosea, Withania (Ashwagandha), Ocimum sanctum (Tulsi, Holy Basil), 20-Hydroxyecdysone (Leuzea, Ajuga), Ginseng (American, Chinese, Korean), Pfaffia paniculata (Brazil Ginseng, SUMA), Aralia manshurica (<i>Araliaceae</i>) Neurologic-Alkaloids, terpenoids, glycosides, coumarins Dis-Adaptive Nutrients- Vitamin C, Vitamin E, Anti-oxidants, NAC, Lipoic Acid, L-arginine,	Anabolics - Bodybuilding exercises and sports like weightlifting, football, shotput, endurance activities and athletics; To enhance and maintain work-output during overnight shifts; To treat muscle atrophy, myopathies, muscle fatigue, moderate to severe COPD, neuro-protective effect in animal models of HD, PD, ALS To improve performance in obese individuals, patients with immunosuppression, cardiovascular and metabolic disorders To relieve long-term stress and combat chronic fatigue during burn-out phases. -same as above- Chronic illnesses like Hypertension, DM, PAOD like Buerger's disease etc. ↓ Muscle fatigue in hemodialysis patients, ↑ myocardial performance in CHF, sarcopenia, cancer cachexia, burn injury, sepsis
V] Pharmacological	Anabolic steroids Eg. (oral- stanozolol, oxandrolone, inj.- nandrolone, testosterone, prohormones-DHEA	Strength dependant sports (wt. lifting), Hypogonadism, Burns, severe PEM, cancer cachexia, aplastic anemia, osteoporosis

	Growth hormone Recombinant - human-EPO Psycho-stimulants- amphetamines, caffeine, cocaine, ephedra alkaloids, narcotic analgesics Beta-blockers (e.g. propranolol, metoprolol) Beta₂ – agonists- clenbuterol	GH-replacement, Turner's syndrome, delayed growth, COPD patients CRF (ESRD), Cancer chemotherapy induced BM depression, Angina & PAD patients Narcolepsy, ADHD, CFS, obesity Moderate to severe COPD Short term high intensity exercise Performance anxiety Archery, shooting Prevention and Rx of Exercise induced asthma, Obesity

Mechanism of action of clinically important ergogens

Antioxidants

Nutritional antioxidants constitutes a very broad range of essential and nonessential nutrients that can purportedly aid in the detoxification of potentially damaging free radicals generated during and after physical exercise. Among the ingestible compounds are vitamins and vitamin precursors (alphatocopherol, ascorbic acid, beta carotene), minerals (copper, selenium, manganese, zinc, iron), and metabolic intermediates (coenzyme Q) that have been tested in athletes as possible ergogenic nutrients. Few of very well studied nutritional antioxidants have been the fat-soluble alpha tocopherol (vitamin E) and beta carotene (a vitamin A precursor) and the water-soluble ascorbic acid (vitamin C). Ergogenic potential of one or more of these nutrients in healthy active people is relatively untested. Some of the metal ions have been essential part of body's important enzymes^{6,9}. For example,

- Manganese in mitochondrial superoxide dismutase
- Zinc in cytosolic superoxide dismutase
- Copper in cytosolic superoxide dismutase
- Selenium in glutathione peroxidase
- Iron in catalase

Blood Doping

The autologous removal of 1-4 units of blood, storage of the blood in cold temperature for 4-8 weeks and the reinfusion of the red blood cells. Reinfusion usually done around 1 week prior to competition increases blood volume, gives hemoglobin maximal O₂ carrying capacity, and improves work performance of endurance activities (aerobic cycle- e.g: marathon race, football). This is found to provide temporary benefit among patients with acute respiratory distress syndrome (ARDS). This blood doping is banned by IOC.

Anabolic steroids

Different anabolic steroids vary in their half-life, and thus individuals typically use each steroid at different intervals of time. A steroid cycle refers to the frequency or schedule of an individual's steroid use. Some individuals also take multiple types of steroids at a time, known as "steroid-stacking"¹³. Examples for Oral- stanozolol, oxandrolone; Injectables- nandrolone, testosterone

These:

- Induce protein synthesis in muscle
- Stimulates release of growth hormone
- Reverses the catabolic effects of cortisol
- Increases Acetyl choline release at synapses & neuromuscular junction hence increasing muscle power
- Have psychological rewarding effect

Growth hormone

- Accelerates incorporation of amino acids into proteins
- Stimulates utilization of lipids from adipose tissue
- Increases plasma Free fatty acids
- Spares muscle glycogen
- Promotes bone & cartilage growth

Recombinant human erythropoietin^{6,9}

- Stimulates erythropoiesis
- Increases maximum O₂ uptake
- Increases time to exhaustion (aerobic activity) hence prolonging activity
- Has psychological rewarding effect

Psycho-stimulants^{1,6}

(amphetamines, caffeine, cocaine, ephedra alkaloids, narcotic analgesics).

These -

- Stimulates sympathetic nervous system
- Improves alertness
- Increases intracellular utilization of free fatty acids
- Improves aerobic endurance,
- Inhibits the inhibitory adenosine receptor, thus acting like a stimulant, blunts pain perception and fatigue
- Causes calcium mobilization from sarcoplasmic reticulum improving contractility

Beta-blockers

(e.g. metoprolol) –anti-tremor and anti-anxiety effects

β₂ agonists

(e.g. clenbuterol)

- Possess CNS and Respiratory stimulatory (analeptic) effect
- Increases glycogenolysis and insulin release
- Causes protein anabolism, increases contractility and exercise tolerance
- Produces 'repartitioning effect'—increases thermogenesis and lean body muscle mass, reduces body fat

Creatine^{1,6,9}

- Increases intracellular ATP
- Increases muscle fiber diameter by 35 %,
- Improves strength and power performance
- Anti-atherogenic & vasodilatory effect
- Raises anaerobic exercise tolerance

Vitamin A, C, E

Muscular free-radicals scavenging during & post endurance activities

L-arginine

Acute intake: increases exercise tolerance, immune function & cell survival

Chronic intake: increases muscle protein synthesis, NO and nocturnal GH

Bicarbonate

- Neutralises lactic acid & carbonic acid which are the metabolic by-products (buffer potential)
- Anaerobic endurance increases (useful to combat metabolic acidosis and among sprinters)

Beta-hydroxy methyl butyrate (HMB)^{9,11}

- Maintains sarcolemmal integrity
- Anti-catabolic
- Inhibits ubiquitin proteasome proteolytic pathway
- m-TOR dependent myofibrillar protein synthesis
- Increases muscle-FA oxidation
- Immune-stimulant

Phosphate loading

- Phospho-creatine system activates ATP synthesis
- Increases exercise endurance, tidal volume and VO Peak

Carnitine^{14,15,16}

- Increases muscle glycogenolysis
- Increases oxidative metabolism (fatty acid transfer into mitochondria)
- Inspiratory muscle strength in COPD patients

Androstenedione

- Protein synthesis in muscle
- Increases release of GH
- Reverses catabolic effects of cortisol

Branched chained amino acids (leucine, isoleucine, valine)

- Increases amino acid transfer to muscles
- Reduces protein degradation leading to increase in intracellular glutamate
- Prevents early lactic acidosis

Choline

It prevents the decline in acetylcholine that occurs during exercise → facilitating transmission of impulses across the neuromuscular junction, hence improving the ability to perform muscular work.

RECENT CONCEPTS

I] Phyto-adaptogens theory

Phyto-adaptogens are novel “anti-fatigue” herbal agents which increase tolerance to mental exhaustion & endurance, thus increasing psychomotor performance.¹⁷

Examples: *Rhodeola rosea* (SHR-5), *Eleutherococcus senticonus*, *Panax ginseng* (animal models), *Cordyceps sinensis* (animal models), Capsaicin (animal models), *Ginkgo biloba* (proven in PAOD patients, not in healthy), Kava & St. John’s wort (no proven efficacy).

Proposed Mechanisms of action of phyto-adaptogens (Figures 6 & 7):

They-

- Reduces sensitivity of “HPA axis” to feedback by cortisol (key role)
- Increases cortisol actions (mimetic)
- Increases chaperones like HSP-16 & -70 to manage “sub-optimal” stress
- Activates c-JNK1, FOX-O mediated DAF-16 – stress resistance & longevity improves
- Reduces stress-induced NO-synthesis

Figure 5: Adaptogenic theory hypothesized with ADAPT-232* - inducing stress resistance and enhancing endurance to stress and possibly, longevity (Source –Internet- <http://cms.herbalgram.org/herbalgram/issue90/images/AdaptogensFig5.jpg>)

Figure 6

(Source- Internet : http://isagenixhealth.net/wp-content/uploads/2012/04/adaptogen_stress.png)

Scope in therapeutics for adaptogens

Various clinical indications have been observed for adaptogens, namely:

1. Mild to moderate depression
2. Chronic fatigue syndrome
3. Alzheimer's & Parkinson's disease: Ginseng is used
4. Asthenia in chronic debilitating illnesses (Cancer cachexia, HIV, Tb etc.)
5. Chemotherapy & radiotherapy induced fatigue
6. Improved exercise tolerance in Cardiac, COPD & PAOD patients
7. Acupuncture –a cardio-ergogenic aid that increases muscle power (neurological conditions and sports).

2. Eugregories (arousal creating drugs)

Modafinilis an agonist at "orexigenic" neurons (hypothalamus) causing norepinephrine and dopamine release. It is used as an "ergogenic aid" in therapy & sports¹⁸.

Their approved therapeutic uses are: narcolepsy, ADHD, shift-work sleep disorder, idiopathic hypersomnia, obstructive sleep apnea syndrome

Off-label uses: Chronic fatigue syndrome, myotonic dystrophy, spastic cerebral palsy

3. Gene Therapy/ Gene doping¹⁴⁻¹⁶

a) EPO- used in Cancer chemotherapy, AIDS associated anemia and chronic renal failure

b) Hypoxia-induced-factors (HIF- α & β)-in cancer (with risk of metastasis due to its angio-genetic potential), chronic infections, angina/MI, stroke, hyperthyroidism etc.

c) IGF-1- Muscular dystrophies (e.g. Duchenne's)

d) Follistatin (myostatin inhibitors)

e) Endorphins & Enkephalins - Angina

f) VEGF- cardio-ergogenic in IHD & PAOD patients

Proven beneficial, safe & legal ergogens^{1,6,9}:

- 1) Fluids
- 2) CHO replacement
- 3) Caffeine-ephedra mixture (over-the-counter medication like Sinarest tablet)
- 4) Antioxidants (e.g.: vitamins A,C,E)
- 5) Beta-hydroxy-methyl-butyrate (HMB)
- 6) Adaptogens - Rhodiola rosea, ADAPT-232

CONCLUSION

Much of the scientific data regarding the aforementioned ergogens are equivocal and contradictory. Many chemical and herbal sources suggest of possessing ergogenic potential.^[19,20] Though a lot of nutritional ergogenics have been a boon to therapeutics in various conditions like cancer, burns, growth disorders and also in improving the nutritional and immunological status among immuno-compromised patients, yet many more of their potential ergogenic efficacies remain largely unexplored. Although most of the literature indicates that prudent supplementation with majority of nutrients is relatively harmless, there have been reports of illnesses (notably with vitamin C) attributed to ingestion of mega dose supplements of antioxidants and L-carnitine induced diarrhea. Hence future research on ergogenic effects of herbs should consider identity and amount of substance or presumed active ingredients administered, dose response, duration of test period, proper experimental controls, measurement of psychological and physiologic parameters, their pharmacokinetic and pharmacodynamic safety studies and clinical measurements of performance pertained to intended uses. The fact that IOC has been stringent and stern through-out in its antidoping regulations is greatly appreciable as the misuse of ergogenic aids in sports is largely minimized. In brief, ergogenic aids to enhance human physical and psychomotor performance has had little scientific study and this represents a large and valid field for future research.

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