

Pharmacological value of Caffeine, Taurine and Arginine in nutritional supplements and their relation to well known socially important diseases

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Abstract: Caffeine, Taurine and Arginine are one of the most widely used supplements from people of all ages. There are lot of controversial information about their proper use and effects and side effects. Our goal is to determine the reasonable boundaries of using these supplements in healthy people and more important in people with socially important diseases like high blood pressure, diabetes and dementia.

Keywords: Caffeine, Taurine, Arginine, Dementia

1. Introduction

Amino acids are important organic compounds. They are so called "building blocks" of our peptides. In mammals amino acids can be divided in: essential, semi essential and non-essential. Arginine is classified as a semiessential or conditionally essential amino acid, depending on the developmental stage and health status of the individuals [1]. It was first isolated from a Lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze [2]. Taurine (2-Aminoethylsulfonic) acid is an amino sulfonic acid, sometimes referred to as an amino acid. It is not amino acid in the usual biochemical meaning of the term, which is referred to compounds containing both an amino and a carboxyl group. Taurine does not link with other amino acids or the building blocks of the proteins hence it does not take part in protein synthesis. It is a major constituent of bile and can be found in the large intestine, and accounts for up to 0,1 % of total human body weight [3]. Caffeine on the other hand doesn't belong to amino acid family and can't be found naturally in human body like Taurine and Arginine. It is white crystalline powder xanthine alkaloid. Caffeine is classified as a CNS stimulant. It is the world's most widely consumed psychoactive drug, but

unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. Caffeine is classified by the Food and Drug Administration as "generally recognized as safe".

2. Caffeine

Caffeine is found in the seeds of coffee plant; the leaves of tea bush and in cola nuts, which are the usual source of caffeine for various energy drinks, nutritional supplements and foods. Other famous sources include guarana and yerba mate. Caffeine is extracted from the plant parts with a process called infusion. Beverages containing caffeine enjoy great popularity nowadays all over the world [4]. Caffeine is the most widely ingested psychoactive drug in the world. Chronic use of caffeine leads to dependence and tolerance. Caffeine in the smokers and heavy caffeine users had a shorter half-life (3.2 and 4.1 hours) than that in nonsmokers and nonusers (5.1 and 5.3 hours). In the caffeine in tolerant group it had a longer half-life, while the cardiovascular effects were similar to those of the other groups [5].

Caffeine in the diet has modest effect to the blood pressure, probably in the region of 4/2mm Hg. However its effects should

not be underestimated, it could be reason for premature deaths in 14% of coronary heart disease and 20% for stroke [5].

Coffee, about two cups/day, is found to be negatively related to the diabetes risk. This although can be applied only to nonelderly people who had previously lost weight and there is also positive dose-response relationship between diabetes risk and weight change [7]. Caffeine/coffee consumption is associated with a decreased risk of diabetes type 2 and possibly also with a decreased dementia risk, although further research is needed [8].

Recent study of psychostimulant actions of chronic use of caffeine (1 mg/mL drinking solution for 30 days) on short and long term memory and brain-derived neurotrophic factor in young and middle-aged rats shows that caffeine use treatment substantially reduced age-related impairments in the two types of memory. In addition chronic use of caffeine increased brain-derived neurotrophic factors in the hippocampus and contribute to the pro-cognitive effects on age-associated losses in memory encoding [9]. Another double-blind placebo-controlled research showed that acute caffeine administration was associated with increased load-related activation compared to placebo in the left and right dorsolateral prefrontal cortex during working memory encoding, but decreased load-related activation in the left thalamus during working memory maintenance. Therefore, the effects of caffeine on working memory may be attributed to both a direct effect of caffeine on working memory processes, as well as an indirect effect on working memory via arousal modulation [10].

A study performed with Alzheimer's disease transgenic mice shows that average daily intake of caffeine per mouse (1.5 mg) was the human equivalent of 500 mg content of caffeine and the amount typically found in five cups of coffee per day lowers hippocampal β -amyloid levels. Moderate daily intake of caffeine may delay or reduce the risk of Alzheimer's disease [11]. Caffeine modulates neuronal activity, 100 mg caffeine 20 min prior to the performance of the working memory task, caused an increased response in bilateral medial frontopolar cortex, extending the right anterior cingulate cortex [12].

3. Taurine

Taurine has many fundamental biological roles, such as conjugation of bile acids, antioxidation, osmoregulation, membrane stabilization, and modulation of calcium signaling. It is very important for cardiovascular function, development and function of skeletal muscle, the retina, and the central nervous system.

Taurine is named after the Latin *tauris* (a cognate of the Greek) which means bull or ox, as it was first isolated from ox bile in 1827 by German scientists Friderich Tiedemann and Leopold Gmelin. Naturally taurine can be found in fish and meat. The mean daily intake from omnivore diets is determined to be around 58 mg and to be low or negligible from a strict vegan diet. Some studies show that taurine intake is generally less than 200mg/day, even in individuals on a high-meat diet. According to Hayes KC and Trautwein EA in

“Modern nutrition in health and disease” taurine consumption is estimated to vary between 40 and 400 mg/day [13].

2-Aminoethylsulfonic acid is a major constituent of bile and can be found in the large intestine and in the tissues of many animals, including humans [14, 15]. Biosynthesis of taurine in mammalian organisms occurs in the pancreas via the cysteine sulfonic acid pathway. In this pathway, the thiol group of cysteine is first oxidized to cysteine sulfinic acid by the enzyme cysteine dioxygenase. Cysteine sulfinic acid, in turn, is decarboxylated by sulfinoalanine decarboxylase to form hypotaurine. Hypotaurine is then oxidized to taurine.

High concentration of taurine exists in skeletal muscles. Taurine has been shown to participate in the excitation-contraction coupling mechanism in skeletal muscle, which means that it affects the transmission of an electrical signal into muscle fibers. Taurine has also been shown to prevent the decrease in structural proteins present in skeletal muscle. Study data report that depletion and repletion of muscle taurine to endogenous levels affects skeletal muscle contractility. In a laboratory experiments the effects of hereditary taurine deficiency on muscle function were examined in taurine transporter knockout mice which resulted in severe skeletal muscle impairment leaving cardiac function uncompromised [16]. Moreover taurine exerts protective properties against ethanol-induced hepatic steatosis and lipid peroxidation during chronic ethanol consumption in rats [17, 18]. The supplement plays an important role in the modulation of cardiovascular function by acting not only within the brain but also within peripheral tissues which is observed in experiments [19].

Taurine is regularly used as an ingredient in energy drinks, with many containing 1000mg per serving [20], and some as much as 2000mg [21]. Following a request from the European Commission, The European Food Safety Authority's (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS) has concluded that exposure to taurine through regular consumption of energy drinks is not of safety concern [22]. A review published in 2008 found no documented reports of negative or positive health effects associated with the amount of taurine used in energy drinks, concluding, “The amounts of guarana, taurine, and ginseng found in popular energy drinks are far below the amounts expected to deliver either therapeutic benefits or adverse events” [23].

The different physiological actions of taurine demonstrate its importance for cardiovascular function, development and function of skeletal muscle, the retina, and the central nervous system [24]. Taurine is conjugated via its amino terminal group with chenodeoxycholic acid and cholic acid to form the bile salts sodium taurochenodeoxycholate and sodium taurocholate. The low pKa [25] of taurine's sulfonic acid group ensures this moiety is negatively charged in the pH ranges normally found in the intestinal tract, thus it improves the surfactant properties of the cholic acid conjugate.

Taurine passes through the blood-brain barrier [26, 27, 28] and is involved in a variety of physiological processes including neurotransmission [29], membrane stabilization [30], protection against glutamate excitotoxicity [31] and prevention

of epileptic seizures [32], long-term potentiation in the striatum/hippocampus [33], calcium homeostasis [34], recovery from osmotic shock [35], feedback inhibition of neutrophil/macrophage respiratory burst, adipose tissue regulation and possible prevention of obesity [36, 37]. Taurine has an antioxidant effect and plays protective role against various toxic substances (for example lead and cadmium) [38, 39, 40, 41]. Additionally, supplementation with taurine has been shown to prevent oxidative stress induced by exercise [42].

In a study conducted by Yanagita and colleagues taurine is found to reduce the secretion of apolipoprotein B100 and lipids in HepG2 cells [43]. Higher concentrations of serum lipids and apolipoprotein B100 (apoB - essential structural component of VLDL and LDL) are major individual risk factors of atherosclerosis and coronary heart disease. Thus there is possibility taurine containing supplements to reduce the risk of these diseases. Taurine has beneficial effects on lipid metabolism in experimental animals fed with high-cholesterol or high fat diets presenting his cholesterol-lowering effect. Furthermore, body weight also decreased significantly with taurine supplementation in these animal studies [44, 45].

There is wealth of experimental information and some clinical evidence available in the literature suggesting that taurine could be of benefit in cardiovascular diseases of different etiologies such as: congestive heart failure, hypertension, ischemic heart disease, atherosclerosis and diabetic cardiomyopathy [46].

In the cells, taurine keeps potassium and magnesium inside the cell while keeping excessive sodium out. In this sense it works like a diuretic. But unlike prescription diuretics, it is not a cellular poison. It does not act against the kidney, but improves kidney function instead. Taurine is very useful in fighting tissue swelling and fluid accumulation. In the brain and the heart taurine stabilizes the cell membrane by regulating the electro-chemical forces. It tends to inhibit and modulate neurotransmitters in the brain and helps to stabilize cell membranes. Because it aids the movement of potassium, sodium, and calcium in and out of the cell, taurine has been used as a supplementation for epileptics as well as for people who have uncontrollable facial twitches [47].

As mention before taurine plays very important role for normal skeletal muscle functioning [16]. Mice with genetic taurine deficiency had a nearly complete depletion of skeletal and cardiac muscle taurine levels and a reduction of more than 80% of exercise capacity compared to control mice. Taurine reverses neurological and neurovascular deficits in experimental type 2 diabetic rats by influencing defects in nerve blood flow, changing the motor nerve conduction velocity, and nerve sensory thresholds [48, 49]. Again in diabetic rats, taurine is found to decreases significantly weight and blood sugar [50]. However according to a single study on human subjects, daily administration of 1.5 g of taurine had no significant effect on insulin secretion or insulin sensitivity [51]. Taurine may exert a beneficial effect in preventing diabetes-associated microangiopathy [52]. It can attenuate hyperglycemia-induced apoptosis in human tubular cells via

an inhibition of oxidative stress and might prevent tubulointerstitial injury in diabetic nephropathy [53].

Taurine is possible safe for adults. It has been used safely by adults in studies lasting up to one year. However, there is one report of brain damage in a body-builder who took about 14 grams of taurine in combination with insulin and anabolic steroids. It is not known if this was due to the taurine or the other drugs taken. Excess taurine is typically excreted by the kidneys.

4. Arginine

Arginine is an important precursor in human body for synthesis of nitric oxide, urea and it is vital for "production" of creatine and glutamate. The last two substances are involved closely with proper brain, cardiovascular and muscle function. In literature exist numerous data showing the positive influence of nitric oxide in brain function. One recent research shows promising results in modulating and improving short term memory by nitric oxide [54]. As we mentioned before Arginine is an immediate precursor in biological synthesis of NO. Another important effect of Arginine in brain function and plasticity is investigated in a in vitro study which shows promising results in slowing age related memory loss in rat models. In a study published in "International Journal of Clinical and Experimental Pathology" found that L-arginine could affect the origination and development of Alzheimer disease. Yet there are still a lot of questions that should be answered about using Arginine as a supplement in diseases that affect brain structures [55].

Clinical data showing also controversial findings about increasing muscle mass and weight gain in patients with tuberculosis supplemented with Arginine [56]. This ability of L-Arginine may be related with another study that shows linkage between oral supplementation of this amino acid and increasing levels in growth hormone [57]. Studies in malnourished patients with head and neck cancer showed lower fistula rates, decreased length of hospital stay, and a trend toward improved survival, while other trials were unable to demonstrate a positive clinical outcome [58]. In a study of patients who had undergone surgery for esophageal cancer, L-arginine given enterally as part of an immuno-enhanced diet with omega-3 fatty acids and RNA was found to inhibit the decrease in platelets following surgery and reduce prothrombin activity and thrombin-antithrombin III complex levels. Additionally, the proportion of T-cells was higher in patients receiving this enteral product on postoperative days 1 and 7. Thus, an immuno-enhanced diet containing L-arginine may be beneficial in patients following surgery for esophageal cancer to reduce the risk for infectious complications [59].

Very interesting trials in patients suffering from Diabetes type 2 shows improvement in their well-being when Arginine was administrated to them. Administration stimulates insulin secretion and enhances insulin-mediated glucose disposal, with various mechanisms suggested: 1. beta-cells in the pancreas take up positively charged L-arginine molecules, resulting in plasma membrane depolarization; 2. metabolism of L-arginine

by arginase yields ornithine and urea; 3. nitric oxide is produced from L-arginine by the enzyme nitric oxide synthase [60, 61]. A long-term study of L-arginine supplementation (9 g/day for 1 month) in patients with type 2 diabetes resulted in improved peripheral and hepatic insulin sensitivity. No changes in body weight, glycated hemoglobin, serum potassium, diastolic blood pressure, or heart rate were demonstrated. Systolic blood pressure decreased in the L-arginine group, low-dose of L-arginine-enriched blood demonstrated a protective effect in ischemia/reperfusion injury, with a lower incidence of perioperative myocardial infarction and a decreased length of stay in the intensive care unit and hospital. Another study shows that low dose of L-Arginine could relax cavernous smooth muscle in the penis for which is required nitric oxide this, suggest the role of Arginine in erectile dysfunction [62]. Studies in rats produced an erectile response and altered vascular tone, but in a human clinical trial, no difference was established between L-arginine 500 mg 3 times daily and placebo [63]. A study of L-arginine in combination with pycnogenol (an extract of French maritime pine bark consisting of procyanidins, catechin, and taxifolin) demonstrated improved sexual function in 80% of treated men. Further increases in pycnogenol amount achieved improvement in 92.5% of men by the end of the study. Treatment with L-arginine was associated with 5% of patients achieving a normal erection [64].

Other reported uses of L-arginine are in Sickle cell anemia and pulmonary hypertension. In 10 patients with sickle cell disease and pulmonary hypertension (mean, 32.7 ± 15 years of age) given oral L-arginine 0.1 g/kg 3 times daily for 5 days, supplementation was associated with a 15.2% mean reduction in pulmonary artery systolic pressure (63.9 ± 13 to 54.2 ± 12 mm Hg, $P = 0.002$). Of the 9 compliant patients, follow-up echocardiography results at 1 month showed that 4 patients reverted back to baseline pulmonary artery systolic pressure values, 1 patient worsened and was admitted for acute chest syndrome, and 4 patients persistently improved; 2 of the patients who improved were started on transfusion therapy, and 1 of these patients continued treatment with L-arginine therapy at a dose of 0.1 g/kg twice daily. The effects in patients with sickle cell disease of L-arginine 0.1 to 0.2 g/kg divided 3 times daily versus sildenafil 25 to 100 mg 3 times daily on safety, cardiopulmonary function, and fetal hemoglobin were assessed [65]. L-arginine did not improve pulmonary pressure or 6-minute walking distances, while sildenafil did. However, fetal hemoglobin levels were insignificantly reduced by $2.9\% \pm 16.1\%$ from baseline in patients receiving L-arginine. In those treated with sildenafil, fetal hemoglobin levels increased [66].

In literature exists a lot of small trials that involve Arginine in cytokine modulation, helping with the problem “sensitive teeth’s” when it is included in toothpaste’s and many other possible uses. That’s why it is very important people who are willing to take Arginine to know it’s interactions save doses in different conditions and side effects. Arginine interactions could be divided in three groups: Major and Moderate. Major : medications for high blood pressure (antihypertensive drugs), medications that increase blood flow to the heart (nitrates). Moderate interactions could be observed with: Sildenafil,

Tadalafil, Vardenafil and cholesterol lowering agents [67]. Dosage could vary between 6 to 30 g/day for a variety of conditions. Parenteral, enteral, intramural, and topical formulations have been used.

5. Conclusion

Arginine and Taurine regulate great number of biochemical processes in our body. On the other hand Caffeine is a xenobiotic that for many people is an essential supplement. All the literature data we collect shows that the difference between toxic and safe effective dosage couldn’t be exactly pointed. In people affected by diabetes, cardiovascular deceases or dementia we recommend consultation with healthcare professional and to use the lowest effective dose of each of these three supplements. The dose has to be defined after thorough evaluation of patient health status.

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