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REVIEW ARTICLE

# Effect of taurine and potential interactions with caffeine on cardiovascular function

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**Abstract** The major impetus behind the rise in energy drink popularity among adults is their ability to heighten mental alertness, improve physical performance and supply energy. However, accompanying the exponential growth in energy drink usage have been recent case reports and analyses from the National Poison Data System, raising questions regarding the safety of energy drinks. Most of the safety concerns have centered on the effect of energy drinks on cardiovascular and central nervous system function. Although the effects of caffeine excess have been widely studied, little information is available on potential interactions between the other active ingredients of energy drinks and caffeine. One of the active ingredients often mentioned as a candidate for interactions with caffeine is the beta-amino acid, taurine. Although taurine is considered a conditionally essential nutrient for humans and is thought to play a key role in several human diseases, clinical studies evaluating the effects of taurine are limited. However, based on this review regarding possible interactions between caffeine and taurine, we conclude that taurine should neutralize several untoward effects of caffeine excess. In agreement with this conclusion, the European Union's Scientific Committee on Food published a report in March 2003 summarizing its investigation into potential interactions of the ingredients in energy drinks. At the cardiovascular level, they concluded that "if there are any interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine." Although these interactions remain to be further examined in humans, the physiological functions of taurine appear to be inconsistent with the adverse cardiovascular symptoms associated with excessive consumption of caffeine–taurine containing beverages.

**Keywords** Caffeine–taurine interactions · Energy drinks · Physiological functions of taurine

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## Introduction

Energy drinks are non-alcoholic beverages that are marketed for their energizing effects and formulated with various ingredients, such as caffeine, taurine and vitamins. Most energy drink brands contain ~300 mg/l caffeine (80 mg per 8.4 fl oz can), which is about the same amount of caffeine that can be found in a home-brewed cup of coffee.

Largely because of the stimulating activity of caffeine, energy drinks are marketed for their ability to supply energy, improve stamina, enhance athletic performance and heighten mental alertness. According to the American Academy of Sleep Medicine, caffeine is effective in increasing mental alertness and improving overall performance after sleep loss (Smith and Phillips 1993). It may also improve safety in the work place, benefit cognitive function and diminish automobile accidents among sleep deprived and fatigued individuals. Athletic performance and endurance have also benefited from consumption of energy drinks.

The energy drink industry has grown exponentially in North America since the introduction of Red Bull in the

United States and Canada in 1997 and 2004, respectively. Worldwide sales of Red Bull in 2012 reached 5.2 billion cans while the 2013 revenue of the second most popular energy drink company, Monster Beverages, was $3.2 billion. Energy drink usage among adults in the United States rose 13 % in 2006 and 17 % in 2012, with Red Bull, Monster Beverage and Rockstar accounting for 92 % of market share. Despite the robust growth of energy drink beverages, 96 % of caffeine consumed is derived from coffee, soft drinks and tea and energy drink beverages only represent 2 % of total daily mean caffeine consumption (Mitchell et al. 2014). Market experts believe that the energy drink industry might be in its infancy, as energy drink consumption is the lowest of all of the ready-to-drink beverages.

Although energy drinks serve an important function, the safety of energy drinks in general and caffeine in particular has recently been questioned. Caffeine overdose is characterized by a series of toxic responses, including cardiac arrhythmias, palpitations, hypertension, irritability, insomnia, tremor and seizures (Pelchovitz and Goldberger 2011; Seifert et al. 2011; Pendleton et al. 2012). Interestingly, the symptoms of caffeine overdose are virtually identical to the common complaints and symptoms (palpitations, agitation, insomnia, tachycardia, hypertension, tremor and gastrointestinal upset) of excessive energy drink exposure recorded by Poison Information Centers (Walsh et al. 2006; Gunja and Brown 2012) and in a study of US military service members consuming energy drinks (Schmidt et al. 2008).

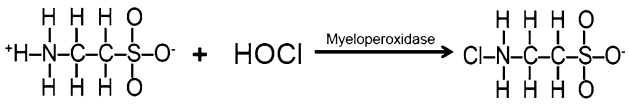
Regulatory agencies and food industry have extensive experience with several of the ingredients found in energy drink beverages, including caffeine, sweeteners and vitamins. In August 2012, the US Food and Drug Administration (FDA) stated that for healthy adults, caffeine intake of up to 400 mg/day is not associated with general toxicity, cardiovascular defects, effects on bone status, calcium imbalance, changes in adult behavior, incidence of cancer, or effects on male fertility. This view is in agreement with Health Canada, who concluded that the general population of healthy adults is not at risk of potential adverse effects from caffeine if limited to 400 mg/day (Nawrot et al. 2003). In addition, the European Food Safety Authority (The European equivalent to the FDA) concluded in its January 2009 opinion on the safety of energy drink ingredients that the exposure to taurine and D-glucurono-γ-lactone at levels presently used in energy drink beverages is not of safety concern and an interaction between D-glucurono-γ-lactone and either caffeine or taurine is unlikely. However, key questions still unanswered are whether caffeine is solely responsible for the adverse response to excessive energy drink consumption or if an untoward interaction develops between caffeine and one or more of the active energy drink ingredients. Interest is therefore focused on one of the biologically active ingredients of energy drink beverages, the amino acid taurine. The present review discusses its biological and physiological actions, the sources of taurine and the claims that taurine might cause toxicity through potential interactions between taurine and caffeine on the cardiovascular system.

## Physiological functions of taurine

Taurine (2-aminoethylsulfonate) is involved in several important physiological functions, including bile acid conjugation, osmoregulation, anti-inflammatory activity, neuromodulation, antioxidant activity and maintenance of normal mitochondrial function and ATP production (Huxtable 1992; Marcinkiewicz et al. 1998; Lang et al. 1998; Schuller-Levis and Park 2003; Kirino et al. 2005; Huang et al. 2006; Wu et al. 2009; Jong et al. 2012; El Idrissi et al. 2013). Most of those actions (bile acid conjugation, anti-inflammatory activity, antioxidant activity and maintenance of normal mitochondrial respiratory chain function) involve a covalent reaction between taurine and another active biological compound.

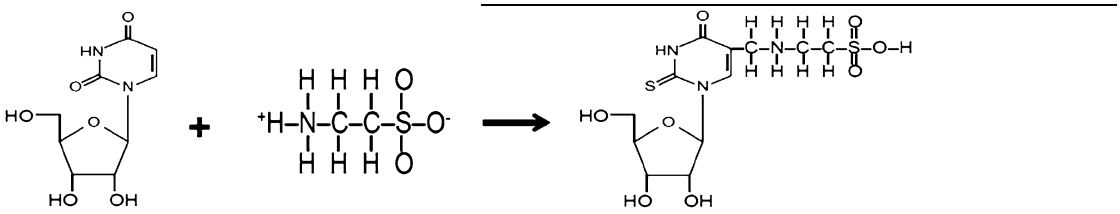
In humans, both taurine and glycine react with bile acids to form a conjugate while in cats, taurine is required for bile acid conjugation. The role of bile acid conjugation is to enhance biliary secretion of the bile acid into bile (Vessey et al. 1983). Because bile acid conjugates are lost daily in the feces considerable amounts of taurine are lost from the body as taurocholic acid.

A covalent reaction between taurine and the oxidant hypochlorous acid contributes to both the anti-inflammatory and the antioxidant activity of taurine. Hypochlorous acid, which is produced by a myeloperoxidase-catalyzed reaction during the respiratory burst of neutrophils, chlorinates both neutrophil and bacterial proteins. However, neutrophils have developed a mechanism that provides protection against the cytotoxic actions of HOCl, one in which taurine substitutes for proteins in a myeloperoxidase-catalyzed reaction involving taurine and HOCl (Thomas et al. 1985).




Not only does taurine and the product of the taurine reaction, taurine chloramine, have less cytotoxic activity than HOCl, taurine chloramines also regulate the inflammatory process by downregulating inflammatory mediators, such as cytokines, cyclooxygenase-2 and inducible nitrix oxide synthase (Kim et al. 1996; Marcinkiewicz et al. 1998; Kontny et al. 2003; Schuller-Levis and Park 2004).

The mitochondrial actions of taurine contribute to both its antioxidant and respiratory chain protective activity. Taurine reacts with the wobble position uridine residue of



$tRNA^{Leu(UUR)}$, generating 5-taurinomethyluridine-$tRNA^{Leu(UUR)}$ (Suzuki et al. 2002; Schaffer et al. 2013). Two codons (UUA and UUG) are capable of interacting with the anticodon AAU*, where U* represents 5-taurinomethyluridine. However, the anticodon (AAU) lacking the taurine modification only interacts normally with the UUA codon. Therefore, the biosynthesis of the UUG-dependent mitochondria encoded proteins, such as ND6, is impaired in taurine-deficient cells and their cellular levels decline (Jong et al. 2012). Because ND6 is a key subunit of complex I, taurine deficiency leads to diminished respiratory chain activity, oxygen consumption, ATP production and conditions that lead to elevations in superoxide generation, as electrons are diverted from the respiratory chain to oxygen (Jong et al. 2012).

Taurine also serves as a neuromodulator, acting as an agonist of the GABA receptor (El Idrissi et al. 2013). It also protects against glutamate toxicity by inhibiting glutamate-mediated calcium overload and oxidative damage (Wu et al. 2009).

The osmoregulatory actions of taurine relate its role as an organic osmolyte. Not only does this action influence the osmotic and ionic balance of the cell (Pasantes-Morales and Schousboe 1997; Hoffmann et al. 2009), but it also affects renal function (Mozaffari et al. 1998) and the expression of various proteins and transporters (Burg et al. 1997; Schaffer et al. 2000). However, recently it has been shown that organic osmolytes also contribute to protein folding and stability (Kumar 2009).

## Sources and pharmacokinetics of taurine

The biosynthesis of taurine is species-dependent, with hepatic synthesis from cysteine being very active in rodents but not in cats and humans (Hayes and Carey 1975; Knopf et al. 1978; Gaull 1986). Because of taurine's fundamental physiological actions, all vertebrates require either a synthetic or dietary source of the amino acid. Hence, cats fed a taurine-deficient diet develop a pathological syndrome, characterized by retinopathy, cardiomyopathy, myopathy, immune deficiency and developmental defects (Hayes and Carey 1975; Sturman 1986; Pion et al. 1987; Schuller-Levis et al. 1990; Ito et al. 2008). In the cat, the loss of taurine is accelerated because the amino acid is lost daily as taurocholic acid. Interestingly, humans do not readily synthesize taurine in the liver, but they do not develop characteristic symptoms of taurine deficiency, largely because the conjugation of bile acids in humans utilizes either glycine or taurine while taurine conjugation is required in taurine-dependent animals, such as the cat (Knopf et al. 1978; Watkins et al. 1983). Humans derive most of their taurine from the diet although a small amount of taurine is synthesized in the liver.

Dietary taurine readily enters the blood, where much of it is rapidly eliminated in the urine, with the elimination rate dramatically enhanced at higher taurine levels (Sved et al. 2007). The normal concentration of taurine in the plasma is very low (e.g. <60 μM in cat) but most tissues contain very high taurine levels (mM range), creating a substantial concentration gradient across the cell membrane. Hence, the taurine transporter located on the cell membrane utilizes energy in the form of the $Na^+$ gradient to drive taurine uptake. However, the taurine transporter acts too slowly to acutely change the size of the intracellular taurine pool. Even after more prolonged taurine supplementation (30–300 mg/kg over a 2 week period), there is little change in taurine levels of the brain and heart (Sved et al. 2007). Without alterations in intracellular taurine levels, it is difficult to explain the biological effects mediated by chronic taurine treatment, as reported for heart and brain (Azuma et al. 1985; Takihara et al. 1986; Ohta et al. 1988; El Idrissi et al. 2003). Four mechanisms might provide an explanation for the positive effect of chronic taurine treatment. First, while acute administration of limited amounts of taurine might have no influence on intracellular taurine levels, prolonged chronic treatment might lead to an elevation in myocardial and brain taurine levels. Second, taurine is compartmentalized within the cell, with the mitochondrial pool serving a different function than the cytosolic pool. Although chronic taurine administration might not alter taurine content of the whole organ it might alter the size of one of the smaller taurine pools, such as those found in the mitochondria. Third, chronic taurine treatment, unlike acute taurine treatment, modulates the expression of certain genes (Park et al. 2006;

El Idrissi et al. 2013). Fourth, elevations in extracellular taurine might influence the function of the cell membrane (Huxtable 1992). At high concentrations, taurine inhibits the enzyme, phospholipid *N*-methyltransferase, preventing the conversion of phosphatidyl-ethanolamine to phosphatidylcholine, a phospholipid change that alters membrane structure and function (Schaffer et al. 1995).

## Potential interactions between taurine and caffeine

According to the European Food Safety Authority, taurine (3–6 g) has been administered daily to a large number of patients (including adults, children and even infants). No adverse health effects have been noted (Scientific Committee on Food 2003). The mean value of taurine intake by adult energy drink consumers in Europe, a group that consumes 2 L/month energy drinks/week, is 272 mg taurine/day (3.82 mg/kg body weight/day) from energy drinks, while the high chronic energy drink consumer (90th percentile—consume energy drinks at least 4–5 times/week for 4.5 L/month) is exposed to 586 mg taurine/day (8.49 mg/kg body weight/day) from energy drinks (Zucconi et al. 2013). However, taurine intake by adult Europeans from an omnivore diet varies from 9 to 372 mg taurine/day, with the average being 58 mg/day. A diet rich in meat and seafood contains fairly high levels of taurine, while a strict vegetarian diet contains little to no taurine. Thus, the intake of taurine by high chronic energy drink consumers is several-fold higher than the intake by individuals on an average omnivore diet. There is no evidence of safety concerns when taurine has been used in dozens of human studies (Aguilar et al. 2009), however, there are case reports implicating taurine–caffeine interactions in untoward responses to energy drinks. The remainder of the review summarizes clinical and basic science evidence for the existence of taurine–caffeine interactions. The possibility of additive effects of the two active agents is also discussed.

### *Potential diuretic and natriuretic interactions of taurine and caffeine*

The Scientific Committee on Food (SCF) raised the possibility that an interaction between caffeine and taurine might enhance diuresis and natriuresis (Scientific Committee on Food 2003). The diuretic actions of caffeine, which appear to be mediated by adenosine receptor antagonism, are well documented (Daly 1993). Caffeine also increases natriuresis by inhibiting tubular sodium reabsorption (Shirley et al. 2002). Although there have been only a few studies examining the diuretic and natriuretic actions of taurine in humans (Gentile et al. 1994), animal studies have established a definitive natriuretic and diuretic action of taurine that appears to involve the modulation of arginine vasopressin activity (Mozaffari and Schaffer 2001).

Because athletes commonly use energy drinks to enhance physical performance, concerns have been raised about the potential for dehydration among athletes using energy drinks. Yet, Riesenhuber et al. (2006) failed to confirm this assumption. They examined 12 individuals, who were prohibited from drinking fluids for 12 h prior to the onset of the experiment. Each individual was then separately administered one of four preparations: (1) 750 ml Red Bull energy drink (containing 240 mg caffeine and 3 g taurine), (2) Red Bull energy drink lacking taurine, (3) Red Bull energy drink lacking caffeine or (4) Red Bull energy drink lacking both taurine and caffeine. Individuals consuming the four variations of the Red Bull energy drink were found to excrete more fluid and sodium in response to caffeine but not in response to taurine. Moreover, taurine had no effect on the diuretic and natriuretic actions of caffeine, suggesting that the interaction (if any) between taurine and caffeine is not a concern for athletes consuming energy drinks.

### *Potential interactions of taurine and caffeine relative to blood pressure*

Caffeine has been shown to elevate blood pressure in both normotensive and hypertensive prone men, in part by inhibiting adenosine action, leading to elevated norepinephrine release and vasoconstriction (Passmore et al. 1987; Lovallo et al. 1989; Sung et al. 1990; James 2004; Savoca et al. 2005; Palatini et al. 2009). By contrast, caffeine also augments endothelium-dependent vasodilation in young, healthy individuals (Umemura et al. 2006). However, the 2001 IOM Report on Caffeine designed for the military stated "despite numerous studies attempting to show a relationship between caffeine and serum lipoproteins, blood pressure, cardiac arrhythmias, and risk of coronary heart disease, results have failed to show a consistent adverse effect of ingestion of moderate amounts of caffeine". The Organization for Economic Cooperation and Development (OECD) reported in 2002 "Though consumption of caffeine (eight cups of regular coffee corresponding to 500 mg caffeine per day) may exhibit acute increases in blood pressure, the long-term effects appear to be minimal. After 1–4 days of regular consumption a tolerance develops, with blood pressure returning to previous levels" (United Nations Environmental Program, http://www.chem.unep.ch/irptc/sids/OECDSIDS/Caffeine.pdf).

Consistent with the actions of caffeine, Steinke et al. (2007) found that healthy, normotensive individuals, having abstained from caffeine for 48 h, exhibit elevations in both systolic blood pressure (10 mmHg) and heart rate

(5–7 beats/min) after consumption of 500 ml of energy drink containing 80 mg caffeine and 1,000 mg taurine. However, the study lacks a proper control group, making a meaningful evaluation difficult. A recent open-label, 2-period crossover pilot study of nine participants by Franks et al. (2012) found that energy drink supplementation elevates both diastolic and systolic blood pressure more than caffeine supplementation only, suggesting a possible interaction between caffeine and other components of energy drinks. However, there was no control group (without caffeine) or coffee group in the study design. The observed effects on blood pressure (max 5–6 mmHg), although statistically significant, cannot be regarded as clinically relevant. Therefore, the authors state "it is unknown whether these blood pressure effects translate into clinically meaningful risk to consumers of energy drinks." In response to those findings, the American Heart Association (2007) issued a warning to hypertensive individuals that energy drink consumption might increase the risk of elevating blood pressure. However, a survey of the literature raises questions regarding the interpretation of the blood pressure results. First, most studies fail to detect an elevation in blood pressure following energy drink consumption (Ragsdale et al. 2010; Geiss et al. 1994; Alford et al. 2001) or co-administration of caffeine and taurine (Bichler et al. 2006). Second, cardiac performance is altered by baroreceptor-mediated reflex bradycardia induced by caffeine (Lane and Williams 1985). Third, caffeine withdrawal is associated with small reductions in blood pressure that are reversed by reintroduction of caffeine (Juliano and Griffiths 2004; Rogers et al. 2003). Fourth, there is overwhelming evidence that taurine treatment reduces blood pressure in both hypertensive animals and humans (Nara et al. 1978; Yamamoto et al. 1985; Hano et al. 2009; Sato et al. 1987; Yamori et al. 2010; Trachtman et al. 1989; Abebe and Mozaffari 2011; Li et al. 1996), while taurine deficiency leads to elevations in blood pressure (Mozaffari et al. 2006). Among the mechanisms implicated in the antihypertensive actions of taurine include either suppression of norepinephrine or enhanced norepinephrine turnover (Hano et al. 2009; Sato et al. 1987), reductions in angiotensin II levels or action (Trachtman et al. 1989; Singewald et al. 1997), elevations in vasodilatory prostaglandin production (Trachtman et al. 1989) and regulation of vascular tone through reductions in $[Ca^{2+}]_i$ (Kohashi et al. 1983; Trachtman et al. 1989).

Two human studies have examined the regulation of blood pressure by taurine. Fujita et al. (1987) completed a double-blind, placebo-controlled trial of young borderline hypertensive patients administered either placebo or 6 g taurine/day. In the taurine-treated group, but not the placebo group, both systolic and diastolic pressure and plasma norepinephrine content fell in response to taurine. The second study is a WHO-coordinated epidemiological study (Cardiovascular Diseases and Alimentary Comparison—CARDIAC) investigating 61 different populations around the world (Yamori et al. 2010). A major finding of the study is that individuals with higher urinary taurine excretion (related to a taurine rich diet) exhibit lower systolic blood pressure, diastolic blood pressure and heart rate. In a related epidemiological study, Yamori et al. (2009) found that high taurine intake is associated with prolonged life expectancy among Japanese. Thus, while caffeine is capable of elevating blood pressure, both animal and clinical studies reveal that taurine reduces blood pressure. In agreement with the above conclusion, in March 2003, the European Union's SCF published a report summarizing its investigation into potential interactions of various energy drink ingredients. At the cardiovascular level, it was noted that "if there are any interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine."

### *Potential interactions between caffeine and taurine relative to ischemic heart disease*

Two case reports have served as impetus for studying the link (if any) between energy drink usage and ischemic heart disease. One case report concerned a 19-year-old who was diagnosed with ST-segment elevation myocardial infarction after consuming 2–3 cans of energy drink/week (Scott et al. 2011). However, normal coronary vessels were seen via coronary angiography. The possibility of taurine-mediated potentiation of caffeine excess was suggested. In the other case report, a 28-year-old male athlete, who had consumed 7–8 cans of an energy drink within 7 h of the athletic event, collapsed shortly after participating in a motocross race (Berger and Alford 2009). The authors suggested that in physiologically predisposed individuals, a combination of excessive ingestion of caffeine and taurine may induce myocardial ischemia by coronary vasospasm. However, their speculation is not based on sound scientific principles. There is no evidence that taurine administration is capable of promoting vasospasms even in the presence of norepinephrine, whose levels are elevated by caffeine (Ristori and Verdetti 1991; Li et al. 1996; Abebe and Mozaffari 2000; Nishida and Satoh 2009). Rather taurine appears to promote vascular relaxation, in part by diminishing norepinephrine- and angiotensin II-mediated vasoconstriction (Abebe and Mozaffari 2011). Taurine deficiency also diminishes $A_2$ adenosine receptor-mediated relaxation suggesting that the amino acid directly acts on the vasculature, perhaps by opening potassium channels, reducing $Ca^{2+}$ mobilization or serving as an antioxidant to elevate nitric oxide levels (Abebe and Mozaffari 2004, 2011). There was also no mention of two studies

concluding that the combination of exercise and caffeine can reduce myocardial blood flow (Namdar et al. 2006, 2009). Although taurine potentiates caffeine-induced muscle contracture, the preparation employed in the contracture studies is saponin-treated tissue rather than intact heart (Steele et al. 1990). Saponin creates holes in the cell membrane, exposing intracellular organelles to the extracellular medium. Addition of caffeine (10 mM) to the extracellular medium allows extremely high concentrations of caffeine to interact directly with the sarcoplasmic reticulum, where it triggers the release of calcium to initiate muscle contracture. The concentration of caffeine used in caffeine-induced contracture studies is several orders of magnitude higher than the median lethal dose of caffeine, which in rats is 200–400 mg/kg (Steele et al. 1990). Therefore, caffeine-induced contracture experiments involve in vitro animal preparations that are not relevant to human studies.

In one report, Higgins (2013) employed flow-mediated dilatation to evaluate endothelial function in a 47-year-old male before and following consumption of an energy drink. The author reported that the percent change in flow-mediated dilatation decreased following administration of an energy drink. Among the mechanisms putatively involved in this effect are inhibition of guanylate cyclase, stimulation of catecholamine release, enhanced production of angiotensin II and interference with adenosine receptors. However, due to the limitations of case reports and study designs, it is unclear from these reports if the alleged effects are attributable to caffeine, taurine or both.

Finally, two publications are sometimes referred to in this discussion. Schneider and Benjamin (2011), referring to a paper by Baum and Weiss (2001), concluded that "taurine has physiologic effects on the intracellular calcium concentration that may cause coronary vasospasms." However, the study by Baum and Weiss (2001) compared myocardial contractile function (not coronary artery contraction) in a double-blind, crossover study in which athletes consumed different beverage preparations (preparation #1 contained caffeine, taurine and glucuronolactone; preparation #2 contained only caffeine and preparation #3 lacked all 3 components). The major conclusion of the study by Baum and Weiss (2001) was that measures of myocardial contractile function (stroke volume and fractional shortening) were significantly elevated after exercise in individuals consuming all 3 active ingredients of energy drinks (caffeine, glucuronolactone and taurine). They concluded that energy drinks (preparation 3) improve maximal performance of the heart while reducing heart rate.

Worthley et al. (2010) examined the possibility that energy drink consumption might promote platelet aggregation, thereby increasing the risk of a thrombotic event. In their study, subjects were fasted overnight and then allowed to consume either a sugar-free energy drink containing caffeine, taurine and glucuronolactone or carbonated water. ADP-dependent platelet aggregation was evaluated 60 min after ingestion of either drink. The group consuming the energy drink exhibited a significant increase in platelet aggregation. However, this finding is not supported by the observation that both caffeine and taurine reduce platelet aggregation (Hayes et al. 1989; Park et al. 2007; Watson et al. 2010; Ijiri et al. 2013). It also must be emphasized that these results represent laboratory results and the clinical implications of increased platelet aggregation in an otherwise fit and healthy cohort of subjects are unclear.

In apparent contrast to those reports, Yamori et al. (2001, 2010) found that individuals with high levels of taurine excretion (correlating to high levels of taurine consumption) have lower risk of coronary heart disease. Moreover, taurine feeding (6 g/day) has been shown to decrease LDL cholesterol among individuals fed a high fat diet (Mizushima et al. 1996). Furthermore, a reduction in the atherogenic index [(total cholesterol−HDL cholesterol)/HDL cholesterol] was observed in a double-blind randomized study of 30 overweight, diabetic college students treated with taurine (3 g/day) for 7 weeks (Zhang et al. 2004). These actions of taurine are related at least in part to the acceleration of cholesterol degradation and to elevations in HDL levels (Yokogoshi et al. 1999; Chen et al. 2004). However, dietary taurine also reduces plasma triglyceride levels (Park et al. 1999; Zhang et al. 2004). According to Murakami et al. (2002), taurine feeding (1 % added to water) diminishes cholesterol levels in hamsters fed a high fat diet by promoting an upregulation of the LDL receptor and increasing LDL turnover levels. Also, the possibility that taurine's antioxidant activity might contribute to the improvement in atherosclerosis deserves further attention (Kondo et al. 2001; Wojcik et al. 2009).

In human trials (Azuma et al. 1985), daily doses of taurine (3–6 g) have been administered to patients with congestive heart failure for between 4 weeks and 1 year, improving the condition of congestive heart failure in the majority of cases with no significant adverse effects reported. Based on that work, taurine is presently used in the treatment of heart failure in Japan.

Regarding caffeine, a recent prospective cohort study in 36740 Swedish women over 10 years, low (<1 cup/day) or no coffee consumption was linked to increased risk of total stroke and ischemic stroke compared to moderate and high intake of coffee in healthy subjects (Larsson and Orsini 2011). In a Japanese prospective cohort study, moderate to high consumption of caffeinated coffee and tea (2–4 cups/day) was even linked to a reduced risk of ischemic stroke (Kokubo et al. 2013).

In a study on 500 hypertensive middle-aged men, the incidence rate of ischemic stroke was higher in men who consumed 2–3 cups of coffee per day than in abstainers (Hakim et al. 1998). However, the study of Hakim et al. (1998) uses caffeine consumption data from the 1960s, which may not be relevant to more recent studies in which caffeine consumption has been updated. For example, a recent meta-analysis including data from seven cohort studies on the association between habitual coffee consumption and cardiovascular events among hypertensive patients did not detect an increase in risk attributable to coffee/caffeine (Mesas et al. 2011).

Together, the clinical and basic science studies provide no evidence of relevant interactions between caffeine and taurine relative to ischemic heart disease or promotion of vasospasms.

### *Potential interactions of caffeine and taurine relative to cardiac arrhythmias*

Several clinical reports have implicated energy drink usage with the development of myocardial arrhythmias. In one case report, a 13-year-old female, who had consumed one energy drink beverage, was referred to a clinic with prolonged $QT_c$ while experiencing palpitations, chest pain, shakiness and dizziness (Higgins 2013). The patient's ECG normalized later that morning. Higgins (2013) also reported that a 47-year-old male experienced a 5.6 % prolongation of the $QT_c$ interval 90 min following consumption of a 24-oz can of energy drink. By contrast, Steinke et al. (2009) observed no significant change in $QT_c$ interval in subjects consuming energy drinks. Moreover, there is no evidence that energy drink consumption is associated with torsade de pointes, an arrhythmia commonly linked to prolonged QT interval. This is not surprising because the "energy drink-mediated changes" in the QT interval are small compared to those commonly associated with initiation of torsade de pointes.

A couple of reports attribute the development of atrial fibrillation to consumption of energy drinks. In one case, a 14-year-old boy, who had consumed an energy drink the previous day, presented with a heart rate of 130 beats/min 2 h after completing a race (DiRocco et al. 2011). The diagnosis was atrial fibrillation with occasional atrial flutter. After treatment with digoxin, normal sinus rhythm was restored. Finally, a 16-year-old volleyball player, who consumed 4–5 cans of energy drink/day, was referred to a university laboratory after becoming orthostatic intolerant, suffering episodes of transient unconsciousness (Terlizzi et al. 2008). The diagnosis was postural tachycardia syndrome caused by exaggerated energy drink consumption; symptoms disappeared 1 week after cessation of energy drink usage.

However, interactions of caffeine and taurine with regard to cardiac arrhythmias are not based on available scientific literature. Pelchovitz and Goldberger (2011) have summarized the results of several human studies examining the effect of caffeine on atrial and ventricular arrhythmias. Although there have been a few cases of increased atrial arrhythmias after ingestion of caffeine (Dobmeyer et al. 1983; Cannon et al. 2001; Peake et al. 2007), the overall conclusion of the Pelchovitz and Goldberger (2011) is that in most individuals, even among those with known or suspected arrhythmias, caffeine in moderate doses is well tolerated and there is no reason to restrict its ingestion.

Taurine, on the other hand, is generally recognized as an antiarrhythmic agent, an effect attributed to the regulation of cation transport (Satoh and Sperelakis 1998). One noteworthy effect is the regulation of the inward rectifying $K^+$ current by taurine, although the taurine effect is complex, being both species and $Ca^{2+}$ dependent. In a related study, Lake et al. (1987) found that myocardial taurine depletion is associated with prolongation of QT interval, suggesting that intracellular taurine content regulates both $K^+$ current and action potential duration. In addition to modulating $K^+$ transport, taurine inhibits fast $Na^+$ current, an effect Satoh (1998) suggested might result in class I antiarrhythmic activity. Through these changes in cation transport, taurine prevents several types of arrhythmias, including those mediated by CsCl, digoxin and epinephrine (Read and Welty 1963; Yin et al. 2012). It is also noteworthy that taurine therapy diminishes the incidence of ventricular fibrillation in isolated rat heart subjected to an ischemia–reperfusion insult (Chahine and Feng 1998).

Three case reports also illustrate the effectiveness of taurine as an antiarrhythmic agent. Prior to taurine treatment, a 64-year-old male had suffered for 6 years from both premature atrial and ventricular contractions associated with periods of tachycardia (heart rates over 150 beats/min) (Eby and Halcomb 2006). When he began consuming 4 g taurine/day the frequency of premature atrial contractions and paroxysmal tachycardia fell 50 %. Upon addition of arginine to the treatment mixture, ectopic beats were reduced to 100/day. In the second report, taurine treatment (10 g/day) of an 82-year-old man was shown to be as effective as verapamil therapy in blocking premature ventricular contractions (Eby and Halcomb 2006). In the final report, therapy consisting of both taurine and arginine nearly eliminated the symptoms of skipped beats and atrial fibrillation (Eby and Halcomb 2006).

Overall, the clinical and basic science studies provide no evidence for relevant interactions between caffeine and taurine relative to cardiac arrhythmias.

*Potential interactions of taurine and caffeine relative to contractile function*

A double-blind, crossover study examining the effect of energy drinks on myocardial performance of endurance athletes before and after exercise revealed that consumption of a complete energy drink containing taurine and caffeine increased contractile function (stroke volume and fractional shortening) in response to exercise, while consumption of a comparable drink containing either caffeine alone or no active ingredients exhibited no alteration in contractile function in response to exercise (Baum and Weiss 2001). There is abundant evidence that taurine mediates a positive inotropic effect associated with elevations in $[Ca^{2+}]_i$ (Chovan et al. 1980; Franconi et al. 1982; Sawamura et al. 1990; Steele et al. 1990; Holloway et al. 1999). However, most of those in vitro studies utilize concentrations of taurine that far exceed the levels achieved following consumption of energy drinks. Nonetheless, evidence that taurine mediates the release of calcium from intracellular stores supports a role for intracellular taurine in the regulation of calcium homeostasis and contractile function.

The positive inotropic effect of energy drinks should benefit exercising subjects by improving delivery of oxygen to skeletal muscle enhancing aerobic metabolism and elevating performance of exercising muscle. Improved contractile function would also promote the elimination of toxic substances by the kidney. Therefore, the combination of caffeine and taurine in the energy drink should provide some benefit to the exercising individual.

**Conflict of interest** Dr. Stephen Schaffer serves as a consultant of Red Bull. All other authors declare that they have no conflict of interest with respect to this manuscript.

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