HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Birth Defects Res. 2017 December 01; 109(20): 1640–1648. doi:10.1002/bdr2.1177.

Taurine, Caffeine, and Energy Drinks: Reviewing the Risks to the Adolescent Brain

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Abstract

Energy drinks are emerging as a major component of the beverage market with sales projected to top $60 billion globally in the next five years. Energy drinks contain a variety of ingredients, but many of the top-selling brands include high doses of caffeine and the amino acid taurine. Energy drink consumption by children has raised concerns, due to potential caffeine toxicity. An additional risk has been noted among college-aged consumers of energy drinks who appear at higher risk of over-consumption of alcohol when the two drinks are consumed together. The differential and combinatorial effects of caffeine and taurine on the developing brain are reviewed here with an emphasis on the adolescent brain, which is still maturing. Key data from animal studies are summarized to highlight both reported benefits and adverse effects reported following acute and chronic exposures. The data suggest that age is an important factor in both caffeine and taurine toxicity. Although the aged or diseased brain might benefit from taurine or caffeine supplementation, it appears that adolescents are not likely to benefit from supplementation and may, in fact, suffer ill effects from chronic ingestion of high doses. Additional work is needed though to address gaps in our understanding of how taurine affects females, since the majority of animal studies focused exclusively on male subjects.

Introduction

Energy drinks are relatively new consumer products that are similar to soft drinks, with additional additives and higher doses of caffeine (Howard and Marczinski, 2010). While typical ingredients found in energy drinks and shots can vary by brand and can be proprietary information, most energy drinks are sweetened carbonated beverages containing 80–320 mg of caffeine per serving, similar to a range seen in a prototypical cup of coffee. In addition to the primary psychoactive ingredient of caffeine that is included in energy drinks to enhance consumer alertness and energy, there are a variety of other compounds in energy drinks, including taurine, ginseng, glucuroncolactone, guarana, and vitamins (Marczinski, 2015). Sales of energy drinks continue to climb worldwide, with sales reportedly nearing

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$50 billion (Fig. 1). They represent 63% of the functional beverage category, with traditional sports drinks comprising only 27% of sales (Datamonitor, 2008). As a category with exponential sales growth, the use of energy drinks has been extremely controversial. The majority of these products are consumed by children, adolescents, and young adults (Malinauskas et al., 2007; Heckman et al., 2010; Wolk et al. 2012). There are health concerns for children and young adults using these products, with a heavy focus on the concerns related to cardiovascular functioning, even though brain development should also be a consideration for these demographic groups. For cardiovascular health, it is known that the acute effects of caffeine and consumption of energy products can moderately increase blood pressure and heart rate (Mesas et al., 2011; Seifert JG et al., 2011; Higgins and Babu, 2013; Marczinski et al., 2014). While moderate elevations in blood pressure after use of energy products may be relatively innocuous in healthy adults, they can be concerning in developing children, who have smaller body sizes and no developed tolerance to stimulant drugs. For this reason, numerous countries have banned the sale of energy drinks to minors, and others are seriously considering doing the same (Ragsdale et al., 2009; Seifert SM et al., 2011). Both the American Academy of Pediatrics and the American Medical Association support restrictions on the sales of energy drinks to minors (AAP, 2011; Thorlton et al., 2014).

Part of the controversy in restricting sales of energy drinks to minors is that caffeine has long been the only psychoactive compound that is legally available to minors. Verster et al. (2013) have argued that safety concerns may be overstated, since caffeinated products are widely used by all age groups. The U.S. Food and Drug Administration limits the caffeine content of carbonated beverages to 71 mg/serving and regulates caffeine in over-the-counter products. However, energy drinks are sold as food supplements, and do not undergo the same regulatory process in the United States in part because caffeine is considered GRAS (generally recognized as safe) and does not require testing before placement in new products (FDA). Therefore, the caffeine content of many energy drinks is often unknown or difficult to determine, especially for newer products. Reissig et al. (2009) reported levels of caffeine ranging from 50 to 505 mg. Thomson and Scheiss (2010) estimated that a single energy drink could push 70% of children and 40% of teenagers past the adverse effect level of 3 mg/kg/day when combined with other dietary sources. Accidental consumption is also an issue. Roughly half of all energy drink-related calls to the United States National Poison Data System (NPDS) between October 1, 2010 and September 30, 2011 involved children under the age of 6 (Seifert et al., 2013). Similarly, more than 45% of caffeine intoxication reports involve children or teenagers (Seifert et al., 2011). However, it remains unclear if caffeine toxicity is the primary reason that energy drinks can be risky products for children and adolescents.

McClellan and Lieberman (2012) reviewed the most common ingredients, other than caffeine, which are found in the most popular energy drinks. They reported levels of the amino acid taurine between 750 and 1,000 mg per serving. Taurine is a non-essential amino acid, and the normal diet typically contains 40 to 400 mg per day (Shao and Hathcock, 2008). The Mayo Clinic recommends no more than 3,000 mg per day (Zeratatsky, 2015). Taurine can modulate calcium release, so there are potential impacts on the brain, heart, and skeletal muscle (El Idrissi and Trenkner, 2003; Seifert et al., 2013). Cardiac effects are

exacerbated when taurine and caffeine are ingested together (Baum and Weiss, 2001) which can be a concern, given that caffeine alone can increase blood pressure and heart rate. A discussion of other common ingredients, such as the stimulants guarana, ginseng, gingko, and glucose is outside the scope of this review and available elsewhere (McClelland and Lieberman, 2012; Wolk et al., 2012; Blankson et al., 2013)

While energy drinks are often consumed alone, energy drinks are also often mixers with alcohol (Fig. 2). While this topic has been reviewed elsewhere (Marczinski and Fillmore, 2014; Marczinski, 2015) and is not the central focus of this manuscript, it should be noted that the use of energy drink mixers increases the abuse potential of alcohol. Elevated rates of binge drinking and risk of alcohol dependence have been associated with alcohol mixed with energy drinks (AmED) versus alcohol alone. Results from laboratory studies indicate that when an energy drink (or caffeine) is ingested with alcohol, the desire (or urge) to drink more alcohol is more pronounced in both humans and animals than with the same alcohol dose alone (Marczinski et al., 2013, Marczinski et al., 2016). Blankson et al. (2013) warned of a “grave danger” of adolescents drinking more alcohol than intended, and being more likely to drive after drinking alcohol mixed with energy drinks. The U.S. Food and Drug Administration took protective action in November 2010 by sending letters to four manufacturers of caffeinated alcohol beverages. The letters warned that caffeine could not be considered “generally regarded as safe” (GRAS) when combined with alcohol, and the products were reformulated to remove caffeine, guarana, and taurine (FDA, 2010; CDC, 2015). Regardless, college students regularly report mixing alcohol and energy drinks, and Bonar et al. (2015) reported that adolescents who mixed energy drinks and alcohol were more likely to need emergency care and more likely to engage in risky behaviors. In this review, we will summarize the unique aspects of high taurine and caffeine consumption on the adolescent and young adult brain, with a focus on cognitive and behavioral effects reported in humans and in animal studies, ending with recommendations for future studies and updated risk assessments for regulatory action.

Caffeine’s effects on brain development and function

Caffeine is a well-known stimulant that affects numerous neurotransmitter and endocrine signaling pathways. By inhibiting phosphodiesterase, caffeine enhances signaling through adrenergic pathways leading to increased heart rate, blood pressure, blood glucose, and bronchodilation. Caffeine antagonizes signaling through adenosine receptors, and increases release of catecholamines. The American College of Obstetricians and Gynecologists recommended that pregnant women limit daily caffeine intake to 200 mg, because caffeine readily crosses the placenta and alters catecholamine levels in the mother (ACOG, 2010). The recommended limit for children is 100 mg per day (AAP, 2011) Although caffeine’s ability to boost cognitive function are widely accepted (Lieberman, 2003), moderate doses of caffeine and caffeine-containing energy drinks have been shown to improve attention, speed reaction times, improve memory, facilitate vigilance, and improve verbal reasoning (Scholey and Kennedy, 2004; Kennedy and Scholey, 2004; Nehlig, 2010; Childs and de Wit, 2008; Einother and Giesbrecht, 2013). However, not all aspects of cognitive performance are enhanced by caffeine. Consumption of caffeinated beverages can impair or have no influence on performance on some cognitive tasks in college-aged students (Howard and

Marczinski, 2010; Marczinski et al., 2014; Boere et al., 2016). Galéra et al. (2016) reported a significant negative correlation between excess caffeine consumption during pregnancy and I.Q. in exposed children, supporting current guidelines not to exceed 200 mg caffeine per day. Thus, caffeine likely enhances cognition via its action on general arousal levels such as mitigating fatigue, and cognitive enhancement is most likely to be observed in fatigued individuals. Together, these findings suggest that the developing brain is uniquely sensitive to caffeine's effects through early adulthood, and fatigue in a developing child is an indicator for the need to rest and not an indication for need for caffeine administration.

Taurine's role in brain development and function

Taurine is a sulfur-containing amino acid with antioxidant properties (Kumari et al., 2013) that is found in high levels in the developing brain, as well as in the adult hippocampus (Shivaraj et al., 2012), cerebellum (Suarez et al., 2016), and hypothalamus (Camargo et al., 2015). Taurine supports proliferation of neural progenitor cells and synapse formation in brain regions required for long-term memory (Shivaraj et al., 2012). Taurine stimulates action potentials in GABAergic neurons and specifically targets the $GABA_A$ receptor (Jia et al., 2008). It can also count-balance the excitotoxic effects of glutamate (Oja et al., 2013). Interestingly, Salimaki et al. (2003) reported that a cumulative dose of 45 mmol/kg of taurine (i.p. injection) significantly decreased extracellular dopamine in the striatum of Wistar rats, with even lower levels on the day following treatment. There were no significant differences in the levels of dopamine metabolites, DOPAC and homovanillic acid, however. Taurine is also found in the inner ear, where it can increase survival of both glia and spinal ganglion neurons (Rak et al., 2014).

Disruptions in taurine homeostasis have been reported in numerous studies of neurological disorders, including epilepsy and autism (Fukuyama and Ochiai, 1982; Junyent et al., 2009; Kuwabara et al., 2013). Taurine levels increase in the brain after stress in an apparent compensatory mechanism (Huxtable, 1992). It has been observed that taurine is released from swollen cells as normal volume gets re-established. This change has been observed in patients with a traumatic brain injury, whereby taurine levels in the cerebral spinal fluid of patients increased to almost double from controls with taurine levels, returning back to control values within 3 days (Seki et al., 2005). Interestingly, the levels of taurine in the brain decreased significantly with age, which led to numerous studies investigating the potential neuroprotective effects of supplemental taurine in several different experimental models (Taranukhin et al., 2012; Ananchaipatana-Auitragoon et al., 2015; Zhang et al., 2017). McClellan and Lieberman (2011) reviewed the evidence for cognitive and physiological benefits and concluded that many human studies were improperly conducted, and the combined evidence from human and animal studies could not support marketing claims of enhanced mental or physical performance. Our findings using two doses of taurine in adolescent and young adult C57Bl/6J mice support those conclusions. Although we found some improvements in Morris water maze that were sex-dependent, we found deficits in novel object recognition at both doses tested, decreased sociality in male mice, and significant differences in alcohol consumption (Brown et al., 2015; Weimer et al., 2016, Weimer et al., 2107; Massie et al., 2017) (Table 1).

Insights from animal studies: What is the evidence for neuroprotection?

Since caffeine is often used in the treatment of apnea in newborn infants, the research supports the view that caffeine is neuroprotective as shown by anti-inflammatory effects in oxidative stress models in rodents. In one study, postnatal day 4 rats received phenobarbital (50 mg/kg) for 3 days with or without 10 mg/kg caffeine (Endesfelder et al., 2017a). The phenobarbital-induced adverse outcomes were partly antagonized by the caffeine. Other findings using similar models indicate that caffeine may be neuroprotective in the developing brain because caffeine has anti-inflammatory, anti-oxidant, and anti-apoptotic properties (Endesfelder et al., 2014; Endesfelder et al., 2017b; Kilicdag et al., 2014). This neuroprotection may also been seen in later behavioral testing (Kumral et al., 2010). However, this literature remains controversial, as other studies have found that caffeine at high doses may actually augment apoptosis, rendering caffeine as a drug that augments neurotoxicity that already occurs with anesthetic drug exposure (Cabrera et al., 2017). A recent review suggests that there is an urgent need to better understand the effects of caffeine on the developing brain using clinically relevant animal models so that the maximal safe dose for a preterm brain can be determined (Atik et al., 2017).

The evidence that caffeine confers neuroprotection may also be true for taurine. There is a consistent body of literature from animal studies supporting taurine supplementation in aged animals and animals dosed with known neurotoxicants; however, the data from studies using adolescent or young adult mice argue against routine supplementation at younger ages. Wistar rats treated with intracebroventricular streptozotocin (ICV-STZ) to mimic Alzheimer's disease showed less cognitive impairments on Morris water maze and in a passive avoidance test when treated with 60 or 120 mg/kg/day taurine (Reeta et al., 2017). Importantly, a control group that received 120 mg/kg/day without ICV-STZ showed no improvements or deficits in any test. The protective mechanism appears to be restoration of normal glutathione levels, consistent with taurine's antioxidant properties. Conversely, Ozan et al. (2012) reported an "antioxidative stress" when guinea pigs were treated with 300 mg/kg (i.p.), with higher levels of DNA damage and 3-nitrotyrosine levels in whole brain homogenates.

Others report unique or additional mechanisms of neuroprotection. Adedara et al. (2017) examined taurine's effectiveness against sodium fluoride toxicity. Doses of 100 or 200 mg/kg/day taurine in drinking water reduced lipid peroxidation and restored acetylcholinesterase activity in male Wistar rats, as well as restoring the activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase. Taurine supplementation in fluoride-treated rats also reduced deficits in negative geotaxis and restored normal locomotor activity, but taurine alone had no benefits. Lu et al. (2014) also reported restoration of normal acetylcholinesterase activity in addition to restoration of choline acetyltransferase activity in male Sprague-Dawley rats exposed to 15 mg/kg manganese chloride during adolescence and early adulthood. Rats treated simultaneously with 200 mg/kg/day (i.p. injection) of taurine performed similarly to control rats in Morris water maze, indicating protection from manganese neurotoxicity.

Jia et al. (2016) also reported restoration of SOD2 and catalase when treating prenatally stressed rats with 2,000 mg/kg/day taurine in drinking water from P21 to P30. There was no protective effect in rats treated with 200 mg/kg/day. The high taurine dose also reduced mitochondrial reactive oxygen species and significantly improved performance in Morris water maze compared with untreated stressed rats and those receiving 200 mg/kg/day taurine. The authors suggest the protective mechanism is activation of the Akt-CREB-PGCIα pathway. Timing appears to be a critical element to neuroprotection against ethanol-induced apoptosis of Purkinje cells in neonatal NMRI mice. Taranukhin et al. (2010) reported that injecting 1,000 mg/kg was sufficient to reduce apoptosis in P7 mice in a model of binge drinking, but not in P4 mice. Although these studies did not measure effects in adolescent animals, they are reported here to provide additional context regarding the differential effects of taurine over the lifespan.

Insights from animal studies: Behavioral effects in young and aged rodents

The value of taurine for neuroprotection extends to aged mice and these benefits are observable with behavioral testing. FVB/NJ mice were tested in a passive avoidance test using 2- and 16-month old animals. There was no difference between controls and those receiving supplemental taurine in drinking water (dose not provided); however, aged animals on taurine showed significantly better performance and retention (El Idrissi, 2008). The differences could be attributed to restoring normal levels of taurine in the brain, which decline significantly over the lifespan (Sturman et al., 1988; Banay-Schwartz et al., 1989). Suge et al. (2007) evaluated differences in C57BL/6 male mice treated with 0.12% taurine in drinking water before and after weaning and in mice treated chronically from birth to 24 weeks of age. The mice exposed for the longest period of time (P1 to 24 weeks) performed significantly worse on a visual discrimination acquisition task, compared with controls while those receiving taurine only after weaning performed better than controls.

Neuwirth et al. (2013) compared the effects of acute taurine (43 mg/kg s.c. injection) with chronic taurine supplementation (0.05% in drinking water from P28 to 6 months of age) in a test of auditory cued fear and context conditioning. All mice were male FVB/NJ with n = 4 per group, which is relatively small for behavioral experiments. Animals treated with acute taurine showed reduced fear, while chronically treated mice showed increased fear compared with controls. The authors also reported increased pain sensitivity in the chronically dosed animals, which is consistent with the findings of Serrano et al. (2002) in aged CD-1 male mice.

Santora et al. (2013) used adult male FVB/NJ mice (age not provided) treated for four weeks with 0.05% taurine in drinking water to examine effects on motor learning. Again, the group size was relatively small (n = 3 per group). Animals were tested on a rotarod after 7 days of training at 24 rpm. Test speeds increased from 5–44 rpm. Taurine-treated mice had significantly shorter latencies to fall at higher speeds and reduced motor learning compared with control mice. In our studies, we found no significant differences in latency to fall when testing male and female C57BL/6J mice treated with 0.12% taurine in drinking water from weaning to P60 when behavior testing began. However, we did find a similar difference in

motor learning, over 5 days of testing. In our tests, the rotarod accelerated from 1–20 rpm over 180 s with a total test time of 300 s (Weimer et al., 2014).

Since caffeine and taurine are co-ingested in humans, it is helpful that various animal studies have examined the effects of this drug combination on various behavioral measures. Kimura et al. (2009) examined the combined effects of taurine and caffeine on locomotor activity using male ddY mice (age not provided). Mice treated with 400 mg/kg taurine and 2 mg/kg caffeine (p.o.) showed significantly higher activity, compared with control mice and mice treated with caffeine alone. This effect was attenuated in mice co-treated with the nitric oxide inhibitor L-NAME, suggesting that the hyperactivity is regulated or modulated by nitric oxide release. Zhang et al. (2017) reported a dose effect for caffeine in locomotor activity using male Kunming mice (age not provided) and a dose range of 0, 1, 3, 10, 30, and 100 mg/kg (i.p.). Mice injected with 10 mg/kg showed the highest total activity, but high-dose mice (30 and 100 mg/kg) showed decreased distance travel, compared with controls. We found a significant sex * (?) treatment interaction when challenging our taurine-treated mice with caffeine. Caffeine-treated males showed an exaggerated response compared with caffeine-treated control males, consistent with Kimura et al. (2009). There was no difference between caffeine-treated control and taurine-treated females (Brown et al., 2015).

Numerous recent studies have examined the combination of energy drinks and alcohol consumption using different rodent models. These studies offer a controlled test of the acute effects of these combinations which are frequently ingested by human underage and young adult drinkers. Takahashi et al. (2015) modeled binge drinking, treating 8–9 week-old male Wistar rats with alcohol, a popular energy drink, or a combination of the two for 6 days. Rats given alcohol alone or alcohol + energy drinks showed impaired performance in novel object recognition. Rats given energy drinks alone had a lower discrimination index compared with controls, but the differences were not significant. There were similar findings in a social recognition test. These results suggest that taurine is not neuroprotective against the effects of alcohol. Of greatest concern for human health was the finding that rats treated with a combination of alcohol + energy drinks showed significantly greater preference for alcohol in a conditioned place preference test. A potential mechanism could be the additive effects of taurine and alcohol on dopamine release in the nucleus accumbens and stimulation of the brain’s reward circuitry, as demonstrated by Ericson et al. (2017) in a rat microdialysis experiment. Interestingly, we have found increased alcohol consumption in taurine-treated C57BL/6J mice, but only in females (Weimer et al., 2017).

A similar study to Takahashi’s (2015) was performed by Krahe et al. (2017) using P40 male and female Swiss mice. Mice receiving the combination of energy drinks plus alcohol had significantly higher locomotor activity, increased anxiety measured as less time in the central region of the locomotor chamber, and shorter latencies to fall off the rotarod. These findings again suggest that the taurine and caffeine in energy drinks is not protective against alcohol’s effects and instead exacerbate them. Genetic differences were explored by Ginsburg and Lamb (2008) who used 8-week-old male C57BL/6J and DBA/2J mice treated with ethanol, taurine, or a combination of the two. Doses ranged from 0.3 to 3 g/kg taurine and from 1 to 4.2g/kg of ethanol i.p.), with control animals receiving saline. Taurine ameliorated the ataxic effects of alcohol in C57BL/6J mice, but there was no beneficial effect seen in DBA/2J

mice. There were no beneficial effects in either mouse strain when assessing the righting reflex.

Unfortunately, there are serious deficiencies in many of the animal studies reported here, which limit their usefulness for risk assessment. They include:

- The use of only male animals
- Incomplete information regarding age
- Inconsistency in the route of administration
- Lack of dose-response data
- Not reporting or accounting for litter effects
- Small sample sizes for behavioral studies
- Limited endpoints (e.g., behavior without neurochemistry, single behavioral test, no gene expression data)

Summary

High consumption of energy drinks and caffeine among teenagers and young adults raises serious concerns about adverse effects on the brain, especially when stimulants are combined with alcohol consumption. We have identified important knowledge gaps in our understanding of the toxicity of these products acutely, chronically, and in mixtures. The literature also suggests that caffeine and/or taurine at the optimal dose and in the right circumstances might confer neuroprotection. Given the wide variety in human lifestyles and potential confounding in human studies, rodent animal models have great value in teasing out differential effects associated with consumption of taurine, caffeine, and alcohol alone and in combination. Animal models have also reproduced behavioral changes observed in human studies with reasonable accuracy and helped to identify potential adverse effects on the adolescent and young adult brain. An additional benefit of animal studies is their use at identifying genetic susceptibilities in metabolic pathways, which are critical to understanding the true risks of food additives in the general population. Considering the easy access to these products and inconsistent ingredient labeling, we strongly recommend ongoing research in both humans and animals to better inform risk assessors and regulators, with a renewed emphasis on collecting data from both males and females, and the use of standardized guidelines, such as ARRIVE (Kilkenny et al., 2010) for animal studies.

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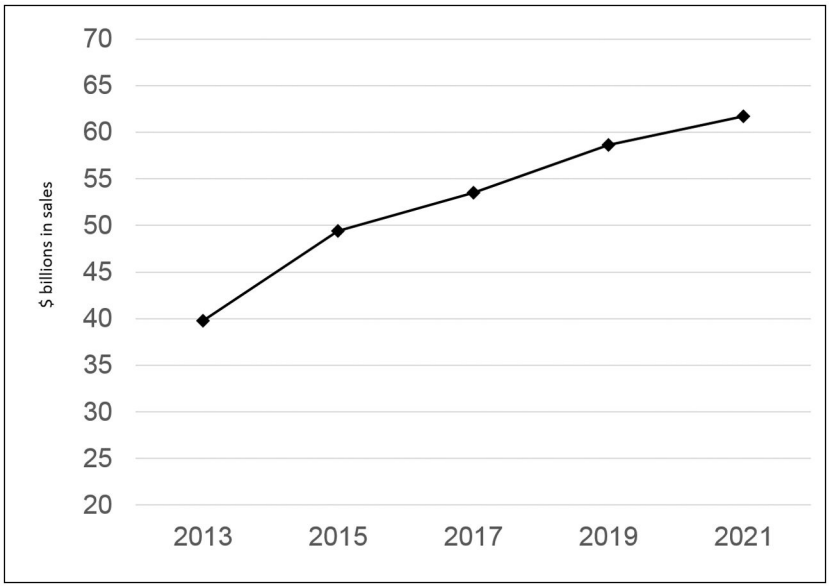

Fig. 1. Projected trends in energy drink consumption

Business forecasts indicate that the current popularity of energy drinks is not likely to subside in coming years. The global energy drink market is expected to top $60 billion within five years (Research and Markets 2015).

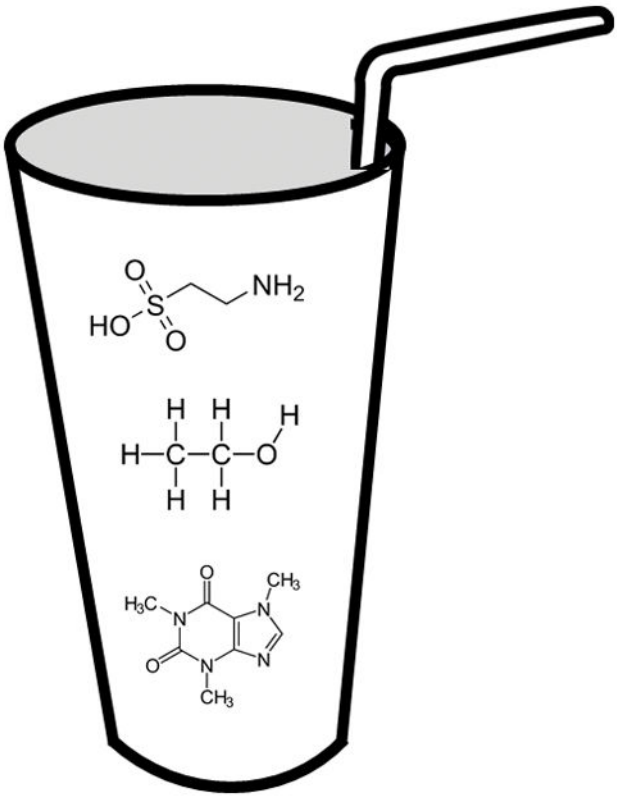

Fig. 2. A new definition of "mixed drink"

Energy drinks, which typically contain high concentrations of taurine and caffeine, are often co-ingested with alcohol. There is also data suggesting that those who consume taurine and caffeine may be at risk of higher alcohol consumption compared with those who do not.

Table 1

Summary of findings from studies of taurine in male and female C57Bl/6J mice

Reference	Dose	Route	Main effects of taurine
Brown et al. 2015	0.12% taurine from P28 to P60	Drinking water	↓ Novel object recognition by males and females ↓ Morris water maze performance by males ↑ Morris water maze performance by females ↑ locomotor activity during caffeine challenge by males
Weimer et al. 2016	0.12% taurine from P28 to P60	Drinking water	↓ cortical dopamine and HVA in males ↑ serotonin in hypothalamus of males and females
Weimer et al. 2017	0.06 and 0.12% taurine from P28 till the end of testing	Drinking water	No differences in anxiety in marble burying test ↓ sociality in males ↓ alcohol consumption in high-dose males ↑ alcohol consumption in low- and hi-dose females
Massie et al. 2017	0.06 and 0.12% taurine from P28 till the end of testing	Drinking water	↓ Novel object recognition by males and females No differences in Morris water maze hidden platform phases with platform present ↓ average distance to target in Reverse Probe trial (no platform) for males ↑ average distance to target in Reverse Probe trial for females