

Taurine and cardiac disease: state of the art and perspectives¹

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Abstract: Taurine is a nonessential amino acid that has received much attention. Two organs, the heart and the brain, are known to produce their own taurine, but in very limited quantities. It is for this reason that supplementation with this amino acid is necessary. Today, taurine is present in almost all energy drinks. A very vast literature reported beneficial effects of taurine in hepatic dysfunction, gastrointestinal injury, kidney diseases, diabetes, and cardiovascular diseases. Most of its effects were attributed to its modulation of Ca^{2+} homeostasis as well as to its antioxidant properties. In this review, we will focus on the current status of taurine modulation of the cardiovascular system and discuss future avenues for its use as a supplement therapy in a specific cardiovascular disease, namely hypertrophy, and heart failure.

Key words: taurine, hypertrophy, heart failure, hypertension, calcium, sodium.

Résumé : La taurine est un acide aminé non essentiel qui a reçu beaucoup d'attention. Deux organes, le cœur et le cerveau, sont connus pour produire leur propre taurine, mais en quantités très limitées. C'est la raison pour laquelle il est nécessaire de fournir une supplémentation pour cet acide aminé. Aujourd'hui, la taurine est présente dans presque toutes les boissons énergétiques. Un très grand ensemble de publications a rapporté les bienfaits de la taurine dans le dysfonctionnement hépatique, les lésions gastro-intestinales, l'insuffisance rénale, le diabète et les maladies cardiovasculaires. La plupart de ses effets ont été attribués à sa modulation de l'homéostasie du Ca^{2+} , ainsi qu'à ses propriétés antioxydantes. Dans cet article de synthèse, nous nous pencherons en particulier sur l'état actuel de la modulation du système cardiovasculaire par la taurine, et nous discuterons des avenues futures pour son utilisation en tant que traitement de supplémentation dans une maladie cardiovasculaire spécifique : l'hypertrophie et l'insuffisance cardiaque. [Traduit par la Rédaction]

Mots-clés : taurine, hypertrophie, insuffisance cardiaque, hypertension, calcium, sodium.

Introduction

Taurine is a nonessential amino acid that has received much attention (Azuma et al. 1992). Two organs, the heart and the brain, are known to produce their own taurine, but in very limited quantities (Schaffer and Kim 2018). In humans, taurine can be found at high concentrations in the plasma (near 50–150 $\mu\text{mol/L}$) (Yamamoto 1996; Trautwein and Hayes 1990), bile, and saliva as well as being very abundant in heart tissue (6 $\mu\text{mol/L}$). The plasma concentration of taurine is known to decrease during human development and aging (Fukuda et al. 1984). This indicates its important role in human development and the dependence of humans on exogenous taurine intake. Although meat is very rich in taurine, its consumption in humans only supplies near 400 mg/day of the amino acid. However, the daily need for the body is close to 3000 mg (Shao and Hathcock 2008), hence the need to recommend an exogenous taurine supplement. The presence of taurine at high concentrations in energy drinks and its use by young people and athletes have renewed the need for better understanding of the beneficial and nonbeneficial effects of taurine as well as its mechanisms of action. One may wonder what is the energizer in these drinks: taurine, caffeine, or sugar or all of them together? The high consumption of taurine-containing energy drinks also renewed the interest in the possible side effects and toxicity of

taurine. However, it does not seem that elevated concentrations of taurine have side effects, at least in the heart, probably due to its elimination in the urine and to the saturable effect of the taurine transporter (Sved et al. 2007). Intracellular taurine concentration is known to be very stable unless there is an osmotic, chemical, or mechanical insult to the cell that decreases the content of the cell by the release of taurine to reestablish the osmotic equilibrium (Sturman et al. 1975). According to what is known about the beneficial effects of taurine and its distribution in the body as well as its chemistry, this osmolyte can be one of the energizers. Also, its main role in these energy drinks is probably to protect the body from high caffeine consumption. The beneficial effects of taurine have been demonstrated in many diseases such as decreased serum low-density lipoprotein, decreased progression of atherosclerosis, and protection against ischemia-reperfusion injury of the myocardium (Schaffer and Kim 2018; Xu et al. 2008; Abebe and Mozaffari 2011; Lambert et al. 2015; De Luca et al. 2015). Besides, the beneficial effects of taurine in diabetic cardiovascular complications are well documented (Franconi et al. 1995, 2004; Inam-U-Allah et al. 2018; Lewis et al. 2014; Manna et al. 2013; Tappia et al. 2011, 2013, 2018; Turan 2010). It has been suggested that taurine increases the high-energy phosphate content of the heart (Schaffer and Kim 2018; Schaffer et al. 2016). Also,

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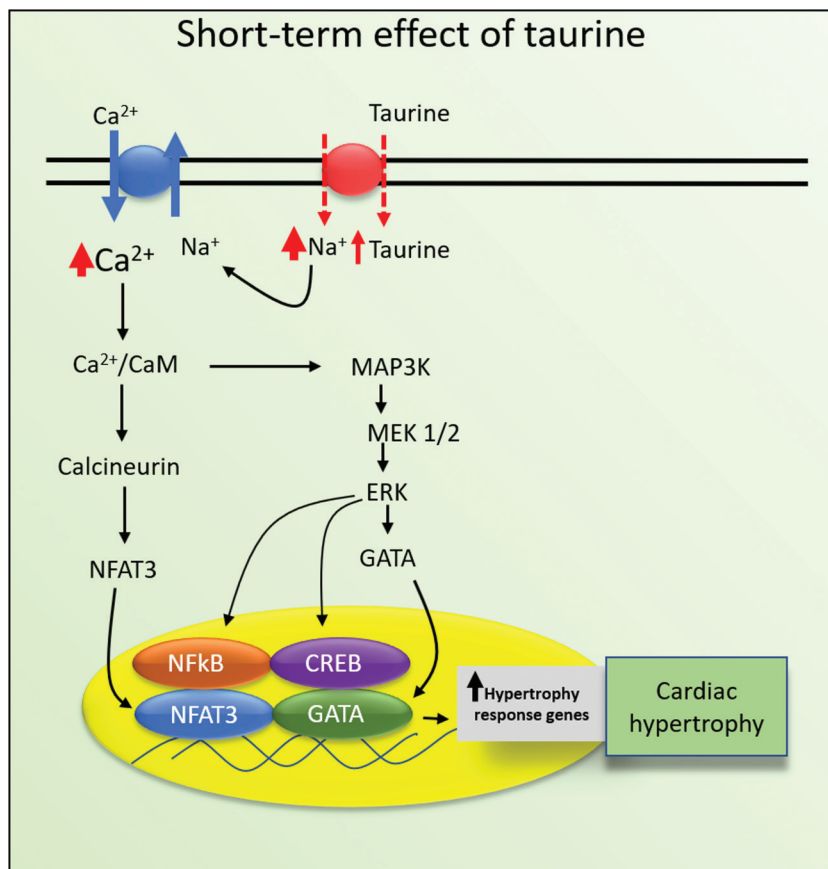
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Fig. 1. Schematic summarizing the short-term effects of taurine on intracellular Na^+ and Ca^{2+} as well as on the proposed indirect and direct Ca^{2+} -dependent second messengers that could be involved in taurine's effect on cardiac hypertrophy. $\text{Ca}^{2+}/\text{CaM}$, calcium-calmodulin; NFAT3, nuclear factor of activated T-cells; MAP3K, mitogen-activated protein kinase kinase kinase; MEK1/2, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; GATA, transcription factor that binds the consensus DNA sequence (T/A)GATA(A/G); NF κ B, nuclear factor-kappa B; CREB, C-AMP response element-binding protein. [Colour online.]



low plasma levels of taurine have been reported in patients with diabetic cardiomyopathy (Franconi et al. 1995, 2004). It has also been reported by Lewis et al. (2014) that the increase in metabolic stress induces a decrease in myocardial taurine. Such cardiac metabolic stress leads to the development of necrosis, hypertrophy, and heart failure. It has also been demonstrated in vitro that taurine antagonizes the effect of Ang II on the hypertrophy of rat cardiomyocytes (Takahashi et al. 1997; Azuma et al. 2000; Mahmoud 2017). Most of the beneficial effects of taurine on cardiovascular diseases, particularly cardiac hypertrophy, were suggested to be due to its action on reactive oxygen species (ROS) as well as on intracellular Na^+ and Ca^{2+} overloads (Bkaily et al. 1996, 1997, 1998; Koyama et al. 1992b). Indeed, taurine is co-transported with Na^+ within the cell via a unidirectional membrane transporter, which directly leads to an intracellular Na^+ overload and indirectly promotes an intracellular Ca^{2+} overload via the stimulation of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (Fig. 1) (Bkaily et al. 1996, 1997, 1998). Such intracellular Na^+ and Ca^{2+} overloads were reported to take place during the development of necrosis, hypertrophy (Fig. 1), and heart failure (Bkaily et al. 2015; Chahine et al. 2005). However, it is not known whether these cardiac pathologies can be prevented by taurine supplementation. Although a large literature in the field reported the antioxidant effect of taurine, still there is no information on how this takes place. This extensive literature gives the impression that all is done for taurine, which does not seem to be the case. Furthermore, it makes it difficult to make a conclusion about any of the reported beneficial and possible toxic effects of taurine, particularly at the cardiovascular

level. In the present work, we tried to make a concise review of what is already known and to propose new avenues for better understanding this "very essential" nonessential amino acid (Ripps and Shen 2012) and its potential future use for the treatment of cardiovascular diseases, particularly those still awaiting treatments such as heart failure and hereditary cardiovascular diseases.

Taurine as an osmolyte

Osmolytes are classified into two categories: inorganic such as ions and organic such as essential and nonessential amino acids including taurine (Ripps and Shen 2012; Pasantes-Morales et al. 1992; Pasantes-Morales 2017). Unlike charged osmolytes, taurine is a neutral zwitterion (Pasantes-Morales 2017; Schaffer and Kim 2018) and consequently does not contribute to membrane surface charge. Also, taurine is one of the most abundant organic osmolytes compared to glycine, alanine, and glutamate (Pasantes-Morales et al. 1992; Bkaily et al. 1998). Upon changes in inorganic osmolyte concentrations, taurine is released by the cells to compensate for any decrease in extracellular osmolarity (Pasantes-Morales 2017). Consequently, in several studies using different cell types, taurine prevented the increase in extracellular inorganic osmolyte-induced cell remodeling (Nakagawa 1990). Therefore, several studies in the literature suggested that taurine can be an efficient osmoregulator (Oja and Saransaari 1992; Pasantes-Morales 2017; Schaffer and Kim 2018). Studies have also shown that an increase in cell volume induces a release of intracellular taurine (Koyama

Fig. 2. Short-term treatment of 10 day old cultured chick heart cells with taurine increased intracellular Na^+ (mainly at the nuclear level). However, long-term treatment with taurine decreased intracellular Na^+ (mainly at the cytosolic level). n is the number of different experiments, and the results are expressed as mean \pm SEM. * $p < 0.05$. Modified from Bkaily et al. (1997). [Colour online.]

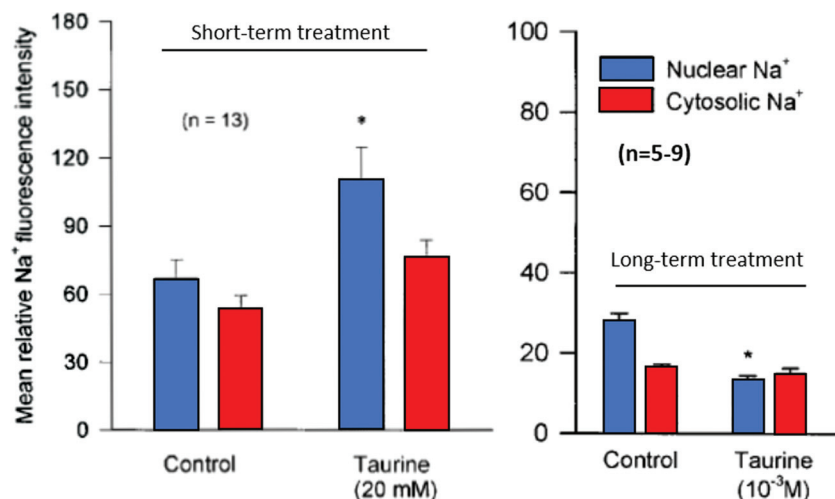
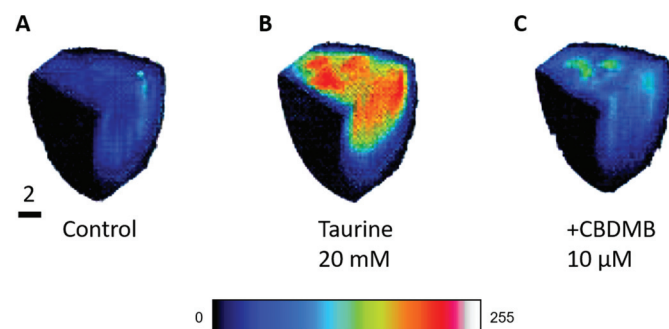


Fig. 3. Steady-state fluorescence image showing the level and distribution of intracellular Ca^{2+} in the (A) absence of taurine as well as in the (B) presence of 20 mmol/L taurine and (C) taurine plus CBDMB ($\text{Na}^+/\text{Ca}^{2+}$ exchanger blocker) in 10 day old embryonic chick heart cells. The pseudocolor bar represents the fluorescence intensity ranging from zero (absence of fluorescence, black) to 255 (maximum fluorescence, white). Modified from Bkaily et al. (1998).



et al. 1992a; Pasantes-Morales and Schousboe 1989; Sanchez-Olea and Pasantes-Morales 1992; Pasantes-Morales 2017). Thus, hyposmolarity would induce the extracellular release of taurine, whereas hyperosmolarity would increase intracellular taurine.

Taurine and intracellular sodium and calcium homeostasis

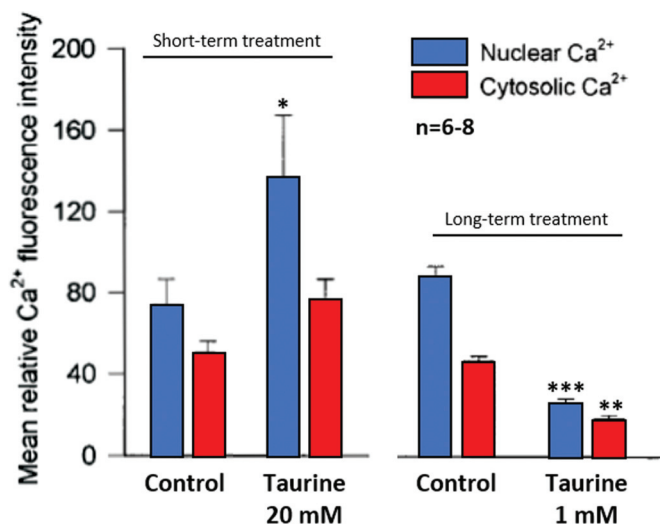
Taurine influx is known to take place via a taurine- Na^+ co-transporter (Bkaily et al. 1998). Thus, the co-transport of Na^+ with short-term treatment with taurine would naturally induce an increase in total intracellular sodium, more particularly at the nuclear level (Figs. 1 and 2). Early studies clearly showed that the short-term treatment with taurine induces a positive inotropic effect and an increase in intracellular Ca^{2+} level in the heart (Figs. 3 and 4) and vascular smooth muscle cells (Bkaily et al. 1996, 1997). This increase in Ca^{2+} was reported to be due to Ca^{2+} influx via the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, as shown in Fig. 3 (Bkaily et al. 1997). The Ca^{2+} influx is due, at least in part, to an increase in intracellular sodium resulting from taurine and Na^+ influx via the taurine- Na^+ co-transporter (Bkaily et al. 1996, 1997, 1998) (Fig. 1). The short-term exposure to taurine was found to increase intracellular Na^+ (Fig. 2) and Ca^{2+} (Fig. 4) levels. The increase in intracellular Ca^{2+} and Na^+ by short-term treatment with taurine was mainly at

the nuclear levels (Figs. 2 and 4) (Bkaily et al. 1996, 1997). Curiously, contrary to short-term treatment, long-term treatment with taurine decreased intracellular Na^+ and Ca^{2+} (Figs. 2 and 4). Furthermore, contrary to short-term treatment, the decrease of total intracellular Na^+ and Ca^{2+} was mainly at the cytosolic level (Figs. 2 and 4). The increase or decrease of intracellular Na^+ and Ca^{2+} respectively by short- and long-term exposure to taurine was suggested to be due to modulation of the minimum Na^+ and Ca^{2+} buffering capacity of the nucleus (Bkaily et al. 1997) as well as, at least in part, to the stimulation of Ca^{2+} efflux via the calcium pump (Michalk et al. 1987; Lima et al. 1992). It is also possible that, since the Ca^{2+} pump capacity is limited, the increase in cytosolic Ca^{2+} by short-term exposure to taurine cannot be evacuated by the plasma membrane and sarcoplasmic reticulum Ca^{2+} pumps. However, long-term exposure to taurine would mask this increase in cytosolic Ca^{2+} due to sufficient time for the Ca^{2+} pump (or increase in Ca^{2+} pump density) to evacuate the Ca^{2+} overload. This is worth being verified in the future. According to our recent work in the field, it is also possible that the decrease in intracellular Ca^{2+} by the long-term taurine treatment could be due, in part, to intracellular taurine overload-induced $\text{Na}^+/\text{Ca}^{2+}$ exchanger reverse mode. The absence of effect of long-term treatment with taurine on cytosolic Na^+ (Fig. 2) could be due to a cytosolic taurine overload-induced reversal of nuclear membrane $\text{Na}^+/\text{Ca}^{2+}$ exchanger, which promotes Na^+ influx into the nucleus. This should also be verified in the future. It is reported that taurine may have a cardiac anti-hypertrophic effect due to its increase of intracellular Ca^{2+} , which promotes stronger contraction. This could be true for its short-term action. However, its long-term effect is supposed to be to decrease Ca^{2+} overload. In this case, one expects a decrease in intracellular Ca^{2+} , which is supposed to further decrease the contractility of the hypertrophic heart, which does not seem to be the case. This awaits to be explained.

Modulation of cardiac ionic transport by taurine

In the late 1980s and early 1990s, the vast literature dealing with taurine was focused on understanding its effect on ionic transport to explain how taurine induces an increase in intracellular Ca^{2+} and, consequently, a positive cardiac inotropic effect (Bkaily et al. 1996, 1997, 1998; Sperelakis et al. 1996; Satoh 1996; Franconi et al. 1989; Sperelakis et al. 1989; Endoh et al. 1989; Lombardini and Liebowitz 1989; Schaffer and Azuma 1992; Sperelakis et al. 1992; Takahashi et al. 1992). Most of these studies used electrophysiological and intracellular Ca^{2+} measurements and were done with

Fig. 4. Effect of short- and long-term treatments with taurine on resting steady-state level of cytosolic and nuclear free Ca^{2+} in 10 day old embryonic chick heart cells using Fluo-3 coupled to quantitative 3D confocal microscopy. The left panel shows an increase in intracellular Ca^{2+} by 20 mmol/L taurine that takes place mainly at the nuclear level. The right panel shows a decrease in cytosolic and nuclear Ca^{2+} levels by long-term treatment with 1 mmol/L taurine. n is the number of different experiments, and the results are expressed as mean \pm SEM. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Modified from Bkaily et al. (1997). [Colour online.]

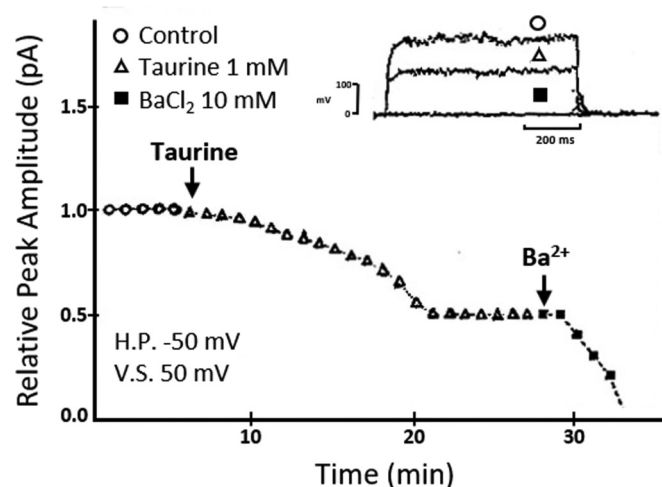


short exposure to taurine. Short-term exposure to taurine was shown to modulate all cardiac and vascular ionic channels. For example, taurine was found to stimulate the slow Na^+ channels (fast component) in early embryonic chick heart cells as well as the T-type Ca^{2+} current (Table 1) (Bkaily et al. 1996). However, taurine inhibited the tetrodotoxin-sensitive fast Na^+ channels, the L-type Ca^{2+} channels, and the delayed outward K^+ channels (Bkaily et al. 1996) (Table 1). All of these effects were accompanied by an increase in intracellular Ca^{2+} (Bkaily et al. 1996). The depressing effect of taurine on fast I_{Na} , L-type I_{Ca} , and I_{K1} (Table 1; Fig. 5) (Bkaily et al. 1996; Sperelakis et al. 1992) cannot explain the increase in intracellular Ca^{2+} and the positive inotropic effect induced by taurine in heart cells. However, it may explain, at least in part, taurine's anti-arrhythmic effect (Lake 1992; Sperelakis et al. 1992). Thus, most studies, including ours, agree that the increase in intracellular Ca^{2+} and the positive inotropic effect induced by short-term taurine exposure could be, as previously mentioned, due to taurine-induced intracellular Na^+ overload, which stimulates the activity of the $\text{Na}^+-\text{Ca}^{2+}$ exchanger and consequently increases in influx of Ca^{2+} through this exchanger (Figs. 1–4) (Bkaily et al. 1996, 1997, 1998). In the mid-1990s, our group reported for the first time that the effect of taurine on intracellular Ca^{2+} and Na^+ homeostasis depends on the time of exposure to this amino acid (Figs. 2 and 4) (Bkaily et al. 1997). As mentioned previously, short-term exposure increased intracellular Na^+ and Ca^{2+} , but long-term exposure decreased both cytosolic and nuclear Ca^{2+} in the absence of changes in intracellular sodium (Bkaily et al. 1997). Since most studies dealing with taurine prevention of cardiovascular pathologies were done with long-term taurine treatments (Negoro and Hara 1992; Bkaily et al. 1998; Ripps and Shen 2012; Schaffer and Kim 2018), the decrease in cytosolic and nuclear Ca^{2+} induced by these treatments may explain the beneficial effects of taurine in these pathologies. More studies should be done to better understand the long-term beneficial effects of taurine in the cardiovascular system.

Table 1. Summary of the actions of taurine on ionic currents of heart cells (modified from Bkaily et al. 1996).

L-type I_{Ca}	Decrease
T-type I_{Ca}	Increase
Fast I_{Na}	Decrease/increase
Slow I_{Na}	Decrease
$I_{\text{Kr/Ks}}$	Decrease
$I_{\text{Na/Ca}}$	No effect

Fig. 5. Effect of short-term exposure to taurine on the inward rectifier K^+ current of vascular smooth muscle cells from rabbit aortas. Whole-cell recordings showing a time-course decrease of K^+ current by 1 mmol/L taurine and the corresponding current traces. The effect of taurine reached a steady-state level after 15 min of exposure to 1 mmol/L taurine. The remaining current was blocked by Ba^{2+} . H.P. is holding potential and V.S. is voltage step to. The bars in the current traces are in ms and mV, respectively. (Modified from Sperelakis et al. 1992). [Colour online.]



Taurine deficiency

Although in humans, taurine is mainly synthesized in small quantities by the heart and brain (Schaffer and Kim 2018), its primary source without any doubt is from the diet such as seafood, eggs, and meat (Wójcik et al. 2010; Abebe and Mozaffari 2011; Ames 2018; Dale et al. 2019). Thus, a lack of taurine consumption may contribute to taurine deficiency. Taurine deficiency was reported to induce several diseases in animal models including retinal degeneration (Negoro and Hara 1992; Ripps and Shen 2012), dilated cardiomyopathy (Lake 1992; Pion et al. 1992; Novotny and Hogan 1992; Schaffer and Kim 2018), deficiency of immune functions (Negoro and Hara 1992; Lake et al. 1992), hypertension (Waldron et al. 2018; Schaffer and Kim 2018), and aging (Schaffer et al. 2015; Ames 2018). For example, in humans, higher incidences of development of hypertension (Xu et al. 2008; Waldron et al. 2018) as well as cardiac diseases (Azuma 1989; Xu et al. 2008) were reported in populations having low-taurine diets (Yamori et al. 2004; Sagara et al. 2015; Schaffer and Kim 2018). Recently, taurine transporter (Taut) knockout mice were used to understand the effects of taurine tissue depletion. This knockout animal model develops multiorgan dysfunction (Han and Chesney 2013; Jong et al. 2017). The group of Schaffer and colleagues extensively used this model and showed that taurine deficiency leads to cardiomyopathy and cardiac abnormalities (Ito et al. 2008, 2010; Ramila et al. 2015). This was attributed to tissue taurine deficiency-induced mitochondrial and endoplasmic reticulum dysfunction (Jong et al. 2017), thus impairing cardiac energy metabolism (Schaffer et al. 2016) and Ca^{2+} -ATPase activity (Ramila et al. 2015).

However, such a complete depletion of tissue taurine has never been reported in humans. All of the studies in the Taut knockout mice demonstrated how taurine supplementation and transport are vital for cell functions and survival. It has to be taken into consideration that circulating and tissue taurine deficiencies will inevitably affect osmolarity, thus affecting cell volume and membrane stability. These two aspects are sufficient to promote cell dysfunction. Finally, depletion of tissue taurine can be closely related to activation of the volume-regulated anion channel (VRAC), which mediates taurine efflux (Zhou et al. 2016). Tissue taurine deficiency can also be due to (1) extracellular hypotonicity, (2) a decrease in taurine synthesis, (3) a decrease in the density of the taurine transporter, and (4) an increase in the activity of VRAC. More studies should be done to understand better how a deficiency in taurine supplementation and transporter contribute to cardiac and vascular failures.

Taurine and reactive oxygen species (ROS)

The antioxidant activities of taurine are detailed by several recent reviews in the field (Ripps and Shen 2012; Burg et al. 2007; Lambert et al. 2015; Schaffer and Kim 2018; Ames 2018). All of the literature in the field of taurine agrees that one of the most important beneficial effects of taurine is its antioxidant property (Banks et al. 1992; Koyama et al. 1992b; Xu et al. 2008; Ripps and Shen 2012; Schaffer et al. 2015; Schaffer and Kim 2018; Ames 2018; Colovic et al. 2018; Rosic et al. 2018). However, most of these studies did not show a direct effect of taurine on oxidants. For example, taurine was shown to be unable to directly chelate certain ROS molecules such as superoxide anions (Aruoma et al. 1988; Lambert et al. 2015). They mostly attributed to taurine a function as an anti-oxidant but not as an anti-oxidant per se. The anti-oxidant-like effect of taurine was reported in many cell types and in many conditions that induce oxidative stress (Banks et al. 1992; Koyama et al. 1992b; Schaffer and Kim 2018 and references within). These anti-oxidant-like effects of taurine were mainly attributed to its mitochondrial protective effect, thus preventing mitochondrial ROS generation. However, its anti-oxidant-like effect was demonstrated in erythrocytes, which do not possess mitochondria. Thus, the mechanism behind the anti-oxidant effect of taurine is still to be determined.

Conclusion and future directions

According to the literature in the field, we can assume that the effect of short- and long-term use of taurine will be via its action as an osmoregulatory organic osmolyte. This will protect the cell from swelling and (or) shrinking. At short-term use, it will contribute to caffeine-induced intracellular Ca^{2+} release by its indirect promotion of Ca^{2+} influx through the Na^+ - Ca^{2+} exchanger. At long term, it would protect the cell from caffeine-induced Ca^{2+} overload. These opposite effects of short- and long-term exposure to taurine still await to be elucidated. In addition, it is possible that one of the long-term effects of taurine could be mediated via its chelation of intracellular Ca^{2+} (Lin et al. 1988) due to its high affinity to calcium. This may explain its membrane-stabilizing effect due to its high binding to extracellular Ca^{2+} , thus increasing the extracellular positive surface charge. The latter would stabilize not only lipid organization but also membrane proteins. Although an extensive literature in the field reported the anti-oxidant effect of taurine, there is still no information about the mechanism involved. The question is whether taurine can be considered as an endogenous anti-oxidant in the heart as well as an exogenous anti-oxidant in other organs with poor taurine content. Besides, one can wonder that if taurine is an endogenous anti-oxidant, could its effect be considered complimentary or additive to other endogenous intracellular anti-oxidants? Several indirect and few direct studies on the short- and long-term effects of taurine under normal physiological and pathological condi-

tions showed opposing results concerning the regulation of intracellular Na^+ and Ca^{2+} homeostasis by taurine. Some work in the field has shown that taurine induces, in certain conditions, an increase in intracellular Ca^{2+} (Sperelakis et al. 1992; Takahashi et al. 1992; Palmi et al. 1996; Bkaily et al. 1996; Cuttitta et al. 2013; Waluk et al. 2013) and in other conditions, a decrease in intracellular Ca^{2+} (Bkaily et al. 1996; Ghosh et al. 2009; Abebe and Mozaffari 2011; Wang et al. 2018). This controversy in the literature regarding the effect of taurine on Ca^{2+} homeostasis may be due to the duration of treatment (short versus long term) with taurine as well as the presence or absence of cardiac pathology (Bkaily et al. 1997). Moreover, this phenomenon can also be influenced by gender and age (Ames 2018). This remains to be elucidated. As previously mentioned, taurine is reported to be an anti-oxidant. However, this has never been proven. Thus, this aspect of taurine should be challenged in the future by demonstrating its direct anti-oxidant properties if there are any. In addition, since most studies reporting an anti-oxidant-like effect of taurine were done in conditions that mimic cardiac pathologies such as Ang II-induced hypertrophy (Takahashi et al. 1997; Azuma et al. 2000; Schaffer et al. 2000; Xu et al. 2008), the question is oes taurine have an anti-oxidant-like effect in nonpathological conditions? Hence, as it stands, according to the current literature in the field, the effect of taurine on ROS seems to be indirect and depends on the type of pathology under study. This effect can also be due, at least in part, to a taurine long-term treatment-induced decrease in intracellular Ca^{2+} overload, which may prevent mitochondrial Ca^{2+} overload and the consequent mitochondrial ROS generation. Finally, ROS generation by cardio- and vasoactive factors is well documented. However, how short- or long-term taurine treatments would affect ROS generation is still a mystery.

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