ACTA PHYSIOLOGICA

Acta Physiol 2015, **213**, 191–212

REVIEW

Physiological role of taurine – from organism to organelle

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Received 19 June 2014, revision requested 1 August 2014, accepted 13 August 2014

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Abstract

Taurine is often referred to as a semi-essential amino acid as newborn mammals have a limited ability to synthesize taurine and have to rely on dietary supply. Taurine is not thought to be incorporated into proteins as no aminoacyl tRNA synthetase has yet been identified and is not oxidized in mammalian cells. However, taurine contributes significantly to the cellular pool of organic osmolytes and has accordingly been acknowledged for its role in cell volume restoration following osmotic perturbation. This review describes taurine homeostasis in cells and organelles with emphasis on taurine biophysics/membrane dynamics, regulation of transport proteins involved in active taurine uptake and passive taurine release as well as physiological processes, for example, development, lung function, mitochondrial function, antioxidative defence and apoptosis which seem to be affected by a shift in the expression of the taurine transporters and/or the cellular taurine content.

Keywords apoptosis, cell volume regulation, hypoxia, lung function, membrane dynamics, mitochondrial function.

Taurine – background

Taurine, originally isolated from the bile acid of the ox (*bos taurus*), accounts for approx. 0.1% of the total body weight (Huxtable 1992). In mammals, the prevailing total taurine pool is a balance between (i) synthesis from methionine/cysteine, (ii) absorption from food in the intestine/reabsorption from the urine in the kidney and (iii) excretion as bile salt (taurocholate) and unconjugated taurine in urine via the kidney. In contrast to human adults who synthesize taurine in the liver and to some extend in the central nerve system (CNS), newborn mammals are unable to synthesize sufficient amounts of taurine and therefore rely on dietary supply. Hence, taurine is often referred to as a semi-essential amino acid. Mice lacking the ability to accumulate taurine in cells, that is taurine transporter (TauT) knockout mice exhibit a reduced exercise capacity, changes in receptor expression and neural activity, loss of retinal photoreceptor function, reduced responsiveness to nociceptive stimulation (Lotsch *et al.* 2014), degeneration of their inner ear, alteration of renal development and function, unspecific hepatitis/liver fibrosis and cardiomyopathy (Ito *et al.* 2010, Han & Chesney 2013) as well as reduced T-cell memory generation (Kaesler *et al.* 2012) and blunted apoptosis in erythrocytes (Lang *et al.* 2003). Besides being involved in bile acid conjugation taurine is often acknowledged for its contribution to the intracellular pool of organic osmolytes, that is a regulator of cell volume, as well as its membrane stabilizing, anti-oxidative, anti-inflammatory and anti-apoptotic effects (Lang *et al.* 2003, Schuller-Levis & Park 2003,

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Lambert 2004, Lambert *et al.* 2008). In a human population, we find individuals that consume taurine lush food (meat and fish based diet) and a fair amount of taurine containing soft drinks as well as vegans that rely on plant diet, which is almost taurine deficient. The question we ask is whether high or low taurine intake will actually affect total body pool/cellular taurine levels and hence physiological processes.

Taurine biophysics

Taurine, β-amino ethane sulphonic acid is in the strict sense not an amino acid, as it lacks the pivotal and less acidic carboxyl group. The acidity of taurine makes the compound also completely zwitterionic over the physiological pH range, which is in contrast to most carboxylic amino acids that are unionized over this range (Huxtable 1992). This zwitterionic nature of taurine gives it high water solubility and low lipophilicity, explaining its impermeability of biological membranes. Due to this impermeability of the membrane, extraordinarily high concentration gradients over membranes can be found in, for example, the retina and Ehrlich ascites tumour cells (EATC), where a cellular to extracellular gradient of 400 : 1 is maintained (Hoffmann & Lambert 1983, Pasantes-Morales *et al.* 1986). The zwitterionic status of taurine, resulting in a high dipole nature, is likely also to account for its many fundamental biological roles such as interaction with cations such as Ca^{2+}, membrane modulatory actions and conjugation with bile acids.

Taurine is often referred to as an amino acid and small polypeptides have been identified which contain taurine (Marnela *et al.* 1984). This incorporation remains, however, a mystery as no aminoacyl tRNA synthetase has been recognized as identifying taurine and capable of incorporating it into a tRNA (Lahdesmaki 1987). In contrast, studies have indicated that taurine instead plays a central role in post-translational modifications of mitochondrial tRNAs, that is, taurine is involved in translation, when a single tRNA can decode two codons through the differences at the third position, so that a pyrimidine is replaced by another pyrimidine or a purine with another purine (Scheper *et al.* 2007). This concept is termed as 'wobble', and an example is the tRNA containing anticodon UAA can decode both codons UUA and UUG (for leucine). Evidence indicates that first base of the anticodon (pairing in antiparallel fashion with the wobble base) of mitochondrial $tRNA^{Leu}$ is post-transcriptionally modified with taurine. Mutational studies in the tRNA indicate that the taurine modification at the 'wobble' uridine in mitochondrial $tRNA^{Leu}$ has a crucial role for translation, probably stabilizing the wobble base pairing making it possible to decode the codons (Scheper *et al.* 2007).

Taurine homeostasis in the body

Taurine homeostasis at the organism level is controlled by multiple layers of regulation and can essentially be divided into absorption, distribution, excretion and synthesis. The nutritional need for taurine in man is met partly by intestinal uptake and partly by biosynthesis, primarily in the liver (Huxtable 1992).

Taurine absorption

Taurine movement across the brush-border membrane of the mammalian small intestine is mediated via the Na^+- and Cl^--dependent, high-affinity, low-capacity transporter TauT (SLC6A6) and the H^+-coupled, pH-dependent, Na^+- and Cl^--independent, low-affinity, high-capacity transporter PAT1 (SLC36A1) (Anderson *et al.* 2009) (see below). The brush-border-mediated taurine uptake was generally believed to be non-regulated; however, data indicate that inflammation may upregulate the transport (Mochizuki *et al.* 2004) and that type 2 diabetes decrease intestinal taurine absorption (Merheb *et al.* 2007).

Taurine distribution

Once the gut has absorbed taurine, it is released into the blood stream presumably using a non-saturable pathway that has not yet been characterized (Roig-Perez *et al.* 2005) resulting in a plasma concentration of approx. 10–100 μM (Huxtable 1992). In the blood stream, taurine is distributed to tissues and cells where it is once again taken up by the TauT or PAT1 transporters. The main uptake is through TauT, as PAT1-mediated transport is not able to compensate to a large degree in the TauT knockout mice where taurine content is reduced by more than 90% in some tissues. The taurine content of tissues varies from 5 to 50 mM (Jacobsen & Smith 1968), with the highest concentration often seen in metabolic active tissues (Wright *et al.* 1986). Skeletal muscle contains the largest pool of taurine in the body, accounting for more than 70% of total body taurine content (Huxtable 1992).

Taurine excretion

Taurine cannot be metabolized by mammals as they lack the enzymes needed for taurine break down. As such, taurine is either excreted by the kidney through urine or conjugated to bile acids which are ultimately

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excreted in faeces. Total body taurine content seems to be regulated rather stringent as cats fed a diet supplemented with high levels of taurine within days will see an upregulation of taurine excretion in the urine (Glass *et al.* 1992). Furthermore, only prolonged increases in taurine intake or taurine depletion seem to cause marked change in taurine plasma content (Trautwein & Hayes 1995). Urinary taurine content has been suggested as a possible marker of dietary seafood intake (Yamori *et al.* 1994, Mori *et al.* 2010). Interestingly, a high taurine intake also increases faecal bile acid excretion (Nishimura *et al.* 2003).

Taurine synthesis

Taurine can be synthesized from cysteine via the sequential actions of cysteine dioxygenase (CDO) and cysteinesulfinate decarboxylase (CSAD), which give rise to cysteinesulfinate and hypotaurine, respectively, followed by oxidation to taurine via an uncertain mechanism (Stipanuk *et al.* 2002). A minor synthesis pathway for taurine is via the breakdown of coenzyme A, resulting in the production of cysteamine, that can be oxidized to hypotaurine by the enzyme cysteamine dioxygenase (ADO; Dominy *et al.* 2007). The liver is the organ mainly responsible for maintaining taurine levels in the organism (Stipanuk 2004), and its capacity for taurine synthesis can change accordingly with regard to dietary intake of cysteine, as high availability of cysteine increase hepatic taurine synthesis. However, a plethora of other tissues, if not all, is also able to synthesize taurine to some extent, and taurine synthesis has been demonstrated not only in liver, but also in brain, lungs, skeletal muscle (Stipanuk *et al.* 2002), adipose tissue (Ueki & Stipanuk 2009) and mammary glands (Ueki & Stipanuk 2007).

Taurine intake

There is great variation in the amount of taurine present in food, with taurine levels ranging from <1 μmol per 100 g wet weight (fruits, plants, vegetables, nuts and legumes) to around 20 μmol per 100 mL (cow milk), 40 μmol per 100 mL (human breast milk), up to 300–500 μmol per 100 g wet weight (beef and pork) to as high as 1000–6000 μmol per 100 g wet weight (dark poultry meat, fish and shellfish; Laidlaw *et al.* 1990, Sturman 1993). It has been estimated that the daily intake of taurine in omnivores is 1000–1500 μmol (125–188 mg) (Laidlaw *et al.* 1990). The estimate of taurine intake in the general population is hindered by the lack of updated food tables, and thus, these values should be considered provisory. In recent years, the intake of energy drinks with a high content of taurine has increased (Reissig *et al.* 2009), with each serving of a taurine containing energy drink (250 mL) usually containing 1 g (8000 μmol) of taurine. Thus, for some people, the estimated intake of taurine may be a magnitude higher than what was estimated previously (Laidlaw *et al.* 1990). For others, their daily taurine intake may be virtually zero, as estimated and measured for a vegan diet (Rana & Sanders 1986, Laidlaw *et al.* 1988, 1990). In fact, it has been observed that vegans have decreased plasma taurine levels by 14–22% as well as a urinary taurine excretion of 2–3-fold less than omnivores (Rana & Sanders 1986, Laidlaw *et al.* 1988). Whether or not this plasma decrease in vegans also causes a change in tissue taurine content is unknown.

Taurine transporters

TauT/PAT1

Cells accumulate taurine via the high-affinity, low-capacity, Na^+-dependent taurine transporter TauT plus the high capacity, proton-coupled but Na^+-independent β-amino acid transporter PAT1, and they release taurine via volume-insensitive plus volume-sensitive leak pathways. Table 1 compares TauT with PAT1, whereas Table 2 compares volume-insensitive with volume-sensitive leak pathways. Figures 1 and 2 show regulation of TauT and the volume-sensitive leak pathway for organic osmolytes respectively.

Taurine transport via TauT is Na^+ and Cl^- dependent, that is, negligible in the absence of extracellular Na^+ and significantly reduced in the absence of extracellular Cl^- (see Lambert 2004, Han *et al.* 2006). TauT has 12 hydrophobic transmembrane (TM) domains and the N- and C-terminal being exposed to the cytosolic compartment. Binding of Na^+ and Cl^- involves the first N-terminal, extracellular loop (Takeuchi *et al.* 2000), whereas gating and ionic binding of taurine to TauT involves an arginine (Arg-324) at the fourth intracellular segment of TauT (Han *et al.* 2006). One to three Na^+ ions are required for accumulation of one taurine (Lambert 1984, Wolff & Kinne 1988, Miyamoto *et al.* 1989, Jones *et al.* 1993, Mollerup & Lambert 1998, Takahashi *et al.* 2003a), and as reduction in the extracellular Na^+ concentration reduces the affinity of TauT to taurine (Lambert 1984, Sakai *et al.* 1989, Thoroed & Fugelli 1993), it is assumed that Na^+ is required for taurine binding and hence initiation of the transport cycle. Na^+ ions are most probably released to the intracellular compartment during the transport cycle as addition of taurine generates a current when added to Xenopus oocytes overexpressing murine TauT (Sarkar *et al.* 2003) and Bergmann glia (Barakat *et al.* 2002). However, TauT-mediated taurine uptake in EATC is electro neutral presumably because Na^+ recycles to the extracellular compartment via the Na^+/

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Table 1 TauT and PAT1 – transport characteristics

	TauT	PAT1
Cloned	Yes*	Yes
Regulation by pH	Transport is stimulated at *alkaline* pH[†]	Transport is stimulated at *acidic* pH[‡]
Na^+/Cl^- dependent	Yes[§]	No[‡]
K_m values	In low μM range	In mM range
Capacity	Low	High
Affinity to taurine	High	Low
Substrates	β-alanine, hypotaurine, taurine[¶]	β-alanine, hypotaurine, taurine** and drugs. Inhibited by dipeptides[††]
Regulation by the membrane potential	Transport is stimulated by hyperpolarization/ negative potential on the *trans* side of the membrane[‡‡]	
Regulation by osmolarity	Transport is downregulated by hypo-osmotic stress and increased by hyperosmotic stress[§§]	
Regulated by ROS	Yes[¶¶]	
Regulated by protein kinases/ phosphatases	Yes***	

ROS, reactive oxygen species.
*Liu *et al.* (1992), Ramamoorthy *et al.* (1994), Smith *et al.* (1992), Uchida *et al.* (1992).
[†]Kromphardt (1965), Lambert & Hoffmann (1993).
[‡]Anderson *et al.* (2009).
[§]Anderson *et al.* (2009), Jones *et al.* (1993), Lambert (1984), Mollerup & Lambert (1998), Wolff & Kinne (1988), Zelikovic & Chesney (1989).
[¶]Holopainen & Kontro (1984), Hruska *et al.* (1978), Lambert (1985), Martin & Shain (1979), Uchida *et al.* (1992).
**Anderson *et al.* (2009), Roig-Perez *et al.* (2005).
[††]Frolund *et al.* (2012).
[‡‡]Barnard *et al.* (1988), Lambert & Hoffmann (1993), Wolff & Kinne (1988), Zelikovic & Chesney (1989).
[§§]Han *et al.* (2006), Hansen *et al.* (2012), Sanchez-Olea *et al.* (1992), Shimizu & Satsu (2000), Uchida *et al.* (1992), Voss *et al.* (2004).
[¶¶]Hansen *et al.* (2012).
***Lambert (2004), Lambert *et al.* (2014), Lambert & Hansen (2011).

Table 2 Taurine release transport pathways

	Volume-sensitive taurine release	Volume-insensitive taurine release
Activation	Osmotic cell swelling	Exposure to LPC
Effect of cholesterol	Unaffected	Blocked
Effect of the anion channels blocker DIDS	Blocked	Unaffected
Effect of antioxidant	Blocked	Blocked
Effect of ROS	Potentiated	Unaffected
Effect of Ca^{2+} mobilization	Potentiated	Unaffected

ROS, reactive oxygen species.

K^+-ATPase (Lambert & Hoffmann 1993). The Cl^- ion is assumed to facilitate binding of the second Na^+ to TauT (Lambert 2004).

The activity of TauT is acutely downregulated following acidification (Lambert & Hoffmann 1993), osmotic cell swelling (Hoffmann & Lambert 1983, Hansen *et al.* 2012), exposure to reactive oxygen species (ROS; Hansen *et al.* 2012) and activation of the serine/threonine kinase protein kinase C (PKC; Voss *et al.* 2004). Activation of PKC reduces the maximal TauT transport activity in a broad range of cells (Han *et al.* 1996, 2006, Mollerup & Lambert 1996, Qian *et al.* 2000, Voss *et al.* 2004, Jacobsen *et al.* 2008), and it has been shown that PKC-mediated phosphorylation of TauT at Ser-332 changes the TauT structure and presumably prevents ionic binding of taurine to Arg-324 (Han *et al.* 2006). cAMP-dependent protein kinase A (PKA) stimulates Na^+-dependent taurine uptake in, for

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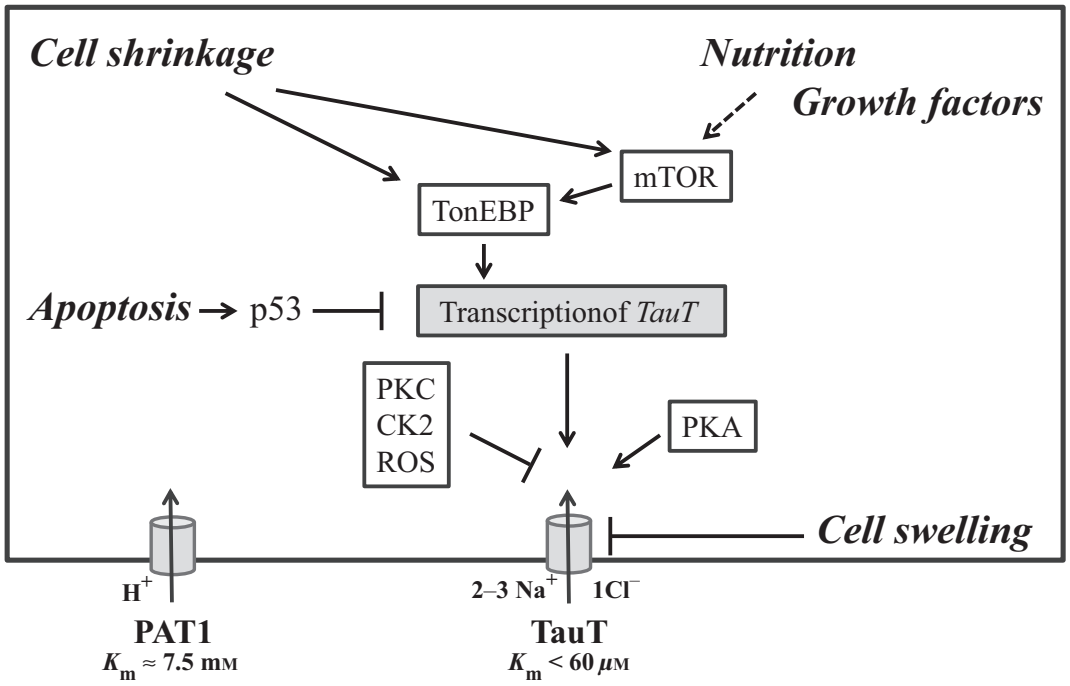

Figure 1 Secondary active taurine transporters. Taurine uptake via PAT1 and TauT is driven by the H^+ and the Na^+ gradient respectively. Short-term regulation of TauT activity involves phosphorylation/dephosphorylation/oxidation of TauT or a putative regulator of TauT by, for example, protein kinases A and C (PKA, PKC), casein kinase 2 (CK2) and reactive oxygen species (ROS). Long-term regulation of TauT involves modulation of gene transcription by protein kinases (mTOR) and transcription factors sensitive to cell shrinkage (TonEBP) or cell death signalling (p53). See text for details.

example EATC, and it has been shown that the PKA effect is abolished following PKC activation (Mollerup & Lambert 1996, 1998), that is, phosphorylation of Ser-332 could reduce PKA accessibility at TauT. Casein kinase 2 (CK2) is an ubiquitously expressed and constitutively active enzyme that restricts TauT activity presumably through phosphorylation of Thr-28, located in close contact with(TM1) at the cytosolic N-terminal part, that is, CK2 inhibition increases TauT′s affinity towards Na^+ and reduces the Na^+/taurine stoichiometry for taurine transport (Jacobsen *et al.* 2008).

Long-term modulation of TauT activity involves modulation of TauT gene transcription, that is, down-regulation of transcription typically follows activation of the tumour suppressor protein p53 and long-term exposure to high extracellular taurine levels (Voss *et al.* 2004) and hypotonicity (Hansen *et al.* 2012). On the other hand, upregulation of TauT gene expression and activity follows exposure to hypertonic medium and involves activation of the tonicity-responsive enhancer binding protein (TonEBP/NFAT5) that binds to and activates the tonicity response element (TonE) in the promoter region to the TauT gene (Han *et al.* 2006). Inhibition of the mammalian target of rapamycin mTOR reduces TauT mRNA abundance, translation as well as TauT activity in primary human trophoblasts (Roos *et al.* 2009), non-malignant NIH3T3 and carcinoma Ehrlich Lettré ascites (ELA) mouse fibroblasts (Lambert *et al.* 2014). As mTOR facilitates transcription of several osmostress response genes including TonEBP (Ortells *et al.* 2012), it has been suggested that increased TauT activity following hypertonic exposure could reflect an increased mTOR-dependent TonEBP activity (Lambert *et al.* 2014).

PAT1 (SLC36A1) is a low-affinity ($K_m = 7 \pm 4$ mM), high-capacity transporter which similar to TauT ($K_m < 60\mu$M) accepts taurine and β-alanine. Reducing extracellular pH from 7.4 to 5.5 increases β-alanine transport via PAT1 (Anderson *et al.* 2009) and as exposure to β-alanine leads to intracellular acidification, it has been suggested that H^+ is cotransported with the amino acid (Thwaites *et al.* 1993). It is noted that PAT1 has been associated with cellular amino acid sensing and cell proliferation presumably through modulation of mTOR activation (Heublein *et al.* 2010).

Volume-insensitive and volume-sensitive taurine transport

During isotonic conditions taurine leaks to the extracellular compartment, and it has been shown that

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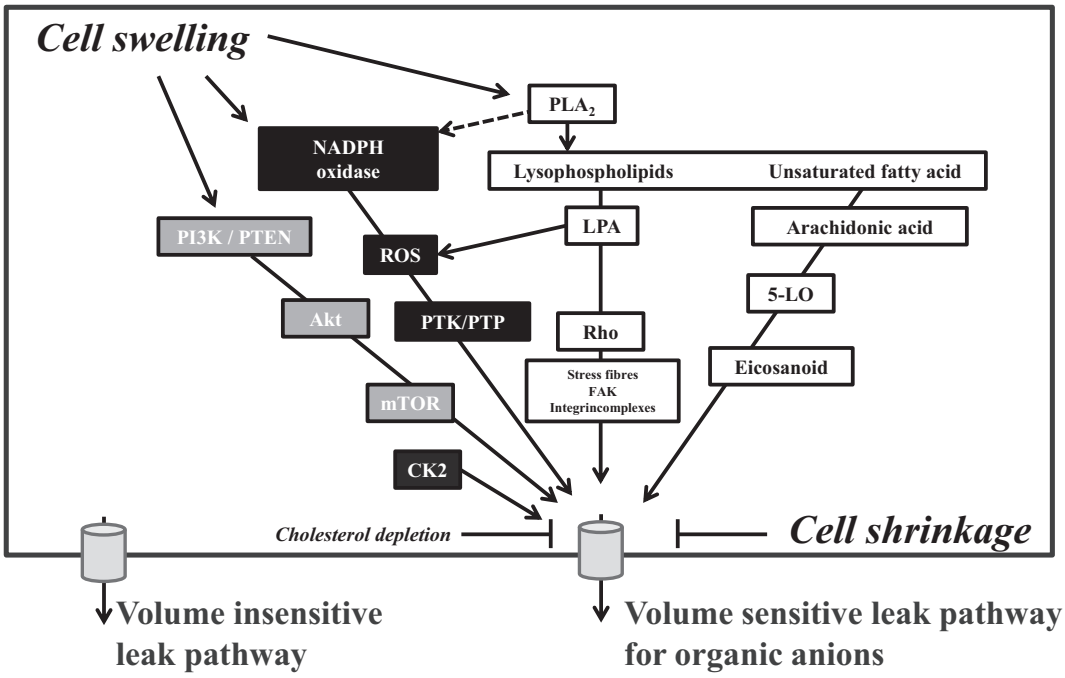

Figure 2 Volume-sensitive taurine release pathways. The model is based on observation from C2C12 cells, Ehrlich ascites tumour cells (EATC), NIH3T3 mouse fibroblasts, and human lung epithelial cell line A549 (Lambert *et al.* 2001, Pedersen *et al.* 2002, Lambert 2004, Lambert & Hansen 2011, Holm *et al.* 2013). The volume-sensitive pathway for organic osmolytes is inactive under isotonic/hypertonic conditions. Swelling-induced activation requires phospholipase A_2 (PLA_2)-mediated mobilization of fatty acids, their oxidation via the 5-lipoxygenase (5-LO) into eicosanoids and subsequently binding of the latter a cysteine leukotriene receptor (CysLT). Once activated the volume-sensitive leak pathway becomes modulated by (i) lysophosphatidic acid (LPA) which acts via a monomeric GTP binding protein (Rho) and structural elements (stress fibres and integrins) and focal adhesion kinases (FAK), (ii) reactive oxygen species (ROS) which are generated by a NADPH oxidase (NOX) and presumably act by amplifying the effect of volume-sensitive tyrosine kinases (PTK) though inhibition of the counteracting phosphatases (PTP) and (iii) kinases (CK2, PI3K, Akt, mTOR) and phosphatases (PTEN), which counteract growth factor/PI3K signalling.

taurine release under these conditions increases in the presence of cholesterol-depleting agents (Villumsen *et al.* 2010), lysophosphatidyl choline exposure (Lambert & Falktoft 2000, 2001, Lambert *et al.* 2001) and during the apoptotic process (Poulsen *et al.* 2010). Release of taurine in unpertubated cells via TauT, that is, TauT working in reverse, seems not plausible taking the low cellular Na^+ concentrations into account (Poulsen *et al.* 2010). However, exposing, for example, EATC to arachidonic acid/eicosapentaenoic acid (Lambert 1991), prostaglandin E_2 (Lambert 1987) or cisplatin (Poulsen *et al.* 2010) increases the Na^+ conductance, and hence, the possibility that cellular Na^+ concentration becomes sufficient to activate TauT as a release system.

Increased release of taurine via the volume-sensitive taurine release pathway, designated volume-sensitive organic anion channel (VSOAC) is seen within minutes following hypotonic exposure. The threshold for the activation of the taurine release has been estimated at 15% cell swelling in NIH-3T3 cells, and the efflux increases exponentially with reducing osmolality (Lambert 2003a). The molecular identity of VSOAC has been controversial, and many candidates have been suggested to represent VSOAC, for example pI, C1C-2, C1C-3, phospholemman, band 3 exchanger and volume-regulated anion channel (VRAC; Hoffmann *et al.* 2009). The complexity of identifying VSOAC has been increased by observations pointing towards that more than one channel is involved in release of organic osmolytes (Mongin *et al.* 1999). However, recently, it was demonstrated that leucine-rich repeat-containing protein 8A (LRRC8A) is an essential VSOAC component as LRRC8A knockdown almost blunts swelling-induced taurine release in HeLa cells (Qiu *et al.* 2014) and HCT116 cells (Voss *et al.* 2014). LRRC8A is a subunit in a multimeric channel complex, and it has suggested that shift in stoichiometry of LRRC8A and other LRRC8 membrane spanning proteins affects channel activity (Voss *et al.* 2014). Hence, difference in the pharmacological profile, that is, sensitivity to cholesterol depletion (Klausen *et al.* 2006, Villumsen *et al.* 2010) and time frame for activation and inactivation of VRAC and

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VSOAC following osmotic cell swelling (Hoffmann *et al.* 2014) could represent heterogeneity in the stoichiometry of LRRC8 components and/or the localization to subdomain of VRAC and VSOAC in the plasma membrane.

Volume-sensitive organic anion channel activation in, for example, EATC (Lambert 2004) and human lung epithelial cells (Holm *et al.* 2013) involves mobilization of arachidonic acid by a phospholipase A_2 (PLA_2), oxidation of the fatty acids to eicosanoids by a 5-lipoxygenase (5-LO) and binding of an eicosanoid to cysteinyl leukotriene receptor 1 (CysLT1). In the case of EATC, leukotriene D_4 has been identified as the agonist in tricking VSOAC following osmotic cell swelling (Lambert 1998). Once VSOAC activity has been evoked it becomes prone for modulation by (i) protein tyrosine, serine, threonine kinases/phosphatases, (ii) phosphoinositide kinases/phosphatases, (iii) Ca^{2+}/calmodulin (CaM), (iv) ROS and (v) nucleotides/Ca^{2+} (Lambert 2004, Pasantes-Morales *et al.* 2006, Hoffmann *et al.* 2009, Lambert & Hansen 2011, Holm *et al.* 2013). PLA_2- and 5-LO-mediated activation of VSOAC is also obtained under isotonic conditions following exposure to the PLA_2 activator melittin (Lambert 2003a), that is, activation of PLA_2 appears to be an upstream event in the volume-sensitive signalling cascade.

Full activation of the 5-LO requires binding of Ca^{2+}, translocation of the enzyme to the nuclear membrane as well as oxidation of the prosthetic iron ($Fe^{2+} \rightarrow Fe^{3+}$) in the catalytic domain by, for example H_2O_2 (Radmark & Samuelsson 2010). The 5-LO inhibitor AA861, which impairs activation of VSOAC in human carcinomic type II pulmonary epithelial cell (A549) (Holm *et al.* 2013), competes with the 5-LO substrate binding to the active site keeping the non-heme iron in the inactive ferrous state (Fe^{2+}) (Pergola & Werz 2010, Steinhilber *et al.* 2010).

Reactive oxygen species production increases within the first minutes of hypotonic swelling in several cell lines (Lambert 2003b, Ørtenblad *et al.* 2003, Varela *et al.* 2004, Diaz-Elizondo *et al.* 2006, Friis *et al.* 2008). Furthermore, exogenous addition of H_2O_2 potentiates the swelling-induced release of taurine, whereas antioxidants or inhibition of antioxidative enzymes, for example catalase, prevents volume-sensitive taurine release (Lambert 2003a, Ørtenblad *et al.* 2003, Lambert *et al.* 2014). It is noted that ROS have no effect on taurine release under isotonic conditions. Hence, ROS favour net loss of taurine under hypotonic conditions through potentiation of taurine release and a concomitant inhibition of TauT (Hansen *et al.* 2012). The swelling-induced ROS production and taurine release are reduced by the NADPH oxidase (NOX) inhibitor diphenylene iodonium chloride and NOX4 small interfering RNA (siRNA) knockdown, indicating that the volume-sensitive ROS production and taurine release are NOX4 dependent (Friis *et al.* 2008). Potentiation of NOX activity occurs downstream to PLA_2 activation (Lambert 2003a) and presumably by lysophosphatidic acid (LPA) that is produced by PLA_2 concomitantly to arachidonic acid mobilization (Friis *et al.* 2008). ROS are suggested to potentiate the swelling-induced taurine release by inhibition of protein tyrosine phosphatase activity and hence enhancement of tyrosine kinase activity (Lambert 2004, Lambert & Hansen 2011).

Extracellular nucleotides are involved in the homeostasis of pulmonary surfactant by modulation the ion and fluid transport as well as ciliary beating (Lazarowski *et al.* 2004). The nucleotide release can be stimulated by shear stress, membrane stretch, hypotonic swelling (Pedersen *et al.* 1999) and hypoxia (Tatur *et al.* 2008). A549 cells release ATP upon hypotonic swelling, and the release is highly dependent on a swelling-induced increase in intracellular Ca^{2+} concentration (Tatur *et al.* 2008). On the other side, ATP is able to induce an intracellular Ca^{2+} release through ATP-gated non-selective cation purinergic receptor channels (P2X1–P2X7) (Hoffmann *et al.* 2002). The role of Ca^{2+} for taurine release is cell type specific where some cell types require increased Ca^{2+} levels other cell types have improved taurine release in the absence of Ca^{2+} (Lambert 2004). It is noted that increase in cellular Ca^{2+} following osmotic cell swelling differs between cell types and that Ca^{2+} contributes to the overall regulatory volume decrease (RVD) response preferentially in cells of epithelial origin (Hoffmann *et al.* 2009). However, Ca^{2+}-mobilizing agents [LPA, leukotriene D_4 (LTD_4), ATP] or ionophores (ionomycin) can potentiate the swelling-induced ROS production and taurine release (Lambert 2004, Friis *et al.* 2008). The Ca^{2+}-signal, affecting the swelling-induced calcium release seems to involve calmodulin, calmodulin-dependent protein kinases II, phosphatidylinositol 3-kinases (PI3K) and Ca^{2+}-dependent PKC (Hoffmann *et al.* 2009).

Inactivation of VSOAC during RVD is likely a consequence of shift in protein tyrosine kinase/phosphatase activities and/or general cell volume restoration. In the case of tyrosine phosphorylation, inhibition of tyrosine phosphatases has been shown to prolong the open probability of VSOAC (Lambert 2007), whereas an accelerated RVD response and a concomitant rapid inactivation of VSOAC has been demonstrated following additions of Ca^{2+} ionophores/Ca^{2+}-mobilizing agents (acceleration of KCl loss due to activation of Ca^{2+}-sensitive K^+/Cl^- channels) and K^+ ionophores (Falktoft & Lambert 2004, Lambert 2007). Furthermore, PKC-mediated phosphorylation/desensitization of the mCysLT1 receptor have recently been assigned

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a role in abrogation of the RVD response (Jorgensen *et al.* 2013).

Taurine transport across epithelia

Absorption via the intestinal epithelium, reabsorption via the renal epithelium as well transport across the placenta contributes significantly to the total taurine pool in the foetus and healthy adults. Figure 3 indicates localization of active and passive transporters involved in cellular and paracellular transport of taurine.

The intestinal epithelium has a high capacity for taurine accumulation (Ahlman *et al.* 1993) and using CaCo-2 cells, that are originally derived from human colon but functionally resemble enterocytes lining the small intestine (Hidalgo *et al.* 1989), it has been shown that taurine transport across the apical (luminal) as well as the basolateral membrane involves a saturable component with typical TauT characteristics (Na^+ and Cl^- dependent, blocked by β-amino acids) and a non-saturable component (Roig-Perez *et al.* 2005). According to Roig-Perez *et al.* (2005) TauT at the basolateral membrane has a lower half-saturation constant (K_m), a lower transport capacity and presumably a lower Na^+ dependence compared with the apical membrane. In addition, it has been demonstrated that PAT1 is coexpressed with TauT in the apical human intestinal epithelium and suggested that PAT1 contributes to taurine accumulation during meals with a solid taurine content (Anderson *et al.* 2009). Hence, net taurine transport across CaCo-2 cells appears to involve accumulation via TauT/PAT1 at the apical membrane and passive release via the non-saturable transport across the basolateral membrane.

In the human foetus and placenta, where enzymes involved in taurine synthesis are lacking, foetal taurine

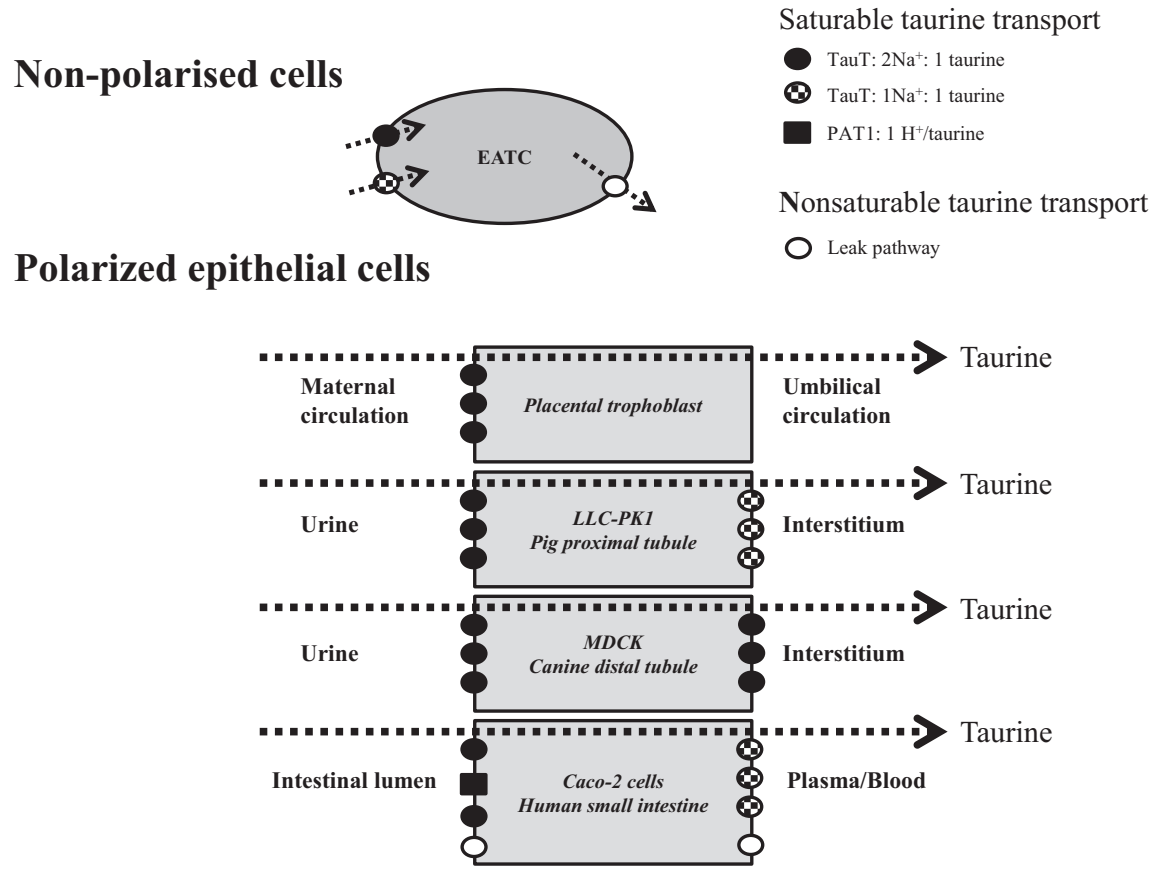

Figure 3 Paracellular taurine transport. Taurine uptake in non-polarized cells involves TauT isoforms with different Na^+ : taurine binding stoichiometry. Taurine transport from the mother to the foetus involves TauT-mediated accumulation of taurine across the membrane of the placental trophoblast facing the maternal blood circulation and presumably leak to the umbilical circulation. Taurine transport across kidney tubule cells involves TauT transporters at the apical/basolateral membranes with different Na^+ : taurine stoichiometry and sensitivity towards tonicity. Taurine accumulation from the intestinal lumen into the intestinal epithelium involves the H^+-coupled, high-capacity transporter PAT1 and the Na^+-coupled, low-capacity transporters TauT, whereas release from the cells to the blood involved TauT and a yet unidentified leak pathway for taurine. See text for details.

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requirement is ensured through taurine transport from the maternal plasma to the foetal plasma, via the syncytiotrophoblast and placenta. TauT is predominantly localized to the maternal-facing microvillus membrane of the syncytiotrophoblast (Norberg *et al.* 1998, Roos *et al.* 2004), that is, the outer epithelial cell layer of the human placenta, where it accounts for accumulation of taurine from the maternal source. Using RNA interference Desforges *et al.* (2013) demonstrated that lack of TauT compromises trophoblast differentiation as well as trophoblast susceptibility to inflammatory cytokines known to be elevated in foetal growth restriction.

Using the continuous renal epithelial cell lines LLC-PK_1 (originated from *proximal* pig renal tubules) and MDCK (originated from the *distal* dog tubule), it has been shown that taurine transport is greatest at the apical surface in LLC-PK_1 and at the basolateral surface in MDCK cells. According to Jones *et al.* localization of TauT in renal cell systems reflects the origin and function of the cells, that is, localization of TauT with a 2Na : 1taurine stoichiometry at the apical membrane and TauT with a 1Na : 1taurine stoichiometry at the basolateral membrane ensures net apical to basolateral taurine transport and hence reabsorption/retention of taurine from urine by proximal renal tubular cells. On the other hand, localization of TauT with a 2Na : 1taurine stoichiometry to the basolateral as well as the apical membrane limits net secretion of taurine although an increased osmo-sensitivity of the basolateral TauT compared with the apical TauT in distal renal cells could be used to regulate cell volume in response shift in the external osmolarity (Jones *et al.* 1993).

Taurine homeostasis in organelles

The two taurine transporters, TauT and PAT1, are both mainly localized to the plasma membrane. However, both have also been observed in the nucleus (Voss *et al.* 2004, Jensen *et al.* 2014) indicating a putative role of taurine in nuclear swelling/shrinking. Furthermore, PAT1 has been observed localized in endosomal and lysosomal membranes (Ogmundsdottir *et al.* 2012), whereas TauT is highly expressed in primary cilia of NIH3T3 mouse fibroblasts, and it has been suggested that TauT or increased taurine influx could be involved in modulation of Ca^{2+}-dependent signalling in the cilium (Christensen *et al.* 2005). There is circumstantial evidence that at least one taurine transporter is present in the mitochondria as isolated mitochondria have been shown to take up taurine (Suzuki *et al.* 2002), and TauT has been observed by western blot in isolated mitochondria (O. H. Mortensen, unpublished results). Interestingly, the size of TauT, as observed by western blot, is larger in the nuclear fraction than in the cytosolic fraction (Voss *et al.* 2004), indicating the possibility of either multiple isoforms of TauT or differences in glycosylation. Recently, a study examined the effect of the competitive taurine uptake inhibitor β-alanine on taurine levels in mitochondria and despite a clear decrease in total cellular taurine content, they found no decrease in mitochondrial taurine content, indicating the possibility of a different source of mitochondrial taurine (Jong *et al.* 2010). This finding is in line with the observation that taurine may be synthesized both in the mitochondria and in the cytoplasm (Ubuka *et al.* 2008). However, the current knowledge regarding regulation and mechanism of organelle taurine uptake is limited, and more research about this topic is warranted.

Physiological role of taurine

Taurine and membrane dynamics

Taurine was first proposed as a membrane stabilizer in 1973 by Huxtable and Bressler, who had observed that the reduction in Ca^{2+} transport and ATPase activity in isolated sarcoplasmic reticulum from rat skeletal muscle that followed incubation with phospholipase C was lifted by addition of taurine to the medium. It has subsequently been shown that taurine mediates a plethora of membrane linked effects in many different tissues (Schaffer *et al.* 1994). To account for these manifold roles of taurine four hypotheses have been proposed: (i) The antioxidant hypothesis, (ii) the protein phosphorylation hypothesis, (iii) the taurine-phospholipid binding hypothesis and finally (iv) phospholipid N-methylation hypothesis (Schaffer *et al.* 1994).

The first hypothesis is based on the observation that taurine reduces the inflammatory response of some cytotoxic oxidants, and hence, it was subsequently proposed that a reduction in the extent of membrane oxidative injury contributes to these cytoprotective actions (Park *et al.* 1993). These effects are for example evident in a recent study on adult rats where taurine oxidative stress induced by endosulfan treatment decreased testes weight, and inhibited spermatogenesis and steroidogenesis. These alterations were, however, effectively prevented by taurine pre-treatment, supporting the role of taurine as a powerful antioxidant (Aly & Khafagy 2014).

The second hypothesis maintains that alterations in protein phosphorylation may underlie certain effects of taurine with a particularly focus on calcium transport. In rat brain taurine (10 mM) blocks PMA-stimulated phosphorylation and taurine stimulates ATP-independent calcium uptake in mitochondrial preparations (Li & Lombardini 1991). Hence, there is a possibility that the reduction in tissue protein

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phosphorylation is downstream to taurine-mediated reductions in cytosolic calcium levels, inhibition of phosphoinositide turnover and altered PKC activity (Li & Lombardini 1991, Schaffer *et al.* 1994).

The third hypothesis argues that the interaction of taurine with the phospholipids leads, among other things, to altered membrane calcium binding and hence functions. This hypothesis is based on early studies reporting that at physiological relevant concentrations of taurine, an interaction develops between taurine and cellular membranes. The binding sites in the membranes for taurine are selective as they bind taurine but not, for example, alanine (Kulakowski *et al.* 1978, 1981, Schaffer *et al.* 1981). Furthermore, the interaction is greatly reduced by proteases and phospholipase C, indicating that both membrane proteins and phospholipids are involved in the interaction (Kulakowski *et al.* 1978, 1981, Schaffer *et al.* 1994). Thus, the hypothesis proposes that taurine directly interacts with membranes, apparently by forming an electrostatic interaction between the amino and the sulfonic acid group of taurine and the phosphate and amino or quaternary ammonium groups of the phospholipids respectively. This interaction appears to cause minor alterations in the lipid bilayer of the cellular membrane, allowing more calcium to bind to the phospholipids (Chovan *et al.* 1979). However, based on electron spin resonance, acute exposure of isolated cell membranes to taurine does not change fluidity of the membranes (Schaffer *et al.* 2010).

The fourth and final hypothesis suggests that the effects of taurine is due to inhibition of phospholipid N-methylation resulting in downstream effects on the membrane composition and structure. Hence, the conversion of phosphatidylethanolamine to phosphatidylcholine is catalysed by the enzyme phospholipid *N*-methyltransferase, and this methylation increases the size of the phospholipid head group, thereby altering the molecular shape of the phospholipid and thus changing the membrane. For example, it has been showed that in human cardiac myocytes taurine inhibits each step in the conversion of phosphatidylethanolamine to phosphatidylcholine, thus changing membrane structure and providing a possible explanation for some of the actions of taurine (Hamaguchi *et al.* 1991, Punna *et al.* 1994). It is clear that all four hypotheses have merit and value, however, none of them can fully explain the membrane actions of taurine found and described in the literature (Hamaguchi *et al.* 1991, Schaffer *et al.* 1994, 2010).

Taurine and cell volume regulation

In recent years, it has become clear that the ability to control cell volume is not only an important factor for regulation of intracellular osmolality and cell morphology but also for defining cellular functions, such as cell migration, cell metabolism and cell death (apoptosis/necrosis) (see Hoffmann *et al.* 2009, Lambert *et al.* 2008). Mammalian cells are highly water permeable due to the presence of water-conducting aquaporins and respond accordingly as almost perfect osmometers following osmotic perturbation. Shift in the intracellular hydration is unfavourable as it affects the intracellular substrate/ion concentrations and hence physiological processes. Consequently, osmotic cell swelling or cell shrinkage is counteracted by volume restoring mechanisms, that is, cell swelling elicits activation of channels and exchange systems for ions as well as VSOAC, which ensures net loss of osmotic material and hence cell water (RVD), whereas cell shrinkage ensures activation of cotransporters/exchange systems for ions and Na^+-dependent transporters for organic osmolytes, which warrants net uptake of osmotic material and hence cell water [regulatory volume increase (RVI)] (Hoffmann *et al.* 2009).

The overall osmolality of the body plasma is tightly regulated by the kidneys, and most cells of the human body are rarely exposed to large changes in osmolality. However, cells of the renal medulla, the epithelial layer of the intestine or airways, are apically exposed to highly anisotonic extracellular media. Furthermore, pathological conditions, for example hypo- or hypernatraemia (disturbance of electrolyte balance in the body), make cell volume regulation crucial. Many studies have focused on the volume-activated release of taurine, as taurine is an abundant intracellular amino acid in, for example, EATC (40–53 mM, Hoffmann & Lambert 1983, Mollerup & Lambert 1998) and skeletal muscle (10–60 mM, Blomstrand & Saltin 1999, Bakker & Berg 2002). The human plasma taurine concentrations are around 40–100 μM and the step outwardly directed taurine gradient provided by the efficient TauT activity and low leak permeability to taurine under isotonic conditions underlines the impact of an increase in VSOAC activity on the overall RVD response following osmotic cell swelling. In EATC, it has been shown that loss of cellular taurine during RVD reflects loss to the extracellular compartment, whereas the concomitant reduction in the cellular pool of glycine and alanine includes an increased oxidative catabolism (Lambert & Hoffmann 1982, Hoffmann & Lambert 1983). It has been estimated that release of taurine and other amino acids accounts for 30% of the total loss of osmolytes in EATC following osmotic cell swelling in medium with 50% of the normal isotonic value (Hoffmann & Hendil 1976). Furthermore, loading cells with radioactively labelled taurine, it has been demonstrated that it is possible to deplete, for example NIH3T3 and HeLa

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cells for tracer, that is, taurine (Moran *et al.* 1997, Lambert & Falktoft 2000).

Taurine release during hypoxia and ischaemia

Taurine together with other free amino acids are released during ischaemia (Kimelberg *et al.* 2004). As blockers of volume-sensitive leak pathway for anions and amino acids, for example, DIDS partially reduce the ischaemia-induced amino acid release (Saransaari & Oja 1998), it is assumed that VSOAC is involved in taurine release under ischaemia. Incubation of rat brain cortical slices in artificial cerebrospinal fluid containing increased levels of taurine prior and during ischaemia and oxygen reperfusion reduce cellular damage (lactate dehydrogenase release), and decrease the amount of oedema in brain tissue (Ricci *et al.* 2009). Recently, it was demonstrated that prevention of taurine loss either by inhibition of VSOAC or by prevention of taurine loss by increasing extracellular taurine reduced hypoxia induced cell death in A549 cells (Holm *et al.* 2013). These observations indicate a protective role of extracellular taurine/retention of cellular taurine during ischaemia. In congruence explanted hearts from rats treated with increased dietary taurine intake are more resistant to ischaemic damage (Sahin *et al.* 2011) and addition of 10 mM taurine to the cardioplegic solution, used to store transplanted hearts in during transplantation surgery, improves preservation of the heart by lowering DNA oxidative stress and apoptosis (Oriyanhan *et al.* 2005). Hence, taurine might have beneficial effects both under ischaemic pathological situations such as stroke and also during organ transplantations.

The mechanism behind the ischaemia-induced amino acid release is thought to be in part due to an ischaemia-induced cell swelling that activates a RVD response and thereby release taurine. When ischaemia is developing in a tissue, the first consequence of a limited blood supply is a decrease in the oxygen level available to the cells. In the lack of oxygen, the oxidative phosphorylation in the mitochondria cannot take place. ATP is produced in an anaerobe process where pyruvate is reduced to lactic acid. Increased amounts of lactic acids in the tissue lower the pH and can lead to acidosis. The acidification of the cell may affect the volume-sensitive pathway. In the absence of oxygen and energy sources, the ATP levels slowly decrease in the cells and the ATP-depending ion pumps get affected. Acute failure of the Na^+/K^+-ATPase leads to intracellular accumulation of Na^+ and at the same time lactic acid, hence cell swelling. This cell swelling activates the RVD response leading to release of osmolytes including taurine. The failure of the ATP-dependent ion pumps leaves the cell unable to keep the Ca^{2+} gradient and the intracellular Ca^{2+} concentration increases. Increased calcium levels can result in activation of wide range of enzymes such as PLA_2 which also have shown be involved in ischaemia- and swelling-induced taurine release (Lambert 2004, Poulsen *et al.* 2007).

Reactive oxygen species are thought to have an important impact on cell damage during ischaemia and reperfusion. The largest increase in ROS production is seen immediately after reperfusion, and a smaller ROS production takes place during ischaemia where superoxide formation is limited due to little or no oxygen available (Galaris *et al.* 2006). The mechanisms responsible for the large increase in ROS following reperfusion are debated, but generation by respiratory chain complexes I and III in the mitochondria and NOX seems to play a major role (Zulueta *et al.* 1997, Schaffer *et al.* 2014). Inhibition or knockout of NOX4 prevents the damage caused by ischaemia reperfusion (Zulueta *et al.* 1997, Nakagiri & Murakami 2009). Jong *et al.* (2012) have recently suggested that taurine function as an indirect antioxidant. Depletion of mitochondrial taurine will have negative impact on the synthesis of the mitochondrial-encoded genes (see Taurine and mitochondrial function) which will affect assembly of the respiratory chain. Due to a reduced activity of the electron transport, chain electrons will consequently be diverted to acceptors such as oxygen thereby increasing the generation of the damaging ROS.

Taurine and development

Taurine is considered to be an essential amino acid during development, as the endogenous synthesis of taurine is inadequate in the human foetus (Hibbard *et al.* 1990). Thus, the foetus is dependent on the maternal supply of taurine. Taurine deficiency leads to a smaller birth weight in both cats (Sturman 1991) and rodents (Ejiri *et al.* 1987). The offspring of cats reared on a taurine-free diet exhibit profound developmental abnormalities, among these being: smaller body weight, smaller brain weight, abnormal hind leg development as well as a degeneration or abnormal development of the retina and visual cortex (Sturman 1991). Furthermore, mice deficient in TauT show a smaller overall size; however, no information regarding birth weight is available (Warskulat *et al.* 2007). TauT knockout mice also show defects in heart and skeletal muscle development, most likely due to mitochondrial effects (Warskulat *et al.* 2004, Ito *et al.* 2008). In humans, a low plasma taurine concentration in the infant has been linked to detrimental mental development (Heird 2004, Wharton *et al.* 2004), something which has been corroborated by animal

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studies (Sturman 1993). Furthermore, taurine supplementation in mice has shown that the exact timing of taurine supplementation during brain development influence the learning ability, with taurine sufficiency being most important during the peri-natal and post-natal period (Suge *et al.* 2007). Experimental animal studies suggest that taurine may be a marker of foetal wellbeing (de Boo & Harding 2007) although a recent study suggests that excessive taurine during gestation may also have detrimental effects later in life (Hultman *et al.* 2007). It is noted that the retina in TauT knockout mouse first degenerates within weeks following birth, indicating a role of taurine in protection against apoptosis (Warskulat *et al.* 2007). It is possible that some of the detrimental effects seen in the TauT knockout mouse and to some extent in the cat is due to developmental taurine deficiency and that these may be corrected in adult life with an adequate taurine supply. However, the nature of the TauT knockout mouse and the difficulty in using the cat as an animal model makes this difficult to examine. Other animal models, like the CDO or CSAD knockout where exogenous taurine can be supplied may be more suitable for examination of these issues.

Taurine and lung function

Taurine has been illustrated as a weak agonist for chloride-permeable gamma-aminobutyric acid type A receptors ($GABA_AR$) and glycine receptors (GlyR). $GABA_AR$ and GlyR are generally thought to be located in the neural synapses, but there is increasing evidence for non-synaptic activity of $GABA_AR$ and GlyR in the central nervous system (CNS; Le-Corronc *et al.* 2011) and even expression outside the CNS, for example lung (Xiang *et al.* 2007, Gallos *et al.* 2012), liver (Minuk 1993) and pancreas (Yang *et al.* 1994).

In the lung, taurine has been suggested to potentiate relaxation of pre-contracted airway smooth muscle cells through the α4-subunit of $GABA_A$ receptors (Gallos *et al.* 2012). Furthermore, expression of apical membrane-located $GABA_AR$ in airway epithelial cells was increased both in mice after inducing an allergic asthmatic reaction with ovalbumin and humans with asthma after allergen inhalation challenge. Intranasal application of selective $GABA_AR$ antagonists suppressed the overproduction of mucus in the lungs (Xiang *et al.* 2007). In this context, it is noted that TauT accepts GABA as substrate and that it has been suggested that the low-affinity transport of GABA via TauT contributes to removal of excess GABA from, for example, retinal interstitial fluid (Tomi *et al.* 2008).

Hypo-osmotic swelling of A549 lung carcinoma cells triggers taurine release through VSOAC via a ROS-dependent activation of 5-LO that leads to autocrine stimulation of CysLT1 receptor. The CysLT1 blocker Zafirlukast, commonly used for maintenance treatment of asthma, prevented the swelling-induced taurine release and RVD in A549 cells (Holm *et al.* 2013).

As described by Mongin (2013), these observations suggest a potential role of taurine both in the general regulation of the lung but also in pathological cases such as asthma. Hypothetically, under normal conditions, a release of taurine may via $GABA_A$ and/or glycine receptors stimulate the relaxation of smooth muscle cells and the secretion of mucus from goblet cells. However, in asthma patients, invading immune cells in the lung are likely to produce large amounts of CysLTs. In turn, this may stimulate the release of taurine and thereby increase mucus secretion. Increased levels of CysLTs, which are potent constricting agents, might at the same time counteract the relaxing effects of taurine on the smooth muscle cells thereby further worsening the symptoms of asthma.

Taurine and mitochondrial function

As mentioned above, taurine conjugation of the mitochondrial tRNA for leucine and lysine is required for effective mitochondrial protein translation making taurine an absolute requirement for mitochondrial function (Suzuki *et al.* 2002), more specifically for the expression of proteins in the electron transport chain (complex 1, 3 and 4) as well as the ATP synthase. Direct evidence that taurine may modulate mitochondrial function can be gained from observations from the TauT knockout mouse where liver mitochondria exhibited a decreased respiratory control ratio indicative of mitochondrial dysfunction (Warskulat *et al.* 2006) as well as from cellular experiments where cellular taurine depletion resulted in a decrease in mitochondrial respiration and activity of electron transport chain complexes I and III. On the other hand, taurine supplementation of neural precursor cells leads to increased cellular proliferation, and an increase in the mitochondrial membrane potential, indicating that taurine may improve mitochondrial function (Ramos-Mandujano *et al.* 2014). The TauT knockout mice are exercise intolerant (Warskulat *et al.* 2007) indicative of a possible energy metabolism dysfunction in skeletal muscle although this phenotypic trait of TauT knockout mice may also be due to a taurine depletion mediated decrease in skeletal muscle force–frequency relationship (Hamilton *et al.* 2006). Likewise, taurine supplementation increase skeletal muscle force output and time to fatigue (Goodman *et al.* 2009), and the authors speculated that this may have been due to a protective effect of taurine upon mitochondrial function.

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Taurine may also have a more direct role in mitochondrial metabolic regulation as taurine depletion has been shown to induce phosphorylation of pyruvate dehydrogenase (PDH) (Lombardini 1998), indicating that taurine depletion may lead to an inhibition of PDH, although this has not been shown experimentally. Taurine-mediated regulation of PDH may be tied to a more complex regulation of sulphur and carbohydrate metabolism, as taurine depletion has recently been shown to increase CDO (Park *et al.* 2014) and the product of CDO, cysteine sulfinate, can be converted to ultimately either pyruvate or taurine (Stipanuk *et al.* 2006). Thus, one may speculate that the taurine depletion-mediated inhibition of PDH may be tied to increased biosynthesis of taurine as the cell tries to favour taurine biosynthesis over pyruvate synthesis in the catabolism of cysteine, although this remains to be determined.

Recently, taurine has been suggested as a pH buffer in the mitochondrial matrix to stabilize mitochondrial beta-oxidation of fatty acids. This oxidative process requires mildly alkaline conditions in the mitochondrial matrix with taurine as optimal pH buffer (Hansen *et al.* 2006, 2010). However, there is no direct experimental evidence that taurine functions as a buffer in the mitochondrial matrix.

Taurine and antioxidative defence

The major culprit of endogenous oxidant-induced cell damage is the ROS which includes superoxide anion ($^{\cdot}O_2^-$) produced as a by-product of oxidative phosphorylation by complex I and III (Li *et al.* 2013). Antioxidants work through one of three mechanisms to prevent oxidative stress and cell damage – either by reducing ROS generation, by scavenging ROS or by interfering with the actions of ROS, and taurine seems to work at all levels.

As such, taurine has been shown to prevent cellular damage caused by among others nitrogen dioxide (Gordon *et al.* 1986) and ozone (Banks *et al.* 1992, Rivas-Arancibia *et al.* 2000) and taurine has been shown to suppress the formation of nitric oxide by interfering with the expression of iNOS (Gurujeyalakshmi *et al.* 2000). However, taurine is unable to directly scavenge ROS products such as hydrogen peroxide or superoxide anion (Aruoma *et al.* 1988) and instead works indirectly to prevent cellular damage caused by ROS. This is performed by increasing or restoring the levels of antioxidant enzymes such as thioredoxin reductase (Yildirim *et al.* 2007), superoxide dismutase (Vohra & Hui 2001) and glutathione peroxidase (Nonaka *et al.* 2001). Taurine also seems to be able to prevent ROS formation, mainly due to its protective effect on mitochondria, as damaged mitochondria produce more ROS. This protective effect is believed to be mediated by the taurine-mediated prevention of intercellular, and especially mitochondrial, calcium overload (El & Trenkner 1999) although the exact mechanism has not yet been established. Furthermore, taurine is able to directly scavenge the antibacterial oxidant hypochlorous acid, an oxidant produced by myeloperoxidase in activated neutrophils and monocytes. These cells also contain high amounts of taurine and hypochlorous acid and can undergo a reaction with taurine catalysed by myeloperoxidase resulting in taurine chloramine, a much less reactive oxidant (Weiss *et al.* 1982).

Recently, a novel mechanism for the antioxidant effect of taurine has been suggested (Schaffer *et al.* 2009). Taurine forms a conjugate with the mitochondrial tRNAs for leucine and lysine (Suzuki *et al.* 2002) making efficient translation of mitochondrial-encoded proteins as well as assembly of the respiratory chain complexes dependent upon a sufficient mitochondrial taurine supply. A reduction in mitochondrial translation and respiratory chain complex formation has been shown to increase mitochondrial ROS production (Ricci *et al.* 2008), and thus, the antioxidant effect of taurine is suggested to be mediated by taurine maintaining efficient mitochondrial protein translation (Schaffer *et al.* 2009). This hypothesis was recently supported by the observation that cellular taurine depletion caused a decrease in mitochondrial proteins specific to the ones encoded by the mitochondrial genome as well as causing a decrease in complex I and III, but not II, activity.

Taurine – cell death and drug resistance

Apoptosis is an orchestrated genetically determined form of cell death that occurs during development and when cells have served their time or been exposed to physiological or cytotoxic stimuli. Typical signs used to indicate apoptotic progression include osmotic cell shrinkage reflecting net loss of intracellular K^+, Cl^-, amino acids and cell water, cytosolic acidification due to inhibition of the Na^+/H^+ exchanger (NHE1), DNA degradation following endonuclease activation, translocation of phosphatidylserine from the inner to the outer part of the plasma membrane, collapse of the mitochondrial transmembrane potential due to opening of a permeability pore, release of cytochrome *c*, formation of the apoptosome (cytochrome *c*, Apaf1 and procaspase 9), activation of pro-apoptotic factors [Smac, DIABLO and HtrA2/Omi (serine protease)], inhibition of IAP (inhibitor of apoptosis) and finally activation of caspase 3 (Elmore 2007). At the end blebs and apoptotic bodies are formed with the latter being removed by neighbouring cells or phagocytes

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leaving no debris that could cause inflammation. Loss of KCl and cell water under isotonic conditions following exposure to, for example, Ca^{2+} mobilizing agonists normally elicits a RVI, that is, reuptake of NaCl uptake via Na^+, K^+, $2Cl^-$ cotransporters and/or Na^+/H^+ plus Cl^-/HCO_3^- exchangers followed by exchange of cellular Na^+ with extracellular K^+ via the Na^+, K^+-ATPase (Hoffmann *et al.* 2009). However, in the case of EATC net loss of KCl and organic osmolytes following exposure to, for example, the platinum-based drug cisplatin exceeds the capacity of the ion transporters involved in RVI and cell shrinkage becomes severe and cell death inevitable within 10 h (Poulsen *et al.* 2010). It appears that it is the decrease in the cellular K^+ concentration, following impairment/inadequate efficiency of the Na^+, K^+-ATPase activity, that causes caspase activation and nuclease activity (Lang & Hoffmann 2012). Resistance to apoptosis-stimulating drugs in mammalian cells has been correlated to upregulation of anti-apoptotic transporters that accumulate osmolytes and/or downregulation of pro-apoptotic transporters that release osmolytes (Table 3). In accordance with findings in kidney cells, where TauT overexpression protects against cisplatin-induced cell death (Han *et al.* 2009), data from EATC and ELA indicate that a functional TauT rather than the cellular taurine level complies with cisplatin resistance in ELA (Tastesen *et al.* 2010). Comparing colorectal cancer cell lines (LoVo, SW480, DLD1, HT-29, HCT116) with normal colonocytes, Yasunaga and Matsumura (2014) have shown that TauT is a colorectal cancer-specific cell surface marker and that TauT knock-down attenuated cell survival/enhanced drug sensitivity, whereas TauT overexpression increased cell survival and drug resistance. It is noted that apoptosis following exposure to hyperosmotic shock or oxidative stress is significantly dampened in erythrocytes from TauT knockout mice compared with wild-type littermates (Lang *et al.* 2003), which most likely reflects a significant reduction in the concomitant cell shrinkage. Furthermore, in drug-resistant EATC, it has been demonstrated that downregulation of VSOAC activity is accompanied by a reduction in TauT expression and activity (Poulsen *et al.* 2002), indicating that downregulation of VSOAC in drug-resistant EATC and hence limitation in the initial cell shrinkage following cisplatin exposure (Poulsen *et al.* 2010) contributes more to cisplatin resistance than modulation of the prevailing capacity/number of TauT copies in the plasma membrane.

Table 3 Anti-apoptotic and pro-apoptotic ion transporters involved in multidrug resistance (Hoffmann & Lambert 2014)

Anti-apoptotic transporters
Plasma membrane Ca^{2+}-ATPases
Na^+/H^+ exchanger (NHE1)
Na^+, K^+-ATPase
Hypertonicity-induced cation channels (HICCs)
Na^+, K^+, $2Cl^-$ cotransporter (NKCC1)
Pro-apoptotic transporters
Membrane bound Ca^{2+} channels (ORAI/Transient receptor potential channels)
K^+ and Cl^- channels

Activation of the tumour suppressor/transcription factor p53 plays an essential role in apoptosis. p53 guards genes that code for proteins controlling DNA repair and cell cycle progression, that is, p53 stimulates expression of $p21^{Waf1/Cip1}$ that via inhibition of cyclin-dependent kinases hinders G1→S and G2→M phase transitions. p53 also regulates apoptosis through cytochrome *c* release due to activation of pro-apoptotic proteins, for example Bax and Bid. Under normal conditions, p53 is inactive due to MDM2 (murine double minute 2) which transfers ubiquitin to p53, hence targeting p53 for degradation by proteasomes. However, following DNA damage ATM (DNA-dependent protein kinase) autophosphorylates, becomes active and phosphorylates p53 (human Ser-15, mouse Ser-20) which subsequently protects p53 from interaction with MDM2, ubiquitination and hence ensures p53 transcriptional activity (Elias *et al.* 2014). Cell shrinkage is part of the apoptotic process, and it has been demonstrated that shrinkage-induced activation of the monomeric GTP binding protein Rac and subsequently the p38 kinase similar to ATM protects p53 (Friis *et al.* 2005). Increased p53 activity during apoptosis would reduce TauT activity either due to uncoupling of *TauT* transcription following p53 interference with the *TauT* promoter or due to p53-mediated recruitment of an AMP-dependent kinase, mTOR inhibition and hence inhibition of TauT (Lambert *et al.* 2014).

Following osmotic cell swelling or ischaemia taurine is released to what would be expected to be a restricted extracellular compartment, and it is speculated that an increase in extracellular taurine concentration will affect physiological processes. Table 4 illustrates that taurine supplementation attenuates stress-induced apoptosis and that taurine seems to interfere with the signalling cascade leading to apoptosis, for example taurine downregulates ligands for the death receptors, prevent apoptosome formation and mitochondrial dysfunction presumably although modulation of Bcl2. It is noted that in EATC and ELA cells, it is modulation of TauT expression and not shift in the cellular taurine concentration that complies with cisplatin resistance (Tastesen *et al.* 2010).

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Table 4 Effect of taurine supplementation on the apoptotic response

Cell system	Stress	Effect of taurine	References
Pancreatic islet	Streptozotocin	Reduced apoptosis Dampens drug induced upregulation of Bax and Fas	Lin *et al.* (2013)
Rat retinal ganglion cells	Hypoxia	Reduced apoptosis Prevention of mitochondrial permeability transition/dysfunction and cytochrome *c* release	Chen *et al.* (2009)
Jurkat T-lymphocytes	CD95(Fas/Apo-1) receptor	Reduced apoptosis Reduction in DNA fragmentation and cell shrinkage	Lang *et al.* (2000)
Retinal glial cells	Exposure to high Glucose	Reduced apoptosis	Zeng *et al.* (2010)
Anti-CD3-activated Jurkat cells	IL-2	Reduced apoptosis Downregulation of FasL protein	Maher *et al.* (2005)
Neonatal cardiomyocytes	Ischaemia	Reduced apoptosis Elevation in cellular Bcl-2	Takahashi *et al.* (2003b)
Cardiomyocytes	Ischaemia	Reduced apoptosis Suppression of Apaf-1/caspase-9 apoptosome assembly	Takatani *et al.* (2004)
Ehrlich ascites tumour cells and Ehrlich Lettré cells	Cisplatin	No effect on apoptosis	Tastesen *et al.* (2010)
Mouse supraoptic and paraventricular nuclei	Ischaemia	Reduces apoptosis Reduction in caspase-8 and caspase-9 expression	Taranukhin *et al.* (2008)
Human umbilical vein endothelial cells	Glucose	Reduced apoptosis ROS inhibition and $[Ca^{2+}]_i$ stabilization	Wu *et al.* (1999)
Rat testis	Doxorubicin	Reduces apoptosis Prevents p53 activity, ROS generation and Ca^{2+} mobilization	Das *et al.* (2012)

ROS, reactive oxygen species.

Lessons from animal models

Several animal models have examined the effect of taurine depletion on taurine homeostasis and pathophysiological parameters. Most prominent is the cat, which has an absolute requirement for taurine as its own biosynthesis is virtually non-existent (Knopf *et al.* 1978). Cats reared on a taurine-free diet become taurine-depleted, most rapidly in plasma and soft tissues, such as liver, lung and spleen, but in the end, all tissues become taurine-depleted, resulting in taurine depletion of muscles and heart as well as nervous tissues, brain and retina. The biological end result includes retinal degeneration, impaired visual function, cardiomyopathy, impaired immune function and severely impaired reproduction in females (Knopf *et al.* 1978, Hayes & Trautwein 1989). Pharmacological inhibition of taurine uptake using either β-alanine or guanidine ethanesulfonic acid has also been used to cause taurine depletion in animals with similar effects to those seen in taurine-deprived cats upon for example retinal degeneration (Gonzalez-Quevedo *et al.* 2003) and cardiac function (Pansani *et al.* 2012).

Several mouse knockout models of taurine depletion have been examined. These include the TauT knockout mouse, which has been produced by two different research groups (Heller-Stilb *et al.* 2002, Ito *et al.* 2008), the full body CDO knockout mouse (Ueki *et al.* 2011), the liver-specific CDO knockout mouse (Ueki *et al.* 2012), and recently the CSAD knockout mouse (Park *et al.* 2014). Of these animal models, only the TauT knockout mouse has been examined in detail, and this animal model presents with similar pathophysiological characteristics as the taurine-deprived cat, namely liver fibrosis and hepatitis, cardiomyopathy, decreased kidney function and destruction of nervous tissue (Warskulat *et al.* 2007). Interestingly, when impairing hepatic taurine production by knocking out the CDO gene in the liver, the animals fully compensated by upregulating the extrahepatic CDO amount and taurine biosynthesis in tissues such as kidney, pancreas and adipose tissue (Ueki

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et al. 2012). The animals were thus able to maintain normal taurine plasma and tissue levels even in the absence of dietary taurine (Ueki *et al.* 2012).

Conflict of interest

The authors report no conflicts of interest.

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