

Chapter 25

Taurine's Effects on the Neuroendocrine Functions of Pancreatic β Cells

Christina M. Cuttitta, Sara R. Guariglia, Abdeslem El Idrissi,
and William J. L'Amoreaux

Abstract Taurine plays significant physiological roles, including those involved in neurotransmission. Taurine is a potent γ -aminobutyric acid (GABA) agonist and alters cellular events via GABA_A receptors. Alternately, taurine is transported into cells via the high affinity taurine transporter (TauT), where it may also play a regulatory role. We have previously demonstrated that treatment of Hit-T15 cells with

C.M. Cuttitta (✉)

Department of Biology, College of Staten Island, Staten Island, NY 10314, USA

Center for Developmental Neuroscience, College of Staten Island, Staten Island, NY 10314, USA

e-mail: christinacuttitta@gmail.com

S.R. Guariglia

Department of Biology, College of Staten Island, Staten Island, NY 10314, USA

Advanced Imaging Facility, College of Staten Island, Staten Island, NY 10314, USA

Center for Developmental Neuroscience, College of Staten Island, Staten Island, NY 10314, USA

A. El Idrissi

Department of Biology, College of Staten Island, Staten Island, NY 10314, USA

Advanced Imaging Facility, College of Staten Island, Staten Island, NY 10314, USA

Center for Developmental Neuroscience, College of Staten Island, Staten Island, NY 10314, USA

Graduate Program in Biology (Neuroscience), Graduate Center, City University of New York,
365 Fifth Avenue, New York, NY 10016, USA

W.J. L'Amoreaux

Department of Biology, College of Staten Island, Staten Island, NY 10314, USA

Advanced Imaging Facility, College of Staten Island, Staten Island, NY 10314, USA

Center for Developmental Neuroscience, College of Staten Island, Staten Island, NY 10314, USA

Graduate Program in Biology (Neuroscience), Graduate Center, City University of New York,
365 Fifth Avenue, New York, NY 10016, USA

Graduate Program in Biochemistry, Graduate Center, City University of New York,
365 Fifth Avenue, New York, NY 10016, USA

1 mM taurine for 24 h significantly decreases insulin and GABA levels. We have also demonstrated that chronic *in vivo* administration of taurine results in an up-regulation of glutamic acid decarboxylase (GAD), the key enzyme in GABA synthesis. Here, we wished to test if administration of 1 mM taurine for 24 h may increase release of another β cell neurotransmitter somatostatin (SST) and also directly impact up-regulation of GAD synthesis. Treatment with taurine did not significantly alter levels of SST ($p > 0.05$) or GAD67 ($p > 0.05$). This suggests that taurine does not directly affect SST release, nor does it directly affect GAD synthesis. Taken together with our observation that taurine does promote GABA release via large dense-core vesicles, the data suggest that taurine may alter membrane potential, which in turn would affect calcium flux. We show here that 1 mM taurine does not alter intracellular Ca^{2+} concentrations from 20 to 80 s post treatment ($p > 0.05$), but does increase Ca^{2+} flux between 80 and 200 s post-treatment ($p < 0.005$). This suggests that taurine may induce a biphasic response in β cells. The initial response of taurine via GABA_A receptors hyperpolarizes β cell and sequesters Ca^{2+} . Subsequently, taurine may affect Ca^{2+} flux in long term via interaction with K_{ATP} channels.

Abbreviations

GABA	γ -Aminobutyric acid
Tau	Taurine
GAD	Glutamic acid decarboxylase
TauT	Taurine transporter
LDCV	Large dense-core vesicles
SLMV	Synapse-like microvesicles
SST	Somatostatin

25.1 Introduction

25.1.1 *The Neuroendocrine Nature of the Pancreas*

The pancreas is a dual function organ with both exocrine and endocrine portions. The endocrine portion contains five cell types, including the α - and β -cells responsible respectively for secreting the peptide hormones glucagon and insulin. These are regarded as two master neuroendocrine cells, responsible for maintaining plasma glucose concentrations. Additional endocrine cells include the PP or F cell that secretes pancreatic polypeptide responsible for actions in the gastrointestinal tract, and G-cells that release gastrin to enhance gastric functions. For glucose

homeostasis, it is the relative plasma concentrations of glucose that dictates which of the exocytotic mechanisms predominates release of glucagon or insulin. However, the molecular machinery involved in the process is typically activated through changes in membrane potential facilitated by binding of neurotransmitters to their ionotropic receptors. The final cell type is the δ -cell, which appears to be a master regulator of all islet cells through its release of somatostatin (SST).

Along with the release of crucial glucose catabolic and anabolic hormones, the islet cells also secrete several neurotransmitters. Additional neurotransmitters synthesized or released by islet cells are glutamate (α -cells) and GABA (β -cells). Other neurotransmitters participate in pancreatic regulation, but these are likely from neuronal input. Therefore, the three major neurotransmitters regulating the endocrine pancreas are glutamate, GABA, and somatostatin.

In α -cells, glutamate is stored in LDCV where it is co-released with glucagon (Hayashi et al. 2003). Glutamate may bind to ionotropic glutamate receptors (AMPA-type receptor variant GluR4c-flip) on δ -cells (Muroyama et al. 2004) to stimulate release of somatostatin (SST). Alternately, glutamate may bind to AMPA/KA receptors on α -cells, serving as a positive autocrine mechanism to further glucagon release (Cho et al. 2010; Koh et al. 2012).

In β -cells, insulin is stored in large dense-core vesicles (LDCV) along with some of the γ -aminobutyric acid (GABA) synthesized in the β -cell, while a significant pool of GABA remains in synapse-like microvesicles (SLMV) (Sorenson et al. 1991; Nathan et al. 1995; Braun et al. 2004; Braun et al. 2007). In vivo, plasma glucose levels of ≥ 2.8 mM are sufficient to stimulate the Ca^{2+} -dependent release of insulin from β -cells (Gilon et al. 1991). Any GABA released along with the insulin may be sufficient to bind to GABA_A receptors on α cells, initiating a hyperpolarization of α -cells and reduce glucagon release (Rorsman et al. 1989; Suckale and Solimena 2010).

SST from δ -cells inhibits the release of the insulin and glucagon from α - and β -cells (Ahren 2009). These neurotransmitters allow for communication between islet cells that is complex and sophisticated in allowing for the cell communication in response to a rise or fall in glucose levels. Additionally, regulation of insulin and glucagon release (and thus glucose homeostasis) is also facilitated aided by SST secreted from the pancreatic δ cells in response to high levels insulin and glucagon (Goldsmith et al. 1975; Efendic et al. 1979; Taborsky 1983).

The initiation of insulin exocytosis includes multiple signaling events in the β -cells beginning with the Na^+ -dependent, electrogenic glucose uptake. Once glucose has entered the cytoplasm, glycolysis is initiated, resulting in the cytoplasmic accumulation of ATP; this increase in cytoplasmic ATP inhibits ATP-sensitive K^+ (K_{ATP}) channels, resulting in a depolarization of β -cells. This depolarization ultimately opens voltage-sensitive Ca^{2+} channels; ensuing Ca^{2+} flux stimulates exocytosis of the LDCV containing both insulin and GABA. GABA then binds to the GABA_A receptor on α -cells, initiating a depolarization of α -cells and subsequent inhibition of glucagon or to GABA_A receptors on β -cells (Gu et al. 1993; Braun et al. 2010).

25.1.2 *Taurine as a Potential Neuromodulator*

Taurine is a conditionally essential amino acid whose role as a GABA agonist in the developing brain has been well documented. Taurine concentrations remain high in the neonatal brain for about 6 weeks, and then drops to adult levels and remains as the predominant free amino acid in some tissues (e.g., retina) or second to glutamate (e.g., brain). It is present in high concentrations in excitable cells (neurons, cardiomyocytes and skeletal muscle fibers) and maintains intracellular osmotic balance. Taurine may be synthesized from cysteine (Agrawal et al. 1971) or taken up into cells via the taurine transporter (TauT). In the brain, taurine acts as a GABA agonist, where it binds to GABA_A receptors. Taurine activation of GABA_A chloride channels alters membrane potential via rapid chloride uptake and subsequent hyperpolarization. Alternately, taurine may also exert a neurotransmitter-like effect through activation of glycine receptors. Although there is speculation of a taurine-specific receptor, to date there is no definitive proof of the existence of such a molecule (Wu and Prentice 2010).

In the pancreas, we and others have shown that release of insulin from β cells may be regulated via the GABAergic signaling system (Kawai and Unger 1983; Satin and Kinard 1998; El Idrissi et al. 2009a, 2010, 2012; Braun et al. 2010; L'Amoreaux et al. 2010). Additionally, we have shown that taurine treatment of β -cell lines is sufficient to induce insulin and GABA release (L'Amoreaux et al. 2010). When plasma glucose levels rise, glucose uptake into β -cells leads to increased exocytosis of LDCV containing insulin and GABA. This calcium-dependent exocytosis relies on the activation of voltage-sensitive calcium channels, which are activated upon depolarization of the membrane potential. The depolarization is driven by inhibition of K_{ATP} channels when cytoplasmic ATP levels rise following glycolytic processing of glucose. Taurine also is able to modulate cytoplasmic ATP levels through its interactions with mitochondria (El Idrissi 2008). Additionally, taurine also interacts with the sulfonylurea receptor subunit of K_{ATP} channels to inhibit channel activity (Tricarico et al. 2000). Inhibition of LDCV exocytosis may be derived by an autocrine feedback via activation of β -cell GABA_A receptors (Braun et al. 2010), GABA_B receptors (Gu et al. 1993), or through SST regulation of β -cell activity (McDermott and Sharp 1993; Doyle and Egan 2003). To date, studies have shown taurine's modulatory effects on cell activities through GABA_A receptors, but not GABA_B. We have previously demonstrated that taurine can lead to an up-regulation of somatostatin expression in brain (El Idrissi et al. 2009b) and pancreatic islets (El Idrissi et al. 2010). Taurine can stimulate release of SST from neurons (Aguila and McCann 1985), but as yet there are no reports of taurine's efficacy in stimulating SST release in pancreas.

Therefore, we sought to examine a system by which taurine may participate in glucose homeostasis via GABA and SST signaling. Here, we used an isolated β cell line (Hit-T15) to investigate the efficacy of taurine in altering SST and GAD expression. Furthermore, we tested the efficacy of taurine in initiating calcium flux in these cells. Together, our data suggests that taurine may participate in glucose homeostasis.

25.2 Methods

25.2.1 *Taurine's Effect on Somatostatin and GAD Levels*

Pancreatic β -cell lines Hit T-15 from Syrian hamster were grown in Ham's F12-K medium. For treatments, cells were plated in complete medium on sterile cover glass at 5,000 cells/cm² until ~80% confluent. Cells were serum starved for 24 h prior to glucose and taurine treatments. The media were aspirated and replaced with glucose-free Ham's medium supplemented with 1 mM glucose, 1 mM taurine, or 3 mM glucose for 24 h. Following treatments with the supplemented media, cultures were fixed in 4% paraformaldehyde in PBS. The cells were then prepared for immunohistochemical analysis using the appropriate antibodies diluted 1:400. Primary antibodies included mouse anti-GAD and rabbit anti-somatostatin (Life Technologies/Molecular Probes, Carlsbad, CA). Primary antibodies were detected using goat anti-mouse IgG conjugated with Alexa 633, and goat anti-rabbit IgG conjugated with Alexa 488 (Life Technologies/Molecular Probes, Carlsbad, CA). Following incubation, the cover glass were placed on a drop of antifade (Slow Fade Gold Plus with DAPI) and sealed. The data were collected by confocal microscopy (Leica SP2 AOBS Confocal Microscope, Germany). Gain and offset for the acquisitions were identical for these three treatments.

25.2.2 *Ca²⁺ Flux*

Hit-T15 cells were grown in Hams F12-K medium as described above. For treatments, cells were plated in complete medium on sterile cover glass at 5,000 cells/cm² until ~80% confluent. Once confluent cells were incubated for 4 h with a 5 μ M/ml solution of the fluorescent Ca²⁺ indicator Fluo-3 (Life Technologies/Molecular Probes, Carlsbad, CA). Following incubation, β -cells were treated with 1 mM glucose, 3 mM glucose, or 1 mM taurine. Live cell imaging (Zeiss Cell Observer; Carl Zeiss, Thornwood, NY), was used to detect Ca²⁺ flux every 15 s for a 5 min period following treatment. Images were obtained using both bright field and FITC filters.

25.2.3 *Statistic Analysis*

Statistical analyses were performed on intensity values using a one-way ANOVA and Bonferroni post hoc analyses (Prism). Values are expressed as the mean \pm SEM. Differences were considered statistically significant when the calculated *p* value was less than 0.05.

25.3 Results

25.3.1 Taurine Does Not Alter Expression of SST or GAD

We report here for the first time the presence of SST in the Hit-T15 cell line (Fig. 25.1). Previous studies have confirmed the presence of a SST receptor in this cell line (Thermos et al. 1990; Seaquist et al. 1995; Cheng et al. 2002; Yao et al. 2005), but to date we find no evidence in the literature confirming the expression of the neurotransmitter within these cells. The *in vivo* role of somatostatin is to modulate exocytosis of LDCV in islets, presumably through the inhibition of Ca^{2+} flux (Yao et al. 2005). We speculate that these transformed cells may express somatostatin to serve as an autocrine regulator of cell function.

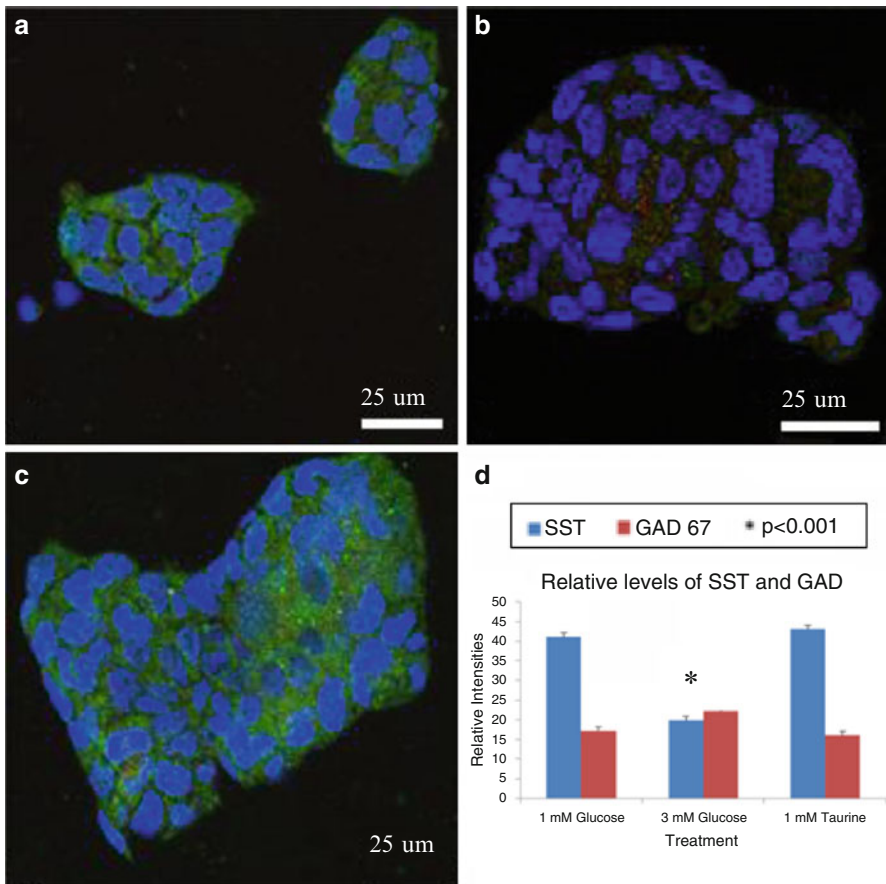


Fig. 25.1 (a) Hit-T15 cells treated with 1 mM glucose. Staining for SST (green) and GAD67 (red). (b) Hit-T15 cells treated with 3 mM glucose. SST levels are decreased and GAD67 increased. (c) Treatment with 1 mM taurine has no effect on the release of SST or expression of GAD67. (d) Only treatment with 3 mM glucose significantly impacted SST levels ($p < 0.001$); neither 3 mM glucose nor 1 mM taurine affected GAD67 expression

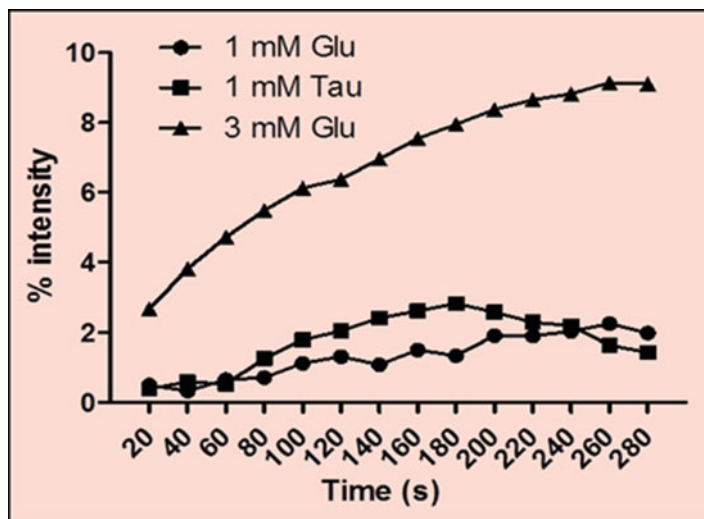


Fig. 25.2 Calcium flux in Hit-T15 β cell line using the fluorescent indicator Fluo-3. Treatment with 3 mM increases Ca^{2+} flux immediately whereas 1 mM taurine exhibited a lag of about 120 s

We also demonstrated here taurine's lack of efficacy in promoting SST release from these cells. Somatostatin levels were significantly decreased ($p < 0.001$) in the presence of 3 mM glucose (Fig. 25.1b, d), but SST levels in the taurine-treated were identical to those cells treated with 1 mM glucose (Fig. 25.1c, d). We also examined the role of taurine in eliciting an increase in GAD67 expression, which we have demonstrated in vivo with taurine treatment (El Idrissi et al. 2009a). We demonstrated that while 3 mM glucose significantly decreased somatostatin and increased GAD levels ($p < 0.05$) compared to those cells treated with 1 mM glucose 1 mM taurine was insufficient in eliciting these responses (Fig. 25.1c, d).

25.3.2 Taurine May Induce a Latent Ca^{2+} Flux

We hypothesized that the exocytosis of LDCV in response to taurine was dependent on the flux of Ca^{2+} . To test the efficacy of taurine in eliciting calcium flux, we pre-loaded Hit-T15 cells with the fluorescent indicator Fluo-3, and then treated cells with subthreshold (1 mM) glucose, suprathreshold (3 mM) glucose, or 1 mM taurine. The 1 mM glucose was insufficient to induce calcium flux, yet 3 mM glucose did cause a significant increase in calcium flux ($p < 0.001$; Fig. 25.2). There were no significant differences in Ca^{2+} flux between 1 mM glucose and 1 mM taurine in the first 60 s following treatment ($p > 0.05$; Fig. 25.2). Following the initial 60 s, there was a significant increase ($p < 0.005$) in Ca^{2+} levels in the taurine-treated cells that persisted for an additional 120 s (Fig. 25.2).

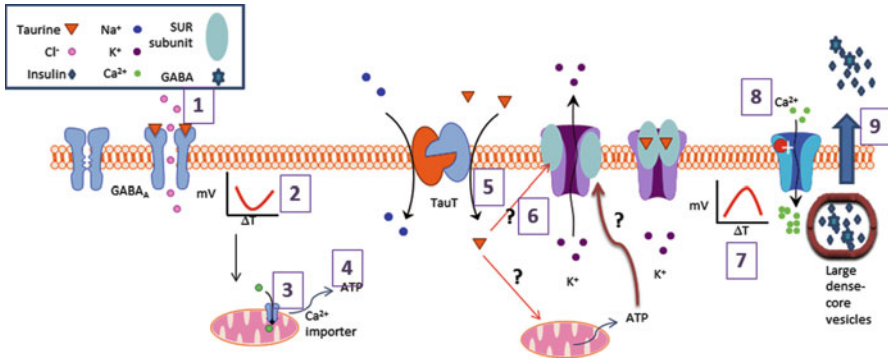


Fig. 25.3 Scheme proposing the dual roles of taurine in eliciting exocytosis of LDCV containing insulin and GABA. In Steps 1–4, taurine elicits sequestration of Ca^{2+} ; in Steps 5–7 either interaction with K_{ATP} channels or cytoplasmic ATP increase via the GABA_A receptor or both activates voltage-sensitive Ca^{2+} channels for Ca^{2+} flux required for exocytosis

These data suggests that taurine may initially initiate calcium sequestration, followed by calcium flux via a second mechanism. The data are similar to findings of taurine's role in calcium sequestration in neurons (El Idrissi and Trenkner 2003; El Idrissi 2008). Taurine increases cytoplasmic ATP levels as a consequence of mitochondrial calcium buffering (Han et al. 2004; El Idrissi 2008). Taurine likely increases cytoplasmic ATP levels by increasing mitochondrial Ca^{2+} influx via the Ca^{2+} uniporter, which increases mitochondrial metabolic function (Han et al. 2004). This strongly suggests that in these studies using a β -cell line, taurine is most likely acting via GABA_A receptors initially. Because β -cells in vivo express GABA_A receptors, we hypothesize that taurine's initial action in intact islets is to bind to GABA_A receptors on β cells, causing both a hyperpolarization of the membrane and calcium sequestration. Following prolonged exposure to taurine, taurine may enter the cell via TauT where we hypothesize that intracellular taurine may bind to the K_{ATP} channel, polarizing the membrane and initiating Ca^{2+} flux that subsequently leads to prolonged exocytosis of the LDCV.

25.3.3 Proposed Model for Taurine's Influence on Insulin Release

We propose that taurine may act through two independent mechanisms, one short term and the other long term (Fig. 25.3). Initially, taurine binds to GABA_A receptors (Step 1), initiating rapid Cl^- influx and hyperpolarization of β cells (Step 2). This hyperpolarization triggers calcium sequestration (Step 3), initially buffering the cell and increasing cytoplasmic ATP levels (Step 4). The timing of these initial four step must be further investigated. It is possible that the initial phase (Steps 1–4) will

permit exocytosis of insulin by increasing cytoplasmic ATP levels and inhibiting K_{ATP} channels. Alternately, this may be a short-term (2 min) mechanism for β cells to retain intracellular insulin. During the subsequent 2 min interval, Ca^{2+} might be sufficient to permit limited release of insulin (Fig. 25.2).

With long-term (24 h) exposure to taurine, TauT takes up the taurine (Step 5), which may then interact with the K_{ATP} channel's sulfonylurea receptor subunit (Step 6) to inhibit the channel (Tricarico et al. 2000; Schaffer et al. 2010). Through either or both mechanisms, taurine treatment increases cytoplasmic ATP levels, inhibiting K_{ATP} channels and triggering a depolarization of β cells (Step 7), which in turn activates voltage-sensitive calcium channels (Step 8) and thus calcium flux and exocytosis of the LDCV (Step 9). Through our work and the work of others, the hypothesis of the modes of action of taurine is certainly plausible. Our laboratory will continue to examine the roles of taurine in eliciting release of insulin from the β cells.

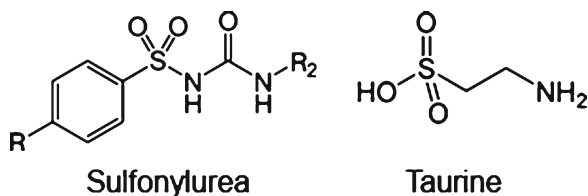
25.4 Discussion

In the *in vivo* environment, when interstitial fluid levels reach ~ 3 mM glucose pancreatic β -cells respond by releasing insulin and inhibiting glucagon release. In our *in vitro* studies, we used 3 mM glucose as our minimal dose required to initiate insulin release. Conversely, 1 mM glucose served as a control dose in which insulin should not be released. When examining the relative fluorescence intensity of insulin and GABA in the Hit cells, abundant signals for both markers were observed (L'Amoreaux et al. 2010). In those studies, we demonstrated that 1 mM taurine alone is effective in lowering plasma insulin and glucose as the values observed were significantly lower than those cells treated with the subthreshold glucose concentration of 1 mM.

Since taurine can affect release of insulin and GABA from LDCV, we demonstrated here that the mechanism by which taurine promotes exocytosis of these vesicles is different from the mechanism by which SST is released. Further, we provided evidence that the taurine-dependent up-regulation of GAD expression requires a feedback mechanism from α cells. We believe that in chronic administration of taurine during early pancreatic development, that a feedback mechanism between α and β cells provide a mechanism through which taurine alters expression of the $\beta 2$ subunits of $GABA_A$ receptors, which leads to a requirement for increased GABA and thus increased GAD expression. As *in vivo* β cells also express $GABA_A$ receptors (Braun et al. 2010), an evaluation of $GABA_A$ receptor expression on this cell line is warranted and is forthcoming.

Taurine likely interacts with pancreatic β cells through two mechanisms. Initially, taurine binds to $GABA_A$ receptors to inhibit exocytosis of LDCV. Taurine is a potent GABA agonist and, as such, is likely playing a role in the feedback mechanism to inhibit further release of insulin via LDCV exocytosis. During a prolonged exposure to taurine, the amino acid is transported into β cells via the TauT transporter.

Fig. 25.4 Comparison of generic sulfonylurea molecule with taurine



Once in the cytoplasm, taurine may bind to the sulfonylurea receptor (SUR) of the ATP-dependent potassium channels. There is strong evidence that taurine can interact with SUR in muscle cells (Tricarico et al. 2000; Schaffer et al. 2010). Use of glibenclamide, a sulfonylurea, in perfused isolated pancreases moderately increases insulin release (Efendic et al. 1979) and also enhances the release of arginine-dependent release of SST (Efendic et al. 1980). Based upon the chemical similarities of the two molecules (Fig. 25.4), it is plausible that taurine may also serve as an antidiabetic agent and work via inhibition of K_{ATP} channels.

25.5 Conclusion

Taurine may serve as a cost-effective treatment for diabetes in that it promotes insulin release from β cells. We present evidence that short-term administration of taurine (such as in the diet) may elicit a response via $GABA_A$ receptors and restrict insulin release. With chronic administration of taurine, binding of taurine to the ATP-dependent potassium channels may elicit insulin release. Further studies are needed to confirm these observations and to determine the role of TauT in regulating insulin release from β cells.

Acknowledgments We thank Jonathan Blaize and Janto Tachjadi for assistance with the confocal microscopy. Support for the confocal microscope comes from the National Science Foundation (DBI 0421046). Support also from the Professional Staff Congress of the City University of New York. We would also like to thank the Organizing Committee of the 18th International Taurine Meeting for the scientific and social programs and the participants that made this a memorable conference.

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