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Reduced Placental Taurine Transporter (TauT) Activity in Pregnancies Complicated by Pre-eclampsia and Maternal Obesity

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Abstract

Taurine is an important nutrient in intrauterine life, being required for fetal organ development and cellular renewal of syncytiotrophoblast (STB), the nutrient transport epithelium of the placenta. As taurine is conditionally essential in human pregnancy, the fetal and placental demand for taurine is met by uptake from maternal blood into STB through the activity of TauT. Pre-eclampsia (PE) and maternal obesity are serious complications of pregnancy, associated with fetal growth restriction (FGR) and abnormal renewal of STB, and maternal obesity is a major risk factor for PE. Here we test the hypothesis that STB TauT activity is reduced in maternal obesity and PE compared to normal pregnancy.

STB TauT activity, measured in fragments of placental tissue, was negatively related to maternal BMI over the range 18–46 kg/m^2 in both the first trimester (7–12 weeks gestation) and at term ($p < 0.01$; linear regression). Neither TauT activity nor expression in the first trimester differed to normal pregnancy at term. STB TauT activity was significantly lower in PE than normal pregnancy ($p < 0.01$). Neuropeptide Y (NPY), a protein kinase C (PKC) activator which is elevated in PE and obesity, reduced STB TauT activity by 20% (50 pM–50 nM: 2 h) ($p < 0.03$). Activation of PKC by phorbol 12-myristate-13-acetate (1 μM) reduced TauT activity by 18% ($p < 0.05$). As TauT activity is inhibited by phosphorylation, we propose that NPY activates PKC in the STB which phosphorylates TauT in PE and maternal obesity.

Reduced TauT activity could contribute to dysregulated renewal of STB and FGR that are common to PE and maternal obesity.

9.1 Introduction

Taurine is a vital nutrient for fetal well-being and animal studies demonstrate a key role for this amino acid in promoting the development of fetal brain, heart, kidney, pancreas, retina, and skeletal muscle (Sturman 1988; Han et al. 2000; Heller-Stilb et al. 2002). In human pregnancy taurine is conditionally essential, as the fetus and placenta lack the enzyme

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required for taurine synthesis (Gaull et al. 1972), and the fetal demand for taurine must be met by placental transfer from maternal blood. Nutrients are transported across the human placenta via the syncytiotrophoblast (STB), a highly specialised multinucleate epithelium with a microvillous plasma membrane (MVM) in direct contact with maternal blood and a basal membrane (BM) in close apposition to the fetal capillary. Taurine is transported into STB by the Na^+-dependent amino acid transporter TauT, which is expressed on the MVM (Roos et al. 2004). TauT accumulates taurine in the cell (STB concentration 10 mM, maternal and fetal plasma 60 and 120 μM, respectively) such that taurine is the most abundant free amino acid in STB (Philipps et al. 1978). This high intracellular taurine provides a driving force for taurine efflux to the fetus, thought to occur through taurine-permeable anion channels (Shennan and McNeillie 1995; Vallejos and Riquelme 2007).

Studies of fetal growth restriction (FGR) suggest that taurine is important for human fetal growth and development. Idiopathic FGR is a condition in which the fetus fails to achieve its growth potential in the absence of genetic or environmental abnormalities and the growth-restricted fetus is at increased risk of neonatal mortality and morbidity (McCormick 1985) and development of metabolic and cardiovascular disease in later life (Calkins and Devaskar 2011; Barker 1999). Plasma taurine concentration is lower in FGR compared to the normally grown fetus (Economides et al. 1989; Cetin et al. 1990) and this is associated with a significantly lower TauT activity in the STB MVM compared to normal pregnancy (Norberg et al. 1998).

Pre-eclampsia (PE) is a serious condition affecting 5% of pregnancies worldwide and is the leading cause of maternal and fetal mortality (Hibbard and Milner 1994; CESDI 1998). Those fetuses that survive are at increased risk of FGR and associated morbidities. The aetiology of the disease is complex but its origin lies in abnormal placental development and function (Roberts and Gammill 2005) and the only treatment for PE is premature delivery of the placenta and baby. The incidence of PE rises with increasing maternal body mass index (BMI) and is four times higher in morbidly obese women compared to their ideal weight counterparts (Mbah et al. 2010). The reason that maternal obesity is a major risk factor for developing PE is not understood but as obesity, and in particular morbid obesity, is increasing in women of reproductive age (Heslehurst et al. 2010; Mbah et al. 2010) the incidence of PE is likely to rise in parallel. Maternal obesity is itself associated with abnormal fetal growth, increasing the risk of stillbirth with FGR fivefold compared to mothers of ideal weight (Nohr et al. 2005).

As normal fetal growth and development depend on the appropriate supply of taurine by the placenta we hypothesised that, in common with idiopathic FGR, a reduction in STB TauT activity in maternal obesity and PE could contribute to the increased risk of FGR evident in these conditions. We determined STB TauT activity in placental villous tissue isolated from first trimester and term pregnancies and related activity to maternal BMI at booking. In separate studies we compared STB TauT activity in PE with normal pregnancy. As TauT activity in renal cells is inhibited by protein kinase C (PKC)-induced phosphorylation (Han et al. 2006), we explored the possibility that TauT activity is modulated by neuropeptide Y (NPY), a hypothalamic peptide that activates PKC in STB (Robidoux et al. 1998), is

elevated in obese individuals (Baltazi et al. 2011), and is higher in maternal plasma in PE compared to normal pregnancy (Khatun et al. 2000).

9.2 Methods

9.2.1 Tissue Acquisition and Ethical Approval

Placentas were obtained with written informed consent as approved by the Central Manchester Research Ethics Committee. First trimester placentas (7–13 weeks gestation) were obtained following elective medical or surgical termination of pregnancy. Gestational age was estimated from the date of last menstrual period and confirmed by ultrasound dating. Term placentas (38–40 weeks gestation) were collected following caesarean section or vaginal delivery from uncomplicated singleton pregnancies. Maternal BMI was determined either at admission (studies of first trimester placentas) or at booking (~12 weeks: studies of term placentas) and women defined as ideal weight (BMI 18.5–24.9), overweight (25–29.9), or obese (>30). Placentas were also collected from women (BMI <30) with PE (defined as hypertension >140/90 mmHg in previously normotensive women plus proteinuria >300 mg/L in a 24-h urine collection after 20 weeks gestation).

9.2.2 Quantitative PCR Analysis of TauT mRNA Expression

Placental tissue was lysed and total RNA extracted using Absolutely RNA Miniprep Kit (Stratagene, USA). RNA was quantified using Quant-iT Ribogreen kit (Molecular Probes) and 100 ng of total RNA from each sample reverse transcribed using AffinityScript cDNA synthesis kit with random primers (Stratagene, USA). mRNA for TauT (SLC6A6) and β-actin were quantified by QPCR using Stratagene's MX3000P real-time PCR machine and Brilliant SYBR Green I QPCR mastermix (Stratagene, USA) as described previously (Desforges et al. 2006). Primers (MWG-Biotech) for SLC6A6 (forward: 5′ CGTACCCCTGACCTACAACAAA 3′, reverse: 5′ CAGAGGCGGATGACGATGAC 3′) and β-actin (Lacey et al. 2005) were used at a final concentration of 200 nM. QPCR data are presented as median values of percentage expression relative to a 40-week placental sample, designated the calibrator, which was included in each QPCR run as an internal standard (Lacey et al. 2005). The data were analysed by Kruskal–Wallis and Dunn's post hoc tests and $p < 0.05$ was considered significant.

9.2.3 Western Blot Analysis

Protein was extracted from placental villous homogenates and Western blot analysis of TauT and β-actin protein expression carried out as described previously (Champion et al. 2004; Desforges et al. 2006) using a rabbit anti-TauT affinity-purified polyclonal antibody (Alpha Diagnostics. 1:400 dilution; 2.5 μg/ml). For a negative control, the purified TauT antigenic peptide was used in 5× excess to pre-absorb the antibody. Primary and horseradish peroxidase-conjugated secondary antibody incubations were performed for 1 h at room temperature. Positive signals were detected using ECL and the density of the immunoreactive species was assessed using a GS 700 Imaging Densitometer (Bio-Rad Laboratories, Hemel Hempstead, UK) with Molecular Analyst software. Data were analysed using a Mann Whitney test and $p < 0.05$ was considered significant.

9.2.4 TauT Activity Measurements and Effect of Neuropeptide Y

Placental villous fragments were dissected and rinsed in a 1:1 or 1:3 mix of Dulbecco modified Eagle medium (DMEM)/control Tyrode's buffer (135 mM NaCl, 5 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM Hepes, 5.6 mM glucose, pH 7.4). Uptake of ^{3}H-taurine (5/10 μM; 0.5/1 μCi/ml) into villous fragments was measured in control and Na^+-free Tyrode's buffer (135 mM choline chloride replaced NaCl, pH 7.4) as previously described (Greenwood and Sibley 2006). The Na^+-dependent component of ^{3}H-taurine uptake, representing TauT activity, was calculated and expressed per mg fragment protein. The uptake of ^{3}H-taurine at initial rate was considered to be a measure of TauT activity in STB. To study the effect of NPY/PMA on TauT activity, placental fragments were incubated for 2 h (37°C) in NPY (5pM-5nM) or PMA (1 μM) prior to measurement of ^{3}H-taurine uptake. TauT activity in treated tissue was expressed relative to the corresponding untreated control and analysed using a Wilcoxon Signed Rank test where $p < 0.05$ was considered significant.

9.3 Results

9.3.1 Placental TauT Expression and Activity in Normal Pregnancy

There were no significant differences in SLC6A6 mRNA expression between 6–9 weeks and 10–13 weeks gestation, or between these gestations and term (Fig. 9.1a). Western blot analysis of first trimester and term placental homogenates (Fig. 9.1b) revealed a single immunoreactive signal at ~ 70 kDa in all samples, which corresponds to the predicted size of TauT (Ramamoorthy et al. 1994). Pre-absorption of the antibody with 5× peptide abolished this signal (data not shown), confirming antibody specificity for TauT. Densitometric analysis revealed no differences in either TauT (Fig. 9.1b) or β-actin (used to indicate protein loading; data not shown) expression in placentas from the first trimester compared to term. Na^+-dependent ^{3}H-taurine uptake (Fig. 9.1c), representing TauT-specific activity, by first trimester and term placental villous fragments was linear over 5–30 min ($p < 0.005$ for both; least squares linear regression) indicating that uptake was at initial rate. TauT activity in the first trimester did not differ to that at term (Fig. 9.1c).

9.3.2 Placental STB TauT Activity in Maternal Obesity and PE

In both the first trimester and at term, there was significant negative relationship between STB TauT activity and maternal BMI (Fig. 9.2a). Comparison of placental TauT activity in obese women (BMI >30) and ideal weight women (BMI 18–24.9) revealed a significant difference at both gestations ($p < 0.05$, MannWhitney-U test). TauT activity was also significantly lower in PE (ideal weight) than normal pregnancy (Fig. 9.2b).

9.3.3 Placental TauT Activity Following Exposure to Neuropeptide Y

Figure 9.3a shows concentration-dependent inhibition of TauT activity (30 min) in term villous fragments by NPY (50 pM–50 nM; 2 h). TauT activity was reduced to a similar extent by the PKC activator PMA (1 μM) (Fig. 9.3b).

9.4 Discussion

The activity of TauT in the MVM of the human placental STB is important to achieve a high intracellular taurine concentration and maintain a gradient that favours taurine efflux towards the fetus. The finding that STB TauT activity and expression are similar in placentas from the first trimester and at term implies that taurine delivery to the fetus is important for fetal growth and development throughout pregnancy.

Maternal obesity and PE are associated with increased risk of poor fetal outcome, including stillbirth and FGR, which might be related to inadequate transfer of taurine across the placenta. In support of this we found that STB TauT activity was inversely related to maternal BMI, recorded at the first antenatal visit, in both the first trimester and at term. Average TauT activity in women with a BMI >30 was 60–70% lower than their ideal weight (BMI 18.5–24.9) counterparts at both gestations. Furthermore, STB TauT activity was ~ 35% lower in placentas of women with PE (BMI < 30) compared to women having normal pregnancy. This reduction in TauT activity could predispose to FGR in these pregnancy conditions but is unlikely to be singularly responsible, as most of the babies born to the women studied were appropriately grown for gestational age.

A reduction in MVM STB TauT activity will lower intracellular taurine in the absence of compensatory changes in taurine efflux. Placental taurine, measured by chromatography, was found to be lower in infants with low birth weight compared to normal (Ghisolfi et al. 1989) and in preliminary studies (Hirst et al. 2012) we showed that the accumulation of radiolabelled taurine in STB at steady state was lower in PE than in normal pregnancy. In addition to restricting taurine efflux to the fetus, a reduction in intracellular taurine has implications for the maintenance of STB. STB is a unique epithelium, being renewed during pregnancy by a process of cellular turnover involving proliferation of the underlying cytotrophoblast cells followed by differentiation, fusion, and incorporation of their nuclei into the STB (Huppertz et al. 2006; Heazell and Crocker 2008). STB volume is maintained by the deportation of aged nuclei into maternal blood. Coordination of STB renewal is critical for normal pregnancy and cellular turnover is dysregulated in PE (Crocker et al. 2003; Heazell and Crocker 2008) and maternal obesity (Higgins et al. 2011). This dysregulation causes the release of toxic material from STB into maternal blood which can initiate a widespread inflammatory response in the mother and trigger PE (Roberts and Gammill 2005). Using cytotrophoblast cells in vitro, we showed that knocking down TauT expression with siRNA inhibited TauT activity, reduced intracellular taurine, and inhibited the differentiation and fusion of cells to form multinucleate syncytia (Parsons et al. 2009). In addition, TauT knockdown increased apoptosis in response to TNFα (Desforges et al. 2010), a cytokine that is elevated in PE (Tosun et al. 2010) and maternal obesity (Challier et al. 2008). Thus, the reduction in TauT activity and intracellular taurine in PE could impair STB renewal and lower cytoprotection to damaging cytokines, leading to reduced nutrient delivery to the fetus and the release of necrotic material to the mother. The fall in STB TauT activity with increasing maternal BMI, particularly in the first trimester, could predispose to abnormal STB renewal later in pregnancy and might in part explain the increased incidence of PE in obese mothers.

The reduction in STB TauT activity in FGR is not associated with a change in expression (Roos et al. 2004) and our preliminary data show that TauT protein expression is also unaffected by PE (Hirst et al. 2012) or morbid obesity (unpublished observation). This suggests that the low STB TauT activity in these conditions of pregnancy is due to post-translational down-regulation of transporter activity. Regulation of TauT activity has not been studied extensively in placenta but in common with other tissues, activity in trophoblast-derived choriocarcinoma cells (JAr) shows adaptive regulation in response to altered taurine concentration (Jayanthi et al. 1995). As maternal plasma taurine concentration is higher in the first trimester of pregnancies that subsequently develop FGR, compared to those that proceed normally (Di Giulio et al. 2004), adaptive down-regulation could contribute to the reduced STB TauT activity in FGR. However, the reduction in STB TauT activity in FGR has been demonstrated at 32–39 weeks (Norberg et al. 1998) and at this later stage of gestation maternal plasma taurine concentration is reported to be unchanged (Economides et al. 1989) or significantly lower (Cetin et al. 1990) in FGR than normal pregnancy. In PE without FGR, maternal plasma taurine does not differ from normal (Evans et al. 2003) and, although it has yet to be measured in obese mothers in late pregnancy, plasma taurine levels are lower in obese individuals in the general population compared to their ideal weight counterparts (Zhang et al. 2004). Therefore it is unlikely that the reduced STB TauT activity in PE and obesity is caused by adaptive down-regulation. It is of interest that, following labour, the taurine concentration in umbilical blood of normally grown fetuses is reported to be higher in PE than normal pregnancy (Evans et al. 2003). Bearing in mind that STB TauT activity was shown to be reduced in PE in the current study, it is possible that higher umbilical plasma taurine arises from altered fetal metabolism and/or reduced uptake of taurine from fetus to placenta in PE. STB basal membrane expresses TauT (Roos et al. 2004) and vesicle studies show that the activity of TauT in this membrane is not affected by FGR (Norberg et al. 1998). In situ, TauT on the BM would transport taurine from the fetus into STB but the influence of BM TauT activity on net maternal-fetal taurine flux has not been determined in normal or compromised pregnancy. Studies of maternal, placental, and fetal taurine levels in PE and maternal obesity following caesarian section delivery, as well as taurine uptake and efflux mechanisms on STB MVM and BM, are required to gain a better understanding of the relationships beween taurine concentration, TauT activity, and delivery of taurine to the fetus.

In renal epithelial cells, TauT activity is down-regulated by PKC-induced phosphorylation of the transporter (Han et al. 2006) and activation of PKC in JAr cells inhibits TauT activity (Kulanthaivel et al. 1991). STB expresses several PKC isoforms (Tertrin-Clary et al. 1990; Ruzycky et al. 1996), and these can be activated in cytotrophoblast cells in vitro by NPY, a hyopthalamic peptide that is also produced by STB, through activation of Y1 and Y3 receptors on the MVM (Robidoux et al. 1998). As NPY levels in maternal serum are higher in PE than normal pregnancy (Khatun et al. 2000), and elevated in obese compared to ideal-weight individuals in the general population (Baltazi et al. 2011), we investigated whether NPY could downregulate TauT activity in STB. NPY treatment of villous tissue (2 h) induced a small but significant reduction in TauT activity at pathophysiologically relevant concentrations (Petraglia et al. 1989). We also confirmed previous reports that the PKC activator PMA reduces STB TauT activity (Roos et al. 2004). It is possible that NPY is a

modulator of TauT activity that is common to both PE and obesity and future work will address whether PCK is activated in PE and obesity and whether there is an increase in phosphorylated TauT compared to normal pregnancy.

9.5 Conclusion

STB TauT activity is lower in placentas of obese mothers compared to mothers of ideal weight and inversely related to maternal BMI in both the first trimester and at term. STB TauT activity is also lower in PE compared to normal pregnancy. We propose that this reduction in TauT activity lowers STB taurine concentration which impairs STB renewal and reduces taurine transfer to the fetus, contributing to the increased risk of FGR in these conditions. The fall in STB TauT activity with increasing maternal BMI in the first trimester could predispose to abnormal STB renewal and development of PE later in pregnancy. The PKC activator, NPY, caused a small but significant reduction in TauT activity and could downregulate TauT in both PE and obesity. Determining the reasons for, and consequences of, reduced placental TauT activity could lead to strategies to improve pregnancy outcome and fetal growth in obesity and PE.

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Abbreviations

TauT	Taurine transporter
STB	Syncytiotrophoblast
MVM	Microvillous membrane
BM	Basal membrane
PE	Pre-eclampsia
FGR	Fetal growth restriction
BMI	Body mass index
NPY	Neuropeptide Y
PKC	Protein kinase C
PMA	Phorbol12-myristate-13-acetate
QPCR	Quantitative polymerase chain reaction

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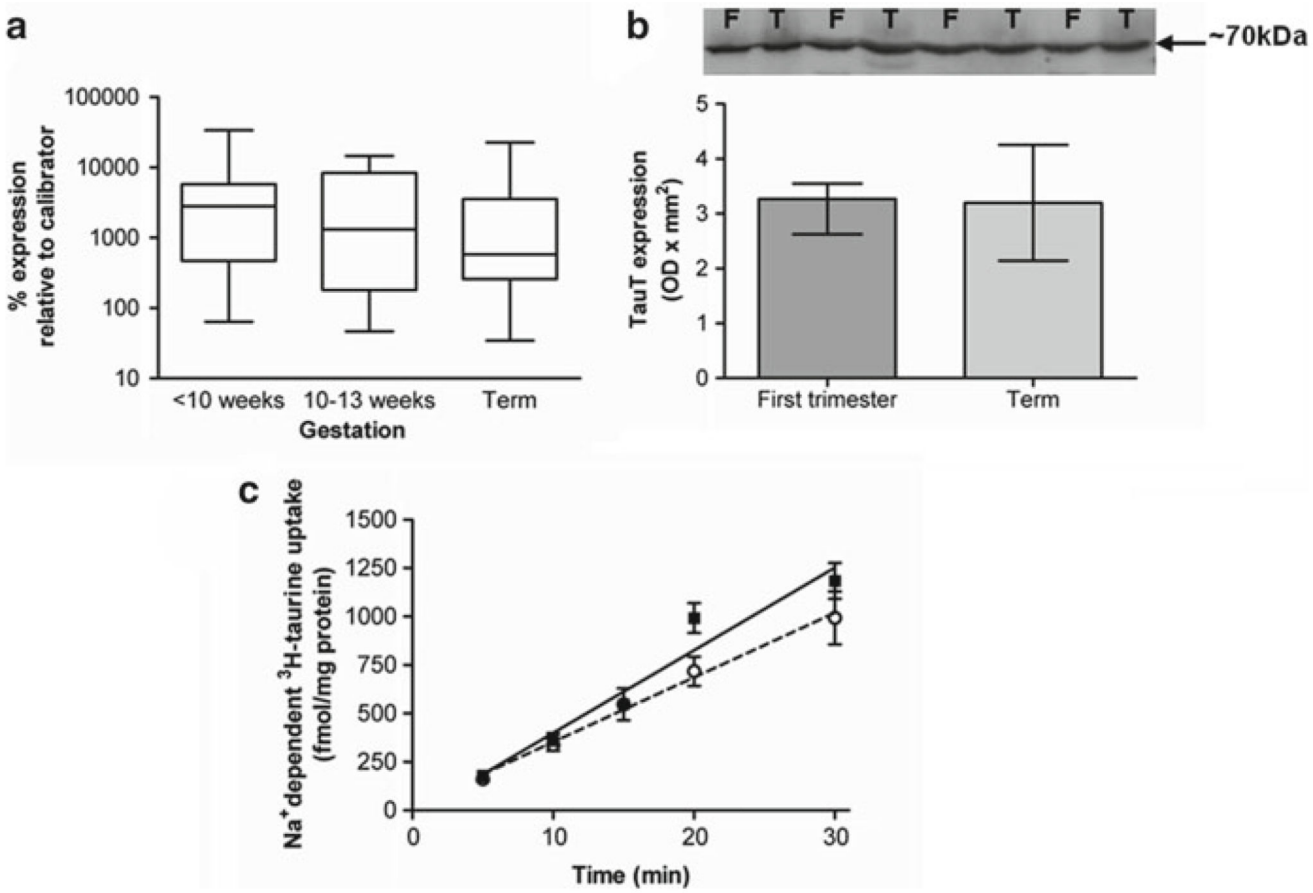

Fig. 9.1.

Placental TauT expression and activity are similar in first trimester and at term. (**a**) TauT mRNA expression relative to a 40-week placental sample, designated the calibrator, included in each run as an internal standard. The groups are early first trimester (6–9 weeks, $n = 23$), late first trimester (10–13 weeks, $n = 12$), and term (38–40 weeks, $n = 21$). (**b**) Western blot of first trimester (F) and term placental (T) samples probed for TauT. A single immunoreactive species was detected at the expected molecular weight of 70 kDa. Bar chart displays densitometric analysis of signal intensity ($n = 4$ for each group, median and interquartile range). (**c**) Na^+-dependent ^3H-taurine uptake by first trimester (*open circles*) and term (*closed squares*) placental villous fragments ($n = 6$ in each group; mean ± SE). At both gestations, ^3H-taurine uptake significantly increased with time ($p < 0.005$; least square linear regression). There was no difference in ^3H-taurine uptake between first trimester and term placenta (2-way ANOVA)

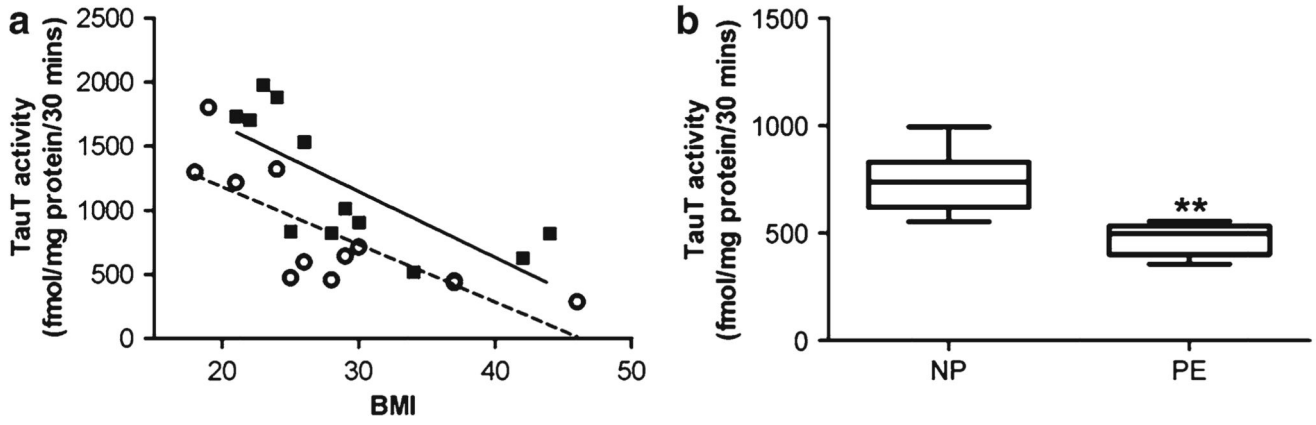

Fig. 9.2.

Placental STB TauT activity is negatively related to maternal BMI and reduced in pre-eclampsia (PE). (**a**) Negative relationship between maternal BMI and TauT activity in first trimester (*open circles*, $n = 12$) and term (*closed squares*, $n = 12$) placental villous fragments. Least square linear regression; $r^2 = 0.60$ and 0.54, respectively, $p < 0.01$ for each. (**b**) TauT activity in normal pregnancy (NP, $n = 9$) and PE (PE, $n = 5$) in women with BMI <30. $p < 0.01$: Mann Whitney-*U* test

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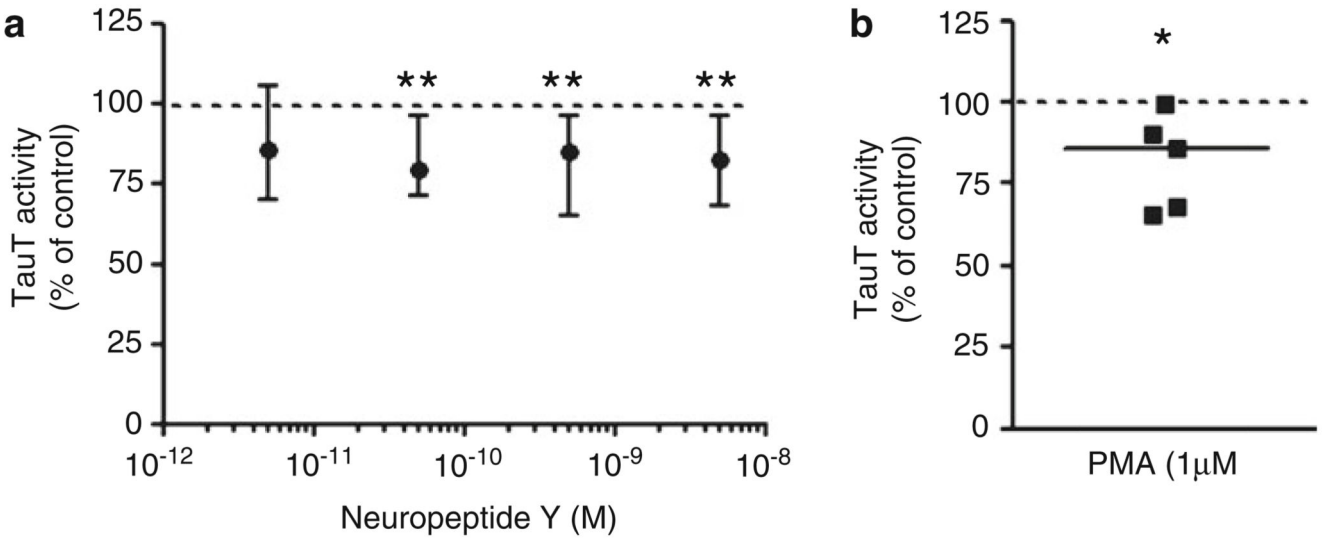

Fig. 9.3.

Placental STB TauT activity is inhibited by neuropeptide Y (NPY) and PMA. Effect of short-term exposure (2 h) to (**a**) NPY (median and interquartile range; $n = 10$) and (**b**) PMA (line at median) on TauT activity in placental fragments (fmol/mg protein/30 min) expressed as % of control. $^{**}p < 0.03$; $^{*}p < 0.05$ vs. 100% (control): Wilcoxon signed-rank test