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European Journal of Pharmacology 495 (2004) 209–215

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Taurine prevents streptozotocin impairment of hormone-stimulated glucose uptake in rat adipocytes

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Received 30 March 2004; accepted 10 May 2004
Available online 19 June 2004

Abstract

Streptozotocin-treated rats were used as models of type 1 diabetes to study the effects of dietary taurine on insulin- and adrenergic-stimulated 2-deoxyglucose uptake by isolated adipocytes. In addition to the well-established impairment of basal and insulin-stimulated 2-deoxyglucose uptakes in adipocytes prepared from streptozotocin-diabetic rats, the α-(phenylephrine) and β-(isoproterenol) adrenergic stimulations of glucose uptake were also abolished. The insulin stimulation of glucose uptake in adipocytes was selectively abolished by the phosphatidylinositol 3-kinase inhibitor wortmannin, whereas that by the adrenergic agonists, phenylephrine and isoproterenol, was inhibited by prazosin and propranolol, respectively. Dietary taurine, 4 weeks before and 4 weeks after streptozotocin administration, prevented the loss of both insulin and adrenergic agonist stimulations of 2-deoxyglucose uptake, without affecting hyperglycaemia. Because insulin and adrenergic activations of glucose transport by adipocytes are coupled to different signalling pathways, it is unlikely that these effects of taurine are related to these disparate postreceptor mechanisms.

Keywords: Diabetes; Isoproterenol; Phenylephrine; Prazosin; Propranolol

1. Introduction

The endogenous amino acid taurine (2-aminoethanesulphonic acid) is present in relatively high concentrations (mM range) in mammalian tissues. Although it is synthesised in the tissues of most mammalian species, diet is a major source for maintaining the large intracellular taurine pools. It appears that taurine may have diverse functions within the tissues, and it has been suggested to act as a neurotransmitter, a GABA-receptor agonist, a regulator of calcium fluxes, an osmoregulator, an antioxidant, and a membrane stabiliser. However, there is no general agreement as to its fundamental role(s) (for reviews, see Huxtable, 2000; Della Corte et al., 2002).

Taurine has been reported to be cytoprotective in several model systems, for example, protecting renal tubular cells (Hizoh and Haller, 2002), endothelial cells (Alfieri et al., 2002), neurones (see Foos and Wu, 2002), and hepatocytes (Kurz et al., 1998) from apoptosis. In contrast, it has been reported to be unable to protect eosinophils against oxidative stress (Wedi et al., 1999), and Schaffer et al. (2002) have reported that taurine depletion protected cardiomyocytes against hypoxia. Furthermore, Herdener et al. (2000) have suggested that taurine may inhibit the specifically targeted apoptosis of transformed fibroblasts.

When administered in vivo, taurine has been reported to act as a thermoregulator and an anticonvulsant (see Huxtable, 2000) and to improve brain function in infants (Benson and Masor, 1994). Dietary supplementation with taurine has also been reported to reduce the risk of a number of diseases, including inflammatory bowel disease (Son et al., 1998), ischemia (McCarty, 1999), and cardiovascular disease (Kendler, 1997), and also perhaps to reduce neurodegeneration in the elderly (Wallace and Dawson, 1990).

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doi:10.1016/j.ejphar.2004.05.004

There is evidence that taurine may have beneficial effects in diabetes. Plasma and tissue levels of taurine are reduced in diabetes (see, e.g., De Luca et al., 2001; Pop-Busui et al., 2001). Dietary supplementation with taurine was shown to protect pancreatic β-cells in the streptozotocin model of type 1 diabetes (Chang, 2000). The hyperglycaemia associated with diabetes is believed to be responsible for many of the longer-term adverse effects of this condition, including increased mortality from related cardiovascular pathologies and an increased risk of developing renal failure, retinopathy, and blindness (see Fuchs et al., 2002). Taurine has been shown to protect the lens against reactive oxygen radical-induced toxicity (Devamanoharan et al., 1998), and it has also been shown to protect renal tubule cells (Verzola et al., 2002) and vascular endothelial cells from high glucose-induced toxicity (Wu et al., 1999).

Taken together, these data suggest that dietary taurine supplementation may be of benefit in the treatment or management of diabetes. In the present study, we have used the well-established streptozotocin model of type 1 (insulin-dependent) diabetes to investigate the effects of taurine supplementation on the insulin and adrenergic stimulation of glucose uptake into the rat adipocyte. Adipocytes are known to be dependent on insulin for the maintenance of their normal functions and to express the GLUT4 glucose transporter (for reviews, see Trayhurn and Beattie, 2001; Rajala and Scherer, 2003). The expression of a number proteins that characterise and sustain the adipocyte phenotype is under the control of insulin, and their metabolic and endocrine functions are also dependent on an adequate level of glucose transport into the cell. These factors result in adipocytes being a good model for studying the functional and metabolic consequences of diabetes. Furthermore, they have been shown to express the taurine transporter, and it has recently been reported that cysteine dioxygenase, a key enzyme of taurine biosynthesis, may be regulated in adipocytes by the levels of insulin (Satsu et al., 2003), making it particularly relevant to study the effects of taurine supplementation in the cells from this tissue.

2. Materials and methods

2.1. Animals and experimental design

Male Sprague–Dawley rats, weighing 100–110 g (Harlan-Nossan, Milano, Italy), were housed under controlled temperature (25–30 °C) and a 12-h light/12-h dark cycle (light on at 8:00 a.m.). All the experiments involving laboratory animals were performed according to the Italian Guidelines for Animal Care (D.L. 116/92), which were also in accordance with the European Communities Council Directives (86/609/ECC). The animals were acclimatised for 1 week before use in experiments then randomly subdivided into the following four treatment groups and kept for 8 weeks with free access to food and water:

Taurine-pretreated Control group ($n=6$): control rats treated with taurine (free access to drinking water containing 3% taurine) for 4 weeks before and 4 weeks after a single injection of vehicle (citrate buffer, pH 4.5) into the tail vein;
Taurine-pretreated Diabetic group ($n=11$): rats pretreated with taurine for 4 weeks before and 4 weeks after the induction of diabetes by a single injection of streptozotocin into the tail vein (65 mg/kg body weight, dissolved in citrate buffer, pH 4.5, immediately before use).
Diabetic group ($n=9$): diabetic rats kept for 4 weeks before and 4 weeks after the induction of diabetes, as described for the Taurine-pretreated Diabetic group.
Control group ($n=6$): control rats kept for 8 weeks without any treatment.

At the end of the 8-week treatment, the animals were fasted overnight and then killed by a blow to the head. Blood samples were collected in heparinised glass capillary tubes and used for the immediate preparation of plasma. The epididymal fat pads were removed and used for the preparation of adipocytes.

2.2. Analysis of plasma taurine and glucose concentration

Proteins were removed from plasma by precipitation with methanol (4:1, v:v) followed by a 5-min centrifugation step (3000 rpm). The content of taurine in the supernatant was then determined by high-performance liquid chromatography with fluorescence detection of the *o*-phthalaldehyde derivative, as described by Bianchi et al. (1999). Plasma glucose was evaluated using a diagnostic reagent kit from Sigma-Aldrich (Milano, Italy).

2.3. Determination of 2-deoxy-D-glucose uptake by adipocytes

Adipocytes were obtained by collagenase digestion, as described by Rodbell (1964). The uptake of 2-deoxy-D-glucose by white adipocytes was measured by filtration assay. An aliquot of 2.5×10^4 cells was distributed in plastic multiwells containing 1% bovine-serum albumin (BSA) and 2 mM pyruvate in glucose-free Krebs–Ringer bicarbonate, pH 7.4 (reaction volume 500 μl). A 10-min preincubation, at 37° in 5% CO_2 atmosphere, was performed before the addition of pharmacological stimuli. After preincubation, insulin (70 nM; Humulin 100 U/ml) was added and further incubated for 45 min before the addition of 2-deoxy-D-[1,2-^{3}H]glucose (40 μM; 111 kBq); the α- and β-adrenoceptor agonists, 10^{-8} M phenylephrine and 10^{-10} M isoproterenol, respectively, were incubated with the cells for 10 min before the addition of labelled glucose. The α- and β-adrenoceptor antagonists, prazosin (10^{-4} M) and

propranolol (10^{-4} M), respectively, were incubated with the cells for 10 min before the addition of their respective agonists. Wortmannin (1 μM) was incubated with the cells 30 min before the addition of insulin or phenylephrine. 2-deoxyglucose uptake, which was linear for up to 30 min, was evaluated 15 min after the addition of labelled deoxyglucose. The reaction was blocked by adding ice-cold buffer (500 μl) to the reaction mixture and was quickly filtered on cellulose nitrate filters (8 μm; Sartorius) under light vacuum. The filters were immediately washed with 10 ml of cold buffer and digested in 5 ml of Filter-Count (Packard BioScience, Pero-Milano, Italy). 2-Deoxylucose uptake was expressed as pmol/10^6 cells/15 min.

2.4. Statistical analysis

The significance of the differences between groups was determined by analysis of variance (ANOVA) followed by Dunnett's multiple comparison test, using GraphPad InStat™. The level of significance was set at $P < 0.05$.

2.5. Chemicals

Streptozotocin, *o*-phthalaldehyde, L-phenylephrine-hydrochloride, L-isoproterenol-hydrochloride, prazosin-hydrochloride, D,L-propranolol-hydrochloride, wortmannin, and 2-deoxy-D-glucose were obtained from Sigma-Aldrich. Insulin (Humulin 100 UI/ml) was obtained from Eli Lilly (Firenze, Italy) and 2-deoxy-D-[1,2-^{3}H]glucose (60 Ci/mmol) was from ICN Biochemical (Segrate-Milano, Italy). Taurine was a kind gift from P.C.A. (Basaluzzo-Alessandria, Italy). All other reagents were of the highest grade available.

3. Results

3.1. Experimental groups

As shown in Table 1, at the end of the 4 weeks after streptozotocin (65 mg/kg) treatment, the diabetic rats were characterised by a significantly lower body weight (65%) and severe regression of the epididymal fat (>98%) and significantly higher plasma glucose concentration (271%) and water consumption (550%), as compared to the control rats.

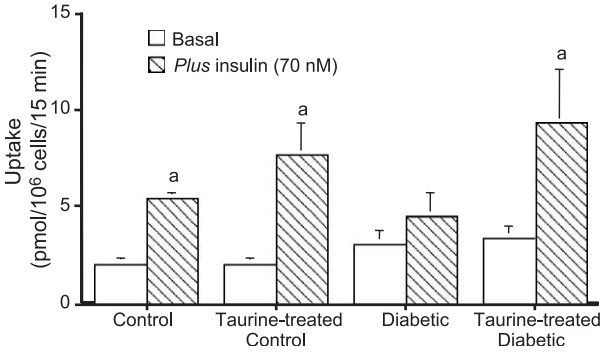

Fig. 1. Effect of insulin on 2-deoxyglucose uptake by epididymal white adipocytes from control (Control), taurine-pretreated control (Taurine-treated Control), streptozotocin-diabetic (Diabetic), and taurine-pretreated diabetic (Taurine-treated Diabetic) rats. 2-Deoxyglucose uptake was determined as described under Materials and methods. Data are means ± S.E.M. of four to seven independent experiments (each done in triplicate). a, $P < 0.05$ vs. basal; (ANOVA and Dunnett's multiple comparison test).

Taurine pretreatment did not significantly affect any of these parameters, either in the control or the diabetic rats.

The very low amounts of epididymal fat pad in the diabetic animals were just sufficient for adipocyte preparation but limited the amount of experiments that could be performed.

The plasma taurine levels were found to be significantly lower in the diabetic rats (61% of control rats). Taurine pretreatment of control rats resulted in significantly higher plasma taurine (413% of control rats). The effect of taurine pretreatment on the plasma taurine levels was even more pronounced in the diabetic rats (the taurine-pretreated diabetic rats were 1921% of diabetic rats and 1170% of control rats). The significantly higher water intake of the diabetic group may have contributed, at least in part, to this effect.

3.2. Basal and stimulated 2-deoxyglucose uptakes

The uptake of 2-deoxyglucose was measured in adipocytes, isolated from the different groups of rats, under basal conditions and stimulated conditions. As shown in Fig. 1, the presence of insulin (70 nM) induced a fivefold increase in 2-deoxyglucose uptake over basal value

Table 1
Mean values ± S.E.M. of body weight, epididymal fat, water intake, glucose, and taurine plasma concentration measured in each treatment group at the end of the experiment

Treatment group	Body weight (g)	Epididymal fat (mg)	Water intake (ml/day)	Plasma glucose (mg/dl)	Plasma taurine (μM)
Taurine-treated Control ($n = 6$)	392 ± 5	4473 ± 424	38 ± 2	83 ± 11	95 ± 13[a]
Taurine-treated Diabetic ($n = 11$)	223 ± 12[b]	78 ± 8	175 ± 7[b]	208 ± 22[b]	269 ± 37[a]
Diabetic ($n = 9$)	247 ± 13[b]	67 ± 7	165 ± 9[b]	222 ± 13[b]	14 ± 2[a]
Control ($n = 6$)	380 ± 7	4367 ± 184	30 ± 3	82 ± 10	23 ± 4

n = Number of rats.
[a] $P < 0.05$ vs. control (ANOVA and Dunnett's multiple comparison test).
[b] $P < 0.05$ vs. taurine-treated control.

($P<0.05$) in adipocytes prepared from taurine-pretreated controls. Wortmannin, a potent inhibitor of phosphatidylinositol 3-kinase (Okada et al., 1994), at a concentration of 1 μM, abolished the stimulation of 2-deoxyglucose uptake induced by insulin (results not shown). Although there was a significant uptake of glucose under basal conditions by adipocytes prepared from diabetic animals, insulin was no longer able to induce any significant stimulation. When adipocytes from taurine-pretreated diabetic animals were tested, basal and insulin-stimulated glucose uptakes were found not to be significantly different from those observed in control taurine-pretreated rat adipocytes (Fig. 1).

Adrenergic-dependent glucose uptake was also studied in adipocytes isolated from control and taurine-pretreated control rats by using phenylephrine (10^{-8} M) and isoproterenol (10^{-10} M) as selective α- and β-adrenoceptor agonists, respectively. As shown in Fig. 2, both phenylephrine and isoproterenol significantly stimulated glucose uptake over basal levels ($P<0.05$). The specificity of these stimulatory effects was tested using the selective α- and β-adrenoceptor antagonists, prazosin (10^{-4} M) and propranolol (10^{-4} M), respectively (Fig. 2). The stimulating effect of phenylephrine was completely abolished by the presence of prazosin, whereas the stimulating effect of isoproterenol was similarly prevented by the presence of propranolol.

Neither phenylephrine nor isoproterenol was able to induce any significant effect on the basal rate of 2-deoxyglucose uptake in adipocytes from the diabetic group (Fig. 3). However, adipocytes from taurine-pretreated diabetic animals maintained their adrenergic responses. Indeed, they showed a significantly higher α-adrenergic stimulation of 2-deoxyglucose uptake ($P<0.05$) compared to the effect observed in taurine-pretreated controls (Fig. 3).

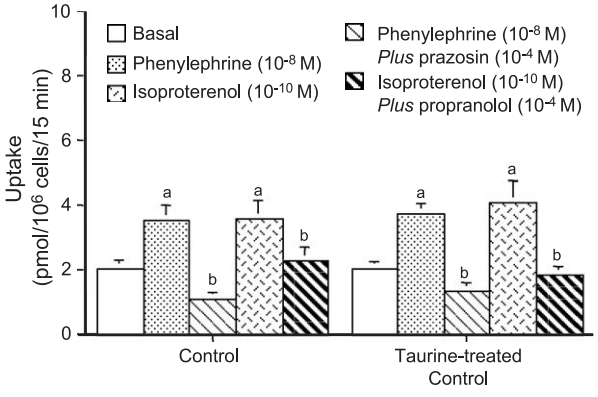

Fig. 2. Effect of adrenoceptor antagonists on 2-deoxyglucose uptake induced by phenylephrine and isoproterenol in adipocytes from control (Control) and taurine-pretreated normoglycaemic rats (Taurine-treated Control). Glucose uptake induced by phenylephrine and isoproterenol was reduced by prazosin (10^{-4}) and propranolol (10^{-4}), respectively. Data are mean values ± S.E.M. of four to six independent experiments (each done in triplicate). a, $P<0.05$ vs. basal; b, $P<0.05$ vs. phenylephrine or isoproterenol (ANOVA and Dunnett's multiple comparison test).

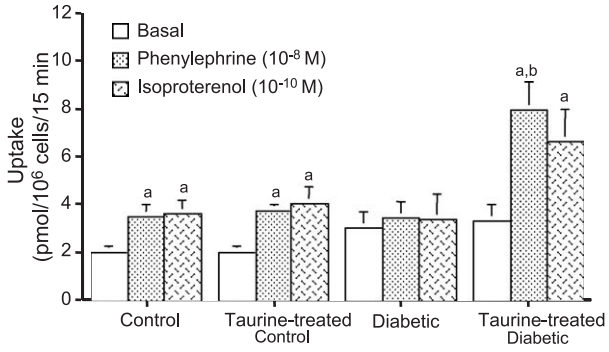

Fig. 3. Adrenergic-induced glucose uptake in adipocytes from control (Control, $n=6$) streptozotocin-diabetic (Diabetic, $n=7–8$) rats, taurine-pretreated streptozotocin-diabetic (Taurine-treated Diabetic, $n=6$) rats, and taurine-pretreated control (Taurine-treated Control, $n=4–6$) rats. Data are mean values ± S.E.M. of n independent experiments (each done in triplicate); a, $P<0.05$ vs. basal; b, $P<0.05$ phenylephrine in taurine-pretreated streptozotocin-diabetic rats (Taurine-treated Diabetic) vs. phenylephrine in taurine-pretreated control (Taurine-treated Control) rat adipocytes (ANOVA and Dunnett's multiple comparison test).

4. Discussion

The impairment of basal and insulin-stimulated 2-deoxyglucose uptakes in adipocytes prepared from streptozotocin-diabetic rats is well established (see Sauerheber et al., 1984). However, to our knowledge, this is the first report to show that streptozotocin treatment also abolishes the α-(phenylephrine) and β-(isoproterenol) adrenoceptor stimulations of glucose uptake in adipocytes. The data reported here show that pretreatment with taurine prevents this loss of both insulin and adrenergic agonist stimulations of 2-deoxyglucose uptake in isolated adipocytes, without affecting hyperglycaemia. Although dietary taurine supplementation has been reported to protect pancreatic β-cells against streptozotocin toxicity (Chang, 2000), the taurine- and streptozotocin-treated animals in the present study were clearly type 1 diabetic by the criteria of hyperglycaemia, weight loss, and fluid intake. It would be of interest in this respect to investigate whether taurine has similar effects on other insulin-sensitive tissues.

There appears to be an interplay between glucose levels and those of taurine. The significantly lower plasma levels of taurine observed in the diabetic rats (Table 1) are in agreement with previous reports of depletion of taurine levels in plasma (De Luca et al., 2001) and/or tissues (Pop-Busui et al., 2001) both in human diabetic subjects and in animal models of diabetes. Physiological concentrations of insulin have been shown to enhance taurine uptake in retina from streptozotocin-induced diabetic rats (Salceda, 1999), which might account for the low internal concentration of taurine induced

by diabetes in that tissue. Furthermore, high glucose concentrations have been shown to decrease the activity of the Na^+-taurine cotransporter and its mRNA abundance rapidly and specifically in retinal cells (Stevens et al., 1999).

The specific receptors mediating insulin and adrenergic activation of glucose transport by adipocytes are coupled to different signalling pathways. The inhibition of insulin-stimulated glucose transport by wortmannin is consistent with phosphatidylinositol 3-kinase being an essential component in the insulin-signalling cascade that stimulates glucose uptake and GLUT4 translocation (Heller-Harrison et al., 1996). Adrenergic stimulation of glucose uptake by adipose cells has been reported to occur, both in vitro and in vivo, through the specific activation of both β_3 adrenoceptors, which are linked to adenylate cyclase (Shimizu et al., 1996), and α_1 adrenoceptors, which involve phospholipase C/protein kinase C activation (Faintrenie and Geloen, 1998). Because pretreatment with taurine prevented the diabetes-induced loss of response to both insulin and the adrenergic agonists, it is likely that post-receptor mechanisms that are common for the three receptors are involved. This would be consistent with the report that insulin receptor levels are increased rather than decreased in diabetes (Kasuga et al., 1978). Further work will be required to show whether the effects involve the GLUT4 transporter itself, its transport mechanisms, or a common feature of the postreceptor signalling pathways. In this context, it would be interesting to study the effects of taurine on lipid breakdown because insulin is antilipolytic whereas isoproterenol promotes lipolysis.

Taurine has been reported to have nonspecific effects on membranes that result in increases in the number of ligand binding sites for several neurotransmitters (Nakashima et al., 1996). Further work will be necessary to show whether it has similar effects on the insulin and α- and β-adrenoceptors in diabetic rats. However, the fact that the treatment of control rats with taurine did not significantly affect the stimulation of deoxyglucose uptake by insulin, phenylephrine, or isoproterenol might indicate such a mechanism to be unimportant under nondiabetic conditions. The present results would suggest the effects of taurine to be a result of the reduction of the toxic effects of hyperglycaemia. Increased oxidative stress has been shown to occur in diabetic and prediabetic individuals and to contribute to the pathogenesis of late diabetic complications, as well as to peripheral insulin resistance. The impaired insulin response has been suggested to involve both receptor and postreceptor mechanisms. Oxidative stress has been reported to result in the inhibition of the compartment-specific activation of phosphatidylinositol 3-kinase, insulin receptor substrate-1 (IRS-1) redistribution, and insulin-induced protein kinase B activation. It has been suggested that each of these effects contributes to the development of impaired insulin-stimulated GLUT4 translocation and glucose transport activity in adipocytes of diabetic subjects (Tirosh et al., 1999). Studies with cultured mesangial cells have suggested that up-regulation of the transforming growth factor-β (TGF-β) system, either directly by high ambient glucose or indirectly through increased oxygen radical formation, is involved in the development of diabetic renal disease through activation of protein kinase C (Studer et al., 1997). Results from in vivo studies, which showed protein kinase C inhibitors to ameliorate the increase of glomerular TGF-β1 mRNA in diabetic rats (Ha et al., 1999; Singh et al., 1999), are consistent with this interpretation. High glucose has also been shown to inhibit the proliferation of primary cultured rabbit renal proximal tubule cells through protein kinase C, oxidative stress, and TGF-β1 signalling pathways (Park et al., 2001).

It has been suggested that taurine prevents apoptosis induced by high ambient glucose in human tubular renal cells by attenuating oxidative stress (Verzola et al., 2002). The antiapoptotic effects of taurine in human vascular endothelial cells have also been ascribed to the attenuation of intracellular reactive oxygen-containing species (ROS), together with stabilisation of intracellular Ca^{2+} concentrations (Wu et al., 1999). Interestingly, macrophage infiltration of pancreatic islets has been shown to precede the development of type 1 diabetes (Sjoholm et al., 2000). The involvement of leucocytes may indicate that respiratory burst formed reactive oxygen species may contribute to the tissue damage, a process that would be attenuated by taurine through its capacity to scavenge hypochlorous acid (Cunningham et al., 1998).

Several pharmacological approaches may be used to counteract either insulin deficiency or insulin resistance (see Bouche and Goldfine, 2003). These are aimed at reducing blood glucose levels, increasing the insulin response, or limiting the tissue damage that arises from sustained hyperglycaemia (Sjoberg et al., 2002; Fuchs et al., 2002). Many studies have stressed the beneficial effects of dietary control (Mann, 2002; Costacou and Mayer-Davis, 2003); it also appears that supplementation may be of value in the control of diabetic hyperglycaemia and/or its complications (see, e.g., Cunningham, 1998; Costacou and Mayer-Davis, 2003). The ability of taurine to protect against diabetic impairment of both insulin- and adrenergic-dependent glucose transports suggests that an increased taurine intake may be a useful addition to procedures aimed at reducing blood glucose levels in the management of type 1 diabetes. Further studies on the effects of taurine supplementation plasma insulin levels, glucose tolerance, ketosis, and the behaviour of other tissues could be of value in this respect. Plasma taurine levels are also reduced in type 2 diabetes (De Luca et al., 2001), and taurine has been shown to improve metabolism in a rat model of that condition by decreasing serum cholesterol and triacylglycerol levels (Nakaya et al., 2000). Thus, taurine may be beneficial in both types of diabetes, although the mechanisms involved may not be the same in the two conditions.

Acknowledgements

We are grateful to Taisho Pharmaceutical (Japan), Ente Cassa di Risparmio (Firenze, Italy), COST D13 (UE), and the Health Research Board of Ireland for their support of this work. KFT gratefully acknowledges support from MIUR (Roma, Italy).

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