COMMENTARY

Curcumin ameliorates hepatic fibrosis in type 2 diabetes mellitus – insights into its mechanisms of action

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A wide variety of beneficial effects have been attributed to curcumin, a major polyphenol from the golden spice *Curcuma longa* known as turmeric, including amelioration of severe complications of type 2 diabetes such as hepatic fibrosis, retinopathy, neuropathy and nephropathy. In the present issue of *BJP*, Lin and colleagues reveal new mechanisms by which curcumin inhibits the activation of hepatic stellate cells *in vitro*, a hallmark of non-alcoholic steatohepatitis and hepatic fibrogenesis associated with type 2 diabetes mellitus. They demonstrated that curcumin suppresses the advanced glycation end-products (AGEs)-mediated induction of the receptor for AGEs (*RAGE*) gene expression by increasing PPARγ activity and stimulating *de novo* synthesis of glutathione. As a result, downstream elements of RAGE-activated pathways are inhibited, which prevents oxidative stress, inflammation and hepatic stellate cell activation. This report suggests that curcumin may have potential as an anti-fibrotic agent in type 2 diabetes and opens the door to the evaluation of curcumin therapeutic effects in liver conditions of different aetiology and in other disorders linked to the impairment of PPARγ activity, such as obesity and atherosclerosis.

LINKED ARTICLE

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Abbreviations

AGEs, advanced glycation end-products; DNMTs, DNA methyltransferases; GSH, glutathione; HSCs, hepatic stellate cells; RAGE, receptors for AGEs; T2DM, type 2 diabetes mellitus

Curcumin (diferuloylmethane) is a bioactive food component present in the golden spice *Curcuma longa* known as turmeric that is an essential component of curry powder. Its chemopreventive and anti-cancer activities have been demonstrated in numerous studies and attributed to its antioxidant and anti-inflammatory properties (Basnet and Skalko-Basnet, 2011; Rogers *et al*., 2011). This polyphenol has been shown to reduce the risk of cancer (Basnet and Skalko-Basnet, 2011), heart disease (Siu, 2010), Alzheimer's disease (Belkacemi *et al*., 2011) and type 2 diabetes mellitus (T2DM) (Aggarwal, 2010). Curcumin supplementation improves diabetes-induced endothelial dysfunction by lowering plasma glucose levels, decreasing superoxide production and inhibiting protein kinase C in rats (Rungseesantivanon *et al*., 2010). By suppressing pro-inflammatory transcription factors

and signal transducers and activating anti-inflammatory signalling pathways, curcumin reverses insulin resistance, hyperglycaemia, hyperlipidaemia and other symptoms linked to T2DM (Kang and Chen, 2009; Aggarwal, 2010; Tang and Chen, 2010). Ongoing clinical trials aim to show the effectiveness of curcumin in the reduction of atherosclerosis events in diabetic patients as well as in the prevention and delay of T2DM in patients with impaired glucose tolerance and insulin resistance.

T2DM results from resistance to insulin action and inadequate insulin secretion. The incidence of this disorder is significantly increasing worldwide. According to the World Health Organization (WHO), today 346 million people have diabetes and the number of diabetes-related deaths is estimated to almost double between 2005 and 2030 (WHO,

Media Centre, 2011). Severe complications associated with diabetes, such as retinopathy, neuropathy, nephropathy, non-alcoholic steatohepatitis and hepatic fibrosis, have been the focus of research in this field in the last decade. Although effective ways of managing these complications are being developed, their molecular basis remains to be elucidated. One of the characteristic features of diabetes is the elevated level of blood glucose, hyperglycaemia, which is considered to be the principal cause of diabetic complications including hepatic fibrosis. The increased availability of glucose leads to the accelerated formation of advanced glycation end-products (AGEs) that are non-enzymatic results of a chain of non-oxidative and oxidative reactions of sugars with proteins and/or lipids. AGEs interact with the receptor for AGEs (RAGE) located on the cell surface which subsequently stimulates different signalling pathways such as MAPK, JAK/STAT and PI3K, and produces pro-inflammatory responses with increased oxidative stress and cell growth (Ramasamy *et al.*, 2009). AGEs-mediated increased proliferation of hepatic stellate cells (HSCs) was observed during hepatic fibrogenesis that was associated with RAGE up-regulation. Evidence has been obtained indicating the efficacy of curcumin at inhibiting the activation of HSCs *in vitro* and *in vivo*, which prevents hyperglycaemia- and hypercholesterolaemia-associated liver fibrosis (Kang *et al.*, 2002; Kang and Chen, 2009; Tang and Chen, 2010). However, the precise mechanism through which curcumin exerts its hepatoprotective effect remains unclear.

In the present issue of the *BJP*, Lin *et al.* (2012) revealed new mechanisms by which curcumin inhibits the activation of HSCs *in vitro*. Curcumin dramatically attenuated AGEs-mediated induction of *RAGE* gene expression, which is crucial for the activation of HSCs. Both PPARγ activity and *de novo* synthesis of glutathione (GSH) are required for the inhibitory effects of curcumin on *RAGE* gene expression. The present findings showed that a PPARγ antagonist diminishes the beneficial effects of curcumin in HSCs whereas agonists have an effect similar to the natural compound. Furthermore, AGEs-induced production of reactive oxygen species and lipid peroxides was attenuated after curcumin exposure and accompanied by an increase in the activity of glutamate-cysteine ligase (GCL) and the intracellular level of the reduced form of GSH. The inhibition of *de novo* synthesis of GSH using a GCL inhibitor partially reduced the effects of curcumin on *RAGE* gene expression. However, the suppression of either PPARγ or GCL did not completely eliminate the effects of curcumin as some inhibition of *RAGE* expression on mRNA and protein levels was still detectable. This suggests the involvement of another mechanism(s), which requires further investigation. Although PPARγ acts as a transcription factor regulating gene expression upon binding to response elements in the promoters of target genes, Lin *et al.* did not find a consensus PPARγ binding site within *RAGE* gene promoter. Their preliminary results from promoter deletion assays indicate the presence of binding sites for other transcription factors, NF-κB and TCF/LEF1, where the latter mediates a nuclear response to WNT signals by interacting with β-catenin. Based on studies that showed the inhibition of NF-κB and disruption of WNT signalling after PPARγ activation in HSCs (Chen and Zheng, 2008), Lin *et al.* suggested that curcumin-induced increase in PPARγ negatively regulates

RAGE gene expression by suppressing NF-κB and TCF/LEF1 activities. Interestingly, PPARs have been demonstrated to be key regulators of glucose and lipid metabolism by regulating transcription of multiple target genes (Bermudez *et al.*, 2010). PPARγ agonists, thiazolidinediones, that increase tissue sensitivity to insulin and maintain plasma glucose level within normal range, are nowadays commonly used in the treatment of T2DM (Bermudez *et al.*, 2010). However, these drugs produce adverse effects including serious heart failures. The opportunity for their replacement with naturally occurring compounds of low cytotoxicity such as curcumin would be an important milestone in the treatment of T2DM.

As shown in the previous studies, treatment of activated HSCs with curcumin increases PPARγ activity and *PPARγ* gene expression (Xu *et al.*, 2003). Yet the mechanism of this action is unknown. The intriguing possibility may be linked to curcumin activity as an epigenetic agent involved in the regulation of activities of DNA methyltransferases (DNMTs). This polyphenol can covalently bind to the catalytic thiol group of Cys1226 present in DNMT1, which causes the inhibition of DNMT1 catalytic activity (Liu *et al.*, 2009). This would explain the decrease in DNA promoter methylation upon curcumin exposure and reactivation of tumour suppressor genes, for example, *RARbeta2* in human cervical cancer cells (Jha *et al.*, 2010). *PPARγ* has been found to be silenced through its promoter methylation in colorectal cancer and this correlated with poor clinical outcome (Pancione *et al.*, 2010). More notably, DNA hypermethylation of *PPARγ* promoter was observed in visceral adipose tissue of mouse models of diabetes and was associated with silencing of *PPARγ* expression that may contribute to the pathogenesis of diabetes (Fujiki *et al.*, 2009).

Given that the present experiments were carried out *in vitro* in cultured HSCs, such studies in human patients are required to confirm the beneficial effect of curcumin in liver injuries developed in T2DM. Nevertheless, the study by Lin *et al.* strongly endorses the potential use of curcumin in T2DM therapy and opens up new avenues for therapeutic applications of this natural compound. It is conceivable that curcumin may confer hepatoprotection developed during the course of other chronic liver diseases. Importantly, the compound may ameliorate patient conditions in disorders where the lack of PPARγ activity contributes to disease pathogenesis such as obesity, atherosclerosis and multiple types of cancer.

Conflict of interest

The author has no conflict of interest to declare.

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