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Effect of Tetrahydrocurcumin Compared to Curcumin in Carbohydrate Metabolism and Glycoprotein Components in Type 2 Diabetes - Systematic Review

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Abstract

Pancreatic β-cell dysfunction and insulin resistance are the two hallmarks of type 2 diabetes mellitus. Treatment of diabetes without any side effects is still a challenge to the medical system. There is an increasing demand by patients to use the natural products with antidiabetic activity, because insulin and oral hypoglycemic drugs are having so many side effects. Curcumin is a biologically active component isolated from the rhizome of Curcuma longa that possess antidiabetic and has been proven scientifically to possess high antioxidant activity and anticancer properties. Tetrahydrocurcumin (THC) is a major curcuminoid metabolite of curcumin, naturally occurring in turmeric. The interest in THC research is increasing because it is superior to curcumin in its solubility in water, chemical stability, bioavailability, and anti-oxidative activity. Many in vitro and in vivo studies have revealed that THC exerts antidiabetic effects through various mechanisms, including modulation of oxidative stress, xenobiotic detoxification, inflammation, proliferation, metastasis, programmed cell death, and immunity. The activities of glycolytic enzymes such as hexokinase and glucose-6-phosphate dehydrogenase were found to be decreased whereas the activities of gluconeogenic enzymes (glucose-6-phosphatase and fructose-1,6-bisphosphatase) and polyol pathway enzyme-sorbitol dehydrogenase were significantly increased in diabetic control rats. In addition, the oligosaccharide moieties of glycoproteins (hexose, hexosamine, fucose and sialic acid) were also significantly increased in plasma and tissues of diabetic control rats. THC and curcumin administration to diabetic rats significantly reversed the above changes when compared to diabetic control rats. In diabetic controls, hepatic and skeletal muscle glycogen content was decreased significantly as compared to non-diabetic controls. Treatment with THC and curcumin increased the hepatic and skeletal muscle glycogen significantly. The antidiabetic and antioxidant effects of THC are more potent than those of curcumin at the same dose. The antihyperglycemic action of THC might be mediated via an enhancement of insulin action, as it is evidenced by the increased levels of insulin in diabetic rats treated with THC, which may be responsible for the reversal of changes in carbohydrate enzymes and glycoprotein components. The THC administration showed more effective than curcumin.

Keywords*: tetrahydrocurcumin, curcumin, streptozotocin, nicotinamide, diabetes, carbohydrate, glycoprotein*

Introduction

Diabetes mellitus is a group of metabolic disorders with one common manifestation called as hyperglycemia. Chronic hyperglycemia causes damage to the eyes, kidneys, nerves, heart and blood vessels. The International Diabetes Federation estimates that in 2003, 194 million people had diabetes, and that by 2025, 333 million people will have this disease (Kun-Ho Yoon et al. 2006). The etiology and pathophysiology leading to the hyperglycemia, however, are markedly different among patients with diabetes mellitus, dictating different

prevention strategies, diagnostic screening methods and treatments. The adverse impact of hyperglycemia and the rationale for aggressive treatment have recently been reviewed (Susman and Helseth, 1997).

Hyperglycemia leads to the worsening of insulin secretion by β-cells and impairment of insulin sensitivity in peripheral tissues. Thus, there is complex inter-relationship among hyperglycemia and insulin action, all of which are involved in the pathogenesis of diabetes. Glucose homeostasis involves the coordinated regulation of several metabolic pathways including gluconeogenesis and glycolysis, which is due to impaired carbohydrate utilization resulting from a defective or deficient insulin secretory response (Reaven, 1998).

Liver is an insulin dependent tissue, which plays a pivotal role in glucose and lipid homeostasis and is severely affected during diabetes (Seifter and England, 1982). The activities of the regulatory enzymes like hexokinase, glucose-6-phosphate dehydrogenase and gluconeogenic enzymes such as fructose-1,6-bisphosphatase and glucose-6-phosphatase are markedly altered during diabetes (Hers et al. 1987).

It is becoming increasingly accepted that the carbohydrate moieties of glycoproteins such as hexose, hexosamine, fucose and sialic acid have an important role in protein stability, function and turnover (Wiese et al. 1997). Glycoproteins continue as a major source to form the structure of extracellular matrix. In the diabetic state, glucose is utilized by the insulin independent pathways leading to the synthesis of glycoproteins and even mild deficiency of insulin influences thickening of basement membrane. The elevation of glycoproteins in diabetics may also be a predictor of angiopathic complications (Konukoglu et al. 1999).

The supplement industry is interesting because some of the most effective ingredients aren't necessarily new, but are instead substances that have been around for centuries. Natural herbs and roots are central in the practices of Ayurvedic and Traditional Chinese Medicine, and many of them have found their way into the world of western supplementation (Pari and Murugan, 2004, 2005). Turmeric one of the most potent natural medicinal plants on the planet, turmeric has been around for ages. In various parts of the world, turmeric is also known as *Curcuma longa*, a plant that hails from the Zingiberaceae family. The turmeric that makes its way into medicinal and health-promoting uses comes from the rhizome of the plant, which is a horizontal underground stem that puts out lateral shoots (Pari and Murugan, 2007a,b).

Turmeric (*Curcuma longa*) is commonly defined as a perennial dietary spice in Indian cuisines, also used as coloring agent in foods and textiles along with wide variety of ailments. Curcumin, the active constituent of turmeric had remarkable medicinal properties and used to treat a wide range of disorders without any side effects even at high doses (Gupta et al. 2012). In fact, its relative abundance in these regions is what ultimately led to its adoption within some of the oldest natural systems in medicine, specifically Ayurvedic and Traditional Chinese Medicine (Murugan and Pari, 2006a).

Curcumin – turmeric's key contributor

Though there are hundreds of individual constituents that reside in turmeric, there are a few particular components that are responsible for much of what turmeric does. There are four of these compounds, collectively called curcumoinoids that carry most of the reported health benefits of turmeric (Murugan and Pari, 2006b).

The main compound within the cuurcumoinoid class of molecules is known as curcumin, which makes up the vast majority of the total curcumoinoid content in turmeric. The other three – demethoxycurcumin, bisdemethoxycurcumin,and cyclocurcumin – contribute somewhat (Kiuchi et al., 1993; Changtam et al., 2010), but not nearly to the same degree as curcumin. These ancillary curcuminoids are simply role players in the overall game, as curcumin dominates the action.

Tetrahydrocurcumin – suped-up curcumin

THC is not only a major metabolite produced during the reduction of curcumin; it may be the primary byproduct responsible for much of its parent compound's capabilities. Structurally, it's very similar to curcumin, with the key differentiator being four additional hydrogen atoms.Visually, the two are different as well: while curcumin has a signature golden hue, THC is notably colorless (Pan et al., 1999). Though these differences seem small to the naked eye, they are a harbinger for something more – a more effective compound (Murugan and Pari, 2007a).

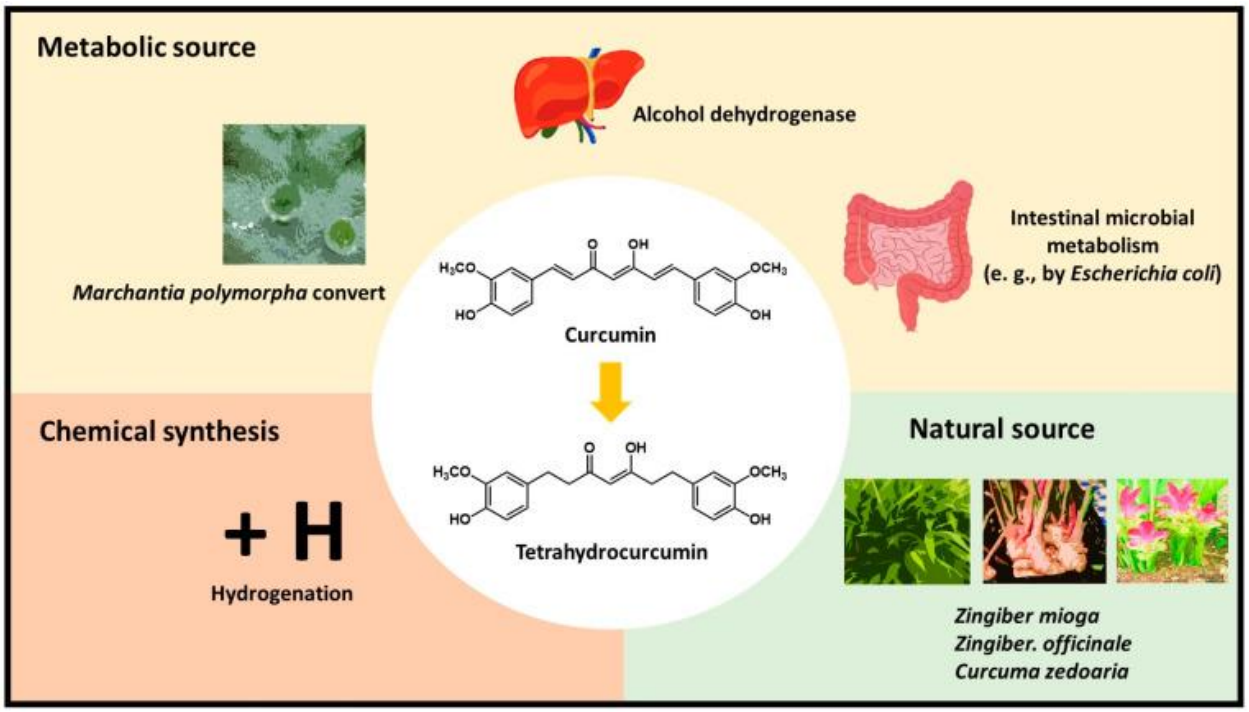

Figure1. Strucure of curcumin and tetrahydrocurcuminn

Tetrahydrocurcumin vs. curcumin

THC is phenolic in nature, acting as antioxidants, protecting against free radicals and preventing the generation of free radicals. Unlike yellow curcuminoids, THC is a colorless compound which can therefore be used in color free cosmetic products that currently employ conventional and synthetic antioxidants. THC, first detected in 1978, (Holder) was quickly tagged as the key bioactive metabolite of curcumin. Research has shown that THC boasts strong bioactivity, as opposed to the other metabolites of curcumin (Aggarwal and Bharat, 2014). Various studies comparing these two differ in conclusion, with some supporting curcumin and many others supporting tetrahydrocurcumin. When looking at either one of them, most people tend to focus on the antioxidant and anti-inflammatory activity of the two ingredients. Luckily, these are the properties central to much of the existing research (Murugan and Pari, 2007b).

THC is a proven, potent anti-oxidant that has been shown to scavenge free radicals, decrease ROS production, and upregulate antioxidant enzymes and thus reduces oxidative stress and pathological conditions in tissues such as liver, kidneys, brain, and blood vessels (Murugan et al., 2008). Many *in vivo* studies have demonstrated that THC potential activity against various toxicants or diabetic-mediated oxidative damage and cellular dysfunction is superior to that of curcumin(Murugan and Pari, 2006a; Pari and Murugan, 2007a).

While both ingredients are active antioxidants, they differ in how they scavenge free radicals in the body, which ultimately dictates how effective each ingredient is against a specific application on the antidiabetic activity of THC and curcumin, in this study we explored the role of THC and curcumin in prevention of streptozotocin (STZ) and nicotinamide induced hyperglycemia and altered carbohydrate metabolic enzymes and glycoprotein components.

Dose dependent effect of THC in STZ-nicotinamide induced diabetic rats

This preliminary study was aimed at selecting the most effective dose of the THC. The type 2 diabetic model was developed according to the description of Masiello et al. (1998). Hyperglycemia was confirmed by the elevated glucose levels in blood, determined at 72 h. The rats with blood glucose concentration more than 250 mg/dl were used for the study. Preliminary studies using THC was done at three doses viz., 20, 40 and 80 mg/kg body weight.

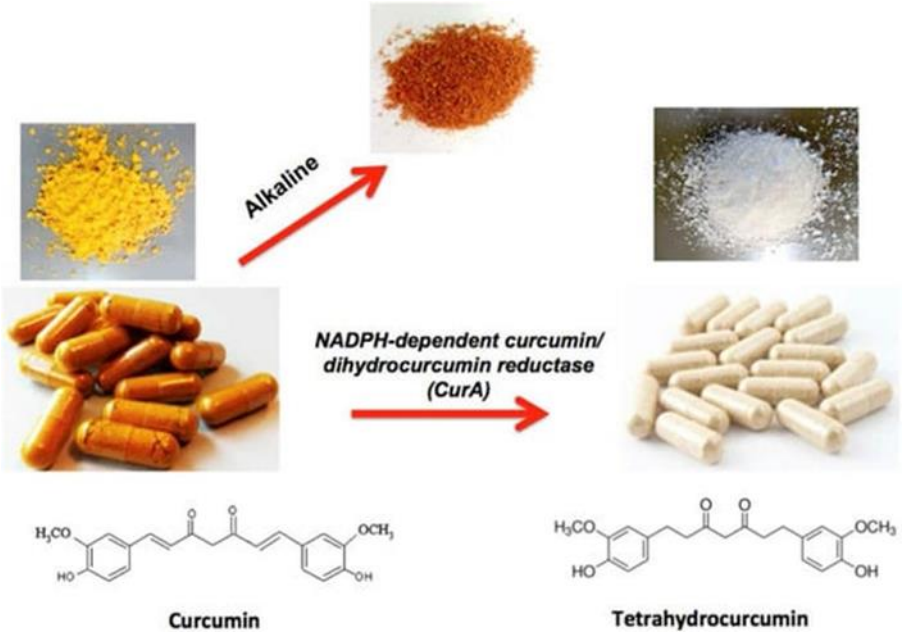

Figure 2. With increasing pH (alkalinity), curcumin changes to red. Curcumin metabolically converts to tetrahydrocurcumin by using the NADPH-dependent curcumin/dihydrocurcumin reductase (CurA) enzyme. Structurally, curcumin has the α,β-unsaturated carbonyl group, but tetrahydrocurcumin lacks α,β dienes.

Effect of THC on blood glucose, plasma insulin, haemoglobin, glycated haemoglobin and urine sugar in normal and experimental rat

This study was aimed at selecting the most effective dose of the THC. In diabetic rats, the blood glucose and glycated haemoglobin levels were significantly increased and plasma insulin, haemoglobin levels were significantly decreased when compared with normal rats. Administration of THC tend to bring the levels of blood glucose and plasma insulin towards normal. In our studies of THC at 80 mg/kg body weight was showed a significant effect than 20 and 40 mg/kg body weight. The effect of THC was more prominent when compared with curcumin. The diabetic control rats showed a significant decrease in the level of total haemoglobin and significant increase in the level of glycated haemoglobin. Oral administration of THC and curcumin significantly restored the level of total haemoglobin and glycated haemoglobin in diabetic rats. Antihyperglycemic effect produced by THC may be due to the stimulation of insulin secretion from the pancreatic β-cells (Murugan, 2021a, b). On the basis of these studies, a dose of 80 mg/kg body weight/day of THC was selected for further evaluation of its effect in diabetic rats and compared with curcumin (Pari and Murugan, 2005).

Body weight changes

The basal values in the normal and diabetic rats were not significantly different from each other. The increase in body weight in THC and curcumin treated groups were not significantly different from each other. The increase in body weight in THC treated rats was significantly higher when compared with diabetic control rats (Pari and Murugan, 2005).

Oral Glucose Tolerance Test (OGTT)

Blood glucose level of normal, diabetic control, THC and curcumin treated rats after oral administration of glucose (2 g/kg body weight). In diabetic control rats, the peak increase in blood glucose concentration was observed after 1h. The blood glucose concentration remained high over the next hour. THC (80 mg/kg body weight) treated rats showed significant decrease in blood glucose concentration at 1 and 2 h when compared with diabetic control rats. The effect was more pronounced at the 2 h interval. THC at a dose of 80 mg/kg body weight was found to be more effective than curcumin (Pari and Murugan, 2005).

Liver and muscle glycogen

Effect of THC on glycogen content in liver and muscle of normal and experimental animals. In diabetic controls, hepatic and skeletal muscle glycogen content was decreased significantly as compared to non-diabetic controls. Treatment with THC and curcumin significantly increased the hepatic and skeletal glycogen (Pari and Murugan, 2005).

Hepatic key enzymes

The activities of carbohydrate metabolizing enzymes in liver of normal and THC-treated diabetic rats. The activities of enzyme hexokinase and glucose-6-phosphate dehydrogenase was found to be decreased whereas the activities of sorbitol dehydrogenase and gluconeogenic enzymes: glucose-6-phosphatase, fructose-1,6-bisphosphatase and sorbitol dehydrogenase were significantly increased in diabetic control rats. THC and curcumin administration to diabetic rats significantly reversed the above changes when compared to diabetic control rats. The THC administration showed more effective than curcumin (Pari and Murugan, 2005).

Plasma and tissue glycoproteins

The levels of plasma and tissue glycoprotein components in normal and experimental rats. There was a significant increase in the level of plasma glycoprotein components in diabetic rats. In liver and kidney of diabetic rats, the level of hexose, hexosamine and fucose were significantly increased where as the level of sialic acid was significantly decreased. Oral administration of THC and curcumin significantly reversed the changes in plasma, liver and kidney glycoprotein components of diabetic rats. The effect of THC was better than curcumin (Pari and Murugan, 2007a).

Discussion

Diabetes mellitus is a disease due to abnormality of carbohydrate metabolism and it is mainly linked with low blood insulin level or insensitivity of target organs to insulin (Maiti et al. 2004). It is the most prevalent chronic disease in the world affecting nearly 25% of the population. Type 2 diabetes (NIDDM) is found to be more prevalent (Home et al. 1998). Major characteristics of type 2 diabetes include impaired utilization of glucose and resistance to the ability of insulin to stimulate glucose uptake and disposal in tissue. Type 2 diabetes is the consequence of a number of defects, including impaired insulin secretion by the pancreatic β-cell, resistance of peripheral tissues to the glucose- utilizing effect of insulin, and augmented hepatic glucose production (Shulman, 2000).

The liver has an important function in maintaining the level of glucose within the physiological limits. In contrast to muscle and fatty tissue, insulin does not directly regulate the uptake of glucose by the liver. Insulin takes part in regulation of glucose metabolism in the liver by stimulating glycolysis, glycogen synthesis and inhibition of gluconeogenesis (Liptakova et al. 2002). In an attempt to gain an insight into the underlying biochemical mechanism on the action of THC, we assayed the key hepatic enzymes, hexokinase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, fructose-1,6-bisphosphatase and sorbitol dehydrogenase in liver of normal and experimental rats, as the liver being the main organ responsible for maintaining glucose homeostasis of the blood.

Blood glucose and plasma Insulin

THC at a dose of 80 mg/kg body weight showed a highly significant effect compared to 20 and 40 mg/kg body weight. The capacity of THC to decrease the elevated blood sugar level to normal glycemic level is an essential trigger for the liver to revert to its normal homeostasis during experimental diabetes. The possible mechanism by which THC bring about its antihyperglycemic action in diabetic rats may be by increasing the pancreatic secretion of insulin from the existing β-cells or insulin release from bound form which was evidenced by the significant increase in the level of insulin in THC treated diabetic rats (Murugan, 2021c,d). Administration of THC and curcumin to normal rats showed a significant decrease in the level of blood glucose and increase in the level of plasma insulin. This clearly shows that the THC has better effect on secretion of insulin from pancreatic β-cells (Pari and Murugan, 2005).

Body weight

Rasch (1980) reported that the rise in body weight was far less in the poorly controlled diabetic rats as compared to well-controlled diabetic rats. A similar observation was made in our study. The loss of body weight may be due to excessive breakdown of tissue proteins during the diabetes (Chatterjee and Shinde, 2002). The daily administration of THC to STZ diabetic rats for 8 weeks caused a statistically significant increase in the body weight when compared with diabetic control rats. This could be the result of improved glycemic control (control over polyphagia and muscle wasting due to hyperglycemic condition) (Grover et al. 2001) produced by THC and/or it could be the result of adipogenesis induced by THC.

OGTT

OGTT is a well accepted and frequently used method to screen antihyperglycemic activity (Alberti and Zimmet, 1998). THC might enhance glucose utilization since it significantly reduces the blood glucose in diabetic rats. From the data obtained with the OGTT, it is clear that blood glucose levels reached a peak and returned to near

normal values after 120 min in both normal and treated rats (80 mg/kg of body weight of THC). Elevated blood glucose levels remained high even after 120 min in diabetic rats. THC administration effectively prevented the increase in blood glucose without causing a hypoglycemic state, and effect due to the restoration of the delayed insulin response.

Haemoglobin, glycated haemoglobin and urine sugar

Glycated proteins are formed post-translationally from the slow, non-enzymic reaction between glucose and amino groups on proteins (Wu and Monnier, 2003). For haemoglobin, the rate of synthesis of glycated haemoglobin is principally a function of the concentration of glucose to which the erythrocytes are exposed. Glycated haemoglobin is the most important glycated fraction of the haemoglobin molecule. In diabetes, there is an increased glycation of a number of proteins including haemoglobin. Haemoglobin is highly susceptible to non-enzymic glycation.

In diabetic condition, the excess of glucose present in the blood react with haemoglobin to form glycated haemoglobin, which has altered affinity for oxygen and this may be a factor in tissue anoxia. Glycated haemoglobin was significantly increased in diabetic rats and this increase is directly proportional to fasting blood glucose. 1% increase in glycated haemoglobin resulted in a 70% increase in proliferative retinopathy and a 20% increase in proteinuria and 10% increase of cardiac events and also anemia is much more common diseases in type 2 diabetes (Murugan and Sakthivel, 2021). The significant decrease in haemoglobin observed in the study was well correlated with results from other studies, which reported that there was a decrease in the level of haemoglobin in experimental diabetic animals (Latha and Pari, 2003; Pari and Saravanan, 2002). Curcumin supplementation prevents the increase of haemoglobin glycosylation and decreases the oxidative stress in erythrocytes exposed to high levels of glucose (Jain et al. 2006). The increase in the level of haemoglobin in rats given THC and curcumin controls the glycation of haemoglobin by its normoglycemic activity and thus decreases the level of glycated haemoglobin in STZ diabetic rats. It may reduce the tissue damage and chronic complications associated with the eyes, kidneys, nerves and cardiovascular system.

Glycogen

Diabetes mellitus is associated with a marked reduction in the level of liver glycogen. In the study, the hepatic and skeletal muscle glycogen content was reduced significantly in diabetic control. Welihinda and Karunanayake (1986) also reported that hepatic and muscle glycogen is reduced significantly in diabetic control rats as compared to non-diabetic control rats. The reduced glycogen content has been attributed to the reduction in the activity of glycogen synthase and increase in the activity of glycogen phosphorylase (Panneerselvam and Govindaswamy, 2002). Administration of THC prevented the depletion of glycogen content but could not normalize it. This prevention is due to stimulation of insulin release from β-cells (Lolitkar and Rao, 1966) or due to insulin mimetic activity of some component of plant resulting in direct peripheral glucose uptake.

Hexokinase

The key enzyme in the catabolism of glucose is hexokinase, which phosphorylates glucose and converts it into glucose-6-phosphate. It causes initial phosphorylation of glucose after it diffuses into liver cells. Once phosphorylated, the glucose is temporarily trapped inside the liver cells and its diffusion is blocked (Bopanna et al. 1997). Hexokinase insufficiency in diabetic rats can cause decreased glycolysis and decreased utilization of glucose for energy production (Vats et al. 2003). Administration of THC of diabetic rats resulted a significant reversal in the activity of hepatic hexokinase. The increased activity of hepatic hexokinase causes the increase in glycolysis and utilization of glucose for energy production. Administration of THC have been observed to decrease the concentration of blood glucose in STZ diabetic rats, which may be due to the increased level of insulin. The decrease in the concentration of blood glucose in diabetic rats given THC may also be as a result of increased activities of hepatic hexokinase, which increased the glycolysis.

Glucose-6-phosphate dehydrogenase

Glucose-6-phosphate dehydrogenase activity was significantly decreased in STZ diabetic rats. A decrease in the activity of glucose-6-phosphate dehydrogenase may also slow down the pentose phosphate pathway in diabetic condition (Abdel-Rahim et al. 1992; Murugan, 2023a). A significant reversal of the hepatic lipogenic enzyme glucose-6-phosphate dehydrogenase by THC with curcumin treatment suggests that the hydrogen shuttle systems and the redox state of the cells become more oxidized, which results in the increased formation of NADPH for increased utilization in lipogenesis and, in turn activation of the enzyme as NADPH, is a strong inhibitor of glucose-6-phosphate dehydrogenase.

Gluconeogenic enzymes

Glucose-6-phosphatase is a crucial enzyme of glucose homeostasis because it catalyses the ultimate biochemical reaction of both gluconeogenesis and glycogenolysis (Berg et al. 2001; Mithievse et al. 1996). The increased activities of glucose-6-phosphatase in diabetic rats provide hydrogen, which binds with $NADP^+$ in the form of NADPH and enhances the synthesis of fats from carbohydrates (i.e. lipogenesis) (Clore et al. 2000; Bopanna et al. 1997) and, finally, contributes to increased levels of glucose in the blood. Increased hepatic production of glucose in diabetes mellitus is associated with impaired suppression of the gluconeogenic enzyme fructose-1,6-bisphosphatase. In the diabetic state, several workers have observed increased activity of gluconeogenic enzymes (Gupta et al. 1999; Zhang and Moller, 2000; Panneerselvam and Govindaswamy, 2002; Murugan, 2023a; Murugan, 2022). The increased activities of two gluconeogenic enzymes from liver may be due to the activation or increased synthesis of the enzymes contributing to the increased glucose production during diabetes, by liver. In the diabetic state, several workers have observed an increase in the activities of gluconeogenic enzymes (Murugan, 2023a; Sochor et al. 1985; Prince et al. 1997). Activation of gluconeogenic enzymes is due to the state of insulin deficiency since insulin function as a suppressor of gluconeogenic enzymes under normal condition.

Administration of THC significantly depressed the activities of gluconeogenic enzymes in diabetic rats. The effect of THC may be primarily modulating and regulating the activities of the two gluconeogenic enzymes, either through regulation of cAMP or any other metabolite activation/inhibition of glycolysis/gluconeogenesis. The redox state of the liver cell is highly reduced in diabetes together with the changes in the energy state (Gupta et al. 1999). ATP levels are lowered in the cytosol and could be the energy source for the higher levels of gluconeogenesis in diabetic liver. Other metabolites especially the substrates for the glucose-6-phosphatase and fructose-1,6-bisphosphatase, glucose-6-phosphate and fructose-1,6-bisphosphate are known to increase in the liver during diabetes due to inhibition of hexokinase, the main regulatory glycolytic enzyme (Sochor et al. 1985). The level of plasma insulin was found to be increased significantly in diabetic rats treated with THC, which may be a consequence for the significant reduction in the level of gluconeogenic enzymes. The reduction in the activities of gluconeogenic enzymes can result in the decreased concentration of glucose in blood.

Sorbitol dehydrogenase (SDH)

The conversion of glucose to sorbitol, which is catalyzed by aldose reductase, in the presence of NADPH that may related to the protection against oxidative stress and abnormalities in NO action (Gey, 1995). NADPH levels are diminished by elevated polyol pathway flux, impairing the glutathione redox cycle (Inouye et al. 1998), which is an important cellular protection mechanism against oxygen derived free radicals (OFRs). The OFRs are markedly increased in diabetes, if not scavenged they cause damage to the vascular endothelium and neutralize NO (Inouye et al. 1998).

SDH catalyzes the conversion of sorbitol to fructose in the presence of NAD. Evidence has shown that the activity of SDH was elevated in diabetic rats, leading to increased availability of fructose and that fructose was 10-fold better substrate than glucose for glycosylation (Brownlee, 1992). In the study, an increase in the activity of SDH in the liver of diabetic control rats was observed. The Increased activity of SDH in diabetic rats has already been reported by Arun and Nalini (2002). As the concentration of glucose in the liver goes up in diabetic rats, more glucose is converted to sorbitol. The observed elevation in the activity of SDH in diabetic rats may have been due to the increased availability of sorbitol. SDH activity was found to be significantly reduced on treatment with THC. The effect produced by THC may be due to decrease in blood glucose by increased activity of plasma insulin, which may prevent the conversion of glucose to sorbitol.

Glycoprotein components

Glycation is a nonenzymatic reaction of glucose and other saccharide derivatives with proteins, nucleotides and lipids (Brownlee, 2001). Non-enzymatic glycation (Maillard reaction) is a complex series of reactions between reducing sugars and amino groups of proteins, which leads to browning, fluorescence and cross-linking of the proteins. The reaction is initiated by the reversible formation of a Schiff base, which undergoes a rearrangement to form a relatively stable Amadori product. The Amadori product further undergoes a series of reactions through dicarbonyl intermediates to form AGEs. Formation of some AGEs combines both the glycation and oxidative steps in a process termed glycoxidation (Thornalley, 2002). Glycation of cellular proteins produce changes in the structure and loss of enzymatic activity. These effects are countered by protein degradation and renewal. Glycation of the extracellular matrix produces changes in macromolecular structure affecting cell - cell and cell - matrix interactions associated with decreased elasticity and increased fluid filtration the across arterial wall and endothelial cell adhesion (Vlassara and Palace, 2002). When the concentration of AGEs increased above a critical level, cell surface AGEs receptors become activated. This is

associated with increased expression of extracellular matrix proteins, vascular adhesion molecules, cytokines and growth factor. Depending on the cell type and concurrent signaling this is associated with chemotaxis, angiogenesis, oxidative stress and cell proliferation or apoptosis (Vlassara and Palace, 2002). These process are thought to contribute to disease mechanisms associated with the development of diabetic complications (Guillot et al. 1994).

Several workers have suggested that elevated levels of plasma glycoprotein components in diabetic rats could be a consequence of abnormal carbohydrate metabolism. Insulin deficiency and high levels of plasma glucose in diabetic condition may result in an increase of glycoproteins synthesis (Patti et al. 1999; Murugan, 2023b;Pari and Murugan, 2007a). The requirement of insulin for the biosynthesis of the carbohydrate moiety of mucoproteins from glucose is thus evident.

The hyperglycemia in diabetic rats lead to decreased utilization of glucose by insulin dependent pathways, thereby enhancing the formation of hexose, hexosamine and fucose for the accumulation of glycoprotein components (Youngren et al. 1996).At the cell surface or inside the cells, there are also carbohydrates such as fucose and sialic acid, which form specific structure, called glycanic chains, covalently linked to lipids or proteins. An increase in the biosynthesis or a decrease in the metabolism of glycoprotein could be related to the deposition of these materials in the basement membrane (Rasch et al. 1995). The basement membrane proteins consist of glycoprotein components and basement membrane thickening may be influenced by insulin deficiency. Thickening of capillary basement membrane is accompanied by the disruption of glycemic control in the diabetes mellitus (Roth et al. 1993). Alterations of those functional glycoconjugates could induce abnormal cellular behavior, as it is frequently described in diabetic microvascular complications (Schiller and Dorfman, 1957). The decrease in the content of sialic acid in tissues may be due to the utilization for the synthesis of fibronectin, which contains sialic acid residues in the core structure. The synthesis of fibronectin was also reported to increase significantly in various tissues of diabetic patients and rats (Blum and Fridovich, 1985).

Cytokines (IL-6 and TNF-α) released by inflammatory cells and damaged endothelia due to angiopathy-associated tissue injury could elicit an acute-phase response, resulting in increased hepatic production of sialylated glycoproteins and other glycoproteins, leading to a rise in acute phase proteins with sialic acid (Crook, 2003). The synthesized glycoproteins are made to circulate in blood. Alternatively, a systemic cytokine response to atherosclerosis could directly cause vasculopathy in diabetes mellitus (Patti et al. 1999).

Conclusion

THC is considered to be a valuable lead compound for developing antidiabetic and treatment therapeutics due to its relatively superior chemical stability and bioavailability, as well as its high structural similarity to curcumin. The antidiabetic effects of THC discussed in this review are proposed to be due to its strong anti-oxidative capability. Administration of THC and curcumin has significant antidiabetic effect in STZ-nicotinamide induced type 2 diabetes. THC and curcumin reversed the abnormalities in the levels of glycoprotein components. THC and curcumin may have beneficial effects in diabetes mellitus, by the enhancement of insulin action, as evident by the increased level of insulin in diabetic rats treated with THC and curcumin, which may be responsible for the reversal of glycoprotein changes. The THC administration was more effective than curcumin. The antidiabetic effect of THC provide sufficient documentation to define its role and action for its potential and promising use in treating diabetes.

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