INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, and the early onset of T2DM is associated with an insulin resistant condition (1; 2). Several previous studies demonstrated that long term consumption of a high-fat diet (HFD) in animal models caused insulin resistance (2-4). Our previous study has shown that 12-weeks of HFD consumption induced not only peripheral but also neuronal insulin resistance, indicated by the impairment of neuronal insulin receptor function (5). Furthermore, previous studies demonstrated that HFD consumption was associated with the cognitive dysfunction and the impaired hippocampal-dependent memory task (6; 7).

Insulin and central nervous system

Insulin is an important hormone to maintain glucose homeostasis (8; 9). It has been known that insulin acts not only in peripheral tissues but also in neuronal tissues such as, in the brain. Several evidence showed that insulin acts on specific brain regions to regulate many brain processors, including energy homeostasis, neuronal survival, learning and memory, and food intake (10). For several decades, neurons and brain were known as "Insulin-insensitive tissue". At present, this statement is no longer true since insulin and insulin receptors have been discovered in several parts of the brain (11). Previous studies have shown the high distribution of insulin receptors (IRs) in many regions of the brain, such as the olfactory bulb, hypothalamus, hippocampus and the cerebellum (8; 9). Moreover, IRs in the brain can be divided into peripheral type, which are found on glial cells, and brain-specific types, which are found on neurons (12). The major sources of insulin in the brain are as following: 1) plasma insulin is secreted from the pancreas and then crossed the blood-brain barrier (BBB) via receptor mediated saturable transport system; 2) insulin is synthesized within neuronal tissues (13-15). Those findings indicate that brain is an insulin-sensitive organ.

Furthermore, recent studies have shown that insulin resistant condition is related to the development of neurodegenerative diseases (16; 17), and correlated with the impairment of learning, memory and cognitive function (18-20).

High fat diet induced peripheral and neuronal insulin resistance as well as related with mitochondrial dysfunction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder, and the early onset of T2DM is associated with insulin resistant condition (1; 2). Insulin resistance (IR) is a pathological condition of the metabolic syndrome, which is characterized by hyperinsulinemia and euglycemia (21). There are several factors correlated with the onset of IR. The common causes of insulin resistance is obesity (4). IR related with obesity often occurs following long term consumption of high-fat-diets (HFD) (3).

High fat diet (HFD) consumption causes not only peripheral insulin resistance but also neuronal insulin resistance (3; 5). A previous study in insulin resistant mice model induced by long term HFD consumption has shown that HFD can trigger insulin resistance by impairing insulin sensitivity, increasing oxidative stress levels and reactive oxygen species (ROS) in liver and adipose tissue (22). That finding well agrees with our previous study showing 12-weeks of HFD consumption in male rats induced peripheral and neuronal insulin resistance as well as elevated neuronal corticosterone levels (5). In addition, previous studies illustrated that HFD intake can reduce insulin transportation via blood brain barrier (BBB) into the central nervous system (CNS) and can reduce hippocampal neurogenesis through the increase of corticosterone levels (23; 24). Those findings indicate that HFD consumption causes peripheral insulin resistance, neuronal insulin resistance and neuronal stress.

Under normal physiological conditions, brain mitochondria are crucial organelles to produce energy for cellular function (25). The byproduct of the respiratory chains from mitochondria, such as reactive oxygen species (ROS), can

cause damage to cells (26). It has been shown that ROS can lead to various pathological conditions in the brain including neurodegenerative diseases (26; 27). In addition, it has been known that brain mitochondria regulate the energy-demanding neurotransmission and calcium homeostasis, which are important mechanisms for the learning and memory process (28). Previous studies also demonstrated the correlation between brain mitochondrial dysfunction and neurodegenerative disease (26; 27). Furthermore, the study of the insulin resistance model by HFD feeding showed that HFD consumption caused the down-regulation of mitochondrial respiratory chain gene expression and increased ROS production in the skeletal muscle (29; 30). Recently, our previous study also demonstrated that 12-week HFD consumption caused brain mitochondrial dysfunction, indicated by an increase of brain mitochondrial ROS, brain mitochondrial depolarization and brain mitochondrial swelling (31).

Metformin

Metformin (N-1,1-dimethylbiguanide) is the drug of choice to treat T2DM, in which its mechanisms are to reduce hepatic glucose output and to increase the insulin mediated utilization of glucose (32; 33). Metformin could improve hyperglycemia and insulin sensitivity in T2DM via decreased gluconeogenesis and glycogenolysis from liver, increased glucose uptake in skeletal muscle, decreased free fatty acid and also decreased intestinal glucose absorption as shown in Figure 1 (34).

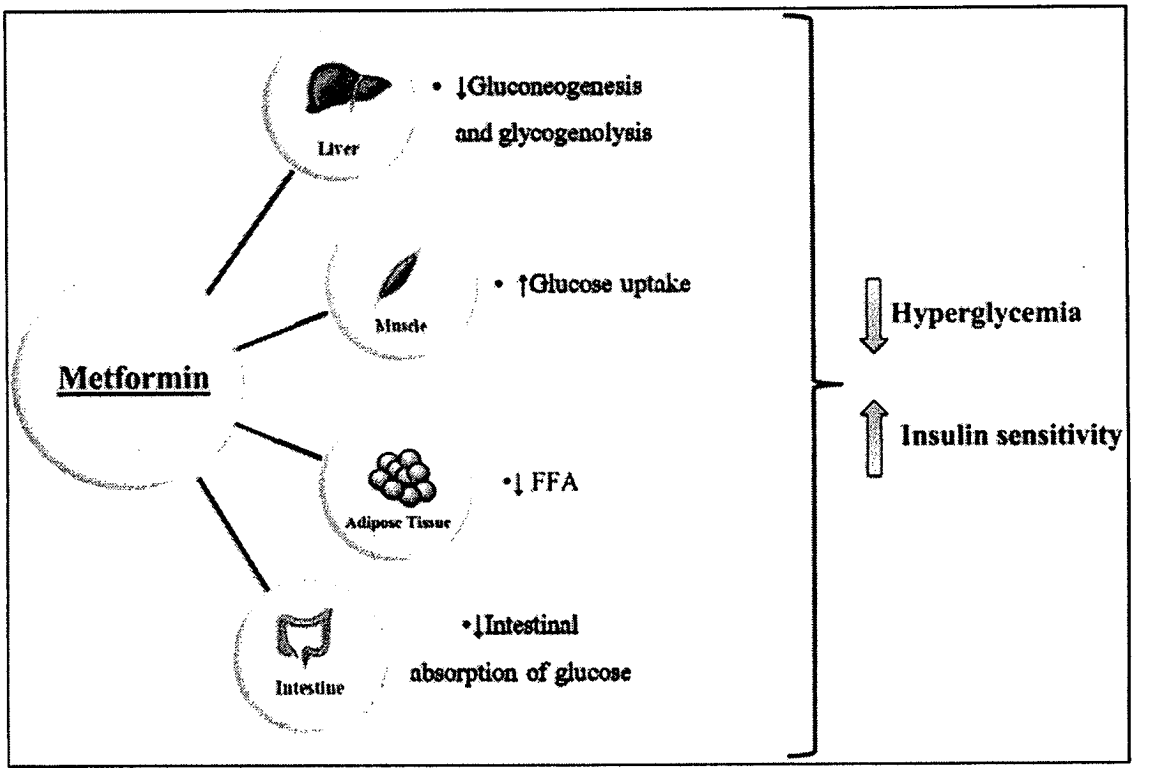

Figure 1: Metformin ameliorates hyperglycemia and enhances insulin sensitivity(Copied from Correia et al, 2008)(34)

Previous studies demonstrated that metformin can rapidly cross the blood brain barrier (BBB) and has several beneficial effects in the brain such as anti-inflammatory and neuroprotective effects (33). Despite its potential benefits, the effects of metformin on the spatial learning behavior and brain mitochondrial function in an insulin resistant model induced by HFD consumption have never been investigated. In the present study, we tested the hypothesis that the administration of metformin can reverse the impairment of spatial learning behavior and brain mitochondrial dysfunction caused by 12-weeks of HFD consumption.