DISSCUSSION

The major findings of the present study are as follows. In long-term HFD fed rats, metformin 1) improved the peripheral insulin resistant condition, 2) decreased plasma and brain mitochondrial oxidative stress, 3) improved brain mitochondrial dysfunction by decreasing mitochondrial ROS production, preventing mitochondrial membrane depolarization, and protecting brain mitochondrial swelling, and 4) restored the learning and memory behaviors impaired by long-term HFD consumption.

Previous studies demonstrated that metformin decreased plasma cholesterol level, plasma insulin level and HOMA index (44; 45), without changing the plasma glucose level (45-47). This finding that metformin improved peripheral insulin resistance is consistent with those previous studies. The mechanisms responsible for these beneficial effects of metformin have been shown to be due to its ability to reduce hepatic glucose production, increase insulin-mediated utilization of glucose (32; 33; 48; 49), restore insulin signaling pathways, and improve insulin sensitivity in peripheral tissues (34; 50).

We previous showed that long-term HFD consumption not only caused peripheral insulin resistance, but also induced neuronal insulin resistance and increased neuronal stress (5). Moreover, previous studies demonstrated that the insulin resistant condition caused by HFD consumption could reduce insulin transportation into the brain (23), reduce hippocampal neurogenesis, and increase oxidative stress in the central nervous system (19). In the present study, oxidative stress was observed in rats with HFD consumption as indicated by an increase in the MDA level in both plasma and brain. Our results demonstrated that metformin completely eradicated brain oxidative stress caused by HFD consumption, and reduced the plasma oxidative stress level. These findings suggest that metformin can act as an anti-oxidant agent. In non-neuronal cell lines, metformin has been shown to prevent oxidative stress-related cellular death (51). In the present study, we found that the anti-oxidative effect of metformin was more effective in the brain than in the circulation since it could completely prevent oxidative stress occurring in the brain but only partially attenuated it in the circulation. This could be due to the lower level of MDA in the brain than in the circulation.

In the present study, we demonstrated that rats with high levels of brain and plasma oxidative stress induced by long-term HFD consumption also developed brain mitochondrial dysfunction as well as the impairment of cognitive function. These findings are consistent with our previous report showing that 12-week HFD consumption caused brain mitochondrial dysfunction (31). Since HFD-induced insulin resistance has been shown to be related to learning and memory decline (7; 19; 52), our findings suggest that the cognitive impairment caused by long-term HFD consumption could be related to brain mitochondrial dysfunction and brain oxidative stress.

Interestingly, we found that metformin completely restored the brain mitochondrial function in rats which was impaired by long-term HFD consumption. In mitochondria, the mitochondrial permeability transitional pore (mPTP) is known as a crucial determinant of mitochondrial integrity (53), and the opening of mPTP can lead to mitochondrial swelling and mitochondrial membrane rupture (54). ROS are known as a trigger of mPTP opening (54). Evidence demonstrated that metformin could inhibit the mitochondrial permeability transitional pore (mPTP) (51; 55), reduce ROS production and lipid peroxidation as well as a decrease in the inflammatory cytokines secretion (51; 56; 57). The prevention of ROS production in brain mitochondria by metformin and its ability to inhibit the mPTP opening could be responsible for the complete protection of brain mitochondrial dysfunction observed in our study.

It has been known that the learning and memory impairment is associated with the impairment of hippocampal neurogenesis, the enhancement of oxidative stress levels in the brain, the reduction of synaptic plasticity in the hippocampus, and the dysfunction of brain mitochondria (19; 58). In the present study, metformin exerted its effect on improving the learning and memory behaviors which were impaired by HFD consumption. This improved cognitive function could be due to the beneficial effects of metformin on improving peripheral insulin resistance, decreasing plasma and brain oxidative stress, and preventing brain mitochondrial dysfunction. Furthermore, since metformin has been shown to rapidly cross the blood brain barrier after oral administration (33), it is possible that metformin could have acted directly as a neuroprotective agent in the central nervous system. Future studies are needed to explore this role of metformin.

CONCLUSION

Our present study demonstrated that metformin attenuated peripheral insulin resistance, decreased plasma and brain oxidative stress, and restored brain mitochondrial function, thus preventing the learning and memory impairment in insulin-resistant rats caused by long-term HFD consumption,. Therefore, metformin could be a possible drug of choice for diabetic patients with the cognitive impairment.