Excess exposure to insulin may be the primary cause of insulin resistance

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TO THE EDITOR: insulin resistance is either a precursor or a key component of numerous major diseases closely linked to the modern lifestyle, which is featured by overeating and/or lack of physical activities. These diseases include obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disorders, and many others. The impact of these problems on the global health and economy could not be more obvious now. The primary cause of insulin resistance is the positive energy imbalance due to overeating and/or lack of physical activities. However, the primary player that converts the positive energy imbalance into insulin resistance and the consequent hyperinsulinemia is still hotly debated. Establishment of this player may provide clear and specific targets for the prevention and treatment of insulin resistance and its associated health problems.

We have observed recently that the basal level of the classical Akt-dependent insulin signaling is increased in mice with insulin resistance and hyperinsulinemia induced by the high-fat diet (HFD) (5). Blunting the increased insulin signaling with the phosphatidylinositol 3-kinase inhibitor LY-294002 during the time when mice slept and did not highly demand insulin completely prevented the development of insulin resistance induced by the HFD (5). Both ectopic fat accumulation and oxidative stress in the liver and skeletal muscles were induced by the HFD, but the induction was prevented by the blockade of insulin signaling with LY-294002 (5). These results indicate that the increased basal insulin signaling causes insulin resistance and hyperinsulinemia through the promotion of ectopic fat accumulation and oxidative stress while working hard to maintain normal blood glucose levels. These results help explain why a majority of subjects with insulin resistance/hyperinsulinemia can maintain their blood glucose at normal or nearly normal levels without ever developing overt diabetes.

Furthermore, we have observed that hyperglycemia does not cause obvious insulin resistance, but administration of long-acting insulin (detemir) causes severe insulin resistance in mice (6). Administration of detemir mimics the continuous hyperinsulinemia induced by the HFD and is accompanied by the ectopic fat accumulation and oxidative stress in the liver and skeletal muscles (6).

In investigating the associated mechanisms, we have found that the mitochondrial production program is reduced by the excess exposure to insulin induced by either the HFD or administration of detemir (5, 6). Blockade of the increased basal insulin signaling reverses the suppression of mitochondrial production (5). Interestingly, macroautophagy (autophagy) may be also inhibited in mice with insulin resistance/hyperinsulinemia induced by either the HFD or administration of detemir (7). Autophagy is normally required for removing the aged/damaged macromolecules and cellular organelles, including mitochondria (7). In cultured hepatocytes, we have observed that prolonged exposure to insulin inhibits both mitochondrial biogenesis and mitophagy (autophagy of mitochondria) (7, 8). These observations imply that the suppressed production of new mitochondria via biogenesis and the reduced removal of aged/dysfunctional mitochondria via autophagy may be major contributors to the increased oxidative stress and insulin resistance induced by the HFD or administration of excess long-acting insulin.

In summary, our recent observations strongly support the notion that insulin may be the primary/necessary player that converts the positive energy imbalance into insulin resistance and associated diseases. Our observations echo some early findings by others that atherosclerosis does not occur or even reverses in the absence of insulin (1–4, 9). Thus, blockade of excess exposure to insulin may be a viable approach to prevent and/or reverse insulin resistance and its numerous associated diseases.

REFERENCES

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