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View Point

Insulin resistance: is it a feedback mechanism or a therapeutic target in type 2 diabetes?

John Thottukadavil Eapen*

Center for Multi-disciplined Research and Development, MEEISATCODE, Dahanu Road, Maharashtra, India

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***Correspondence:**
Dr. John T. Eapen,
E-mail: Jeteapen@gmail.com

ABSTRACT

Insulin resistance is an essential pathological condition leading to hyperglycemia of blood, and hence insulin resistance is considered as a therapeutic target. The experimental evidence of studying the effect of naphthalene on *Anadara granosa*, a bivalve, indicated mitochondrial dysfunction and osmolarity change in them. This communication tries to suggest whether insulin resistance is a feedback mechanism to protect the influx of nutrients into the cells demanding osmoregulation of cells.

Keywords: Electron transport chain inhibitors ,Insulin resistance, Mitochondrial dysfunction process, Type 2 Diabetes

INTRODUCTION

Type 2 Diabetes, characterized by hyperglycemia in the blood is the most common metabolic disease in the world.[1] Insulin, a hormone produced by the β cells of the pancreas facilitates glucose into the cells. Glucose transporter proteins mediate the transport of glucose across the muscle cell plasma membrane, and two isoforms (GLUT1 and GLUT4), are expressed in muscle. Insulin acutely increases glucose transport in muscle by selectively stimulating the recruitment of the GLUT4 transporter (but not GLUT1) from an intracellular pool to the plasma membrane.[2] Due to some unknown reason, the entry of glucose into the cells is hindered even in the presence of an adequate amount of insulin, and this condition is known as insulin resistance. Insulin resistance is defined as a reduced response of targets such as the skeletal muscle, liver, and adipocytes, to insulin.[3] It has traditionally been associated with type 2 diabetes.[1] The defects in the insulin responsiveness of skeletal muscle and liver are responsible for insulin resistance, and if it persists over time, then glucose-stimulated insulin secretion by pancreatic β cells gets defected.[4] In addition to this, prolonged hyperglycemia of blood may affect the functioning of different organs, leading to morbidity. Due to these reasons, insulin resistance is considered an important pathological condition that may lead to diabetes and it is a therapeutic target to control hyperglycemia.[1]

Recent reports indicate the association of mitochondrial dysfunction and insulin resistance.[4,5] However, when ambient blood glucose levels were near normal in diabetes, no defect in mitochondrial function was apparent.[1] It raises a question, whether mitochondrial dysfunction causes insulin resistance, or result from insulin resistance.[1,5]

In this communication, author wants to suggest that insulin resistance may be a protective feedback mechanism that prevents nutritional overload and deposition of metabolic intermediates in the cells

demanding complicated osmoregulation of cytoplasm of the cells.

Rationale for the hypothesis

Present study on the effect of naphthalene, a toxic component in the petroleum that caused mitochondrial dysfunction and osmolarity change of the tissues and hemolymph of *Anadara granosa*, a bivalve that lives in muddy shores of Sewri and Trombay in Mumbai, has shed some insights into the physiological changes that may occur during mitochondrial dysfunction in the cells of other animals.[6-10]

Physiology of intertidal animals

Intertidal animals are covered by seawater during high tide and respires aerobically utilising oxygen as the final electron acceptor. During low tide, the water recedes, and they live without water for many hours. During low tide or hypoxia in the bivalves, the energy production is facilitated through an anoxic endogenous oxidation mechanism.[6,7] This mechanism is present in the lipochrome pigments of cytosomes, which function as an oxygen store through conjugated double bond binding.[11] The unsaturated fatty acids perform the electron transfer function. Unsaturated fatty acids accept electrons from hydrogen donors like NADPH or NADH and become saturated.[6,8]

Experimental evidence

A. granosa exposed to 5, 10 and 15 ug. ml-1 of naphthalene dissolved in filtered seawater and their physiological and biochemical responses were studied. Naphthalene-induced mitochondrial dysfunction by inhibiting ubiquinone (Coenzyme Q10). It resulted in anaerobic metabolism in *A. granosa* though they were living in seawater. Anaerobic metabolism led to the accumulation of specific metabolites and ions in the cells and hemolymph. *A. granosa*, being an osmo-conforming bivalve, adjusted the change in osmolarity with water and resulted in tissue hydration.[6-10]

Importance of osmoregulation

The osmolarity of the cytoplasm alters with influx and deposition of specific metabolites from outside or intermediate metabolites generated within the cells. Osmoconformation is very important to the cells, and in the aquatic animals, water molecules from the environment play a significant role. Water is essential to life.

Physiological and biochemical modifications in animals depend on the availability of water. (e.g. Ammonia, a nitrogenous waste, is disposed of in aquatic animals into the water, though solubility of ammonia is low in the water. In terrestrial animals ammonia is converted to urea, uric acid or guanine that excretes with little water).

Importance of insulin-mediated transport

Since water is scarce for terrestrial animals, author believes that the entry of glucose, an important nutritional metabolite, into the cells is transported with insulin hormone. It could facilitate switching off the insulin receptors in the cells during hyperglycemia of the blood to avoid overloading of cells with nutrients, leading to osmolarity change in the cytoplasm. Under this condition, the osmolarity of the blood is easily adjusted with water, to match the osmolarity of cytoplasm in the cells. It may explain the polydipsia observed during hyperglycemia. When the level of blood glucose comes down the excess water may be removed by polyuria.

Due to the reasons mentioned above, author wants to suggest that insulin resistance could be a feedback mechanism to prevent nutrition overload in the cells and it may not be considered as a therapeutic target to control hyperglycemia. The reason for hyperglycemia could be something else.

Mitochondrial dysfunction: Could it be the root cause?

The association of mitochondrial dysfunction (oxidative stress) and type 2 diabetes is known and there are reports suggesting insulin resistance and β cells dysfunction arise out of mitochondrial defects. An important question that remained unanswered was: Is the reduction in mitochondrial function in vivo due to mitochondrial loss, functional abnormalities in the mitochondria or both? Based on our observation of naphthalene acting as electron transport inhibitor, author wants to propose that mitochondrial functional defect could be the triggering point for insulin resistance leading to hyperglycemia in many cases.[4-5]

Electron transport chain inhibitors

Many pesticides and derivatives inhibit electron transport chain at different levels. The effects of some food additives in processed food may also have a role in the inhibition of the electron transport chain. Generally, their concentration in food is allowed on Allowable Daily Intake (ADI) of that compound concerning its toxicity. However, some of them may have an inhibitory effect at low levels over a while. At low concentrations, the inhibitory effect may be temporary as seen in *A. granosa* exposed to 5ug.ml-1naphthane. The endangered animals behaved like control animals when they were in clean seawater without naphthalene for some time. It allowed depuration of naphthalene from them. This observation gives hope that mitochondrial dysfunction could be reversible if probable electron transport inhibitors are reduced or avoided in nutrition.[6,10,12-14]

Clinical evidence to support the hypothesis

At this juncture, author wants to share a clinical experience where a patient managed his hyperglycemia

for the last ten years just by having home cooked food and avoiding processed food as far as possible including refined salt.[15] He used common salt available from the local market. However, he used to walk at least 2 kms daily. In his life, he took medicines for diabetes just for a month when doctors diagnosed nine years ago. This case study points out that mitochondrial dysfunction is reversible.

Could ageing be a contributing factor for mitochondrial dysfunction?

Ageing may also cause mitochondrial loss leading to reduced mitochondrial dysfunction.[16] This author believes that wherever man faces a challenging situation, the intuition shows a way to counteract the challenge.[17] In many population groups, ginger, a herb, is used in their tea and coffee.[18] The "Chukku Kappi" (coffee with dry ginger powder) was used by the elderly as their morning beverage in South India, and it may have helped the elderly.[19] Ginger is known to increase mitochondrial biogenesis, and this may have helped the elderly to counteract mitochondrial dysfunction associated with ageing.[20]

CONCLUSION

In summary, author wants to propose that mitochondrial dysfunction could be the triggering factor for the hyperglycemia and it could be caused by different electron transport inhibitors in the environment or food. Insulin resistance could be a feedback mechanism preventing nutritional overload in the cells. Mitochondrial dysfunction is reversible if electron transport inhibitors are avoided. Administration of insulin to counteract insulin resistance may cause obesity in patients where the glucose entering into the cells get converted into fatty acids instead of going through the Krebs cycle if mitochondrial dysfunction (oxidative stress) persists in the patient.

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