Medicine Journal
2014; 1(1): 8-12
Published online February 28, 2014 (http://www.openscienceonline.com/journal/med)

A perspective on interaction between lipid and branched chain amino acids (BCAA) in developing insulin resistance

Sheriff D. S*; Younis, M. Y. G; Elshaari F. A; Negia Abdalla Mohamed; Hanan Issa Ali El Kuwaila; Sara Ali Sh. Abdalla; Rajea Elfaghi

Department of Biochemistry, Faculty of Medicine, Benghazi University, Benghazi, Libya

Email address

dhastagir@yahoo.ca (Sheriff D. S)

To cite this article

Sheriff D. S; Younis, M. Y. G; Elshaari F. A; Negia Abdalla Mohamed; Hanan Issa Ali El Kuwaila; Sara Ali Sh. Abdalla; Rajea Elfaghi. A Perspective on Interaction between Lipid and Branched Chain Amino Acids (BCAA) in Developing Insulin Resistance. *Medicine Journal,* Vol. 1, No. 1, 2014, pp. 8-12.

Abstract

There is a reciprocal relationship between glucose and fatty acid oxidation. Over nutrition or obesity causes perturbation in this reciprocal metabolic interrelationship leading to "metabolic inflexibility" resulting in mitochondrial dysfunction causing insulin resistance. Excess fat intake in obesity results in an inhibition of fatty acid oxidation in the adipose tissue accompanied by increased BCAA catabolism in skeletal muscle. This results in an increase in the levels of acyl carnitines which impair insulin action. It is suggested that serum acyl carnitine levels could therefore be taken as markers of insulin resistance.

Keywords

Branched Chain Amino Acids(BCAA), Metabolic Inflexibility, Acyl Carnitines, Insulin Resistance (IR)

1. Introduction

Oxidation of carbohydrates, fats and proteins produce acetyl Co. A. Whose oxidation result in the formation of NADH, FAD. 2H which by oxidative phosphorylation produce energy in the form of ATP.(Stage I to III depicted in the Fig 1.). 1 These processes take place in mitochondrial matrix, inner mitochondrial membrane apart from the mitochondrial proteins present in outer mitochondrial membrane as carriers or transporters. Therefore, the structure, function and its content in a tissue determine the oxidizing potential of a specific tissue linking carbohydrates, lipid and protein metabolism. A co-ordinated interplay between the tissues in whole body metabolism are regulated by insulin and its counter regulatory hormones particularly glucagon or epinephrine and cortisol. A disconnect between these metabolic activities may be due to loss of hormonal action or vice-versa. For example an excess of fat intake may result in accumulation of intramyocellular triglycerides and its metabolites, such as long-chain fatty acyl-CoAs. An increase in the levels of long chain fatty acyl Co As is reported to cause impaired insulin signaling and insulin resistance 2. This effect of high fat intake seen in obesity or type 2 diabetes (T2DM) is associated with possibly a defect in mitochondrial structure or in density which may be associated with skeletal muscle experiencing insulin resistance or insulin inaction. It may lead to oxidative stress releasing more super oxide anions which impair or aggravate insulin resistance.

Recent studies have shown that increased fatty acid oxidation in muscle in response to high-fat intake is associated with concomitant increase in TCA cycle activity. Such a disconnect between fatty acid oxidation and TCA cycle will results in accumulation of incompletely oxidized fatty acids in the mitochondrial matrix. This will result in mitochondrial matrix stress and interfere with insulin action. Therefore in this short review an attempt has been made to bring out the role of mitochondrial dysfunction causing an imbalance between adipose tissue, skeletal muscle and liver

metabolism orchestrated by insulin and its counter regulatory hormones.[3-5]

2. Insulin Resistance (IR)

Insulin resistance can be defined as resistance to insulin action on metabolism of carbohydrates and lipids. It influences glucose uptake, metabolism and storage. In other words it promotes uptake of glucose in skeletal muscle and adipose tissue through Glucose transporter 4 (GLUT 4). It promotes glycogenesis in muscle and liver and also glycolysis to provide energy. Insulin also promotes lipogenesis and inhibits lipolysis. Its action involves induction of lipoprotein lipase activity (LPL) which breaks down chylomicrons or VLDL attached triglycerides into fatty acids and Lipoprotein remnants. The liberated fatty acids are taken up by the adipose tissue and stored as triglycerides. It inhibits lipolysis by inactivating Hormone sensitive lipase (HSL) the key enzyme of triglyceride breakdown. It promotes fatty acids synthesis by activating acetyl co A carboxylase, the key enzyme of fatty acid synthesis. The increased formation of malonyl Co A during fatty acid synthesis inhibits the uptake of fatty acids into mitochondria by inhibiting carnitine shuttle involved in fatty acid transport. (inhibits carnitine palmityl transferase I (CPAT I). [1] General metabolic effects of insulin and glucagon actions are depicted in Fig.2.

2.1. The Mechanism of Insulin Action

The mechanism of action of insulin involves the binding of insulin to insulin specific receptors activating tyrosine kinase activity intrinsic to Beta chains of insulin receptor. This in turn activate insulin receptor substrates (IRS I and 2) by phosphorylation of multiple tyrosine residues. These phosphorylated tyrosine residues become docking sites for many proteins including the regulatory subunit of phosphoinositide 3' kinase (PI3K). Functional defects in insulin resistance may be due to impaired insulin signaling in all three target tissues i.e. in adipose tissue, skeletal muscle and liver. In both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of IRSs are reduced. Recent studies have indicated that defective signaling from the insulin receptor is an important component of insulin resistance associated with obesity in humans.

There are also tissue-specific alterations observed in adipocytes of obese humans, IRS-1 expression is reduced, resulting in decreased IRS-1-associated PI3K activity, and IRS-2 becomes the main docking protein for PI3K.[6]

In contrast, in skeletal muscle of obese individuals, IRS-1 and IRS-2 protein levels are normal but PI3K activity associated with both IRSs are impaired.[7]

2.2. Metabolomic Profiling Studies

The introduction of metabolic profiling of biochemical parameters (Metabolomics) has resulted in trying to understand the role of proteins, particularly amino acids in developing insulin resistance (IR). It has been shown that branched chain amino acids (BCAA) have a special role in the interaction between glucose, fatty acid and α- keto acid derivatives' oxidation and utilization.[8, 9]

2.3. Effect of Diet and Dietary Components- a Reciprocal Relationship between Carbohydrate and Lipid Metabolism

Diet and dietary components' effect on whole body metabolism is regulated by insulin and its counter regulatory hormones (glucagon, epinephrine and cortisol). The secretion and release of these hormones are usually dependent on the continued feed-starve stimulus on islet cells (β and α cells). [10]

During starvation the increased glucagon levels causes an increase in lipolysis releasing free fatty acids into the circulation which is oxidized to provide energy to the peripheral tissues including skeletal muscle. The intermediates of fatty acid oxidation inhibit glycolytic enzymes and therefore glucose oxidation and its utilization. During the fed state insulin will promote lipogenesis and fatty acid synthesis. The high levels of malonyl Co A the key metabolite of fatty acid synthesis will inhibit fatty acid oxidation and vice-versa. This reciprocal relationship help to maintain and balance glucose and lipid metabolism.[11,12].

2.4. Over Nutrition and Metabolic Inflexibility

Over nutrition or obesity causes perturbation in reciprocal metabolic interrelationship leading to "metabolic inflexibility" resulting in mitochondrial dysfunction causing insulin resistance. (Fig 3.) 13

2.5. Excess Fat and Sloth

An excess accumulation of fat accompanied by a sedentary lifestyle (Sloth) is reported to bring about a disconnect between fatty acid oxidation and TCA cycle.(Fig.4) This causes an accumulation of lipid intermediates like acyl carnitines which impair insulin action.[8,14]

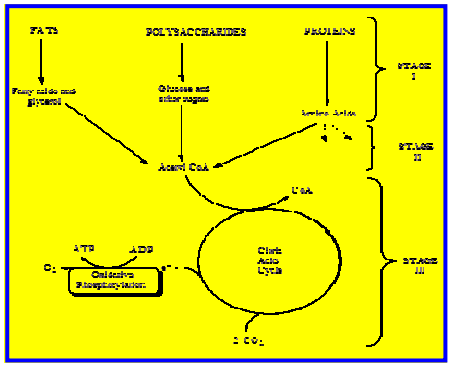

Fig 1. *Acetyl Co.A production, oxidation and production of Energy in the form of ATP.*

Metabolic Action	Insulin	Glucagon
Glycogen synthesis	↑	↓
Glycolysis (energy release)	↑	↓
Lipogenesis	↑	↓
Protein synthesis	↑	↓
Glycogenolysis	↓	↑
Gluconeogenesis	↓	↑
Lipolysis	↓	↑
Ketogenesis	↓	↑

Fig 2. *Metabolic Effects of Insulin and glucagon (stimulates; inhibits).*

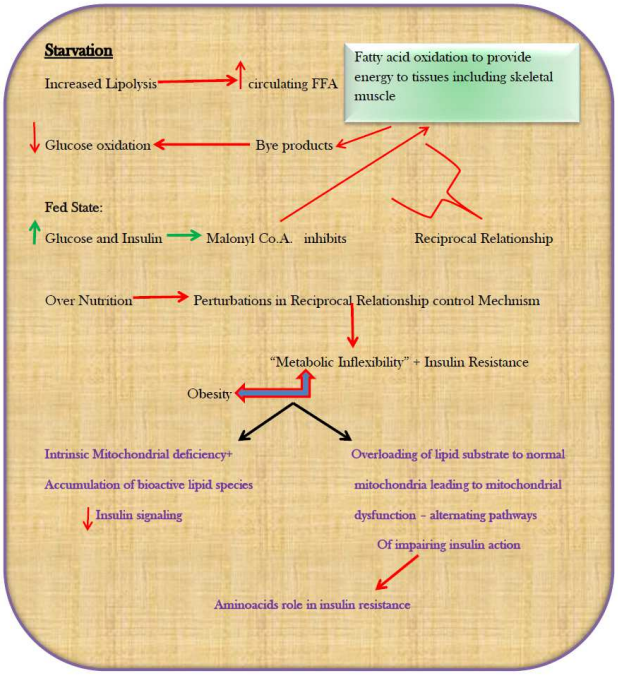

Fig 3. *Metabolic Relations and its impairment in Obesity leading to alternate pathways to influence insulin action.*

2.6. Branched Amino Acids(BCAA)

Most of the amino acids can be transaminated and degraded in the liver effectively, with the exception of BCAA's (Valine, Leucine and isoleucine). Large percentages of the BCAA are oxidized by the muscle tissue and some by adipose tissue [15] The liver oxidizes α-keto acid derivatives formed from BCAA catalyzed by mitochondrial dehydrogenase and branched-chain keto acid dehydrogenase (BCKADH).(Fig.5)

2.7. Mitochondrial Stress-Accumulation of Acyl Carnitines

With mitochondrial stress and inhibition of active fatty acid oxidation, BCAAs like valine and isoleucine are transaminated and catabolized liberating increased levels of propionyl Co A which gets converted to succinyl Co A flooding the TCA cycle with intermediates (anaplerosis). Increased levels of propionyl Co A and succinyl Co A allosterically inhibit citrate synthase which in turn inhibits glucose oxidation and its utilization causing glucose intolerance.[16] Excess fat intake in obesity results in inhibition of fatty acid oxidation in the adipose tissue accompanied by increased BCAA catabolism in skeletal muscle. Propionyl Co A and succinyl Co A accumulation cause succinylation of mitochondrial proteins which hampers the cross talk between glucose, fatty acid and BCAA oxidative pathway. This expands the serum pool of BCAA which spills into other tissues including skeletal muscle generating more of C3 and C5 acyl carnitines. (Figs 4, 5.)[17] There is now considerable evidence to show the connection between BCAA metabolism and insulin resistance in obese and diabetic patients.[18, 19] Therefore accumulation of C3 and C5 acyl carnitines in plasma could be taken as a marker of insulin resistance. (Figs.6)

3. Conclusion

In general obesity, sedentary life style, aging, genetics, glucotoxicity and increase in free fatty acids are considered to cause IR. Now it is seen that branched amino acid metabolism and its defect could also result in IR> Though .few studies are available about the role of BCAA metabolism in obesity and obesity-related disorders it will be worthwhile to study the role of BCAA metabolism in a cross section of population with different geographical, cultural and life styles. Further studies may also help to define the possible role of acyl carnitines as biomarkers of IR and their overall effect on whole body metabolism in health and disease.

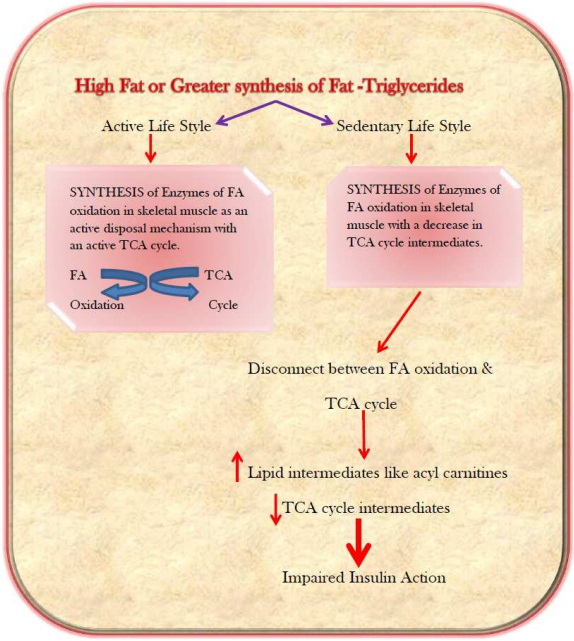

Fig 4. *High Fat Diet and Life style influence on Glucose and Fatty Acid Oxidation.*

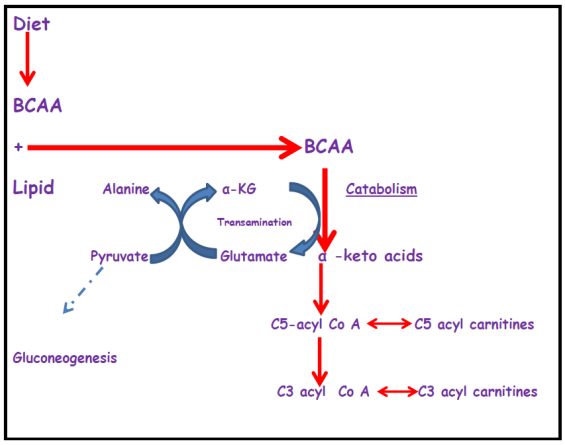

Fig 5. *Over nutrition related to obese subjects, circulating branched-chain amino acids (BCAA) rise, leading to increased flux of these amino acids through their catabolic pathways.*

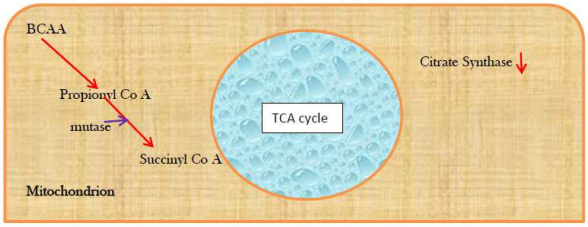

Fig 6. *Increased catabolism of branched chain aminoacids (BCAA) and loading of succinyl Co A into TCA cycle.*

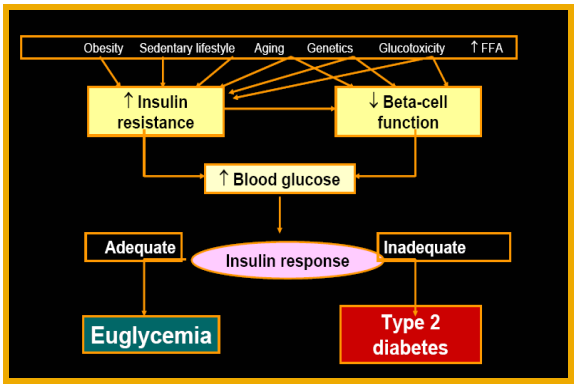

Fig 7. *Possible causes of insulin resistance.*

Note: There is no funding or any conflict interest with respect to the above submission.

References

[1] Sheriff D.S. Introduction to metabolism. In. Medical Biochemistry (Text Book), Jaypee Medical publishers, New Delhi.2004

[2] Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, Neschen S, White MF, Bilz S, Sono S, Pypaert M, Shulman GI. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. J Clin Invest 2005;115:3587–3593

[3] Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002;51:2944–2950

[4] Ritov VB, Menshikova EV, He J, Ferrell RE, Goodpaster BH, Kelley DE. Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. Diabetes 2005;54:8–14.

[5] Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med 2004;350:664–671

[6] Rondinone CM. Insulin receptor substrate (IRS) 1 is reduced and IRS-2 is the main docking protein for phosphatidylinositol 3-kinase in adipocytes from subjects with noninsulin-dependent diabetes mellitus. Proc Natl Acad Sci USA 1997; 94: 4171-4175.

[7] Kim YB, Nikoulina SE, Ciaraldi TP, Henry RR, Kahn BB. Normal insulin-dependent activation of Akt/protein kinase B, with diminished activation of phosphoinositide 3-kinase,in muscle in type 2 diabetes. J Clin Invest 1999; 104: 733-741

[8] Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. Nature 2006;440:944–948

[9] Bains JR, Stevens RD, Wenner BR, Ilkayeva O, Muoio DM and Newgard CB. Metabolomics applied to diabetes research: moving from information to knowledge. Diabetes 2009;58: 2429-2443.

[10] Koves TR, Li P, An J, Stentz D, Ilkayeva D, Akimoto et al. Peroxisome proliferator activated receptor –gamma co-activator 1 alpha ; metabolic remodeling of skeletal myocytes mimcs exercise training and reverses lipid-induced mitochondrial inefficiency. J Biol Chem 2005;280: 33588-33598.

[11] Stephen L. Aronoff, Kathy Berkowitz, Barb Shreiner, and Laura Want, Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum 2004 ;17:183-190

[12] Randle DJ. Regulating interaction between lipid and carbohydrate ; the glucose-fatty acid cycle after 35 years. Diabetes Metab Rev 1998;14:263-283.

[13] McGarry.J.D. Banting lecture.2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes mellitus. Diabetes 2001;51: 7-18.

[14] Kelley DE and Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a re-examination. Diabetes 2000;49: 677-683.

[15] Sparks LM, Xie H,Koza R, Mynatt R, Hulver MW, Bray GA et al. A high fat diet coordinately down regulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. Diabetes 2005;54: 1926-1933.

[16] Gaitanos, G.C., C. Williams, L.H. Boobis, and S. Brooks (1993). Human muscle metabolism during intermittent maximal exercise. J. Appl. Physiol.1993 75:712–719

[17] Guillet C, Delcourt I, Rance M, Giraudet C, Walrand S, Bedu M, Duche P, Boirie Y.J Changes in basal and insulin and amino acid response of whole body and skeletal muscle proteins in obese men. Endocrinol Metab. 2009; 94(8):3044-50.

[18] NewgardCB,An J, Bain JR, Muehlbauer ,J, Stevens RD, Lie n LF, Haqq AM, et al.. A branched chain amino acid- A branched related metabolic signature that differentiate obese and lean humans and contributes to insulin resistance. Cell Metab 2009;9: 311-326.

[19] Yazmin Macotela, Brice Emanuelli, Anneli M. Ba˚ng, Daniel O. Espinoza, Jeremie Boucher, Kirk Beebe , et al. Dietary Leucine - An Environmental Modifier of Insulin Resistance Acting on Multiple Levels of Metabolism. PLoS ONE 2011; 6 (6):e21187.