Introduction

It has been aptly said: “yesterday’s research is today’s practice and today’s research is tomorrow’s practice of medicine”. Applying this dictum to T2DM the knowledge gained about proinsulin, C peptide, glucagon, adiponectin, AMPK and TNFα in the last 10-15 years should be reflected in the current thinking about managing T2DM. Even the latest consensus statement of ADA and EASD on Medical Management of hyperglycemia of T2DM (Nathan DM et al 2009) does not reflect the importance of these players – which are not even mentioned in the whole statement, hence the need for this critical review.

Proinsulin

Proinsulin (9000 mol wt. peptide) is synthesized on the ribosomes of pancreatic islet β cells and then transferred to Golgi apparatus, where during the process of maturation of secretory granules, proinsulin is cleaved by endo-peptidases PC3 (type 1) and PC2 (type 2) into insulin (6000 mol wt) and C-peptide (3000 mol wt.). normal cleavage sites are Arg. 31-32 and Lys 64, Arg 65 at the A Chain (Fig. 1).

During this processing, conversion intermediates are produced – type1 intermediates in which C peptide/ A chain has been cleaved and C peptide remains attached to the B chain (des Lys64 Arg65 proinsulin); and type 2 intermediate in which C peptide / B chain has been cleaved and C peptide remains attached to the A chain (des Arg31 Arg32 proinsulin).

Starr and Rubenstein (1974) have studied the metabolism of endogenous proinsulin and insulin in humans. Compared to insulin, human proinsulin has low biological potency, low avidity for insulin receptors and prolonged half life in circulation. Studies with I-123 labeled human proinsulin (HPI) have shown that intact HPI is extracted only by the kidneys (while majority of insulin is extracted by the liver) : Type 1 (des 64.65 proinsulin) is mainly extracted by the liver, partly by the kidneys. Type 2 (des 31-32 proinsulin) is extracted by both liver and kidneys (F. Sodoyez- Goffanx et al 1988).

Gabbay et al (1976) described familial hyperproinsulinemia, an autosomal dominant defect in which C peptide remains attached to A chain (site of cleavage Arg 32 glu 33 of B chain) and in which Arg 65 has been replaced. Total immunoreactive insulin

Abstract:

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may be as high as 100 μU/ml of which 75-90% is proinsulin. The subjects remain euglycemic, since type 1 intermediates have intermediary biological activity while type 2 intermediates have low biological activity.

Ahmad et al (1991) showed that (-) epicatechin an active principle in the watery extract of the bark of an Ayurvedic herb Vijayasar (Pterocarpus marsupium) increases the cAMP content of rat islet β cells, associated with increased conversion of proinsulin to insulin and increased insulin release. The response was more pronounced in immature (one month old) than mature (12 months old) rats. A recent ICMR clinical trial by Vijayasar in T2DM patients surprisingly did not include estimation of proinsulin and insulin before and after therapy. This illustrates the need and scope for more imaginative thinking based on available information, while planning clinical trials.

**Proinsulin to insulin ratio**

Serum proinsulin is disproportionately elevated both in the basal state and after an oral glucose load in T2DM with an increase in the proinsulin to insulin ratio (normal 15%). Duckworth et al (1972)\(^2\), Gordon et al (1974)\(^4\) and Mako et al (1977)\(^7\), Ward et al (1987)\(^9\) experimentally confirmed the hypothesis that a greater demand for insulin secretion in response to insulin resistance, when accompanied by β cell secretory dysfunction leads to hypersecretion of pro-insulin by β cells. Dexamethasone (6 mg/d for 3 days) raised the proinsulin : insulin ratio from normal 13% to 21% in control and from 29% to 57% in T2DM patients. Seaquist et al (1996)\(^11\) provided further evidence of “increased demand theory” of proinsulin secretion. Healthy donors for pancreatic transplantation had pre-hemipancreatectomy base line fasting proinsulin level 6.24 + 1.14 pmol/mL. At one year post-donation the basal proinsulin was 34.63 + 17.47 pmol/ml. A healthy control group showed normal level (5.78 ± 1.12 pmol/ml) initially and one year later.

Yoshioka N et al (1988)\(^12\) have shown that apart from T2DM, subjects with impaired glucose tolerance (IGT) also showed increased proinsulin. They suggested that β cells release immature granules richer in proinsulin content as well as mature granules, in the over-stimulated state.

Yoshioka N et al (1989)\(^13\) studied the effects of dietary treatment on insulin and proinsulin response in newly diagnosed T2DM. On a diet of 25 – 30 K Cal/kg. ideal body weight, plasma glucose decreased from 197 + 35 to 113 + 10 and proinsulin to insulin ratio decreased from 32% to 24%.

**Predictive value of proinsulin**

Haffner SM et al (1993)\(^14\) suggested increased proinsulin as a cardiovascular risk factor in non-diabetic subjects. Yudkin (1995)\(^15\) showed that a proinsulin : insulin ratio > 20% is a predictor of future T2DM. The same was shown by Ramachandran et al (1988)\(^16\) Warham NJ et al (1999)\(^17\), Lele RD et al (2006).\(^18\) A large epidemiological study (IRIS-1, 4265 patients) confirmed that fasting hyperproinsulinaemia is a highly specific marker of insulin resistance (Pfutzner et al 2004)\(^19\) hence therapy should focus on reducing insulin resistance. Proinsulin stimulates plasminogen activator inhibitor 1 (PAI-1) secretion and blocks fibrinolysis, thereby increasing risk of cardiovascular micro and macrovascular disease. I have urged the Indian diabetologists to routinely measure proinsulin to insulin ratio in epidemiological studies. This suggestion has been accepted by for the Chennai Rural & Urban population study (Mohan et al 2006). Predicting future T2DM provides a 10 year window of opportunity for preventive measures (regular physical exercise, weight reduction, dietary modification with EPA / DHA and antioxidants).

Rachman J. et al (1997)\(^20\) showed that the relative hyperproinsulinaemia of T2DM persists despite the reduction of hyperglycemia with insulin and SU therapy. This may reflect an additional defect in the converting enzymes PC3 and PC2 as in familial hyperproinsulinaemia. In a study of 35 T2DM and 50 healthy controls, 3 examples of defective PC enzyme were detected with low insulin and high proinsulin (Lele RD et al 2006).

Hansen BS et al (1988)\(^21\) suggested another mechanism viz. effect of IL-1 on biosynthesis of proinsulin and insulin in isolated rat pancreatic islets. The high levels of TNFα found in T2DM and their correlation with proinsulin (Lele RD 2006) suggest a testable hypothesis that TNFα acts similar to IL-1, in the islet cells, inhibiting insulin biosynthesis and attenuating the rate of conversion of proinsulin to insulin.

**C peptide**

C Peptide is a measure of endogenous insulin secretion, Normal fasting level is 1-4 ng/ml which rises after meals eg. Fasting 1.2 ng/ml → 4.7 ng/ml pp 1.8 ng/ml → 5 ng/ml pp 2 ng/ml → 6.8 ng/ml pp

Strowig SM et al (2004)\(^22\) studied 28 patients of T2DM with fasting C peptide > 2 ng/ml, who were given insulin + TZD therapy for 4 months, all gained weight 4.4. + 2.7 kg.

In an analysis of 400 T2DM patients who were being considered for insulin therapy because of poor glycemic control at Jaslok Hospital & Research Centre, Mumbai during 2007 and 2008, only 5 patients were seen to have fasting C peptide less than 1 ng/ml. 5 patients showed C peptide more than 5 ng/ml, highest being 9.8 ng/ml in a male aged 50. All others had C peptide in the normal range, clearly indicating that they have insulin resistance and need strategies for overcoming insulin resistance (discussed in the last section of this review). By putting these patients on insulin there will be a predictable gain in weight (5 kg, over next 3-12 months) and more episodes of hypoglycemia (both undesirable effects). I have been urging that C peptide < 1 ng/ ml fasting or < 2 ng post meal should be the basis of starting insulin therapy for T2DM. Unfortunately this dictum is totally ignored by most practicing diabetologists world-wide who do not consider estimation of C peptide necessary -- an amazing "blind spot" in their vision ! Even Harrison's Principles of Internal Medicine 17th ed. (2006) mentions C peptide estimation only in the context of insulinoma.

A biological role for C peptide was suggested by the clinical observation that T1DM with some measurable C peptide have less long-term complications than T1DM patients totally deficient in C-peptide. Pancreatic / islet cell transplant restored both insulin and C peptide, resulting in amelioration of diabetic nephropathy and neuropathy. Short-term C peptide infusion as well as oral replacement therapy for 3 months was shown to reduce albuminuria by 40% and improvement in nerve conduction velocity by 80% C peptide at physiological concentrations (0.9 mmol/l) releases NO in vascular endothelial cells in a time and concentration –dependent manner and increase intracellular Ca++. The effects are abolished by pertussis toxin suggesting Gi/Go-linked protein interaction in C peptide signaling. (Wahren J et al 2007)\(^23\) These benefits are seen in C
peptide deficient states only. Excess C peptide like excess insulin and proinsulin causes undesirable activation of several protein kinase isoforms (MAPK, NFkB).

**Beta cell preservation therapy**

There is a progressive deterioration in β cell function and mass in T2DM. At the time of diagnosis β cell function is already 50% of normal with a reduction in β mass of about 60% (shown in necropsy). Several factors- glucotoxicity, lipotoxicity, proinflammatory cytokines (IL-1, TNFα), leptin and islet cell amyloid, accelerate β cell apoptosis. Interventions to preserve or rejuvenate β cells are reviewed by Wajchenberg (2007). They are:

1. Short-term intensive insulin therapy of newly diagnosed T2DM.
2. Induce β cell rest by selective activation of ATP-sensitive K+ (KATP) channels using drugs such as diazoxide.
3. Anti-apoptotic drugs such as thiazolidinediones (TZDs) and incretin mimics/enhancers, which stimulate β cell proliferation and inhibit β cell apoptosis.

The only objective way of testing the effectiveness of these therapies is by serial measurements of C peptide (fasting and post-prandial) and proinsulin / insulin ratio. It is worth emphasizing that intensive insulin therapy does nothing to alter the basic underlying defect viz. insulin resistance, as measured by HOMA-IR and Mitsuda Index (Chen HS et al 2008). Hence the need for a paradigm shift: use of insulin sensitizers to overcome insulin resistance, in preference to exogenous insulin, which can exacerbate weight gain as well as hypoglycaemia (Fonseca V. et al 2007).

**Glucagon**

If glucagon had been discovered earlier than insulin, T2DM would well be defined as a state of hyperglucagonemia resulting in hyperglycemia due to glucagon-induced hepatic gluconeogenesis. Hyperglucagonemia is a characteristic of both T1DM and T2DM. Unger RH (1971, 1974, 1977) has discussed the role of pancreatic islet α and β cell inter-relationship in health and disease and the role of glucagon in diabetes. The normal reciprocal response of insulin and glucagon regulates post-prandial glucose levels. Impaired α cell regulation leads to excessive glucagon release in the fasting and post-prandial state, with increase hepatic glucose production (HGP) and hyperglycaemia. The incretin concept was put forward by Crutzfeldl W et al in 1979 indicating the role of two incretins – Glucagon-like peptide1 (GLP-1) secreted by intestinal L cells, and Glucose-induced insulinogenic Polypeptide (GIP) secreted by intestinal K cells in regulation of islet α and β cell function. Nauck ME et al in 1993 showed a new approach to achieve normalization of fasting hyperglycemia with exogenous GLP-1 in T2DM and the ability of GLP-1 to increase post-prandial insulin secretion and suppress post-prandial glucagon secretion.

Dunning BE et al (2005) have discussed α cell function in health and disease and the role of incretins GLP-1 & GIP in regulation α and β cell function. Meier JJ et al (2006) have shown that the inappropriate post prandial hyperglucagonemia in T2DM is due to loss of intra islet post-prandial suppression of glucagon secretion by insulin. Pancreatic α cells express insulin receptors at high levels. Intra islet release of insulin exposes α cells to insulin concentration of ~ 400 nmol/l which suppresses post-prandial glucagon secretion. Impaired insulin secretion leads to loss of intra-islet insulin – driven suppression of glucagon secretion.

Banarier S et al (2002) have suggested that intra islet hyperinsulinemia prevents the glucagon response to hypoglycaemia despite an intact autonomic response.

Because of the rapid inactivation of GLP-1 by dipeptidyl peptidase 4 (DPP4) several incretin analogs were developed: GLP-1 receptor agonist exenatide (synthetic extendin 4); and liraglutide (conjugation of GLP-1 with circulating albumin). The acute effect of GLP-1 and GLP-1 receptor agonists on β cells is stimulation of glucose dependent insulin release, followed by enhancement of insulin biosynthesis through stimulation of insulin gene transcription. The chronic action is stimulation of β cell proliferation, induction of islet β cell neogenesis and inhibition of β cell apoptosis, thereby promoting expansion of β cell mass as observed in rodent diabetes and cultured β cells. Exenatide and Liraglutide enhanced post-prandial β cell function. Orally active DPP4 inhibitors sitagliptin and vildagliptin also promoted β cell proliferation & neogenesis and inhibited β cell apoptosis in rodents. (Xu HG et al 1999; Farilla L et al 2002).

The recent availability of incretin enhancers (inhibitors of DPP4 which normally inactivates incretins) and incretin mimetics have brought a new approach viz. glucagon suppression to control hyperglycemia in T2DM (Holst JJ, 2002; Drucker DJ, 2003; Ahren B 2005).

I. V. infusion of exenatide not only promotes glucose- induced insulin secretion, it counter-regulates insulin secretion during hypoglycaemia (Degen KB et al 2004). Incretin mimetics (Exenatide – Byetta, and Liraglutide) have to be injected, while DPP4 inhibitors (sitagliptin, vildagliptin) can be given orally. These agents are antihyperglycaemic, not hypoglycaemic (unlike insulin and sulfonyl ureas), and do not cause weight gain (unlike insulin and Thia Zolidines T2Ds).

Post-prandial glucagon suppression can also be achieved by pramlintide (amylin analog) when injected 15 minutes before meals.

A novel approach is therapeutic anti-sense oligonucleotide drug (ISIS 325568) directed to the glucagons receptor (GCGR) to reduce hepatic glucose production.

Data on animals regarding protective effects of incretin mimetics and enhancers has to be reproduced in human clinical studies. This evidence can be created only by measuring C peptide and proinsulin and amylin before and after therapy. Therapy for β cell preservation will assume great importance in future. (Wajchenberg BL 2007).

**TNFα**

Hostamisligil GS et al (1995) showed increased adipose tissue expression of TNFα in human obesity and insulin resistance. Suzawa M et al (2003) showed that IL-1 and TNFα inhibit the expression and activity of PPARγ which is highly expressed in adipose tissue and is the trigger for adipocyte differentiation and proliferation. Newly formed adipocytes produce adiponecint while distended hypertrophied adipocytes produce leptin, resistin TNFα and IL-6. Lihn AS et al (2003) have shown that increased TNFα and IL-1 inhibit adipose tissue expression of adiponectin mRNA by 80 per cent thereby lowering plasma adiponecint levels.

In a study of 35 Asian Indian T2DM, high levels of TNFα were a striking feature Normal range of TNFα is 1-20 ng/ml. 19 patients ranged 40-100 ng/ml, 8 more than 100 ng/ml and
another 8 more than 200 ng/ml. Equally significant was the low adiponectin (< 6 mg/l) and high proinsulin in all of them. (Lele RD et al 2006).

A positive correlation has been found between abdominal obesity and circulating levels of TNF-α. Adipose tissue macrophage number increases in obesity. Compared to lean individuals obese adipose tissue produced more proinflammatory cytokines by the macrophages as well as stromal vascular cells (SVCs) in adipose tissue. Kupffer cells of the liver are also a major source of TNFα.

The molecular mechanism of TNF-α induced insulin resistance has been explained (Hostamisigil GS 19996, Shulman GI (2000)61 TNFα causes serine phosphorylation of IRS-1 in muscle and IRS-2 in liver thereby abrogating the IRS-P13K- AKT signaling pathway of insulin action which is necessary for GLUT4 translocation glucose transport and glycogen synthesis. In the liver, reduced AKT activity decreases phosphorylation of forkhead box protein O (FOXO) which leads to activation of PEPCK and G6Pase and increased gluconeogenesis. Mitochondrial glycerol-3 phosphate acyl transferase (mt. GPAT) is a key enzyme in denovo fat synthesis in the liver, leading to fatty liver.

Obese mice lacking TNFα function have shown protection from developing insulin resistance.

Role of nutrients

Kavanagh K et al (2007)46 in a unique monkey experiment lasting for 6 years, showed that trans fatty acids (TFAs) in the diet used in the preparation of fast food, with elaidic acid (t18 : 1 n 9) as a major component, induce abdominal obesity and insulin resistance, through impaired post receptor binding signal transduction. TFAs enhanced intra-abdominal deposition of fat even in the absence of caloric excess.

Calder P (2002)47 has emphasized the important role of omega 3 PUFAs EPA and DHA in the diet in the suppression of proinflammatory cytokines. Increased EPA in cell membrane phospholipids suppresses production of prostanoids (PGI2, TXA2, PGD2, PGE2, PGF2α) while increasing the production of prostacyclin and TXA3 which inhibit platelet aggregation. EPA produces 5- series LT (LTA5, LTB5, LTC5, LTD5, LTE5) which are anti-inflammatory, unlike the LT4 series produced by arachidonic acid, which are proinflammatory.

The adverse impact of replacement of the traditional fat sources in the Indian diet (ghee, mustard oil, coconut oil which have an ideal W6-W3 ratio of 2 : 1) with refined vegetable oils with a very high W6-W3 ratio (even 120 : 1) has contributed to the sharp rise in the metabolic syndrome (Raheja BS 1993).48 Correction of this distortion by dietary supplements of EPA/ DHA has shown improvement (Das UN 2003).49 PUFAs of marine origin induce adiponectin in mice fed on a high fat diet (Flachs K et al 2006).48

Vit. D inhibits adipogenesis through a vitamin D receptor (VDR) dependent inhibition of CCAAT enhancer binding protein alpha (CEBPα) and PPARγ expression, and a decrease in PPARγ induced activation in pre-adipocytes. This is due to a Vit. D induced decrease in endogenous PPARγ ligand availability and a competition between VDR and PPARγ for a limiting amount of retinoid X receptor (RXR) a common heterodimeric binding partner of both nuclear receptors.

Retinoic acid, the carboxylic acid form of Vit. A, is a transcriptional activator of the genes encoding uncoupling proteins and a determinant of whole body thermogenic capacity. Retinoic acid also influences adipocyte differentiation and survival: low doses promote adipogenesis while high doses inhibit it.

PGC-1 a transcriptional coactivator of PPARγ and other nuclear hormone receptors, plays a key role in energy homeostasis, especially in adaptive thermogenesis, adipogenesis and oxidative metabolism.

The association of PGC-1 gene polymorphism with insulin resistance and T2DM in the Asian Indian population has been shown for the first time by Vimaleshwaram KS et al (2005).51

Adiponectin

Adiponectin, a 244 aminoacid protein produced exclusively by adipocytes, has important role in health and disease. Normal levels (males 7.9 + 0.5 mg/ml females 16.6 + 5 mg/ml). Adiponectin circulates in multimeric forms. Recent reports have focused on high molecular weight (HMW) adiponectin, which is found to be lower in Asian Indian pregnant women compared to Caucasians (Retna Karon R et al 2006).52 Asian Indian T2DM have low adiponectin levels with higher risk for CAD. (Mohan V, et al 2005)53

Adiponectin receptors Adip R1 and Adip R2 expressed on vascular endothelial cells, interact with APPL-1 an intracellular protein to mediate eNOS activation & NO production and vasodilatation (Cheng K et al 2007).54 Hypoadiponectinemia is linked to endothelial dysfunction in hypertension, CAD and T2DM. Ouchi N et al (2000)55 showed that adiponectin inhibits endothelial NFKB signaling through a CAMP dependent pathway.

Kadowaki and Yamauchi (2005)56 have proposed the adiponectin hypothesis for insulin resistance, metabolic syndrome and atherosclerosis. Reduced adiponectin levels (< 6 mg/ml in males; < 10 mg/ml in females) can be caused by genetic defects (such as SNP 276 in the adiponectin gene on chromosome 3Q27) or caused by lifestyle changes causing obesity such as high fat diet. Reduced adiponectin plays a causal role in the development of insulin resistance. T2DM and atherosclerosis. Adiponectin knock-out mice show the characteristics of the metabolic syndrome- insulin resistance, hyperlipidemia, glucose intolerance, hypertension and atherosclerosis.

Langenfeld MR et al (2004)57 studied 500 T2DM to compare the specificity and sensitivity of fasting intact proinsulin, adiponectin and the proinsulin/ adiponectin ratio as markers for insulin resistance as assessed by HOMA score > 2 Elevation of proinsulin seemed more specific (96%) and sensitive (70%) marker for insulin resistance and increased cardiovascular risk than suppression of adiponectin.

Adiponectin activates PPARα and AMPK and UCP2 and inhibits acetyl CoA Carboxylase (ACC). Adiponectin is a regulator of energy homeostasis (Wolf G 2003).58

Upgradation of plasma adiponectin or the development of Adipo R agonists are appropriate therapeutic strategies.

PPARγ agonists such as TZDs stimulate adipocytes to secrete adiponectin TZDs suppress macrophages production of proinflammatory. Cytokines (TNFα, IL-6 IL1β, PAI-1, INOS).

Osmotin a member of a large PR-5 protein family is ubiquitous in fruits and vegetables and is a homologue of mammalian adiponectin (Narasimhan LM et al 2005)59. The beneficial effects of a diet containing 400 g. of fruits and vegetables may partly be due to the osmotin content apart from the anti-oxidants and high fibre low fat content. Osmotin activates AMPK via
Adipo R. Further research examining the similarities between osmotin and adiponectin may facilitate development of potential adiponectin agonists.

**Molecular mechanisms of insulin resistance**

Using invivo NMR Spectroscopy (H1, C13, P31) Peterson, Shulman et al 2003 have shown that T2DM patients as well as their thin, non-smoking normoglycemic young offsprings have:

1. Decreased insulin-stimulated GLUT-4 transporter expression, glucose uptake & glycogen synthesis in the muscle by over 50%.
2. Decreased insulin-stimulated mitochondrial ATP synthesis by 30% Insulin is an important regulator of mitochondrial biogenesis in skeletal muscle.

Increased intramyocellular lipid (IMCL) assessed by H1 MRS was even a better predictor of insulin resistance in skeletal muscle both in adult T2DM and their healthy children. Fasting plasma FFA was the best predictor of insulin resistance in the healthy cohorts. Increased IMCL increases LCF Acyl Co A and diacyl glucorol (DAG) which activates protein kinase C (PCKG) which causes serine- threonine phosphorylation of IRS1 and IRS-2 thereby abrogating the IRS- PI3K AKT signaling pathway. PKC knock out mice are protected from fat induced insulin resistance in skeletal muscle.

**AMPK : cellular energy sensor and regulator**

The AMP-activated protein kinase (AMKP) system acts as a sensor of cellular energy status and plays a key role in maintenance of energy balance at the whole body as well as cellular level.

The insulin / IGF1 signaling pathway is activated when nutrients are available whereas AMPK pathway is activated when cells are starved for a carbon source. Insulin promotes lipid, protein and glycogen synthesis whereas AMPK inhibits those biosynthetic pathways.

Glucose deprivation ishcaemia and exercise activate AMPK which inhibits ACC and malonyl CoA via malonyl CoA decarboxylase (MCD), thereby inhibiting Triglyceride synthesis, and the same time increasing fatty acid oxidation in the mitochondria. AMPK is an important regulator of mitochondrial biogenesis, mediating its effects through MEF2 and CRFB-mediated PGC1a and PGC1b (peroxisome proliferator – activated receptor coactivators). There is also increased expression of UCP2 in adipose tissue and UCP3 in skeletal muscle.

Major effects of AMPK activation on glucose and lipid metabolism are in the muscle, liver and adipose tissue.

In processes that regulate plasma glucose levels the insulin and AMPK pathways work in the same direction. In the skeletal muscle both increase GLUT4 translocation to the plasma membrane and increase glucose transport by different mechanisms: AMPK activated GLUT-4 is not suppressed by
Wartman (inhibitor of insulin- PI3K) but by compound C, a selective inhibitor of AMPK. The subsequent fate is different: glycosyn synthesis (anabolic insulin effect): glycolysis / and increased β oxidation of fatty acids (catabolic AMPK action), thereby decreasing intramyocellular lipid (the cause of insulin resistance in muscle).

Uptake of glucose into skeletal muscle accounts for more than 70% of glucose disposal in humans hence this process is a paramount importance for normal glucose homeostasis.

AMPK activation underlies many of the health benefits of regular physical exercise. There are also new indications that AMPK system is involved in the beneficial effects of caloric restriction on life-span lengthening.

In the liver AMPK activation (1) decreases PEPCK and G6 Pase thereby reducing gluconeogenesis; (2) increases β oxidation of fatty acids and decreases triglyceride and cholesterol synthesis and reverses fatty liver.

In the adipose tissue AMPK activation decreases PPARγ expression, decreases adipogenesis and lipogenesis and increases lipolysis; decreases release of TNFα and IL-6 from adipocytes and enhances their degradation and increased adiponectin secretion. The molecular mechanisms of AMPK effects are depicted in Fig. 2.

Intriguingly, in at least 3 animal models that are resistant to diet-induced obesity viz. mice over-expressing UCP1, UCP3 or mice with a knockout of stearoyl CoA desaturase 1 there is persistent activation of AMPK.

Leptin, adiponectin, metformin and AICAR (5 aminoimidazole 4 carboxamide ribonucleoside)- an experimental drug all activate AMPK. Adiponectin is a regulator of energy homeostasis through activation of AMPK and PPARα in the liver and skeletal muscle (Wolf G 2003).

AMPK is a key player in the development of new treatments for obesity, T2DM and the metabolic syndrome (Towler MC and Hardie DG 2007).61

Conclusion

This article emphasizes (1) the utility of routine measurement of pro-insulin to insulin ratio as a specific marker of insulin resistance and predictor of future T2DM, HT and CAD. (2) routine C-Peptide estimation to determine which T2DM needs insulin and to monitor the effects of newer drugs which promote β cell regeneration (3) routine estimation of adiponectin and TNFα and monitor response to thiazolidines drugs which increases adiponectin and decreases TNFα production by adipocytes (4) crucial role of AMPK – Cellular energy sensor in mediating the beneficial effects of exercise as well as drugs (adiponectin, metformin) in T2DM (5) Availability of glucagon suppressors will eliminate the need for giving insulin to T2 DM with normal C Peptide levels which inevitably causes undesirable weight gain and hypoglycemia.

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