Invited Article

Ancient Indian Insights and Modern Discoveries in Nutrition, Exercise and Weight Control

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Introduction

Ayurveda ("Science of Life") the ancient Indian System of Health Care represents experiential wisdom of over 5000 years. The following description from "Charak Samhita (600 BC) sounds refreshingly contemporary:

"A person who is habituated to pampering his belly even when a previous meal has not been thoroughly digested; who is addicted to a habit of sleeping in the day or leading a sedentary life, who is averse to taking any sort of physical exercise, will suffer from excessive stoutness. He is likely to be afflicted by many diseases that invariably terminate in death, due to obstruction of internal channels due to deposition of fat. Hence all things and conditions which foster the growth of abnormal fat should be carefully avoided."[1]

"The excessive corpulence is caused by over eating, lack of exercise, lack of mental exertion and by inherited tendency".

"The corpulent person is afflicted with eight disabilities viz. dimunition of lifespan, lack of agility, debility, difficulty in sex act, fetor, distressing sweats, excessive appetite and excessive thirst".

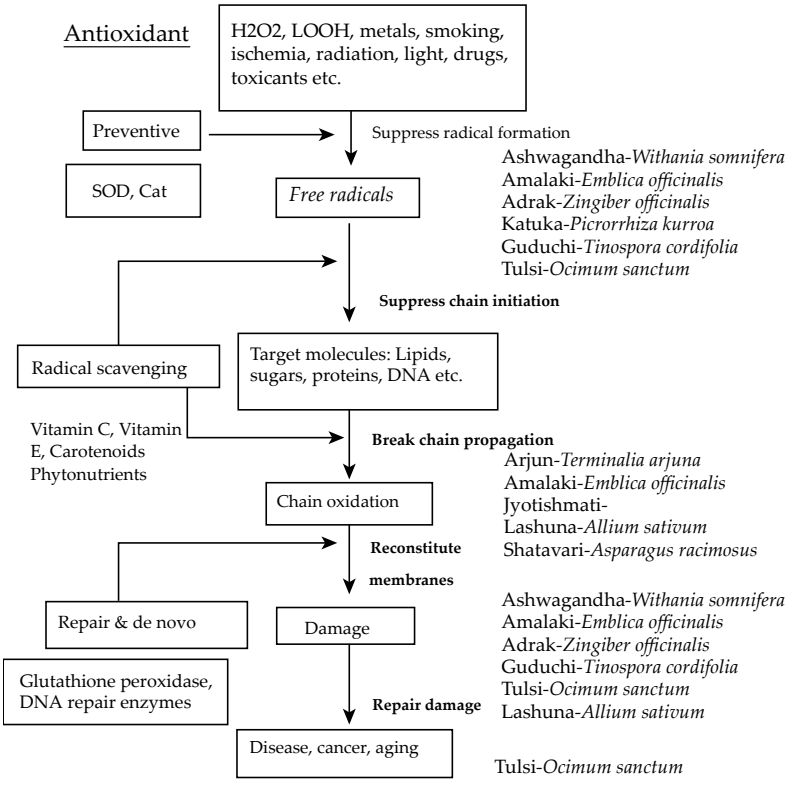

Fig. 1 : Depicts the Ayurvedic anti-oxidants according to the various levels at which they act. (Devasagayam et al 2004)[2].

Importance of "Ahar" – Diet

Charak Samhita discusses "Wholesome" and "unwholesome" food. "The use of a wholesome diet is the only factor that promotes the healthy growth of humans; and the factor that makes for disease is the indulgence in unwholesome diet". "That class of food which helps the harmonised body elements to retain their state of equilibrium, and the discordant body elements to gain equilibrium, is the wholesome one; and the unwholesome one to be that which acts in the opposite manner".

Regarding Energy requirements, Charak States: "Even light, easily digested and nutritious food should not be taken in excess of bodily requirements, or after the appetite has been satisfied. Food difficult to digest should not be taken habitually. Even if used the quantity should not exceed a fraction of a full meal". "An excess or surfeit of food is markedly harmful unless the gastric fire is increased by hard exercise".

Shushruta, who described Diabetes (Madhumeha) for the first time in the history of medicine advised the corpulent diabetic to indulge in vigorous physical exercise (such as walking 20 "yojanas" or physical effort (digging a well). At the same time Shushruta exorted the thin diabetic not to exert too much.

Ayurveda describes 3 kinds of "ahar" or diet – "satwik", "rajasik" and "Tamasik":. The "Rishis" took "Satwik ahar" consisting of kanda, moola, phala" (vegetables and fruits) and lived for hundred years. In today's parlence, this represents a 1300 caloric diet (which causes the least oxidative stress), high fibre, low fat, low sodium, high potassium & minerals and plenty of anti-oxidants (Figure 1). Excessive oxidative stress is central in most human disorders including ageing process as shown by increased levels of F2 Isoprostanes in peripheral blood and urine, and increased F4 neuroprostanes in the CSF.

Osmotin, a recently discovered plant analogue of mammalian adiponectin, is abundant in fruits & vegetable and acts through adiponectin receptors (Narsimhan LM et al 2005)[3] Adiponectin and osmotin act via AdipoR1 receptors in muscles and Adipo R2 receptors in liver and act as insulin sensilizers and regulators of energy homeostasis via AMPK activation (Wolf G 2003)[4]. Part of the beneficial effects of fruits and vegetables is due to their osmotin content, which

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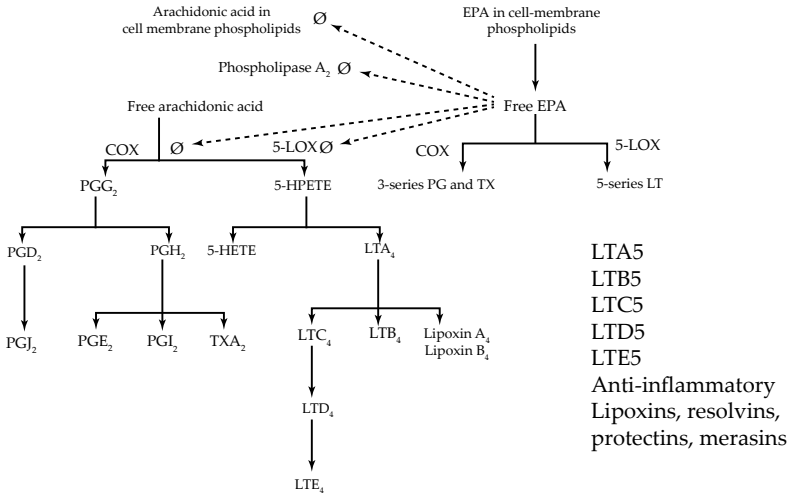

Fig. 2 : Beneficial effects of EPA/ DHA in cells membrane phospholipids

remains stable in the digestive tract.

Kashyap Samhita (which deals with paediatrics) stresses the importance of breast milk as essential promoter of growth and development and tonic for all tissues. "If the mother does not have enough breast milk, it is better to employ a "Dhatri" (wet nurse) as no other milk can compete with human milk".

Ayurveda also gives details of the qualities of Cow's milk, also milk from buffaloes, goats, sheep, camels, horses and elephants.

The insight about mother's milk is fully vindicated today in terms of its ideal content of essential fatty acid EPA/ DHA and their effects on the composition of the cell membrane (as discussed in the next section).

Essential Fatty Acids

Polyunsaturated fatty acids of omega 6 class linoleic acid (LA) and omega 3 class (alphalinolenic acid (ALNA) are essential dietary sources since they cannot be synthesized by the organism. W6 are present in maize, sunflower and sesame oil; W3 are present linseed oil, nuts, soyabeans, wheat and cold water fish.

All cell membranes contain W6 arachidonic acid and W3 Eicosapentanoic acid EPA and docosa-hexanoic acid DHA (Fig. 2). The ideal ratio of W6 : W3 is 2:1, maximum 6:1 Any higher ratio is detrimental since it leads to increase in the arachidonic-acid induced proinflammatory cytokines (PGE1, IL-1, IL-6, IFNγ and TNFα) EPA/DHA lead to decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory lipoxins, resolvins and protectins and IL-10, which play active role in the resolution of inflammation (Ariel and Serhan 2007)[5] (Bannenberg and Serhan 2010).[6]

EPA is a source of resolvins (rvE1, E2), DHA (RvD1D2D3D4) and protectins (PD1 and NPD1) DHA derived Neuroprotectins (NPD1) protect against neuronal decline through excessive oxidative stress and apoptosis, while promoting cell survival and maximising cognitive function throughout the human life span (Uavy & Dangour 2006)[7].

W3 FAs maintain membrane fluidity and longer residence of transporters such as GLUT. Brain cell membranes have a high content of EPA/DHA, essential for neurotransmission, brain development and function including learning tasks.

Epidemiological data indicates the association of low EPA/ DHA with depression (with higher levels of inflammatory markers including hsCRP, ICAM-1, Il-6) and coronary Heart Disease (Empana JP et al 2005).[8] Some epidemelogical data supports a relationship of higher fish intake and lower depression and suicide (Colin A et al 2003).[9] Dietary supplement of DHA for three months prevented young students from developing aggressive behaviour during time of stress (Hamazaki et al 1996).[10]

EPA/DHA play essential role in maintaining normal endothelial function and inhibiting endothelial inflammation, the starting point of atherosclerosis. The EARLY study evaluated the role of DHA in restoring endothelial function in children with hyperlipidemia, as measured by increased flow-mediated vasodilation (FMD) (Engler MM et al 2004)[11].

Higher concentrations of EPA/DHA improve brachial artery dilatation in patients with coronary artery disease. (Tagawa H et al 1999)[12].

Red cell membrane EPA/DHA level of 5% of total fatty acids is associated with a 70% reduction in the risk of primary cardiac arrest (Siscovick DS et al 1996)[13]

Higher concentrations of EPA/DHA decrease the risk of sudden cardiac death (Albert et al 2002)[14] EPA/DHA ensure plaque stability via reducing abundance of macrophages (Thies et al 2003)[15]. Low EPA/DHA is associated with acute coronary syndrome (Block RC et al 2008).[16]

Dietary PUFAs function as fuel partitions, inducing FA oxidation and reducing fatty acid synthesis and reduce fat deposition. High intake of trans-fatty acids (TFAs) in cafeteria foods, bakery and meat products, margarine, frying oils and desserts reduce the conversion of ALA to DHA, and promote abdominal obesity hence reducing the dietary intake of TFAs is an important health goal. (Kummerow FA et al 2004).[17]

Diet and Inflammation

Prof. PC Calder (2002)[18] has given an excellent review of inflammation in health and disease. He has emphasized the important role of dietary essential fatty acid omega 3 PUFA EPA and DHA, in the suppression of pro-inflammatory cytokines and production of anti-inflammatory lipoxins, resolvins and protectins in the resolution of inflammatory response (Fig. 2). This is crucial in many disease states including inflammatory disorders (such as arthritis), atherosclerosis, asthma and cancer.

Zinc, selenium, Vit. A, Vit. C, Vit. E, folic acid Vit, B6 and Vit B12 are important nutrients whose deficiency affects susceptibility to infection and host immune response. The role of Vit. D. in relation to immune competence has only recently been discovered. Dendritic cells and macrophages have receptors for Vit. D. Deficiency of Vit. D and Vit. D receptor polymorphism increase susceptibility to tuberculosis (Wilkinson 2000).[19]

There is a two-way interaction between nutrients and human genes (Roche HM 2004).[20] How genetic variation influence response to nutrients and how nutrients influence gene expression, transcription and metabolism are the subject of Nutrigenomics. The effect of maternal malnutritional on suppression of foetal insulin IRS-PI3K, AKT pathway is well known as the basis of Metabolic Syndrome and insulin resistance with consequent hyperuinsulinemia.

Diet and Chemoprevention of cancer:

Diet contains several non-nutritional phytochemicals whose active principles have been identified: Haldi (Curcumin), red chilli peper (capsaicin),ginger (gingerol), green tea

Table 1 : Mode of action of dietary phytochemicals.

1. Curcumin:	Inhibits TNFα induced COX2 gene transcription and NFKB & AP1 activation; anti-proliferative, pro-apoptotic and anti-metastatic activities via suppression of B Catenin.
2. Capsaisin:	Blockade of IKbα degradation and NFKB Translocation into nucleus; induces apoptosis by activation of CJUN. NH2 terminal kinase (JNK) and p 38.
3. Gingerol:	Inhibits EGF-induced AP.1 activation and neoplastic transformation.
4. EGCG: Epigallocatechin 3 Gallate	Blocks activation of AP1 & NFKB, inhibits PI3K. AKT-NFKB and HER2 / NEU receptor tyrosine phosphorylation; inhibits VEGF, β catenin expression . G0/G1 phase arrest and apoptosis.
5. Genistein:	Inhibits AP1, cFOS and ERK activity, inhibits AKT mediated NFKB activation.
6. Resveratrol:	Inhibits PMA-induced COX-2, PKC and AP1, MMP-9 NFKB; induces apoptosis via activation of p53 via ErK and p. 38 Down-regulates β catenin.
7. Procyanidin:	Naturally occurring polyphenolic bioflavonoid in grape-seed & pine bark; powerful antioxidant.
8. Caffeic acid phenethylester (CAPE):	Disrupts the NRF2-KEAP1 complex. Decrease β Catenin expression; suppress NFKB activation.
9. Diallyl sulphide:	Prevents mutagenesis by suppressing ROS
10. Indole - 3 Carbinol:	Decreases β catenin, inhibits adhesion, migration and invasion of cancer cells
11. Sulphoraphane:	Directly interacts with KEPA1; stimulates nuclear translocation of NRF2 which subsequently activates ARE for expression of many anti-oxidant or detoxification enzymes.
12. Lycopene	Anti-oxidant-suppresses ROS.

(epigallocatechin), honey (caffeic acid) garlic (diallylsulphide), cabbage (indol-3-carbinol) broccoli (sulpharaphane), carrot (β carotene), grapes (resveratrol), grape seeds and pine bark (procyanadine), tomatos (lycopenes). Their mode of action at the moleuclar level is described in Table 1. Non-nutrient dietary phytochemicals exert their substantial anti-mutagenic and anti-carcinogenic properties by blocking cell signalling pathway that regulate cell proliferation an differentiation- such as the family of mitogen activated protein kinases (MAPKs), NFKB- API, NRF2 as well as β catenin a component of cell-cell adhesion machinery. Carcinogenesis is a multi-step process, the initiation of which can be blocked or suppressed by dietary phytochemicals. They can also halt or retard the progression of pre-cancerous cells into malignant cells (Surh YH 2004).[21]

How dietary phytochemicals can modify gene expression or transcriptional gene silencing is the subject of nutrigenomics and epigenetics.

Current Knowledge about Adipose Tissue

Ability to store energy in excess of what is required for immediate use is essential for survival. White adipose tissue plays a central role in the regulation of energy balance and conservation of body heat through thermogenesis. Functions of adipose tissue include (1) storage of triacylglycerol in the body, and aromatizaion of sex steroids, storage of fat soluble vitamins and (2) protection of vital structures- orbits, palms & soles, vulva, perineal, periarticular, pericalyceal and epidural regions. It is interesting to note that this supportive function of fat is preserved in lipodystrophy suggesting separate embryonic origin and genetic regulatory mechanisms of supportive fat. (3) Adipose tissue is an endocrine organ which produces several adipocytokines. leptin, visfatin, adiponectin, resistin, TNFα, IL-6 PAI-1 etc. (Fig. 3).

Newly formed adipocytes produce adiponectin, an insulin sensitizer while distended adipocytes produce leptin, resistin, TNFα, IL-6. TNFα induces insulin resistance by causing serine phosphorylation of IRS-1in muscle and IRS-2 in liver thereby abrogating the IRS-PI3K-AKT signalling pathway necessary for GLUT4 translocation, glucose transport and glycogen synthesis in muscle.

Adipose tissue is a dynamic structure with a good blood supply. The stored fat in adipose tissue is continuously undergoing lipolysis (hydrolysis) and lipogenesis (re-esterification). These two processes are not forward and reverse phases of the same reaction but have entirely different pathways in the control of synthesis and hydrolysis. Insulin plays a central role in stimulating lipogenesis and preventing lipolysis. Due to differences in receptors and post-receptor events between human visceral (omental) and subcutaneous adipose tissue, antilipolytic effects of insulin are 3 fold higher in subcutaneous fat than omental. Although the receptor number is similar (~ 300,000 sites per cell), receptor affinity is higher in subcutaneous fat. I-125 labeled insulin dissociates more rapidly from omental than subcutaneous adipocytes.

There is a remarkable heterogeneity in the distribution and metabolic response in adipose tissue in different sites. At any BMI adult females have more body fat than males as reflected in plasma leptin levels. Insulin stimulates adipogenesis and prevents lipolysis at all sites. Growth hormone reduces truncal fat and promotes fat deposition in palms and soles. Estrogen promotes fat deposition in hips, legs, breasts and subcutaneous tissue. Prolactin promotes adipogenesis in femorogluteal & mammary regions. Androgens favour visceral and subsutaneous abdominal fat deposition. Male hypogonadism is associated with increased adipose tissue distribution in female pattern. Glucocorticoids promote re-distribution of fat from peripheral to central location-truncal and supraclavicular (buffalo Halo hump). Lipodystrophy related to HIV treatment resembles Cushing's syndrome but cortisol levels are not high.

B adrenoreceptor agonists (isoprenalin) accelerate lipolysis while α2 adrenoreceptor agonists (clonidine) retard lipolysis, more in females. Noradrenaline – induces lipolysis is ten fold more in abdominal than gluteal fat- this difference is 20 fold in females. Regional differences in nor-adrenaline induced lipolysis are not seen when post receptor acting compounds are used such as forskolin (adenylylcyclase & CAMP), enprofyline (phosphodiesterase) or dibutyryl cAMP (protein kinase). (Bolinder J et al)[22]. Visceral adipose tissue cells grow slower

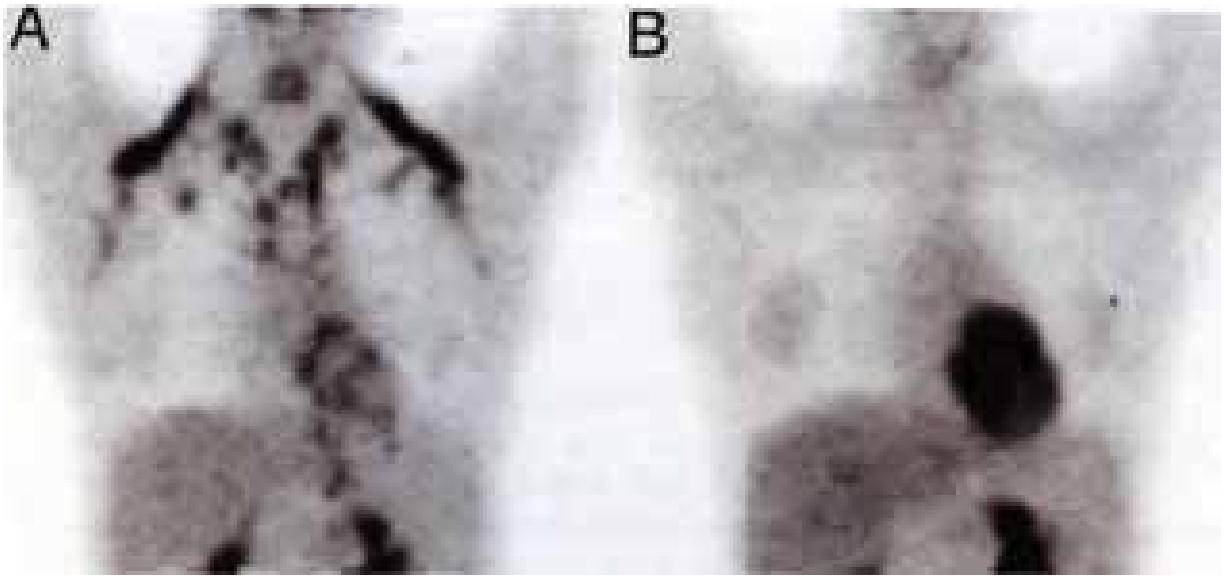

Fig. 3 : Brown fat seen on image A. Disappears after giving Propranolol in image B.

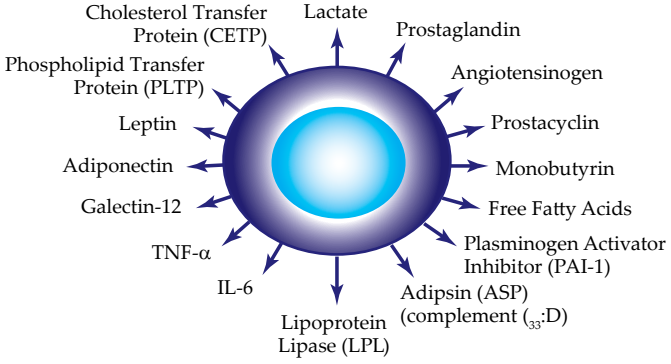

Fig. 4 : Adipocytokines

in culture than subcutaneous adipose cells Thiazolidine drugs cause proliferation of subcutaneous adipose tissue (but not visceral adipose tissue) and increased UCP2 mRNA expression.

Understanding Obesity at the Molecular Level

Obesity can occur as a result of genetic and acquired changes in three main types of biochemical processes which are now understood at the molecular level (Palou A et al 2000).[23]

1. Feeding control, which determines the sensation of satiety and hunger through processes that depend on an interplay between internal signals (notably leptin) and environmental factors. Leptin regulates food intake by central action inducing expression of SOCS-3 mRNA in the hypothalamus and it stimulates fatty acid oxidation in adipose tissue
   i. by reduction in SREBP-1 (sterol regulatory element binding protein) an insulin – stimulated lipogenic transcription factor.
   ii. by upregulation of carnitine palmitoyl transferase1 (CPT-1), acyl CoA oxidase (ACO), PPARα, PGC1α, UCP-1, UCP-2 and UCP-3 in WAT and liver, causing fatty acid oxidation and disappearance of fat store within adipocytes and liver.

   However, leptin resistance is a feature of obese humans. Excessive SOCS-3 activity in leptin responsive cells is a potential mechanism of leptin resistance. Proteintyrosine phosphatase PTP1B regulates leptin signalling pathway probably by targeting the Jak2 protein molecule, a characteristic feature of human obesity. PTP1B may be a novel target to treat leptin resistance in obesity.
2. Energy efficiency, particularly activation of UCP-1, UCP-2 and UCP3, convert calories contained in food as heat instead of accumulating them as fat.
3. Adipogenesis, controlled by an interplay of transcription factors including PPARα, PPARγ, C/EBP and ADD families.

   The knowledge of a growing number of genes and molecules implicated in these 3 types of processes and of their metabolic relationship provides a molecular level understanding of body weight regulation and suggesting new methods of obesity control.

   (TFA) found in extensive in cafeteria foods, margarine, frying oils, desserts, bakery products, promote abdominal obesity.

Human Obesity Gene Map

As of October 2005, 176 human obesity cases due to single gene mutations in 11different genes were reported. There are 244 genes that when mutated or expressed as transgenes in mouse, result in phenotypes that affect body weight and obesity. 253 QTLs for obesity-related phenotypes have been mapped from 61 genome-wide scans. The obesity gene map shows putative loci on all chromosomes except Y. The electronic version of the map with links to useful publications and relevant sites can be found at the Pennington Biomedical Research Centre Human Genomics Laboratory. http://obesity.pbrc.edu

Vit. A and Vit. D

Vit. A has a role in the regulation of the level and functioning of body fat reserves. A low vitamin A status favours increased fat deposition (Bonel ML et al 2003).[24]

Vit. D. inhibits adipogenesis through VDR – dependent inhibition of C/ EBPα (CCAAT enhancer binding protein-alpha) and PPARγ (Wood RJ. Et al 2008)[25] Vit. D deficiency and Vit. D receptor polymorphism leads to obesity, through increased PPARγ induced, pre-adipocyte proliferation & differentiation.

Thermogenesis: Energy Expenditure

Regulation of body weight involves coordination of intake and expenditure of calories. Uncoupling of oxidation and phosphorylation in mitochondria via uncoupling proteins may act as energy buffers in humans. Uncoupling proteins provide new clues for causation of obesity (Gura T 1998).[26]

UCP-1 is expressed exclusively in brown adipose tissue (BAT). Transgenic mice with reduced BAT are obese. BAT is abundant at birth but progressively disappears in adults. Recent availability of FDG PET / CT has demonstrated the presence of BAT in a substantial proportion of adult humans and is primarily located in supraclavicular and neck region (Fig. 4). BAT is seen in cancer patients undergoing FDG PET/CT. This BAT may contribute to cancer-induced cachexia . FDG uptake by BAT can be reduced pharmacologically using β blockers (propranolol), reserpine, benzodiazepine & fentanyl. The tumour uptake of FDG is not affected by such pre-medications. Role of BAT in human obesity is discussed by Cinti (2006).[27]

Tertaterol, a new β3 adrenoreceptor agonist increases mRNA of UCP-1 and down regulates PPARγ and aP2 gene in adipose tissue thereby increasing thermogenesis.

UCP-2, a homolog of UCP-1 is expressed in numerous tissues including WAT, BAT and muscle. The UCP-2 locus on human chromosome 11 and mouse chromosome 7 is linked to obesity and hyperinsulinism (Fleury CV et al 1997)[28] possibly UCP-2 expression determines development of obesity. Leptin regulates UCP2 expression in adipose tissue.

UCP-3 is expressed in skeletal muscle (Kubota T et al 1998).[29] Single nucleotide polymorphism in UCP-3 gene influences fat distribution in women of European & Asian origin (Bass et al 1997)[30] (Cassell PG et al 2000).[31]

Increased UCP2 and UCP3 mRNA expression occurs during fasting in obese and lean humans.

Increased UCP3 expression in skeletal muscles decrease muscle energy efficacy and affects thermoregulation and substrate oxidation (Klaus S et al 2005).[32]

UCP3 is the mediator of thermogenesis regulated by thyroid hormones, β3 adrenergic agonists and leptin (Gong DW et al 1997).[33]

Muscle as a Target of Insulin Resistance

Muscle is the largest tissue in the human body (less than 25% at birth more than 40% in young adults and about 30% in the aged). Skeletal muscle protein is the major non-fat store of energy. Prolonged caloric under nutrition leads to large losses in muscle mass.

Insulin is anabolic for muscle, the mechanism of which has been studied by Chow et al.[34] One snag in the interpretation of BMI > 25 as a measure of obesity is the assumption that the increase in mainly due to fat. Lele et al (2007)[35] emphasized the importance of assessing the muscle component of BMI by simple somatoscopy or somatotyping. Unlike Western populations, only 25 percent of Indian T2DM have BMI > 25, 75 percent of Indian T2DM have a normal or low BMI (< 23) but they have increased visceral fat as indicated by increased waist girth (> 90 cm in adult males, > 85 cm in adult females). Strong muscle component in overweight females with T2DM and CAD has been shown (Goldberg & Gordon 1964)[36] (Lele RD 1965)[37].

Glucose transport via GLUT4 is a critical insulin-dependent rate- controlling step for glucose uptake by muscle and insulin-stimulated glycogen synthesis in muscle. Glygogenin is a protein primer for glycogen synthesis and is a determinant of maximum glycogen storage capacity. In T2DM there is a marked decrease in muscle glycogen synthesis (as determined by C-13 MRS and C-13 glucose-1) this defect is also seen in first degree relatives and offsprings of T2DM patients.

Increased intramyocelluler lipid (IMCL) is a feature of insulin resistance. This is seen also in lean healthy offsprings of T2DM.

Insulin stimulated rate of glucose uptake by muscle is 60% lower in insulin resistance compared to normal. There is 80% increase intramyocellular lipid (IMCL) and 30% reduction in mitochondrial oxidative phosphorylation, as assessed by P-31 MRS (acquisition time 120 minutes). Rate of ATP synthesis (ratio of inorganic phosphate to phosphocreatine in soleus muscle) is reduced by 20% which reflects a lower ratio of type 1 fibres (mostly oxidative) to type 2 fibres (mostly oxidative) in insulin resistance.

Increased number of type IIb muscle fibres in overweight, insulin resistant first degree relatives of T2DM patients with reduced ratio of type I to type II in muscle fibres indicates reduction in mitochondrial content lean insulin- resistante off springs of T2DM patients also show impaired mitochondrial activity (Peterson KF et al 2004).[38]

PGC1α (cold-inducible PPARγ coactivator of nuclear receptors) has important role in mitochondrial biogenesis, thermogensis and gluconeogenesis. Upregulation of PGC1α converts WAT to BAT.

External physiological stimuli activate PGC1α which in turn activates. NRF1 and NRF2 with increase in mt TFA- direct regulator of mt DNA replication / transcription.

Since skeletal muscle is the primary site of insulin resistance, greater the muscle mass, greater the importance of physical exercise to overcome the insulin resistance and greater the importance dietary supplements of omega-3 PUFA to optimize the phospholipid composition of the muscle membrane (increasing residence of GLUT 4 in the plasma membrane).

Skeletal Muscle Membrane Phospholipids: Role of Dietary PUFA

The fatty acid composition of skeletal muscle membrane phospholipids is altered by n-3 PUFA (EPA and DHA), increasing the fluidity, thereby permitting prolonged residence of GLUT-4 in plasma membrane. Mothers with insulin resistance have children with less EPA and DHA in their muscle membrane and at increased risk for development of insulin resistance. (Baur et al 1999)[39]. Pima Indians have reduced capacity to incorporate n-3 PUFA into muscle membrane, EPA and DHA induce UCP2 and UCP3 expression which induce fatty acid oxidation in both liver and skeletal muscle, suppress hepatic lipogenesis, reduce hepatic triglyceride output. Peroxisomal fatty acid oxidation and mitochondrial uncoupling of oxidation & phosphorylation are both thermognic.

Although the amount of peroxisomal fatty acid oxidation in skeletal muscle is unknown, the large size of muscle mass and a two fold increase in the peroxisomal oxidative capacity of skeletal muscle suggests that the peroxisomes could be a significant site of fatty acid oxidation and diet- induced thermogenesis. N3 PUFA in diet induces thermogenic pathways and reduce fat deposition by 25 percent. Transfat induces abdominal obesity

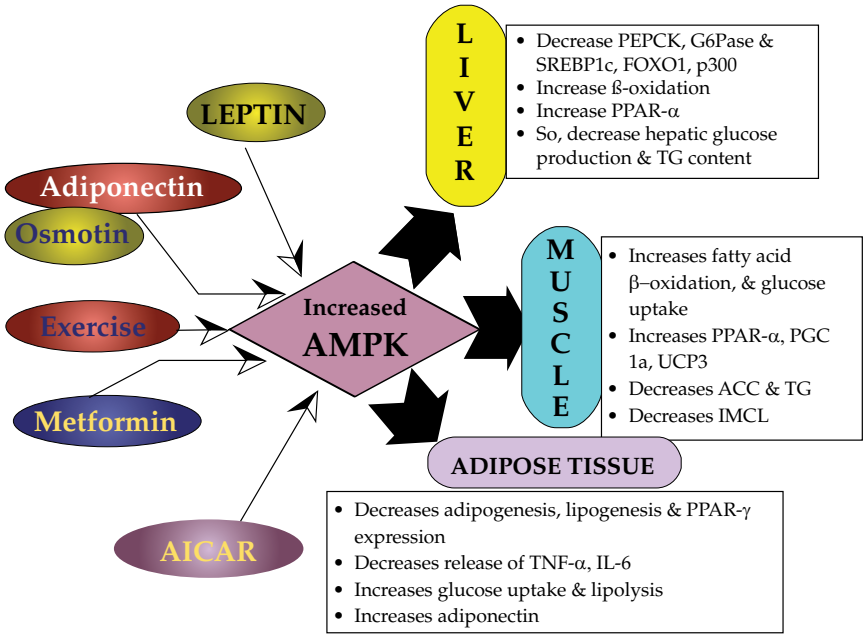

Fig. 5 : AMPK actions

and changes insulin sensitivity in monkeys. Interestingly enhancement of fatty acid oxidation and thermogenesis by dietary PUFA is associated with an improvement in the glucose uptake and insulin sensitivity of muscles.

Ingestion of PPARα ligand is accompanied by an increase in expression of skeletal muscle UCP3 and decrease in hepatic expression of SREBP-1 and decrease in hepatic triglyceride synthesis.

AMPK: Cellular Energy Sensor and Regulator

Regulating energy levels is fundamental process in every living organism. At a cellular level ATP must be maintained at relatively high levels (normally about ten-fold above the concentration of ADP) in order to drive essential metabolic processes. AMPK is activated in response to ATP depletion, which causes a concomitant increase in the AMP : ATP ratio. Activated AMPK causes switching off of ATP- utilizing pathways (eg. Fatty acid synthesis) and switching-on of ATP generating pathways eg. fatty acid oxidation. AMPK is a sensor as well as regulator of cell energy status and plays a key role in maintenance of energy balance at the cellular as well as whole body level. (Towler and Hardie 2007).[40]

$SIRT_1$, activated by AMPK, plays an important role in metabolic function and longevity in mammals. Both act in concert with PGC-1α which interacts with multiple transcription factors to stimulate mitochondrial metabolic capacity. Fibroblast Growth factor-21 regulates energy metabolism by activating AMPK-SIR1-PGC1α pathways. In animal models of obesity FGF21 reduced abdominal fat by 50% (Chau CM et al 2010) Further research is needed to expand our understanding of the diagnostic and therapeutic relevance of FGF21-dependent pathways in humans, and the potential to ameliorate both obesity and diabetes.

AMPK activity in the hypothalamus regulates feeding behaviour Ghrelin activates AMPK and NPY leading to increased food intake and decrease in energy expenditure. Leptin by suppressing AMPK &NPY decreases food intake and increases energy expenditure in periphery. α Lipoioc acid, a naturally occurring co-factor of mitochondrial dehydrogenases, inhibits AMPK in hypothalamus while activates AMPK in skeletal muscle (Kim MS et al 2004)[41](Carling D 2005).[42]

When nutrients are available, the Insulin/IGF-1 signalling pathway is activated. When cells are starved of carbon source, the AMPK pathway is activated- glucose deprivation, ischemia, exercise activate AMPK which inhibits ACC and malonyl CoA via malonyl CoA decarboxylase thereby inhibiting TG synthesis and simultaneously increasing FA oxidation in the mitochondria. AMPK is an important regulator of mitochondrial biogenesis, mediating it's effects through MEF2 and CRFB- mediated PGC1a and PGC1b.

AMPK also increases expression of UCP2 in adipose tissue and UCP3 in skeletal muscle. AMPK activation of GLUT-4 in muscle is not suppressed by wartmanin (inhibitor of Insulin-IRS-P13K) but by compound C, a selective inhibitor of AMPK.

AMPK activation underlies many of the health benefits of regular physical exercise, as well as beneficial effects of caloric restriction.

In atleast 3 animal models of resistance to diet induced obesity(UCP-1,UCP-3 overexpression or mice with a knock out of stearoyl CoA desaturase 1), there is persistent activation of AMPK.

Leptin, adiponectin and osmotin (plant homolog of adiponectin), AICAR, metformin and exercise all activate AMPK (Fig. 5).

AMPK is a key player in the development of new treatments of obesity and metabolic syndrome (Lele RD 2010).[43]

Importance of Physical Exercise

Charak states "Physical exercise increases the body's strength and firmness. It should be practised regularly in the right measure. Lightness, capacity for work, firmness, tolerance to hardship, subsidence of humoral discordance and stimulation of gastric fire accrue from exercise". "Fatigue, exhaustion, wasting thirst, asthma, cough, fever & vomiting result form over-exercise".

A normal man at rest inhales between 6 and 8 litres of air per minute, from which about 0.3 litre of oxygen is transformed in the lung alveoli to the blood. During maximal physical activity the same man takes in 100 litres of air per minute and extracts five litres of oxygen. Hill studied the effects of breathing pure oxygen during exercise. The immediate effect is to lower considerably the rate of ventilation. Athlets who have breathed oxygen- enriched air during exercise reported a pronounced relief of subjective distress and a decrease in ventilation. Oxygen breathing extended the work capacity of trained athelets. On the other hand the Mexico Olympics showed the adverse effects of high attitude and hypoxia on competitive athletics.

When the body is at rest, the muscles take up no more than about 20 per cent of the total body oxygen consumption (60 to 70 ml of O2 per minute out of 300 ml per minute). During exercise, as in running or swimming the active muscle needs about 3000 ml per minute or about 50 times their resting requirement.

Thanks to the presence of myoglobin the special oxygen store, the muscle cell is extraordinarily tolerant to a temporary shortage of oxygen supply. The amount of myoglobin in muscle tissue can be increased by physical training.

The increased fuel requirements of exercising muscles (FFAs and glucose) are ensured by the production of 3 hormones noradrenaline, adrenaline and glucagon abetted by growth hormone and cortisol. Physical training results in improved myocardial performance, improved oxygen transport as well as increased oxygen extraction by muscle- the myoglobin levels are elevated, mitochondrial size and numbers increase so also their enzyme content and activity. Exercise increases fibrinolytic activity in plasma which is important in diabetic patients.

Skeletal muscle contains 2 types of fibres: type 1 (slow twitch) fibres are red because they contain myoglobin (a reservoir of oxygen) and high number of mitochondria. They maintain relatively sustained contraction (such as maintaining of posture) and their metabolism is aerobic.

Type II (fast twitch) and have very few mitochondria, exhibit short duration of contraction and derive their energy from phospho creatine and anerobic glycolysis of glycogen.

Athletes training for marathons have increase in the number of type 1 fibres in certain leg muscles, whereas 100 meter sprinters have a increased in number of type 2 fibres.

Exercise increases GLUT-4 and hexokinase II and glycogenin expression in human skeletal muscle. (Kranion Y et al 2000).[45] In human skeletal muscle exercise results in increased mitogen-activated protein kinase (MAPK) activity and activation of down stream targets of MAPK. Impact of exercise training on insulin sensitivity and physical fitness and muscle oxidative capacity has been shown in healthy first degree relatives of T2DM patients (Ostergard T et al 2006).[46] Physical exercise is the most physiological way to overcome insulin resistance in muscle.

Benefits of exercise have not only be shown in metabolic syndrome but also in cancer. Female breast cancer patients who did regular physical exercise lived longer on chemotherapy compared to sedentary patients (Valenti M et al 2008).[47]

Immunomodulatory effects of aerobic training in obesity have been demonstrated. Thomas Nickel et al (2011)[48] have analyzed the effects of 10 week intensified exercise training (ET)in obese subjects. There was significant reduction in waist circumference and oxidized LDL levels and increase in serum adiponectin levels, and up-regulation of BDCA-1dendrilic cells and (DCs) TLR-4 and TLR-7, indicating an enhanced immunocompetence with higher antibacterial, antiviral and antitumor activity.

The traditional Indian practice of "Surya Namaskar" is an excellent combination of 12 Yogasanas (which maintain flexibility of all tendons and joints in the body) with dynamic aerobic exercise and deserve to be promoted universally.

The Future

Effects of stress management training and dietary changes in treating ischaemic heart disease have been shown (Ornish DM et al 1983).[49] Beneficial efforts of Yoga life style on reversibility of ischaemic heart disease have been documented in a prospective study of 80 patients with CAD (Yogendra J et al 2004).[50]

To educate and motivate the general public to adopt a healthy life-style including diet (caloric restricted diet with400 g. fruits & vegetables and essential fatty acids and avoidance of trans-fats), regular physical exercise, avoidance of tobacco and alcohol use and stress management, takes time and persistent effort. To educate and motivate the patient to implement the advice takes at least 10 minutes per visit, while it takes only ten seconds to write a drug prescription. There is a very powerful drug lobby but no lobby to promote nutrition exercise and stress control. The medical community should be reminded that the word "doctor" is derived from "docere"- to teach.

A unique feature of Ayurveda is emphasis on promotion of positive health, physical, mental and social and spiritual. "The wise man should control the impulses of greed, grief, fear, anger, vanity, impudence, jealousy, malice and excessive attachment".

"He alone can remain healthy, who regulates his diet, exercise and recreation, who controls his sensual pleasures, who is just, generous, truthful and forgiving and who can get along with his kins".

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