Chapter 1 : Energy metabolism and obesity | Read by QxMD

Finally, it can be argued that a focus on energy metabolism as a possible explanation of obesity is unlikely to yield interesting information because of the wide range in energy expenditure in the population even after adjusting for body composition.

 Abstract A wide range of adipokines identified over the past years has allowed considering the white adipose tissue as a secretory organ closely integrated into overall physiological and metabolic control. Apelin, a ubiquitously expressed peptide was known to exert different physiological effects mainly on the cardiovascular system and the regulation of fluid homeostasis prior to its characterization as an adipokine. This has broadened its range of action and apelin now appears clearly as a new player in energy metabolism in addition to leptin and adiponectin. Apelin has been shown to act on glucose and lipid metabolism but also to modulate insulin secretion. Moreover, different studies in both animals and humans have shown that plasma apelin concentrations are usually increased during obesity and type 2 diabetes. This mini-review will focus on the various systemic apelin effects on energy metabolism by addressing its mechanisms of action. A rapid modification of energy balance leads to obesity that in turn is a crucial cause of insulin resistance. Several mechanisms linking obesity to insulin resistance have been proposed. Among them, adipocyte-secreted factors or adipokines have been shown to play an important role. Alteration of their production excess or deficit could directly promote or delay the onset of insulin resistance. The role of leptin and adiponectin has been extensively studied for review see Lafontan and Viguerie, ; Tishinsky et al. In Tatemoto et al identified apelin as the ligand of the APJ receptor, a G protein coupled receptor Tatemoto et al. Apelin gene encodes for a 77 amino acid preproprotein and the apelin propeptide contains several doublets of basic amino acids implicating potential proteolytic cleavage sites for endopeptidases which give rise to several bioactive carboxy-terminal fragments including apelin, apelin, and apelin but also the pyroglutamate apelin which is protected from exopeptidase degradation Masri et al. The group of Tatemoto has described the presence of apelin in rat adipose tissue Wei et al. Apelin and its receptor APJ are widely expressed in several tissues stomach, heart, lung, skeletal muscle, etc. Neither the effects of apelin on the regulation of cardiac and vascular functions, fluid homeostasis and angiogenesis, Chapman et al. This mini-review will discuss the recent advances concerning the role of apelin on energy metabolism particularly in pathophysiological situations obesity, type 2 diabetes and will try to establish a link between plasma apelin concentrations and metabolic diseases in humans. Apelin and glucose metabolism One of the first apelin effects observed on glucose metabolism, apart from that on insulin secretion Sorhede Winzell et al. This decreased glycemia has been shown to be mainly due to increased glucose uptake in target tissues such as skeletal muscle and adipose tissue Dray et al. Since the muscles represent the main entry of glucose, apelin effect was studied in isolated soleus muscle. Apelin stimulated glucose transport and its effect was additive to that of insulin Dray et al. Later on, the study of Yue et al. This discrepancy could be due to the fact that NOS inhibitors were used in the study of Yue et al. In addition, apelin also increased Akt phosphorylation in muscle manner both ex vivo Dray et al. Interestingly, apelin is still able to stimulate glucose uptake in muscle of obese and insulin-resistant mice. This leads to an overall better insulin sensitivity Dray et al. Even though apelin-induced glucose transport has not yet been reported in isolated mouse adipocytes, apelin stimulates glucose transport in an AMPK-dependent way in human adipose tissue explants Attane et al. Skeletal muscle and adipose tissue are not the only tissues where apelin stimulates the entry of glucose. Apelin also increases glucose transport in vitro, in H9C2 cardiomyoblasts Xu et al. A role of apelin has also been shown in intestinal glucose absorption. Ingested glucose can rapidly induce the secretion of apelin in the intestinal lumen in mice Dray et al. This study also shows that, when apelin is administered orally, the amount of glucose transporters SGLT1 is decreased in enterocytes, whereas that of Glut2 is increased due to AMPK activation. This results in

an increased intestinal absorption of glucose. These data suggest that glucose arrival in the intestine causes its own absorption by inducing the paracrine secretion of apelin. A transient increase in blood glucose levels in the portal vein could induce rapid secretion of insulin Fukaya et al. Thus, apelin could also regulate glucose metabolism, by promoting glucose absorption by the enterocytes and then by increasing portal blood glucose and insulin secretion. This could be in agreement with the fact that apelin was shown to increase GLP-1 secretion Wattez et al. Although all studies did not report a significant decrease in fasting blood glucose in obese and insulin resistant mice in response to apelin, decreased insulinemia has frequently been observed. This may be the result of improved insulin sensitivity or a direct effect of exogenous apelin on the pancreas. Accordingly, apelin was shown to decrease insulin secretion stimulated by different glucose concentrations Guo et al. Thus, by activating AMPK and bypassing insulin signaling, apelin exerts direct anti-diabetic effects, which could have an important impact in insulin resistant conditions. Apelin and lipid metabolism Few publications describe acute effects of apelin on lipid metabolism. These results were confirmed by Than et al. However, in human adipose tissue explants or human isolated adipocytes, apelin had no effect on basal or isoproterenol-stimulated lipolysis Attane et al. Effects on adipose tissue and lipolysis were also found in vivo after a chronic apelin treatment in standard or high-fat diet HFD fed mice. Indeed, Higuchi et al. Similar results were obtained in transgenic mice over-expressing apelin Tg-apelin mice fed a HFD Yamamoto et al. Chronic apelin treatment, in obese and insulin resistant mice, was also shown to increase fatty acid oxidation in muscles through AMPK activation Attane et al. More recently, chronic apelin treatment has also been shown to prevent reduction of fatty acid and glucose oxidation in a model of obesity-related decline of cardiac function Alfarano et al. In addition to stimulate the utilization of lipids, apelin treatment increases mitochondrial biogenesis in skeletal muscle Attane et al. Increased mitochondrial DNA content in skeletal muscle was also found in Tg-apelin mice Yamamoto et al. Interestingly, the resistance to obesity of Tg-apelin mice was correlated with an increase in vessel formation in skeletal muscle. Thus, apelin might also prevent development of obesity through the maintenance of vascular integrity. Energy expenditure in response to apelin treatment has also been studied via thermogenesis. However, food intake was not altered in both models. All together, these studies clearly show that apelin, by itself, exerts metabolic functions such as glucose uptake but also improves insulin sensitivity since, for example, at the end of chronic apelin treatment, insulin-induced glucose transport was increased in skeletal muscles and there is an overall better insulin and glucose tolerance Attane et al. Therefore apelin could be proposed as an interesting therapeutic target in the treatment of type 2 diabetes. Apelin and [pyr-1]-apelin may represent the predominant forms in plasma De Mota et al. During the last years, additional information was provided by assays performed especially in diabetic patients and in patients involved in weight loss intervention studies. Interestingly, plasma apelin has been shown to be a novel biomarker for predicting diabetes in Han Chinese subjects Ma et al. Plasma apelin concentrations were higher in women than in men but they were associated with a risk of diabetes only in men Ma et al. Recent data have also shown that apelin concentrations were significantly higher in type 1 diabetic patients than in control subjects and even higher than in type 2 diabetic patients Habchi et al. All together these studies pointed out the role of systemic apelin in metabolic diseases. What is the meaning of elevated apelinemia? Is obesity a main determinant of elevated plasma apelin concentration? Different elements could be provided. Increased concentrations of apelin in type 1 diabetes could be an attempt to compensate for the lack of insulin and to overcome insulin resistance. However patients were also treated with insulin, which could as well explain this rise, since insulin is one of the most important regulator of apelin expression and secretion Boucher et al. Moreover, type 1 diabetic patients are not obese, suggesting that obesity is probably not the main determinant of increased apelin levels. In line with this point, an absence of correlation between plasma apelin concentrations and BMI has often been described Castan-Laurell et al. The recent study of Krist et al. They aimed to investigate whether changes in circulating apelin, in a context of weight loss, are primarily due to a reduced body fat mass or reflect the improved insulin sensitivity. First, all the different weight loss intervention studies hypocaloric diet, bariatric surgery or exercise program reduced the elevated serum apelin concentration determined in different cohorts of obese and diabetic patients as previously reported Heinonen et al. Secondly, significant BMI-independent correlations between reduced apelin levels

and improved insulin sensitivity were found Krist et al. Thus, it could be hypothesized that the increased plasma apelin observed in type 2 diabetic patients, is, as in type 1 diabetes, a compensatory mechanism devoted to directly decrease insulin resistance since apelin exerts different metabolic actions itself. When insulin resistance is decreased, this may lead to decreased apelin levels. It has thus been proposed that lower apelin serum concentrations in healthy lean individuals may be a consequence rather than a cause of normal insulin sensitivity Krist et al. Still, there remain many questions and many tools need to be developed. Long term apelin treatment studies, in both healthy and pathological conditions, need a more integrative view including cardiac, vascular and central effects. The methods used for apelin quantification include enzyme immunoassays and radioimmunoassays but give a wide range of basal values depending on the studies. More reliable assays, easy to use, are necessary. It will also be important to know whether the elevated serum apelin concentrations correspond to active apelin and what are the predominant forms of apelin in metabolic diseases and their variations. Finally, selective agonists and antagonists for APJ started to be developed but they need to be tested on metabolic tissues and their signaling more largely described. All these points are important in order to validate the promising anti-diabetic properties of apelin.

Chapter 2 : Obesity and the regulation of fat metabolism

Energy Metabolism and Obesity: Research and Clinical Applications is a compilation of highly informative reviews written by undisputed leaders in the field. These authors elucidate the most important aspects of genetic background, neuropeptide secretion and action, neuronal pathways, adipokines, gut hormones, and environmental influences.

Diabetes Back cover copy Energy Metabolism and Obesity: Research and Clinical Applications is a compilation of highly informative reviews written by undisputed leaders in the field. These authors elucidate the most important aspects of genetic background, neuropeptide secretion and action, neuronal pathways, adipokines, gut hormones, and environmental influences physical activity, pharmacologic agents, and surgical alteration of the gastrointestinal tract , as well as the complex interactions among them. Understanding the physiology of energy storage and partitioning has become quite a daunting task. This title enables researchers and clinicians to face the challenge of understanding this complex topic and applying the information to the practice of obesity prevention and treatment. The excellent overviews in this book will undoubtedly provide readers with a better understanding of the multifaceted entity of obesity. Research and Clinical Applications Editor: Chung and Rudolph L. Benoit, and Deborah J. Neuroendocrinology and Pathology Robert H. Franks and Stephen M. Stimson and Brian R. Treatment of Insulin Resistance in Youth: Readers from many levels will find this review helpful, including students, researchers, and others seeking to get an overview of the state of the science of obesity-related research. In addition, practitioners seeking an understanding of the direction in which obesity treatment might be moving will also find this book helpful. All chapters are illustrated by several tables, figures, schemes, photos and color plates of high instructive value and supported by more than references which considerably increase the information level of this monograph and offer to the reader a The titles include reviews on leptin, adiponectin, melanocortin, gastrointestinal hormones, growth hormone and ghrelin. Topics related to obesity include syndromic obesities, Prader Willi syndrome, antipsychotic drugs, as well as the surgical approach to obesity. Concise and clearly written overviews. For clinicians and researchers. Each chapter is comprehensive and can serve as an independent reference for its specific topic Donohue has constructed a comprehensive, well-organized and ably-prosed reference To the graduate student her book would be a valuable blueprint to guide study in the now inter-disciplinary field of obesity research. To the expert her digest offers ease of access, novel information and integrative understanding. Sherry, Psychoneuroendocrinology, August, Review quote From the reviews: Donohoue Energy Metabolism and Obesity presents an up-to-date overview of the many aspects of energy balance and its relationships to disease processes resulting from excess energy consumption and storage. Topics covered include energy storage and partitioning, control of feeding and physical activity, adipocyte biology, and the development of obesity-related comorbidities.

Chapter 3 : Center for Metabolism & Obesity Research

The Metabolism, Energy Balance, and Obesity program supports basic and clinical studies related to energy balance and physiological mechanisms modulating weight gain, loss, and maintenance.

CMOR is an interdepartmental and interdisciplinary center established to support the advancement of our understanding of the basic biological mechanisms that regulate metabolism, and how they are dysregulated in disorders such as obesity, diabetes, stroke, and cancer. While these may seem to be divergent themes, they share common root causes in disordered energy balance, which can affect many biological systems. Thus, while CMOR investigators approach these problems from within their individual disciplines, the Center provides an opportunity to explore common scientific themes and collaborate. CMOR also works to facilitate the translation of discoveries to applied knowledge for therapeutics in these fields. We also provide extensive protocols in biochemistry and tissue culture to assist all investigators and students in exploring the diverse biology that is metabolism. CMOR is an integrative and collaborative center that combines research into the molecular and cellular mechanisms of metabolism with a wide range of physiological and behavioral studies. Addressing topics such as nutrient sensing, bioenergetics, and endocrine regulation, the center employs both cutting edge technologies and fundamental basic science to advance our understanding of the biology that regulates metabolism and how it is dysregulated in attendant disorders such as obesity, diabetes, cancer, and stroke. Mission To lead in the study and support of integrative research in the field of metabolism and obesity to advance our understanding of the biological mechanisms that regulate metabolism and how they are dysregulated in attendant disorders, such as obesity and diabetes. Understanding how specific metabolic pathways influence biological outcomes and behavior is the goal of metabolism in our era, and is a common foundation for systems and behavioral biology. The overall goal of CMOR is to develop an infrastructure to facilitate cutting-edge research into the fundamental basic science of metabolism. Goals To provide an infrastructure for scientific interactions among faculty and community. To integrate research using model organisms and metabolic profiling. To develop service and technological resources. To enhance the education of trainees. To foster interactions between CMOR and agencies that support research in metabolism and obesity. To disseminate knowledge to the public in the form of graduate education and to facilitate translation of this knowledge to therapeutic strategies. Bioenergetics entails the conversion of catabolized molecules into energy ATP and reducing equivalents NADH , the availability of which dictates the biological anabolic processes that may occur. Endocrine regulation denotes the humoral and neuroendocrine responses that occur to maintain homeostasis, often in relationship to nutrient availability. For example, molecules such as insulin, leptin, and hypothalamic neuropeptides respond to peripheral and central metabolic cues to sense energy balance and affect behavior. At the cellular level, these metabolic systems influence cell survival, cell cycle regulation, the expression levels of diverse proteins required for cellular functions, and cellular senescence. At the organismal level, nutrients, endocrine profiles, and bioenergetics affect reproduction, exercise capacity, CNS activity, feeding behavior, and longevity. Dysregulation of these pathways results in some of the most devastating diseases that we face, including obesity, diabetes, cancer and stroke. As we discover new regulatory roles for these metabolic pathways, we seek to apply this information towards therapeutic strategies, making the Center a timely undertaking. Most importantly, this theme provides flexibility, allowing the Center to adapt as needed in response to future needs. Follow Johns Hopkins Medicine.

Chapter 4 : Apelin and energy metabolism

Body metabolism is a complex relationship of the energy necessary to perform life-sustaining functions, adaptive thermogenesis, the thermic effect of food, and activity. It has been postulated that obese patients have a slower metabolism than those patients who are not morbidly obese.

Whitson, MD; and Todd A. This article serves as an update of an article on the same topic published in Bariatric Times in September, Ikramuddin S, Kellogg, TA. Energy Metabolism and Biochemistry of Obesity. Bariatric Times ; 2 5: It is true that obesity is now occurring at epidemic proportions. In parallel, efforts to treat obesity are increasing. Currently, surgery is the only proven treatment resulting in sustained weight loss for the morbidly obese. It is no wonder that investigators are using bariatric surgical techniques as models to try to ascertain the mechanism of massive weight loss and improvement of type 2 diabetes T2DM. In turn, these observations can yield important new targets for non surgical or medical interventions for the treatment of morbid obesity. We learn more about the mechanisms of morbid obesity every day; however, though an estimated , bariatric procedures are performed annually, we still have a great deal to learn. The Central Nervous System Chief among the centers of the brain is the ventral hypothalamus. The ventral hypothalamus serves as the central organizing area that controls eating behaviors. A key area of the ventral hypothalamus is the arcuate nucleus. The arcuate nucleus contains two opposing sets of neurons: Stimulation causes an increase in appetite and a decrease in metabolism through antagonism of melanocyte stimulating hormones MSH. These hormones in the hypothalamus will decrease appetite and increase energy conservation. Secondary neurons from these sites then feed to the nucleus tractus solitarius NTS , which influences eating behaviors through a variety of mechanisms, including the sympathetic nervous system. Figure 1 Adipocytes Adipocytes produce cytokines, such as tumor necrosis factor alpha TNFa , resistin, leptin, adiponectin, and Acpr30 adipocyte complement-related protein of 30 kDa , all of which have profound effects to varying degrees in the central nervous system to influence metabolism. Understanding of adipocyte biology is probably 10 years behind that of the endothelial cell. The fat cell is equally, if not more, complex. Originally, the adipocyte was thought of as a passive storage depot for fat, and that there were a fixed number. Today there is evidence to suggest that the number of adipocytes can increase in number based on obesity. When the obesity decreases, the adipocytes can potentially differentiate, although the evidence for this is still somewhat inconclusive. Adiponectin Adiponectin is secreted by adipocytes and is a mediator of insulin sensitivity, is protective, and has anti-inflammatory effects. Plasma adiponectin concentration in obese patients is decreased in comparison to non obese patients. In many previous studies, the postoperative levels of adiponectin after gastric bypass have been shown to increase at 6 and 12 months. Leptin is a product of the OB gene that was first identified in mice. Leptin has been found to suppress NPY neurons in the hypothalamus. There have been very few reported human cases of leptin deficiency and this defect is not a significant contributor to obesity in humans. There are only rare monogenic causes of obesity related to either leptin deficiency or deficiency of the leptin receptor. Those related to leptin deficiency are associated with a family of South Asian origin who were extremely obese and responded very well to recombinant leptin. Somewhat paradoxically, leptin is positively correlated with total body fat and stimulates satiety and increased energy expenditure. Today it is felt that leptin is chiefly involved in long-term regulation of obesity, and its role in short-term obesity is thought to be less important. Leptin receptors are located on pancreatic beta cells resulting in decreased insulin production when stimulated. Resistin contributes to insulin insensitivity and plasma resistin concentration correlates with the level of insulin resistance. In a study of 45 T2DM and 34 non-diabetic patients, the resistin levels of the diabetics were approximately 20 percent higher than the non-diabetic patients. In a study of 12 T2DM and 77 non-diabetic controls, there was no association of resistin and diabetic status. Data available describe changes evident in the postoperative response of obese patients in general. Vendrell and colleagues showed no correlation of resistin levels comparing preoperative to postoperative status. Vendrell also found that resistin was correlated to BMI, fat-free mass, weight, and tumor necrosis factor receptor. Considerable interest now surrounds the hormone known as ghrelin. Ghrelin is an orexigenic hormone that is produced by

the stomach, pancreas and probably the proximal portion of the small intestine. It was identified by a group looking for a growth hormone releasing hormone analogue. Following the gastric bypass operation, ghrelin levels will not rise as much, suggesting a period of satiety. The ghrelin levels appear to be dynamic and are more likely associated with total energy balance than satiety. This is interesting because those patients who undergo gastric bypass typically will see resumption of some degree of hunger between nine months and one year. Figure 3 The glucagon-like peptides GLP are important anorexigenic peptides. GLP1 levels rise following the gastric bypass operation as well as the biliopancreatic diversion BPD , otherwise known as the Scopinaro procedure. The RYGB results in prompt delivery of food to the terminal ileum thereby enhancing satiety, slowing motility, and increasing GLP-1 release. These effects may act synergistically to enable the effective weight loss seen with the RYGB. The levels do not increase after the vertical banded gastroplasty. GLP1 has certain important functions within the body, which include reduced gastric emptying, increased insulin sensitivity, reduced hepatic gluconeogenesis, and reduced pancreatic glucagon secretion. Levels increase and remain elevated for 20 years following these procedures. GLP1 analogues have been useful in the treatment of type 2 diabetes and are currently being tested in ongoing clinical studies. The effects of GLP1 administration can be overcome by administration of ghrelin. Peptide Y for example may be is administered intranasally that may have central action at the neuropeptide Y receptors in the arcuate nucleus to inhibit appetite. Additionally, GLP-1 induces satiety. Non-significant changes have been seen at delayed times from surgery in patients undergoing RYGB or jejuno-ileal bypasses. After RYGB, not only is weight loss attributed to restriction and malabsorption, but it also has been theorized that the more rapid transit time of food into the ileum enhances peptide YY and GLP-1 release with a more rapid insulin response postprandially. Our data suggest that there are minimal effects of surgical status on GIP levels. This has been noted by Rubino and colleagues as well. This may make any subsequent postprandial changes following the gastric bypass of less significance. We were able to show non-significant decreases postoperatively in both diabetics and non-diabetics. Again, Rubino and colleagues have demonstrated similar non-significant decreases in NPY levels. The postoperative levels of insulin have been reported to be significantly as well as non-significantly reduced after surgery. Some of this data are made more confusing for those patients who are postprandial. The multiple stimuli for insulin secretion and the diabetic and operative status of the patients make these data difficult to interpret. Another product of the intestinal L cells is PYY. An outstanding review of this topic was recently published by Ballantyne, et al. Its secretion is stimulated by numerous factors such as cholecystokinin and vasoactive intestinal peptide VIP. Incidentally DPP-IV inhibitors are an important class of medications used in the treatment of type 2 diabetes. Unlike GLP-1 mimetics these medications can be administered orally. There are two active forms that are produced which can cross the blood brain barrier. PYY acts centrally at the ventromedial hypothalamus to stimulate appetite and to decrease metabolism. PYY has the opposite effect. In the gut PYY decreases gastrointestinal motility as well a pancreatic exocrine and endocrine secretion. Generally speaking, PYY levels are depressed in obese patients in comparison to their lean counterparts. A discrete linear relationship has not been shown. Response to a mixed meal is blunted in obese patients in that they require more calories to elicit a similar response to lean subjects. Small bowel resections produce an increase in the level of PYY in many cases. PYY levels appear to increase somewhat following restrictive surgery. Following the gastric bypass basal levels remain low but there is an increase in the stimulated response in comparison to obese controls. Implications for the bariatric surgical population are unclear. Metabolism Body metabolism is an important aspect of the regulation of body weight. Body metabolism is a complex relationship of the energy necessary to perform life-sustaining functions, adaptive thermogenesis, the thermic effect of food, and activity. It has been postulated that obese patients have a slower metabolism than those patients who are not morbidly obese. However, when adjustments are made for fat-free mass, it appears that the metabolism of morbidly obese people is in fact equal to that of those who are not morbidly obese or are of normal weight. Interesting observations have occurred in those patients who are perhaps on the way to becoming morbidly obese. A role has been postulated for those patients who are hypometabolic at one stage of their life, and as they gain weight, their metabolism comes to rest in a normal phase for their body weight in comparison to thin patients. In addition, some evidence exists that with weight loss there is a slowing of

metabolism, which can be reversed by weight gain and the presence of excessive weight in weight-stable patients. However, when patients begin to gain weight above 10 percent of their resting weight stable weight , body temperature will rise and energy expenditure will increase to a non-energy conservation mode. This is interesting, considering that energy production is tightly coupled to adenosine triphosphate ATP production; in patients who have gained weight, there appears to be an uncoupling of the energy production and electron transfer gradient, which is likely due to the action of uncoupling proteins. Following gastric bypass-associated massive weight loss, there does not appear to be the expected slowing of metabolism out of proportion to the change in fat-free mass. Genetics Genetics most likely play a role in morbid obesity. As mentioned earlier, there are several causes for monogenic obesity. These include defects in the leptin receptor, defects in the leptin protein, and transcription of the melanocortin gene or the melanocortin receptor. There are also defects in sim1 gene production, which codes for the supraoptic nuclei. There are over genetic abnormalities that support a polygenic cause of obesity, which probably form the bulk of most obesity cases.

Chapter 5 : Energy Metabolism and Biochemistry of Obesity : Bariatric Times

ENERGY METABOLISM AND OBESITY thermic effect of exercise) is the term frequently used to describe the increase in metabolic rate that is caused by use of skeletal muscles for.

This is because down-regulation of insulin signaling confers an extended adult lifespan as well as promoting dauer formation, the larval hibernation stage see aging and dauer chapters in Post-embryonic development section of WormBook. Increased fat accumulation and altered metabolism are hallmarks of the long-lived, stress resistant dauers. Similarly, loss of function of daf-2 , the C. Measurements of metabolic rate, as assessed by CO2 release, biochemical activity assessment of several key enzymes, microarray and serial analysis of gene expression, have all indicated global shifts in metabolic pathways associated with dauer larvae and daf-2 mutant adults Braeckman et al. In general, these shifts are reminiscent of metabolic adjustments observed in nutrient deprived or fasting mammals. These adjustments favor energy conservation, fat storage, and utilization of stored reservoirs. One complexity in interpreting these studies is that they analyze mRNAs and proteins extracted from whole animals. Since different tissues play different roles in energy balance, it is likely that identical metabolic pathways are modulated differentially in separate tissues. Regulation of growth and metabolism by insulin signaling in C. This promotes growth and reproduction. Nutrient limitation down regulates signaling through the insulin receptor allowing activation of DAF In an early larval stage, DAF activity promotes dauer formation. In adults, DAF reduces reproductive rate, enhances lifespan and causes fat accumulation. Activated component of insulin signaling in different contexts of nutrient availability is shown in green. Genetic alterations of metabolic enzymes profoundly impact fat levels in C. Similarly, inactivations of fatty acid synthesis e. Inactivation of fatty acid oxidation genes causes either decreased or increased fat levels Ashrafi et al. The basis for this paradoxical result is not yet clear but likely reflects compensatory and homeostatic mechanisms. Not surprisingly, inactivation of oxidative phosphorylation and ATP synthesis components is generally associated with profound reductions in fat levels concomitant with growth defects K. Inhibition of fat-5 , fat-6 , and fat-7 genes encoding delta-9 fatty acid desaturation enzymes is associated with reduced fat levels. Interestingly, RNAi inactivation of fat-7 causes fat reduction and shortened lifespan, phenotypes not seen in a fat-7 deletion mutation Brock et al. This discrepancy may be explained by the observation that loss of function mutations in fat-6 or fat-7 cause compensatory transcriptional responses in the remaining delta-9 desaturase genes. Accordingly, triple fat-5 ; fat-6 ; fat-7 are embryonic lethal Brock et al. Mammalian delta-9 stearoyl-CoA desaturase-1 SCD-1 has emerged as a therapeutic target for obesity and metabolic disorders. SCD-1 is a target of leptin signaling. One proposed mechanism is that SCD-1 inhibition results in accumulation of saturated fatty acylCoAs which cause feedback inhibition of acyl-CoA carboxylase ACC , the rate-limiting enzyme of fatty acid synthesis. ACC inhibition results in reduced accumulation of its product, malonylCoA, which in turn, relieves inhibition of carnitine-palmityol-transferase CPT shuttle. Whether similar mechanisms account for fat reduction of C. However, as in mammals, C. Coordination of fat synthesis and breakdown pathways by malonyl-CoA. AcetylCoA is the building block of fatty acids that are assembled into storage triglycerides through step-wise enzymatic processes. Inhibiting delta-9 desaturase activity SCD-1 in mammals, fat-5 , fat-6 , and fat-7 in C. Metabolic sensors and coordinated regulation of metabolic pathways The capacity to coordinately adjust energy flux through various catabolic and anabolic pathways in response to changing nutritional status is critical for cellular and organismal survival. Metabolic sensing mechanisms are thought to coordinate these responses Lindsley and Rutter, How alterations in energy status are sensed is a vibrant field of research. On a cellular level, metabolic sensors respond to altered concentrations of macronutrients, e. In multicellular organisms, energetic status of different tissues is further coordinated through hormonal signals Lindsley and Rutter, ; Salway, Recent studies in mammals indicate that some of these cellular metabolic sensors also function in the nervous system to regulate behavioral responses Minokoshi et al. RNAi inhibition and loss of function mutations in C. Thus far, analysis of candidate sbp-1 targets in C. Additionally, sbp-1 regulates expression of elo-5 and elo-6 , two fatty acid elongation enzymes required for synthesis of monomethyl branched chain fatty acids Kniazeva et al. Further conservation of

function for sbp-1 has emerged from studies in which sbp-1 stimulated transcription of mammalian SREBP targets in a human cell line. Moreover, in both mammalian cells and C. One function of cholesterol in mammalian cells is to regulate membrane fluidity. Interestingly, Drosophila melanogaster, also a cholesterol auxotroph, regulates its membrane fluidity through an SREBP-mediated transcriptional program that produces phosphotidylethanolamine Seegmiller et al. It is likely that a similar mechanism regulates membrane fluidity in C. Also, it remains to be determined if, as in mammals, C. Interestingly, changes in expression patterns of fat metabolic genes caused by nhr inactivation overlap with expression changes noted after 12 hours of food deprivation Van Gilst et al. Thus, nhr responds to nutrient signals and functions as a regulatory node of metabolic gene expression. Several other NHRs, whose mechanisms of function are unknown, are also required for wild type intestinal fat deposits Ashrafi et al. TOR, AMPK, and hexosamine pathways TOR target of rapamyacin is an evolutionarily conserved phosphatidylinositol kinase related family member that couples cell size and proliferation to nutrient levels, particularly amino acids and hormonal signals such as insulin Inoki and Guan, ; Lindsley and Rutter, In Saccharomyces cerevisiae, Drosopholia melanogaster and mammalian cells, TOR activity promotes translation through direct activation of translational machinery. The precise nature of the nutrient signal that elicits TOR activity remains elusive. Loss of function mutations as well as RNAi inactivation of C. In Drosophila melanogaster and mammals, the TSC tumor suppressor complex provides a mechanism of cross talk between the insulin and TOR signaling pathways. Thus, despite differences in cross talk mechanisms, insulin and TOR pathways interact in C. ATP ratio as well as upstream kinase cascades Kahn et al. AMPK activation causes numerous cellular changes, that together down-regulate energy-consumptive pathways and up-regulate energy-generating pathways. In mammals, neuronal AMPK also functions downstream of leptin and insulin signaling to modulate food intake Kahn et al. Genetic analysis has linked the C. These studies have focused on adult lifespan as a read-out. Direct investigation of the effect of C. O-linked N-acetylglucosamine O-GlcNAc is thought to function as a dynamic posttranslational modification of many proteins Lindsley and Rutter, ; Love and Hanover, Flux through the hexosamine pathway is tuned to cellular energy levels. Defects in this pathway are associated with numerous diseases including Type II diabetes. Moreover, insulin mediated dauer pathways are affected in ogt-1 and oga-1 mutant animals Forsythe et al. Development of fat storage capacity During mammalian adipogenesis, hormonal cues initiate transcriptional programs that guide the differentiation of multipotent mesenchymal stem cells into mature adipocytes. SREBP is also required for lipogenic programs of differentiating adipocytes. Despite the fact that C. Electron microscopic examination of a deletion mutation of sbp-1 , lpd-1 gf1 , revealed that, intestinal cells of these animals maintain overall normal ultrastructural appearance including intact microvilli McKay et al. This suggests that fat storage capacity of intestinal cells is distinct from developmental program of these cells as enterocytes. Chemical inhibition of complex I and complex IV by rotenone and NaN3 causes reduction of lipid accumulation in 3T3-L1 cells, a murine tissue culture adipocyte model system. Moreover, lpd-3 encodes a novel but conserved gene expressed in C. The mammalian counterpart of lpd-3 is strongly expressed in brain, testis and embryonic fat tissues. Inactivation of mammalian lpd-3 by shRNA in 3T3-L1 cells that had been induced to undergo adipogenesis prevented lipid accumulation despite appearance of adipocyte differentiation markers McKay et al. Mammalian homologs of these genes mediate fatty acid transport across various lipid bilayers and intracellular shuttling of fatty acylCoAs. In mammals, altered expression of putative fatty acid transport proteins is associated with obesity and insulin resistant states Chawla et al. Loss of function of a FATP-like transporter causes a reduced fat phenotype only in the context of mutations that confer increased fat storage K. Additionally, RNAi inactivations of specific family members of OCT-type transporters, a lysosomal transporter, an amino-acid permease and glucose transporters cause altered fat accumulation Ashrafi et al. Mechanisms of function underlying these phenotypes are not known. GFP-reporter fusions for each of these genes are exclusively expressed along the apical membrane of intestinal epithelia. These functions are required for appropriate acidification of intestinal cells, which in turn, powers a variety of proton-coupled nutrient uptake systems. The best characterized lipid uptake and transport system in C. A mixture of fats and cholesterol are loaded onto vitellogenins, yolk proteins with functional and structural similarities to LDL-type proteins. Vitellogenins are secreted from the intestinal cells into the pseudocoelum

and then taken up by developing embryos via receptor-mediated endocytosis Fares and Grant, This ACBP modulates vesicular transport in the intestine, hypodermis and oocytes and, when inactivated, impairs receptor-mediated endocytosis Larsen et al. Neuroendocrine fat and feeding regulatory pathways In mammals, the nervous system functions as a central coordinator of both metabolic pathways and behaviors associated with food consumption. Molecular components of these pathways are extensively covered elsewhere. Thus, this pathway responds to environmental conditions and function as a central regulator of C. Similarly, many of the C. In mammals, insulin signaling has both peripheral and central actions on fat homeostasis see Figure 6. Importantly, tissue-specific knockouts or reconstitution of the insulin receptor in mice has begun to reveal contributions of different tissues to glucose and fat homeostasis. For instance, neuronal insulin receptor knockout and muscle insulin receptor knockout mice are obese while fat cell insulin receptor knockout mice are lean and resistant to diet induced obesity Biddinger and Kahn, Similarly, insulin signaling in different C. For instance, reconstitution of the insulin receptor in neurons but not in muscle partially rescues the increased fat content of insulin receptor knockout animals Wolkow et al. Systemic actions of insulin signaling in mammals. In response to nutrients e. Concomitantly, insulin inhibits triglyceride and glycogen breakdown pathways in these tissues. Similarly, insulin inhibits hepatic gluconeogenesis and glycongenolysis while promoting glycogen synthesis.

Chapter 6 : Energy Metabolism and Obesity : Patricia A. Donohoue :

Overall, this book does a good job of bringing together an abundance of data to help readers understand the complex interplay of the various pathways involved in energy metabolism, satiety, hunger, and ultimately obesity.

Chapter 7 : Metabolism, Energy Balance & Obesity | NIDDK

The reduction in melatonin production, as during aging, shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chronodisruption leading to obesity.

Chapter 8 : Energy metabolism, fuel selection and body weight regulation

Melatonin, energy metabolism, and obesity: a review. Abstract: Melatonin is an old and ubiquitous molecule in nature showing. multiple mechanisms of action and functions in practically every living.