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REVIEWS: CURRENT TOPICS

Is metabolic syndrome X a disorder of the brain with the initiation of low-grade systemic inflammatory events during the perinatal period?

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Abstract

An imbalance between pro- and anti-inflammatory molecules occurs in metabolic syndrome X. High-energy diet, saturated fats and *trans*-fats during perinatal period could suppress Δ^6 and Δ^5 desaturases both in the maternal and fetal tissues, resulting in a decrease in the concentrations of long-chain polyunsaturated fatty acids (LCPUFAs): arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that have a negative feedback control on inflammation. EPA, DHA and AA augment endothelial nitric oxide synthesis, potentiate insulin action both in the peripheral tissues and brain and alter leptin production. LCPUFAs are essential for brain growth and development and synaptogenesis and modulate the action of several neurotransmitters and hypothalamic peptides. This suggests that metabolic syndrome X could be a disorder of the brain due to suboptimal LCPUFAs during perinatal period that triggers low-grade systemic inflammation, implying that perinatal strategies are needed to prevent its development.

Keywords: Metabolic syndrome X; Long-chain polyunsaturated fatty acids; Leptin; Serotonin; Dopamine; Neuropeptide Y; Arachidonic acid; Eicosapentaenoic acid; Docosahexaenoic acid

1. Introduction

Abdominal obesity, atheroslcerosis, insulin resistance and hyperinsulinemia, hyperlipidemias, endothelial dysfunction, essential hypertension, type 2 diabetes mellitus and coronary heart disease (CHD) are components of metabolic syndrome X. Other features of metabolic syndrome X also include hyperfibrinogenemia, increased plasminogen activator inhibitor 1, low tissue plasminogen activator, nephropathy, microalbuminuria and hyperuricemia [1]. Subjects with abdominal obesity, hypertension, type 2 diabetes, hyperlipidemias, CHD and stroke show insulin resistance and impaired glucose tolerance (IGT). Hyperinsulinemia may be a consequence of this. During early stages of metabolic syndrome X, insulin resistance is restricted to muscle tissue, whereas adipose tissue is not [2]. Exercise decreases insulin resistance and enhances glucose utilization in the muscles, which explains why exercise is beneficial in metabolic syndrome X. In addition, exercise is anti-inflammatory in nature [3,4]. Exercise not only decreased the levels of proinflammatory cytokines interleukin (IL) 6, tumor necrosis factor α (TNF-α) and C-reactive protein (CRP) but also enhanced the

Abbreviations: ATP, Adenosine triphosphate; CHD, Coronary heart disease; LCPUFA, Long-chain polyunsaturated fatty acid; AA, Arachidonic acid; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; IGT, Impaired glucose tolerance; TNF-α, Tumor necrosis factor α; CRP, C-reactive protein; MIF, Macrophage migration inhibitory factor; HMGB1, High-mobility group box 1; IL, Interleukin; Mn-SOD, Manganese superoxide dismutase; eNOS, Endothelial nitric oxide synthase; VMH, Ventromedial hypothalamus; NPY, Neuropeptide Y; VMH, Ventromedial hypothalamus; NA, Noradrenaline; 5-HT, Serotonin or 5-hydroxytryptomine; PVN, Paraventricular nucleus of hypothalamus; GK, Glucokinase; AgRP, Agouti-related peptide; POMC, Proopiomelanocortin; GABA, Gamma-aminobutyric acid; DMN, Dorsomedial nucleus of hypothalamus; α-MSH, α-Melanocyte-stimulating hormone; CART, Cocaine- and amphetamine-regulated transcript; CNS, Central nervous system; ICV, Intracerebroventricular; K_{ATP} channel, ATP-sensitive K^+ channel; IRS, Insulin receptor substrate; IGF, Insulin-like growth factor; GLUT, Glucose transporter; SNARE, Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor; SNAP25, Synaptosomal-associated protein of 25 kDa; NMDA, *N*-methyl-D-aspartate; ACh, Acetylcholine; RAR, Retinoic acid receptor; ARH, Arcuate nucleus of hypothalamus; RA, Retinoic acid; RXR, Retinoid X receptor; PPAR, Peroxisome proliferator-activated receptor; LXR, Liver X receptors; FXR, Farnesoid X receptor; PS, Phosphatidylserine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; ICV, Intracerebroventricular; NAE, *N*-aceyl-ethanolamine; CB, Cannabinoid; EPSC, Excitatory postsynaptic current; IPSC, Inhibitory postsynaptic current.

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concentrations of anti-inflammatory cytokines IL-4, IL-10 and transforming growth factor β [4]. In experimental animals, exercise significantly reduced the magnitude of myocardial infarction, and this cardioprotective action paralleled the increase in manganese superoxide dismutase (Mn-SOD) activity [5]. The administration of antisense oligodeoxyribonucleotide to Mn-SOD abolished this cardioprotective action, implying that ability of exercise to enhance the activity of Mn-SOD is crucial to this protective action. This increase in Mn-SOD activity is in response to exercise-induced free radical generation, suggesting that, under certain circumstances, free radicals have beneficial actions. Paradoxically, administration of antibodies to TNF-α and IL-1 abolished the cardioprotective action of exercise and activation of Mn-SOD, indicating that exercise-induced increase in the production of proinflammatory cytokines augment the production of free radicals that, in turn, enhance Mn-SOD activity that is responsible for the cardioprotective action of exercise. This is supported by the observation that circulating levels of extracellular SOD are lower in subjects with CHD [6]. Furthermore, SOD enhances the half-life of nitric oxide (NO), a potent vasodilator, platelet antiaggregator and antiatherosclerotic molecule. It is noteworthy that supplementation of antioxidant vitamin E counteracted the beneficial effects of exercise, suggesting that stimulation of endogenous Mn-SOD is more critical to the beneficial actions of exercise, and this benefit cannot be imitated by exogenous administration of antioxidants.

In addition, it was reported that exercise increases cholinergic activity in the brain [7] and enhanced acetylcholine (ACh)-induced vascular relaxation and expression of endothelial nitric oxide synthase (eNOS) protein in experimental animals and humans [8,9]. These results indicate that some of the beneficial actions of exercise are mediated through central nervous system (CNS). ACh is known to have anti-inflammatory actions and suppress the production of proinflammatory cytokines [10]. In this context, it is important to note that low-grade systemic inflammation has a role in the pathobiology of metabolic syndrome X, implying that exercise and metabolic syndrome X are closely related to each other.

2. Low-grade systemic inflammation in metabolic syndrome X

Plasma levels of CRP, TNF-α and IL-6, markers of inflammation, are elevated in subjects with obesity, insulin resistance, essential hypertension, type 2 diabetes and CHD both before and after the onset of these diseases [11–16]. Weight reduction and exercise decrease serum concentrations of TNF-α. A negative correlation exists between plasma TNF-α, glycosylated hemoglobin, serum insulin concentrations and high-density lipoprotein cholesterol, which explains why CHD is more frequent in obese compared to healthy or lean subjects [14].

CRP levels greater than 3.0 mg/L was significantly associated with increased incidence of myocardial infarction, stroke, coronary revascularization or cardiovascular death [16]. CRP activates complement that leads to increases in the size of myocardial and cerebral infarcts [17]. Recent studies showed that 1,6-bis(phosphocholine)-hexane, a specific small molecule inhibitor of CRP, abrogated the increase in infarct size and cardiac dysfunction produced by injection of human CRP in rats [17], suggesting that CRP is not only a predictor of metabolic syndrome X but also could be a therapeutic target. This evidence clearly indicates that metabolic syndrome X is a low-grade systemic inflammatory condition [18]. Since exercise increases brain ACh levels [7], ACh, in turn, enhances endothelial NO (eNO) generation [8], and as exercise suppresses inflammation [3,4], I propose that metabolic syndrome X is a disorder of the brain and that it has its origins in the perinatal period.

3. Ventromedial hypothalamus and type 2 diabetes mellitus

Ventromedial hypothalamic (VMH) lesion in rats induces hyperphagia and excessive weight gain, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia and IGT [19,20]. Intraventricular administration of antibodies to neuropeptide Y (NPY) abolished the hyperphagia and *ob* mRNA (leptin mRNA) in these animals, suggesting that increased release or action of NPY plays a role in hyperphagia and obesity observed in VMH lesioned animals and that *ob* gene is up-regulated even in non-genetically obese animals [21,22]. Increased NPY concentrations were noted in the paraventricular, ventromedial (VMH) and lateral hypothalamic areas of streptozotocin-induced diabetic rats [23]. Streptozotocin-induced diabetes produced significant decreases in extracellular concentrations of noradrenaline (NA), serotonin or 5-hydroxytryptomine (5-HT) and their metabolites, a pronounced increase in extracellular γ-aminobutyric acid (GABA), in the VMH [24]. Long-term infusion of norepinephrine plus serotonin into the VMH impairs pancreatic islet function in as much as VMH norepinephrine and serotonin levels are elevated in hyperinsulinemic and insulin-resistant animals [25]. Streptozotocin-induced diabetes caused an increase in NA concentrations in the paraventricular nucleus of hypothalamus (PVN), with a concurrent increase in serum corticosterone, and increased the concentrations of NA, dopamine and serotonin in the ARH and NA concentrations in the lateral hypothalamus, VMH and suprachiasmatic nucleus [26]. Treatment with insulin completely reversed these effects, while leptin treatment was unable to decrease diabetes-induced increase in NA concentrations in the VMH. The restoration of serotonergic activity to normal by insulin therapy suggests that serotonin concentrations depend on the levels of circulating insulin more than on noradrenergic activity. These results indicate

that dysfunction of VMH impairs pancreatic β-cell function and induces metabolic abnormalities similar to those seen in type 2 diabetes.

Glucokinase (GK) is the critical glucose sensor of pancreatic β cells. GK activity is high in the arcuate nucleus; moderate or low in the ventromedial nucleus, lateral hypothalamic area and paraventricular nucleus and very low in the cortex. GK activity and GK mRNA level in the arcuate nucleus of streptozotocin-treated rats were lower than those of control rats, suggesting that prolonged hyperglycemia induced by diabetes decreased the activity of GK in the arcuate nucleus [27]. This decrease in glucokinase activity in the hypothalamic neurons may interfere with the central regulatory mechanisms of insulin secretion by pancreatic β cells. Thus, hypothalamic neurons and neurotransmitters play a crucial role in the regulation of insulin secretion and glucose metabolism, suggesting that metabolic syndrome X may very well be a disorder of the brain [28]. If this is true, it is likely that development of appetite regulatory centers that occurs during the perinatal period is critical to the occurrence of metabolic syndrome X in adult life.

4. Development of appetite regulatory centers during perinatal period

Hypothalamic appetite regulatory centers develop predominantly after birth. NPY is present within the fetal ARC from as early as 14.5 days of gestation; NPY/agouti-related peptide (AgRP) projections between the ARC and dorsomedial nucleus of hypothalamus (DMN) develop around 10–11 days after birth, whereas NPY containing projections to the PVN develop around 15–16 days [29,30]. Hence, it is expected that factors that influence brain growth and development will have substantial impact on the development of appetite regulatory centers that, in turn, determine food intake in later life. For instance, postnatal overnutrition in rats led to an increased early weight gain and fat deposition, hyperphagia, obesity, hyperleptinemia, hyperglycemia, hyperinsulinemia and insulin resistance. These indices of metabolic syndrome X seen in the over fed rats were found to be accompanied by alterations in the concentrations and actions of the appetite regulatory neuropeptides. These changes in the neuropeptides included decreased mean areas of neuronal nuclei and cytoplasm within the PVN, ventro medial hypothalamic nucleus (VMN) and ARC; a significant increase in the number of NPY-containing neurons within the ARC and decreased immunostaining for both proopiomelanocortin (POMC) and α-MSH [30–32].

Genes for the neuropeptides NPY, AgRP, POMC and cocaine- and amphetamine-regulated transcript (CART) are highly expressed in the ventromedial portion of the ARC of the fetal sheep hypothalamus by 110 days of gestation. NPY projections are present in the fetal PVN during late gestation, and the messenger RNA for the long form of the leptin receptor is also expressed in both the ARC and VMN of the fetal sheep and, to a lesser extent in the DMN, consistent with the reported pattern of expression in the adult sheep [33]. These neuropeptides showed significant changes in their concentrations in the various regions of the hypothalamic nuclei, in response to intrafetal infusion of glucose between 130 and 140 days of gestation [34], suggesting that neuropeptides that regulate appetite centers and their responses to stimuli such as glucose, insulin and other stimuli is "programmed" in the fetal and perinatal stages of development. This implies that factors that govern the growth and development of brain and biochemical stimuli such as glucose, insulin and fatty acids (both saturated and unsaturated fatty acids that may include both short-chain and long-chain fats) may have long-lasting impression or programming effects on the appetite regulating centers. This ultimately influences the dietary preferences and the development of obesity and metabolic syndrome X in later life. In this context, it is important to note that brain is rich in insulin receptors through which it regulates food intake, neuronal growth and differentiation, neurotransmitter release and synaptic plasticity in the CNS [35–37].

5. Insulin and insulin receptors in brain

Brain is rich in insulin receptors, especially in the olfactory bulb, the hypothalamus and the pituitary. Diazoxide, a potent inhibitor of insulin secretion, attenuates the thermogenic response to a carbohydrate meal. In contrast, injection of insulin into the VMN and PVN increased body temperature and energy expenditure and reduced food intake [38,39]. Infusion of insulin-specific antibodies or antisense oligonucleotides directed against insulin receptor into the third ventricle reduced hepatic sensitivity to circulating insulin and increased hepatic glucose production, suggesting that the action of insulin in the brain regulates liver glucose metabolism [40]. Insulin receptor substrate (IRS)-2 is abundant in the arcuate nucleus [41], and mice lacking IRS-2 in the hypothalamus exhibit increased food intake and body fat deposition and a major impairment of reproduction [42,43]. Intracerebroventricular (ICV) insulin infusion blocked the effects of both fasting- and streptozotocin-induced diabetes to increase expression of NPY mRNA in the arcuate nucleus [44] and increased hypothalamic POMC mRNA content, while SHU-9119, a melanocortin receptor antagonist, blocked the ability of ICV insulin to suppress food intake [45]. Subthreshold doses of insulin and leptin, when administered in combination, showed additive effects on short-term food intake [46]; both insulin and leptin suppressed NPY/AgRP neurons in the arcuate nucleus while activating POMC/CART neurons. This cross-talk between insulin and leptin, especially in the brain, apart from sharing the common ability to suppress anabolic, while activating catabolic, regulatory neurocircuitry suggests their role in the pathobiology of metabolic syndrome X [47] and indicates that metabolic syndrome X has its origins in the brain.

Insulin acts on adenosine triphosphate (ATP)-sensitive K^+ channels (K_{ATP} channels) of hypothalamic neurons, especially in the mediobasal hypothalamus [48], and may act downstream of NPY and POMC neurons and play an integrating role for peripheral and central energy homeostasis. Leptin, like insulin, activates K_{ATP} channels in glucose-responsive hypothalamic neurons [49]. Glucose-responsive neurons from Zucker fatty (*fa*/*fa*) rats that develop obesity, which have a leptin receptor mutation, are insensitive to both insulin and leptin, which explains why ICV insulin inhibits neither food intake nor NPY gene expression in these *fa/fa* rats [50,51].

Glucose transporter (GLUT) 4, GLUT-8 and glucokinase, the glucose sensor of the β-cell, are present in several areas of the brain. In the arcuate nucleus, >75% of NPY-positive neurons express glucokinase [52] that function as glucose sensors in both glucose-responsive (also referred to as glucose-excited) and glucose-sensitive (also referred to as glucose-inhibited) neurons. Glucokinase-expressing neurons coexpress K_{ATP} channels, and coexpression of GLUT-4 with insulin receptor mRNA is reported in glucose-responsive neurons [53], suggesting that an interaction exists among glucose sensing, ion channel function, neuropeptide gene expression and neuropeptide release.

Food deprivation induced increase in NPY levels in the paraventricular nucleus (PVN) and returned to the control range following insulin injections, which did not alter blood glucose levels. Similar decrease in NPY release in the PVN of food-deprived rats was noted in response to peripheral insulin injections. Both insulin and insulin-like growth factor (IGF) II decreased the release of NPY in a dose-dependent fashion from the PVN in vitro, suggesting that the site of insulin action on the hypothalamic NPY network is at the level of NPY nerve terminals and that both insulin and IGF-II decrease NPY release from the PVN [54]. NPY is a potent orexigenic signal, and insulin and IGF-II decrease hypothalamic NPY, suggesting that presence of adequate amounts of insulin, insulin receptors and IGF-II in the brain reduce appetite, control obesity and hyperglycemia. Obviously, this interaction between insulin, IGF-II and neuropeptides depends on the health of the neurons in the brain, their respective receptors and the presence of adequate synaptic connections between various neurons.

Insulin receptor tyrosine kinase substrate p58/53 and the insulin receptor are components of synapses in the CNS [55]. IGF-1 and insulin antagonize neuronal death induced by TNF-α [56,57]. IGF-I and insulin enhance ACh release from rat cortical slices [58]. ACh inhibits the synthesis and release of TNF-α both in vitro and in vivo [10], enhances eNO production [59] and, thus, shows anti-inflammatory actions. ACh and eNO are not only neuroprotective in nature but also interact with other neurotransmitters. Thus, insulin, IGF-I and ACh protect brain from insults induced by TNF-α and other molecules.

Since brain growth and development occurs from early pregnancy till the first few years of life, it is essential that the integrity of various neurons and their synaptic connections have to be borne and maintained during this critical period of growth for which long-chain polyunsaturated fatty acids (LCPUFAs) are essential. Furthermore, there is substantial evidence to indicate that LCPUFAs have a regulatory role on *N*-Methyl-D-aspartate (NMDA), GABA, serotonin and dopamine-secreting neurons; alter leptin levels and influence of leptin on NPY/AgRP and POMC/CART neurons and, thus, may participate in programming hypothalamic "body weight/appetite/satiety set point," as discussed below.

6. LCPUFAs activate syntaxin and participate in brain growth and development

For proper neuronal development and increase in cell membrane surface area, growth of neurite processes from the cell body is critical [60]. Nerve growth cones are highly enriched with arachidonic acid (AA)-releasing phospholipases, which have been implicated in neurite outgrowth [61,62]. Cell membrane expansion occurs through the fusion of transport organelles with plasma membrane, and syntaxin 3, a plasma membrane protein that has an important role in the growth of neurites, has been shown to be a direct target for AA, docosahexaenoic acid (DHA) and other LCPUFAs [63]. It was reported that AA, DHA and other LCPUFAs but not saturated and monounsaturated fatty acids activate syntaxin 3. Of all the fatty acids tested, AA and DHA were found to be the most potent, compared to linoleic acid (LA) and alphalinoleic acid (ALA), whereas eicosapentaenoic acid (EPA) was not tested. Even syntaxin 1, which is specifically involved in fast calcium-triggered exocytosis of neurotransmitters, is sensitive to AA [64], implying that AA is involved both in exocytosis of neurotransmitters and neurite outgrowth. It is interesting that synaptosomal-associated protein of 25 kDa (SNAP25), a syntaxin partner implicated in neurite outgrowth, interacted with syntaxin 3 only in the presence of AA that allowed the formation of the binary syntaxin 3–SNAP25 complex. AA stimulated syntaxin 3 to form the ternary soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which is needed for the fusion of plasmalemmal precursor vesicles into the cell surface membrane that leads to membrane fusion. These results clearly demonstrated that AA and DHA change the α-helical syntaxin structure to expose SNARE motif for immediate SNAP 25 engagement and, thus, facilitate neurite outgrowth.

7. RAR-RXR nuclear receptors, LCPUFAs and neuronal growth

Retinoic acid (RA) is essential for the development of vertebrate limb and nervous system and in epithelial cell differentiation. These actions of RA are transduced by its binding to a nuclear RA receptor (RAR), which, in the presence of ligand, is transformed into a transcription factor.

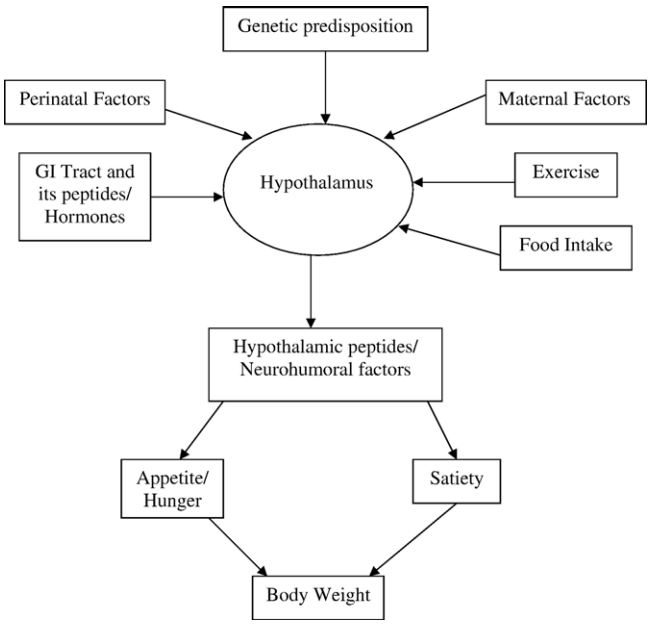

Fig. 1. Scheme showing simplified relationship between genetic factors, maternal factors, diet, gastrointestinal tract and hypothalamus to body weight.

RAR gene family: RAR-α, RAR-β and RAR-γ, have been described, and differential expression of these receptors is important for correct transduction of the RA signal in various tissues. The other subtype of retinoid receptor is the retinoid X receptor (RXR), which could be α, β and γ. RXRs are transcription factors that act as ligand-dependent and ligand-independent partners for RARs and other nuclear receptors. RAR-RXR dimers act on the β-catenin signaling pathway to produce some of their actions. RAR-RXR nuclear receptors are essential for the development brain and other neural structures [65]. AA, DHA and EPA serve as endogenous ligands of RAR-RXR and activate them [66,67]. Several RXR heterodimerization partners such as peroxisome proliferator-activated receptors (PPARs), the liver X receptors (LXR) and farnesoid X receptor (FXR) are essential for regulating energy and nutritional homeostasis and in the development of brain and other neural structures. AA, DHA and EPA modulate these and other regulatory events by binding to RAR-RXR, LXR, FXR and other nuclear receptor heterodimers (Fig. 1).

8. AA/EPA/DHA are involved in neuronal growth and synapse formation

DeWille and Farmer [28] reported that mRNA level of genes involved in myelination were affected by a diet lacking essential fatty acids. Puskas et al [68–71] noted that ω-3 DHA/ALA diets altered genes included those involved in synaptic plasticity, cytoskeleton, signal transduction, ion channel formation, energy metabolism and regulatory proteins. Genes that participate in signal transduction, like *RAB6B*, small GTPase, calmodulins, α- and γ-synuclein and D-cadherin genes were up-regulated in response to ALA/DHA-rich diet, which are specifically enriched at synaptic contacts that play a significant role in neural plasticity, development and maturation of neurons [72]. Perinatal supplementation of ω-3 fatty acids (especially DHA) enhanced the expression of genes coding for cytochrome C and TNF receptor (TNFRSF1A). Berger et al. [73] noted that AA and EPA/DHA supplementation increased the expression of serotonin receptor and POMC in hypothalamus. 5-HT_4 receptor increases in expression are known to augment hippocampal ACh outflow. Thus, AA and EPA/DHA feeding influences hypothalamic function and control energy metabolism.

TNF-α produced by glial cells enhances synaptic efficacy by increasing surface expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. Continued presence of TNF-α is required for preservation of synaptic strength at excitatory synapses [74,75]. In contrast, TNF-α production is suppressed by EPA/DHA, whereas excess TNF-α induces apoptosis of neurons [56,57]. Insulin, which is needed for neuronal growth and differentiation and synaptic plasticity in the CNS [35–37], stimulates the formation of AA/EPA/DHA by activating of Δ^6 and Δ^5 desaturases and suppresses TNF-α production [76,77]. Calorie restriction activates Δ^6 and Δ^5 desaturases and promotes formation of AA/EPA/DHA [77] and mitochondrial biogenesis by inducing the expression of eNOS [78], a neurotransmitter and vasodilator that may aid rapidly growing brain during perinatal period. Furthermore, insulin and AA/EPA/DHA stimulate eNO formation. Thus, a close interaction exists between TNF-α, EPA/DHA, insulin, Δ^6 and Δ^5 desaturases, eNO and mitochondrial biogenesis. Furthermore, TNF-α is needed for synaptic strength, whereas AA/EPA/DHA is needed for the activation of syntaxin 3 and neurite outgrowth. These evidences suggest that growth of neurons and synaptic formation will be optimum only when TNF-α and AA/EPA/DHA are present in physiological concentrations. This implies that when AA/EPA/DHA concentrations are suboptimal, TNF-α levels will be high. Elevated TNF-α concentrations induce neuronal death especially to VMH neurons that will lead to hyperphagia, hyperglycemia, hyperinsulinemia, hypertriglyceridemia and IGT [19]. Thus, TNF-α may participate in the pathogenesis of metabolic syndrome X by two mechanisms: (a) inducing peripheral and central insulin resistance and (b) interfering with the action of VMH neurons.

9. AA/EPA/DHA modulates NMDA, GABA, serotonin and dopamine levels and action in brain

Rats fed purified diets containing safflower oil, a rich source of LA; soybean oil as a source of LA and ALA and high fish oil, rich in DHA, through gestation showed that offspring of rats fed fish oil had significantly higher DHA in their brain nerve growth cone membrane phosphatidylserine (PS), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) than the soybean oil group. Serotonin

concentration was significantly higher in brain of offspring in the safflower oil, compared with the soybean oil group. The newborn brain dopamine was inversely related to PE DHA and PS DHA but positively related to phosphotidylcholine (PC) AA. These results suggest that maternal dietary fatty acids alter fetal brain growth cone fatty acid content and neurotransmitters involved in neurite extension, target finding and synaptogenesis [79].

Piglets fed diets deficient in LA and ALA from birth to 18 days not only had lower amounts of AA in frontal cortex PC and PI and lower DHA in PC and PE but also had significantly lower frontal cortex dopamine; 3,4-dihydroxyphenylacetic; homovanillic acid; serotonin and 5-hydroxyindoleacetic acid concentrations. These indices were restored to normal or were even higher in piglets that received AA and DHA, suggesting that dietary LCPUFAs affect frontal cortex neurotransmitters in rapidly growing piglets and that these changes are specifically due to AA and/or DHA [80]. These results, coupled with the observation that both AA and DHA influence the expression of dopamine receptor genes and their products [81], modify monoaminergic neurotransmitters in frontal cortex and hippocampus [82,83] and facilitate release and actions of GABA [84,85] and ACh [86,87], lends support to the concept that LCPUFAs have a modulatory influence on the release, action and properties of various neurotransmitters in the brain. Exogenously added AA (20–160 μM) stimulated dopamine uptake when preincubated for short times (15–30 min), whereas at 160 μM, AA inhibited following longer preexposures (45–60 min) in glioma cells [88]; markedly stimulated, in a dose-dependent manner, the spontaneous release of dopamine; inhibited, in a dose-dependent manner, dopamine uptake into synaptosomes but still stimulated dopamine spontaneous release in the presence of dopamine uptake inhibitors in purified synaptosomes from the rat striatum, indicating that AA both inhibits dopamine reuptake and facilitates its release process [89].

It is important to note that, in obesity, a decrease in the number of dopamine receptors or dopamine concentrations occurs [90], and obesity is a common feature of metabolic syndrome X. Both in obesity and type 2 diabetes mellitus, plasma concentrations of AA, EPA and DHA are decreased [91–95]. An association between poor fetal growth and adult insulin resistance and increased incidence of type 2 diabetes mellitus and metabolic syndrome X has been reported. In both muscle and liver, the ratio of DHA to docosapentaenoic acid was reduced in low protein offspring. Δ^5 desaturase activity in hepatic microsomes was reduced in the low protein offspring that was negatively correlated with fasting plasma insulin. These results suggest that the activity of key enzymes involved in the desaturation of LCPUFAs could be programmed by perinatal factors such as maternal protein intake [96]. LCPUFA composition of skeletal muscle membranes and insulin sensitivity are closely related [91–95]. Maternal protein restriction decreases Δ^5 desaturase activity, resulting in a decrease in fetal tissue content of LCPUFAs that could program development of insulin resistance and metabolic syndrome X during their adult life, a mechanism linking fetal growth retardation to insulin resistance. Maternal factors (such as maternal protein restriction) could also influence LCPUFA content in the brain. Since LCPUFAs such as AA and DHA have profound influence on the secretion and actions of various neurotransmitters, it is likely that alterations in the concentrations of various LCPUFAs in the brain (especially in the hypothalamus) during the perinatal period could lead to changes in the levels and actions of dopamine, serotonin, ACh and food intake regulating peptides NPY, AgRP (agouti related peptide), POMC (pro-opio-melanocortin) and their receptors and insulin action in the brain (as discussed above). In addition, neurotransmitters are known to influence the metabolism and actions of LCPUFAs. For instance, in the intact rat brain, D2 but not D1 receptors are coupled to the activation of phospholipase A_2 and the release of AA [97]. This suggests that there is both positive and negative feedback control between LCPUFAs and various neurotransmitters and their actions. In this context, it should be noted that an interaction exists between LCPUFAs, leptin, NPY, AgRP and melanocortins.

10. Maternal essential fatty acid-deficient diet lowers plasma and tissue leptin levels

Diet rich in LCPUFAs increases leptin levels in diet-induced obese adult rats [98], suggesting that the type of diet during pregnancy and lactation might significantly modulate fetal and neonatal growth and development by leptin-associated mechanisms, since leptin influences NPY/AgRP and POMC/CART neurons and their connections [99,100]. Plasma and adipose tissue leptin levels were found to be low in the lactating dams fed the essential fatty acid (EFA)-deficient diet and their suckling pups, compared with controls [101,102], suggesting that maternal EFA deficiency decreases leptin levels in several tissues and, possibly, even in the hypothalamus. These low leptin levels during the perinatal period alter NPY/AgRP and POMC/CART homeostasis [99,100] that could lead to the development of metabolic syndrome X in adulthood (Fig. 2).

11. Leptin influences NPY/AgRP and POMC/CART neurons and programs hypothalamic "body weight/appetite/satiety set point"

In obese (*ob/ob*) mice, which lack leptin, obesity due to persistent hyperphagia and decreased energy expenditure is seen [103]. Leptin also functions as a signaling molecule in neuroendocrine response to starvation [104], the timing of puberty [105] and regulation of the hypothalamic-pituitary-adrenal axis [106] and plays a role in the development of central nervous system and maturation of neuronal pathways [107–109]. A 5–10-fold increase in leptin levels was seen in female mice during second postnatal week

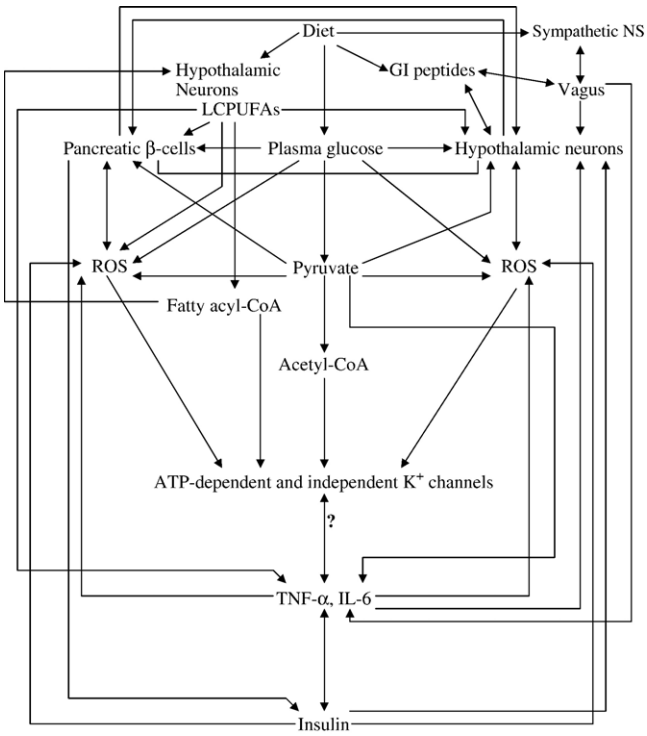

Fig. 2. Scheme showing the relationship between diet, hypothalamus and β cells and the effect of fatty acyl-CoA, pyruvate and ROS on insulin secretion and plasma glucose levels. For further details, see text.

independent of fat mass and declined after weaning, and this rise preceded the establishment of adult levels of corticosterone, thyroxine and estradiol. During this early postnatal period, food deprivation did not alter leptin levels. In adult mice, circadian rhythm of leptin, corticosterone and thyroxine was maintained by food intake, whereas in *ob/ob* mice, the basal concentrations of corticosterone were high, and leptin deficiency did not prevent nocturnal rise in corticosterone [110], suggesting that leptin is involved in the maturation and function of the neuroendocrine axis.

In adults, leptin suppresses food intake. In contrast, a pronounced surge in leptin levels is seen during the first few weeks of life [110], which is not associated with a corresponding decrease in food intake in neonatal mice, indicating that the neonatal brain is relatively insensitive to leptin. In leptin-deficient (Lep^{ob}/Lep^{ob}) mice that are deficient in leptin, the outgrowth of nerve fibers projecting from the arcuate nucleus to the parvocellular part of the PVN (paraventricular nucleus) was disrupted. The distribution pattern in the PVN in Lep^{ob}/Lep^{ob} mice and wild-type littermates were similar, suggesting that leptin deficiency alters the density but not the pattern of innervation. Similar reductions in the density of nerve fibers from the arcuate nucleus of hypothalamus (ARH) to the dorsomedial hypothalamic nucleus, lateral hypothalamic nucleus and other terminal fields of Lep^{ob}/Lep^{ob} mice were seen, indicating that leptin deficiency causes extensive disruption of ARH projections. Leptin deficiency did not produce widespread disruption of hypothalamic circuitry but specifically affected the development of ARH projections to its major terminal fields [111]. Treatment of neonatal Lep^{ob}/Lep^{ob} mice with recombinant leptin restored the density of the nerve fibers in the paraventricular nucleus of hypothalamus (PVH) to normal, and exposure of isolated explant cultures derived from neonatal mice to leptin produced a significant induction of neurites from the ARH explants compared to control, suggesting that leptin acts on ARH neurons to promote axon elongation and proliferation [111].

In adult mice, leptin stimulates ARH neurons that contain α-melanocyte-stimulating hormone (α-MSH)/POMC, CART and anorexigenic peptides and inhibits neurons that coexpress NPY and AgRP, the orexigenic peptides; this ultimately results in reduced food intake. Lep^{ob}/Lep^{ob} mice have reduced density of α-MSH and AgRP-immunoreactive fibers in the PVH. Treatment of adult Lep^{ob}/Lep^{ob} mice with leptin did not restore the density of α-MSH and AgRP-immunoreactive fibers in PVH to normalcy, unlike the restoration of the density of the nerve fibers in the PVH to normal and the density of AgRP and α-MSH fibers in the PVH to normal levels in the leptin-treated neonatal Lep^{ob}/Lep^{ob} mice [111]. These results suggest that leptin is essential for brain development and formation of hypothalamic pathways and critical for the development of ARH projections, especially during the "critical neonatal period," a period during which ARH axons are guided to their specific targets. Thus, the purpose of neonatal surge in leptin production is to establish ARH projections to its major terminal fields and restore normal balance between anorexigenic and orexigenic neurons.

Exogenous administration of leptin to Lep^{ob}/Lep^{ob} mice and humans decreases food intake and reduces body weight by increasing the firing rate of POMC neurons in the ARH [112]. In the ARH, the signaling form of leptin receptor is coexpressed with NPY/AgRP and POMC/CART neurons. In general, increased NPY/AgRP activity and reduced POMC/CART activity increase feeding and fat deposition, whereas reduced NPY/AgRP activity and increased POMC/CART activity decrease feeding and body mass. Thus, leptin, by increasing the firing rate of POMC and CART in ARH decreases food intake. This is supported by the observation that in the *ob/ob* mice, the NPY RNA content is increased, whereas the RNA content of POMC is decreased, and these changes reverted to normal after leptin treatment [113,114]. Furthermore, NPY/AgRP neurons produce GABA and send collateral inputs to inhibit the activity of POMC/CART neurons. Under normal physiological conditions, NPY neurons of the wild-type mice showed similar number of excitatory (EPSCs) or inhibitory postsynaptic currents (IPSCs), whereas POMC neurons showed nearly twice as many IPSCs as EPSCs. In contrast, *ob/ob* mice showed reciprocal alterations in the inputs to NPY and POMC neurons, with a marked net increase in inhibitory tone onto the POMC neurons and an increase in excitatory tone onto the NPY neurons, observations that are consistent

with increased food intake noted in these animals, which are in support of the known effects of these peptides on food intake. Furthermore, (i) wild-type mice showed more inhibitory synapses onto the NPY neurons than excitatory ones, whereas *ob/ob* mice had more excitatory synapses than inhibitory ones; (ii) the number of excitatory synapses was more, and inhibitory synapses, less, onto the *ob/ob* NPY neurons, compared with wild-type, a finding consistent with the increased excitatory tone onto the NPY neurons from *ob/ob* mice; (iii) the excitatory synapses were more numerous than inhibitory ones on the POMC cells of wild-type mice, whereas the POMC cells on *ob/ob* mice showed significantly greater number of inhibitory inputs and (iv) a significantly reduced number of excitatory synapses were seen onto the *ob/ob* POMC neurons, compared with wild-type. In summary, both electrophysiology and electron microscopy studies suggest that there is a net increase in excitatory tone onto the NPY neurons and a net increase in inhibitory tone onto the POMC neuron in *ob/ob* mice, which is the opposite of what is seen in the wild-type mice [115]. Leptin treatment of *ob/ob* mice rapidly normalized the synaptic density within 6 h of its administration, both in the NPY and POMC neurons in the hypothalamus, much before leptin's effect on food intake. On the other hand, ghrelin, an orexigenic peptide, produced a significant decrease in the number of excitatory inputs to the POMC neurons in wild-type mice, with no changes in the number of either excitatory or inhibitory inputs onto the NPY neurons, changes that are opposite of that induced by leptin [115]. These findings suggest that leptin, ghrelin and other peptides have rapid and potent effects on the wiring of key neurons in the hypothalamus and elsewhere that may account for some of their behavioral effects. These results raise the interesting possibility that perinatal deficiency of leptin and other peptides not only produce structural aberrations in the hypothalamus but are also possible to produce rapid rewiring of the various hypothalamic neurons by changing the afferent inputs to key neurons, implying that synaptic plasticity might underlie "hypothalamic memory" concept that under- and overnutrition during critical periods of hypothalamic development may induce body weight/appetite/satiety set point that is long-lasting and potentially irreversible onto adulthood [116]. Such a concept may explain the relationship between perinatal and in utero nutrition and its long-term effects into adulthood (Figs. 1 and 2).

12. Conclusion

Based on the preceding discussion, it is evident that there is a critical neonatal window period during which adequate amounts of LCPUFAs — EPA, DHA and AA should be available to prevent metabolic syndrome X and its associated conditions in later life. The negative correlation noted between breast-feeding and insulin resistance and type 2 diabetes mellitus supports this view since human breast milk contains significant amounts of LCPUFAs. Although infants synthesize longer-chain fatty acids from LA and ALA, the rate of their formation is inadequate in the early stages of life, especially in preterm infants [117–119]. Hence, LCPUFAs formed are inadequate to support optimal neural development. As a result, development, expression and maintenance of NPY/AgRP, POMC/CART neurons and insulin receptors will be defective; plasma, tissue and hypothalamic concentrations of leptin will be inadequate, whereas the concentrations of proinflammatory cytokine TNF-α will be high [120], which may affect neuronal plasticity [74,75]. High TNF-α levels may result in inadequate development of the critical hypothalamic neurons that may predispose to the development of metabolic syndrome X, as seen in the neuron-specific insulin receptor knockout mice, VMH lesioned rats and Lep^{ob}/Lep^{ob} mice. Thus, a marginal deficiency of LCPUFAs during the critical phases of fetal and infant growth can have a major effect on subsequent health. This is analogous to the observation that DHA deficiency in the perinatal period results in hypertension in later life even when animals were subsequently replete with this fatty acid [121].

LCPUFAs serve as ligands for the RXR that have a significant role in brain development and growth. LCPUFAs regulate food intake by modulating the concentrations of endogenous lipids *N*-aceyl-ethanolamine (NAEs, anandamide) and 2-acylglycerols, the ligands of cannabinoid (CB) receptors. Piglets fed diets with AA and DHA during the first 18 days of life showed increased amounts of corresponding biologically active polyunsaturated NAEs in various regions of the brain [122]. These polyunsaturated NAEs bind to CB1 and CB2 receptors and regulate food intake [123]. Furthermore, defective leptin signaling was found to be associated with elevated hypothalamic levels of endocannabinoids in obese *db/db* and *ob/ob* mice and Zucker rats. Leptin treatment reduced anandamide and 2-arachidonoyl glycerol concentrations in the hypothalamus. EPA and DHA modulate leptin gene expression and levels both in vitro and in vivo [101,102,124]. This suggests that LCPUFAs, endocannabinoids and leptin act in concert with other neurotransmitters NPY/AgRP and POMC/CART to control food intake, obesity and metabolic syndrome X.

Direct support to the concept that PUFA content of hypothalamic neurons control food intake and energy homeostasis comes from the observation that infusion of oleic acid (18:1 ω-9) in the third ventricle resulted in a marked decline in plasma insulin concentration and a decrease in the plasma glucose concentration, compared with control within 1 h from the start of the infusion [125], suggesting that intracerebroventricular (ICV) oleic acid enhances insulin sensitivity. Oleic acid markedly suppressed the rate of glucose production by activating K_{ATP} channels in the hypothalamus similar to leptin and insulin [126–128]. In this context, it is interesting to note that fatty acid synthase inhibitors reduced food intake and hypothalamic NPY mRNA levels [129]. Fatty acid synthase inhibitors

increase the concentration of malonyl CoA, a potent inhibitor of the entry of long-chain CoAs into the mitochondria via inhibition of the activity of the enzyme carnitine palmitoyl-transferase-1 [130,131]. This results in elevation of cytoplasmic long-chain fatty acyl-CoAs and diacylglycerol that play a role in signaling the cells about the availability of fuels. One possible role for malonyl-CoA could be to mediate nutrient-stimulated insulin secretion in the pancreatic β cell. Since both β cell and glucose-sensing neurons have many features in common, such as expression of glucokinase and the ATP-sensitive K^+ channels, it is likely that malonyl-CoA may signal fuel status in the hypothalamic neurons. In addition, similar to the fatty acid synthase inhibitors, ICV injection of oleic acid also inhibited hypothalamic expression of NPY [125]. These results indicate that PUFA content of the hypothalamic neurons have the ability to regulate NPY, and probably that of other neuropeptides, expression and, thus, regulate food intake and the development of metabolic syndrome X.

Regulation of ATP-sensitive K^+ channels is a common pathway by which nutrients and other factors modulate neuronal sensing of fuels. This is so since a primary increase in hypothalamic glucose levels lowers blood glucose through inhibition of glucose production, and this effect of glucose requires its conversion to lactate, followed by stimulation of pyruvate metabolism, which activates ATP-sensitive K^+ channels [132]. Pyruvate has antioxidant and anti-inflammatory actions [it inhibits nuclear factor kappa B (NF-κB) activation, TNF-α, IL-6, macrophage migration inhibitory factor (MIF) and high-mobility group box 1 (HMGB1) production] and is an insulin secretagogue [133], indicating that both glucose and pyruvate influence glucose sensing by neurons through a free radical-dependent process since both (glucose and pyruvate) modulate free radical generation.

Hypothalamic slices ex vivo exposed to 5–20 mmol/l glucose-generated ROS and glucose-induced increase in neuronal activity in arcuate nucleus and insulin release could be suppressed by antioxidants. This implies that brain glucose-sensing mechanism involves ROS signaling [134]. In addition, ATP-sensitive K^+ channels control transmitter release in dorsal striatum through an H_2O_2-dependent mechanism [135] and that a variety of ROS-sensitive and nonselective cationic channels are known to exist [136,137]. It is possible that glucose-sensing mechanisms could be similar in pancreatic β cells and hypothalamic neurons [138,139] (see Fig. 2).

Peripheral tissues, muscle, adipose cells, etc., pancreatic β cells and hypothalamic neurons communicate with each other to maintain energy homeostasis, although the exact mechanism on how this takes place is not clear. Immediately after food intake, gut peptides such as ghrelin, cholecystokinin (CCK), etc., are secreted, which interact with hypothalamic neurons and signal hunger and satiety sensations. CCK reduces food intake by acting at CCK-1 receptors on vagal afferent neurons. Leptin mRNA has been reported in vagal afferent neurons, some of which also express CCK-1 receptor, suggesting that leptin, alone or in cooperation with CCK, might activate vagal afferent neurons and influence food intake via a vagal route. A much higher prevalence of CCK and leptin sensitivity amongst cultured vagal afferent neurons that innervate stomach or duodenum than there was in the overall vagal afferent population was reported. Almost all leptin-responsive gastric and duodenal vagal afferents also were sensitive to CCK. Leptin, infused into the upper GI tract arterial supply, reduced meal size and enhanced satiation evoked by CCK, indicating that vagal afferent neurons are activated by leptin and that this activation participates in meal termination by enhancing vagal sensitivity to CCK [140]. Injection of adeno-associated viral vectors encoding leptin (rAAV-lep) injection increased hypothalamic leptin expression in the absence of peripheral leptin in *ob/ob* mice; suppressed body weight and adiposity; voluntarily decreased dark-phase food intake; suppressed plasma levels of adiponectin, TNF-α, free fatty acids and insulin, concomitant with normoglycemia and elevated ghrelin levels for extended period. Leptin administration rapidly decreased plasma gastric ghrelin and adipocyte adiponectin, but not TNF-α levels, thereby demonstrating a peripheral restraining action of leptin on the secretion of hormones of varied origins. Ghrelin administration readily stimulated feeding in controls, but it was completely ineffective in rAAV-lep-treated wild-type mice. Thus, leptin expressed locally in the hypothalamus counteracted the central orexigenic effects of peripheral ghrelin [141]. In addition, incubation of hypothalamic explants with ghrelin significantly increased NPY and agouti-related peptide (AGRP) mRNA expression [141], suggesting that ghrelin and NPY interact with each other to regulate energy homeostasis and metabolism. Ghrelin facilitates both cholinergic and tachykininergic excitatory pathways, consistent with activity within the enteric nervous system and the vagus nerve [142]. Thus, both sympathetic and parasympathetic (especially vagus nerve) nerves carry messages from the peripheral tissues and β cells to the hypothalamus and vice versa, where messages are integrated, codified and relayed to target tissues to maintain energy balance.

Adenovirus-mediated expression of PPAR-γ2 in the liver induces acute hepatic steatosis while markedly reducing peripheral adiposity, changes that were accompanied by increased energy expenditure and improved systemic insulin sensitivity. Hepatic vagotomy and selective afferent blockage of the hepatic vagus reversed, whereas thiazolidinedione, a PPAR-γ agonist, enhanced these changes [143]. These results suggest that afferent vagus from the liver and efferent sympathetic nerves to adipose tissues is involved in the regulation of energy expenditure, systemic insulin sensitivity, glucose metabolism and fat distribution between the liver and the periphery. The “cholinergic anti-inflammatory pathway” mediated by ACh inhibited the production of TNF, IL-1, MIF and HMGB1 and activation of NF-κB expression [10,144,145]. The effects of PPAR-γ agonist and

vagus nerve stimulation are similar in that both improved systemic insulin sensitivity, reduced TNF-α production and showed anti-inflammatory actions [143,144]. Since, ACh is a neurotransmitter and has regulatory role on serotonin, dopamine and other neuropeptides [146], whereas LCPUFAs influence ACh release [147–149] and insulin sensitivity [150–157], it is clear that a complex network of interaction exists between these molecules in the regulation of energy homeostasis. Thus, peripheral and central mechanisms communicate through both neuronal and humoral pathways to maintain energy homeostasis, which ultimately affects food intake. Any perturbation(s) in this communication system can ultimately affect food intake and energy expenditure and lead to the development of metabolic syndrome X. LCPUFAs seem to play a vital role in this communication system.

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