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Hypothalamic Inflammation and Glioses as Aetiopathogenetic Factor in High Fat Diet Induced Obesity and Various Therapeutic Options to Resolve it

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ABSTRACT

We reviewed the literature relating to hypothalamic inflammation (HI); gliosis in relation to high-fat diet (HFD) and that how this could be reversed with various types of therapies. We searched PubMed articles with the MeSH terms "*hypothalamic inflammation*", "*gliosis*", "*HFD*", "*obesity*", and "*treatments*" used. During HFD intake, we found that the ventromedial hypothalamus (VMH) astrocytes uses fatty acids (FA's) to generate ketone bodies which are then exported to neurons where they produce excess adenosine triphosphate (ATP) and reactive oxygen species (ROS), which overrides CD36 mediated FA sensing and role of astrocyte-derived ketone bodies in reducing calorie intake in diet resistant but not diet-induced obese strains was emphasized. The further role of HAM-RS2-a special starch, resolvins abscisic acid, KBH1, unsaturated fatty acid receptor targeting GPR120/GPR40. Hepatic clock genes were effective in tackling obesity. We found that in rodents hypothalamic inflammation and glioses were found to occur immediately with HFD consumption before any significant weight gain. Sensitivity or resistance to diet-induced obesity in rodents also correlates with the presence or absence of hypothalamic inflammation and reactive glioses. Further functional interventions with the increase or decrease inflammation in neurons and glia alter diet associated weight gain. Various human magnetic resonance imaging (MRI) studies have found glioses and disrupted connectivity in obese humans. Various factors which can be used to tackle obesity like HAM-RS2-a special starch, resolvins, abscisic acid, KBH1, unsaturated fatty acid receptors, GPR120 and GPR40 are some of the explored routes by which these pathways may be explored to prevent the further extension of the HFD and one may get newer answers for arresting obesity development.

KEY WORDS: Hypothalamic inflammation; Glioses; Obesity; Resolvins; Abscisic acid; KBH1; Hepatic clock; Astrocytes; Ketone bodies.

ABBREVIATIONS: HI: Hypothalamic Inflammation; HFD: High Fat Diet; VMH: Ventromedial Hypothalamus; FA: Fatty Acids; ATP: Adenosine Triphosphate; ROS: Reactive Oxygen Species; BAT: Brown Adipose Tissue; MBH: Mediobasal Hypothalamus; MRI: Magnetic Resonance Imaging; CNS: Central Nervous System; IHC: Immunohistochemistry; GFAP: Glial Fibrillary Acidic Protein; DIO: Diet-Induced Obese; HAM-RS2: High amylose maize-resistant starch type 2; AUC: Area Under Curve; TDZ: Thiazolidenediones; GIT: Gastrointestinal Tract; SCFA: Short Chain Fatty Acids; PYY: Peptide YY; FGF21: Fibroblast Growth Factor; AARE: Amino Acid Response Elements; VMN: Ventromedial Nuclei; ARC: Arcuate Nuclei; IKK: Inhibitor of Kappa Kinase; ER: Endoplasmic Reticulum.

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INTRODUCTION

In our previous articles on trying to elaborate aetiopathogenetic factors in obesity we discussed various aspects of factors causing obesity, including microRNA's, role of brown adipose tissue (BAT) metabolism, fibroblast growth factor 21 (FBG21) and in reviewing nutrient metabolism, special stress on fatty acid metabolism was emphasized and how hypothalamic inflammation (HI) precedes the development of obesity in high fat diet (HFD).[1-8] We further highlighted the role of gliosis with HI in this article along with various ways of considering therapeutic action to counter these changes as an effective way of tackling obesity.

HYPOTHALAMIC INFLAMMATION (HI) AND GLIOSIS

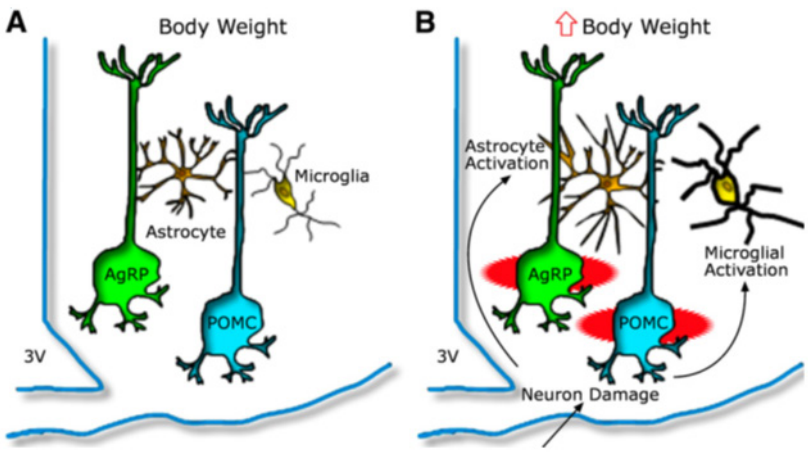
A growing literature in rodent models suggests that obesity is associated with inflammation of and injury to hypothalamic areas critical to the control of energy balance and glucose imbalance.[9-13] Histologically, this response is characterized by gliosis, the proliferation, and activation of glial cells induced by the response to central nervous system (CNS) injury. Microscopically, gliosis means infiltration of microglia and astrocytes and astrocytic proliferation including the increased density of astrocyte processes on the cell bodies of neurons.

Feeding HFD to rodents triggers inflammation and gliosis in the arcuate nucleus located in the mediobasal hypothalamus (MBH), even before obesity occurs[9,12] and eventually reduces proopiomelanocortin cell number.[9] Such changes are associated with both obesity and impaired glucose homeostasis in rodents[13-15] and they offer an explanation for obesity-associated resistance of hypothalamic neurons to humoral signals like leptin and insulin.[16,17] Even though evidence exists from animal studies, the significance of this hypothalamic glioses in humans had largely been unknown (Figure 1).[18]

A core concept of current research is that glioses can be detected in humans using magnetic resonance imaging (MRI) by assessing for increased signal brightness on a T2 weighted image.[19-21] Clinically the visual identification of increased T2 signal intensity is used to detect CNS insults like stroke and multiple sclerosis (MS),[20,21] but quantitative techniques can detect more subtle alterations in CNS tissue characteristics.[11,22] One prior retrospective study on humans utilized clinical MRI examination and found a positive association between body mass index (BMI) and ratio on the T2 signal in the MBH as compared to the amygdale.[9] Thus Schur et al in recent studies utilized a quantitative MRI technique to measure T2 relaxation time in the MBH, employing a dedicated sequence not typically utilized in clinical imaging protocols. Using a similar sequence they found longer MBH T2 relaxation times in diet-induced obese (DIO) mice compared to chow-fed controls.[11,22] Thus using 2 separate studies they sought evidence for MBH gliosis in human studies. In study 1, an *in vivo* MRI study it was hypothesized that MBH gliosis when present would be associated with obesity and insulin resistance. In study 2, a postmortem study of human brain tissue hypothesized that T2 relaxation time would be related to immunohistochemistry (IHC) measures of astrocytes in the MBH.

Schur et al examined 67 patients undergoing a fasting blood draw and MRI. Cases with radiologic evidence of MBH gliosis [n=22] were identified as the upper tertile of left MBH T2 relaxation time and were compared to controls [n=23] from the lowest tertile. Besides a separate postmortem study brain slices [n=10] through the MBH was imaged by MRI and stained for glial fibrillary acidic protein (GFAP). In all the participants, longer T2 relaxation time in the left MBH was associated with

Figure 1: Model Depicting the Hypothalamic Response to an HFD in Animals Predisposed to DIO A) AgRP and POMC Neurons are Integral Components of Energy Balance Neurocircuitry Located in the ARC Nucleus, Situated Adjacent to Third Cerebral Ventricle (3V) Along the Floor of the Hypothalamus. The Activity of these Neurons is Sensitive to Input from Circulating Hormones (e.g., Leptin and Insulin) and Nutrients, and it Plays an Important Role to Establish the Defended Level of Body Weight. B) Recent Evidence Suggests that During HFD Feeding these Neurons may be Injured *Via* Unknown Mechanisms, and that this Injury Triggers Activation of Local Glial Cell Populations (Astrocytes and Microglia). This Neuron Injury and Reactive Glioses Can, in Turn, Impair Homeostatic Control of Body Fat Stores, Leading to Increased Body Weight.[81]



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higher BMI (p=0.01). As compared to the control cases, the participants had longer T2 relaxation times in the right MBH (p<0.05) as well as higher BMI (p=0.05), fasting insulin concentrations (p<0.01) and HOMA IR values (p<0.01) adjusted for sex and age. Elevations in insulin HOMA IR were also independent of BMI. In the postmortem study, GFAP staining intensity was positively associated with MBH T2 relaxation time (p<0.05) validating an MRI based method for the detection of MBH gliosis in humans. Hence they concluded that these findings links hypothalamic gliosis to insulin resistance in humans and suggests that the link is independent of the level of adiposity.[23]

ASTROCYTES AND HYPOTHALAMIC GLIOSES

Data from recent studies suggests that neuronal inflammation may be a downstream event during DIO, with recruitment and activation of hypothalamic glial cells being more proximal response to HFD exposure.[9,11,24-26] This gliosis process involves accumulation and multiplication of activated microglia and astrocytes in the region of MBH.[9,11,25-27] Various studies have implicated microglia in the development of diet-induced inflammatory signals along with metabolic dysfunction,[14,28] but a similar role for astrocytes is not clear. Buckman demonstrated a modest role of astrocytic inflammation to caloric intake on the first day of HFD feeding but there was no analysis of susceptibility to DIO.[29] There are abundant astrocytes throughout the CNS and involved in many fundamental processes like synaptic transmission, neurovascular coupling, and blood-brain barrier maintenance.[30] Additionally, astrocytes participate in CNS immune responses, when they take an activated phenotype having raised GFAP expression and release of proinflammatory cytokines which can enhance neurotoxicity and neurodegenerative disease progression.[30-32] Hence, astrocytes have the basic requirement to affect energy homeostasis regulation in health and disease. MBH astrocytes modulate feeding behavior on pharmacological activation[33,34] and show dynamic responses to circulating signals of nutrient availability like insulin and leptin.[35-38] Also, MBH astrocytes become activated with obesity and HFD feeding in rodents and humans,[9,23] which raises the possibility that astrocyte inflammation disrupts the hypothalamic regulation of energy balance and promotes DIO.

The group of Thaler et al developed a mouse model with an inducible astrocytic specific deletion of IKKβ with the use of tamoxifen. With this approach, they showed that decreasing the astrocytic signaling protects mice from HFD induced HI and decreases susceptibility to DIO and glucose tolerance. The results highlight the importance of non-neuronal cells in obesity pathogenesis and suggest the possibility of newer target for therapy.[39]

ROLE OF HAM-RS2

Diets high in fibers may lower obesity risk and its morbidities.[40,41] Zero point four percent decreases in body weight is reached by consumption of most dietary fibers for 4 weeks.[42] The amount of weight loss was proportional to the physical and chemical properties (i.e., solubility, viscosity, and fermentability) of each type of fiber. Mechanisms by which weight loss is caused by fibers are changes in gut motility, prevention of absorption of nutrients and decrease in the total caloric input, which are associated with the physicochemical properties.[41,43] Various fibers which can be fermented are under scrutiny, as the metabolites obtained after fermentation by bacteria in the gastrointestinal tract (GIT) may influence body weight. Short-chain fatty acids (SCFA) are produced from these fibers in the distal intestine which stimulates the release of GLP1 and peptide YY (PYY), which acts in synergy with leptin to induce satiety, which further regulates through the CNS.[44-46] Although, SCFA's are produced by fiber fermentation there is an inconsistent relation between GLP1 and PYY on satiety and food intake in humans. After eating a standard breakfast in the morning immediately following 3 days of consecutive intake of a barley kernel based bread with resistant starch, fasting plasma GLP1, and postprandial PYY concentrations were increased in healthy adults.[47] But there was no change in appetite sensations like in satiety, hunger, desire to eat.[47] Also, overweight women who had taken an enzyme hydrolyzed arabinoxylan from flax at breakfast did not show a postprandial subjective satiety although there was an improvement of GLP1 and PYY, which corresponded to increased subjective satiety following maltodextrin intake in healthy humans.[48] But there was no suppression of energy intake in spite of these changes. In a recent trial, there was improvement in PYY which corresponded with satiety along with 14% decrease in food intake in healthy adults who took 15 g unripe banana flour rich in resident starch for 6 weeks.[49] Why there are differences in satiety peptides and satiation responses relates to fermentability patterns, nature, amount and duration of fiber intake along with gut microbe composition of individuals? Besides the blood, gut peptide concentrations may be very low to be able to cross the blood-brain barrier or the individual might be having a hypothalamic resistance which can occur from a HFD even *in lieu* of obesity.[50]

High amylose maize-resistant starch type 2 (HAM-RS2) comprises an insoluble, nonviscous fermentable fiber, which has been shown to improve glucose homeostasis,[51] or those with metabolic syndrome.[52-54] Yet many of trials of long duration did not report or show improvements in blood concentration of gut peptides, satiety responses or changes in food intake. The beneficial effects of HAM-RS2's may be on glucose metabolism by increasing SCFA in blood to alter FFA and glycerol release from adipocytes and increased fat oxidation[55] by affecting bile acid metabolism,[56] or changing the gut microbiota profile.[57] Earlier trials reported that the effects of HAM-RS2 on glucose homeostasis in healthy individuals or those with MS.[12-15] Thus Maziaiz et al tried to determine the impact of daily consumption of 30 g HAM-RS2 incorporated into muffins for 6 weeks on glucose homeostasis in normoglycaemic healthy overweight adults at risk of developing glycemic abnormalities. They used a randomized control, placebo arm, a double-blind design with 18 overweight healthy adults consuming either muffins enriched with 30 g

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HAM-RS2 (n=11) or 0 g HAM-RS2 (control; n=7) daily for 6 weeks. Both HAM-RS2 and control muffins were similar in total calories and available carbohydrates. They found at baseline total PYY concentrations were significantly higher 120' following the consumption of study muffins in the HAM-RS2 group than control group (p=0.043). Within the HAM-RS2, the area under curve (AUC) glucose (p=0.028), AUC leptin (p=0.022), and postprandial 120' leptin (p=0.028) decreased independently of changes in body composition or overall energy intake at the end of 6 weeks. Fasting total PYY increased (p=0.033) in the HAM-RS2 group but changes in insulin or total GLP 1 were not observed. Mean overall change in subjective satiety score did not correlate with mean AUC biomarker changes which suggested that the satiety peptides did not elicit a satiation response or change in overall total caloric intake. The metabolic response from HAM-RS2 occurred despite the habitual intake of a moderate to HFD (mean range 34.5% to 39.4%) of total calories. Thus, they concluded that consuming 30 g HAM-RS2/day x 6 weeks can improve glucose homeostasis, lower leptin concentrations and increase fasting PYY in healthy overweight adults without impacting body composition and may help in the prevention of chronic disease. However, between groups, differences in biomarkers were not seen and warrants future research before making specific recommendations.[58]

ROLE OF FGF21

It was believed that FGF21 was the hormone associated in response to nutrient restriction *in lieu* of increase during fasting, starvation and a ketogenic diet.[59-62] But, recent data suggested that the decreased protein intake is the primary regulator of FGF21 during those interventions and FGF21 deficient mice failed to exhibit the increases in food intake and increases in energy expenditure and reductions in growth observed in wild-type mice consuming low protein diet (LPD).[63] The mechanisms linking reduced protein intake to increased hepatic FGF21 expression and secretion are not clear but there is an implication of amino acid GCN2 sensor.[63,64] GCN phosphorylates eIF2α in response to depletion of cellular aminoacids[65] which lead to inhibition of general protein synthesis while increasing translation of transcription factors such as activation transcription factor 4 (ATF4). This links amino acid availability to metabolism specifically in the liver.[66,67] The FGF21 promoter contains amino acid response elements (AARE) and both depletion of amino acid's and activation of this Eif2α/ATF4 pathway increases FGF21.[64,68-70] Thus, it was shown that hepatic Eif2α phosphorylation is induced by multiple settings of dietary protein restriction and that low protein (LP) induces increases in FGF21 and Eif2α phosphorylation are blunted in GCN2 deficient mice.[63] Since FGF21 is required for metabolic and behavioral responses to protein restriction and GCN contributes to the increase of FGF21 in this setting, Laegar et al hypothesized that GCN2 deficient mice would fail to respond to reduced protein intake and thereby recapitulate this phenotype of FGF21 KO mice. They demonstrated that there is a persistent and essential role of FGF21 in the metabolic response to protein restriction. FGF21 KO mice were fully resistant to LP inducing changes in food intake, EE, body weight gain and metabolic gene expression for 6 months. GCN2KO mice recapitulate phenotype but LP induced effects on FI, EE, body weight begin to appear after 14 days on diet. They showed that this delayed emergence of LP induced metabolic effects in GCN 2KO mice coincides with a delayed but progressive increase of hepatic FGF21 concentration over time. Thus, they concluded that the data indicated that FGF21 is essential for the metabolic response to protein restriction but then GCN2 is only transiently required for LP induced FGF21.[71]

ROLE OF ASTROCYTES AND KETONE BODIES

The mechanisms by which HFD leads to obesity development are still poorly understood. Body weight regulation involves 2 mechanisms namely hunger and satiety. The brains actions regarding regulating these are influenced by nutrients, hormones, peptides and other related signaling molecules which cross the BBB and change the activity of particular metabolic sensing neurons which are dispersed in various anatomical sites in the brain. The mature human brain weighs only 2-3% of total body weight.[72] Neurons store very little energy and hence are dependent upon the continuous exogenous supply of glucose as the primary metabolic substrate for most of brains energy requirements.[73,74] Recently, importance of glia, of which mainly astrocytes have gained importance for giving this metabolic support to neurons.[75,76] Since astrocytic foot processes directly impinge on brain microvessels they are the first cells which nutrients face on entering the brain.[77,78] Astrocytes have important metabolic functions including neuronal transmission,[79-82] glycogen storage and lactate production for neuronal metabolism mainly during increased activity of neurons.[83,84] In the ventromedial hypothalamus (VMH), ventromedial nuclei (VMN) and arcuate nuclei (ARC) astrocytes also produce ketone bodies from free fatty acids (FFA).[85,86] Although, lactate production, occurs as a continuous process[84,87] the ketone production from astrocytes occurs mainly if blood FA levels increase secondary to dietary intake.[85,86] Recently, role of local production of ketones by VMH astrocytes as regulators of food intake during intake of HFD has been highlighted. Also, novel hypothesis by which astrocytes can regulate FA turnover in the VMH and mechanism by which astrocyte produced ketone override normal neuronal FA sensing to regulate feeding is described.

Le Foll et al tried to understand mechanisms of long-term and excessive HFD intake in obesity development. VMH is a major site involved in the regulation of glucose and energy homeostasis where metabolic sensing neurons integrate metabolic signals from the periphery. FA modulates, VMH neuronal activity through the use of FA translocator/CD36 which plays a critical role in the regulation of energy and glucose homeostasis. During LFD intake FA are oxidized by VMH astrocytes to fuel their ongoing metabolic needs. But HFD intake causes VMH astrocytes to use FA to generate ketone bodies. Thus they postulated that these astrocyte-derived ketone bodies are exported to neurons where they produce excess ATP and ROS, which over-

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rides CD36 mediated FA sensing and acts as a signal to decrease short-term food intake. On a HFD, VMH astrocytes produced ketones reduced elevated calorie intake to LFD levels after 3 days in rats genetically predisposed to resist (DR) DIO but not leptin resistant DIO rats. This gives a suggestion that while VMH ketone production on a HFD can contribute to protection from obesity, the inherent leptin resistance overrides this inhibitory action of ketone bodies on food intake. Thus, astrocytes and neurons form a tight metabolic unit that is able to monitor circulating nutrients to alter FI and energy homeostasis.[88]

ROLE OF RESOLVINS

Infectious agents, trauma or chemical stimulus cause an acute inflammation and its prompt resolution is needed to prevent chronicity and undesired tissue damage which could lead to an unrestrained response to the original harmful stimulus.[89] Lipoxins,[90] resolvins,[91,92] and protectins[93] are families of endogenously produced lipid-derived substances which act in the resolution phase of acute inflammatory processes.[94] Resolvin D2 (RvD2) is one of the members of the resolvin family is produced from the ω-3-polyunsaturated fatty acid docosahexaenoic acid (DHA) as a result of a series of reactions which get catalyzed by lipoxygenases.[91] The anti-inflammatory and pro-resolution effects of RvD2 are mediated at least in part by the pertussis sensitive G protein-coupled receptor (GPCR), GPR18, by signaling mechanism yet to be fully elucidated.[95,96] Though most studies have explored the role of resolvins in acute inflammatory conditions, a recent study had provided evidence that both RvD2 and resolvin D1(RvD1) can modulate the chronic inflammatory process that takes place in the adipose tissue of obese subjects.[97] Also, treatment with 17 hydroxy docosahexaenoic acid (17HDHA), a precursor of Rv D2, reduced inflammation and corrected IR in obese diabetic rodents.[98] Obesity is one of the most prevalent diseases worldwide. Saturated fatty acids present in the diet induce an inflammatory response in the hypothalamus leads to dysfunctional regulation of caloric intake and energy expenditure,[99-103] which plays an important role in the genesis and perpetuation of obesity.[9,104] Number of pharmacological and genetic approaches used to decrease obesity linked H I leads to reversal of the obesity phenotype in animal models[9,100-102,105] increase the content of ω3 fatty acids can decrease obesity linked HI, increase POMC neuron-specific neurogenesis and attenuate the obese phenotype.[106,107] As ω3 fatty acids are precursors of RvD2, Pascal et al examined the activity of this system in the hypothalamus of obese rodents. Male Swiss mice were fed either chow or a HFD. RvD2 receptor and synthetic enzymes were evaluated by real-time PCR and immunofluorescence. RvD2 was determined by mass spectrophotometry. Both dietary and pharmacological approaches were used to modulate the RvD2 system in the hypothalamus and metabolic consequences were determined. All enzymes involved in the synthesis of RvD2 were detected in the hypothalamus and were modulated in response to the consumption of dietary saturated fats leads to a reduction of hypothalamic RvD2. GPR18, the receptor for RvD2 which was detected in POMC and NPY neurons was also modulated by dietary fats. The substitution of saturated by polyunsaturated fats in the diet leads to increased hypothalamic RvD2 which was accompanied by decreased body mass and improved glucose tolerance. The ICV treatment with docosahexaenoic acid leads to increased expression of the RvD2 synthetic enzymes increased expression of anti-inflammatory cytokines and improved metabolic phenotypes. ICV treatment with RvD2 caused decreased adiposity, improved glucose tolerance and increased hypothalamic expression of anti-inflammatory cytokines. Thus, they concluded RvD2 is produced in the hypothalamus and its receptor and synthetic enzymes are modulated by dietary fats. The improved metabolic outcomes of RvD2 make this substance an attractive approach to treat obesity.[108]

ROLE OF PUFA RECEPTORS GPR120 AND GPR40

Intake of large quantities of dietary fats is one of the most important environmental factors leads to obesity.[108-110] Long chain saturated fatty acids trigger inflammation through the activation of toll-like receptor 4 and the induction of endoplasmic reticulum stress (ER).[111-113] The low-intensity inflammation generated in this context can act both systemically and on selected anatomical regions to affect insulin and leptin action,[114] insulin production,[115,116] lipid metabolism[117] and a number of other parameters related to whole body energy homeostasis. Since metabolic inflammation plays a part in the pathogenesis of insulin and leptin resistance, it has been hypothesized that means by which inflammation is attenuated could be beneficial for obesity, T2DM.[118-120] Genetic and pharmacological approaches aimed at reducing inflammation have produced encouraging outcomes in various experimental models.[116,119] Recently, in a clinical trial salsalate was used to target the inhibitor of kappa kinase (IKK) which leads to a marked decrease in glycated hemoglobin levels in patients with T2DM.[121] Polyunsaturated fatty acid (PUFA) receptors GPR120 and GPR40 have been found to be attractive targets for the treatment of IR.[122-125] Activation of GPR120 by PUFA or synthetic ligands engages an atypical signaling system which suppresses the metabolic inflammation in obesity and T2DM.[126] A recent study has reported the beneficial effect of a synthetic agonist of GPR120 in improving glucose intolerance and hepatic steatosis in an animal model of DIO.[127] Additionally, a lot of studies have shown the influence of targeting GPR40 systemically in T2DM.[128] A new anti-inflammatory mechanism was described by Oh et al regarding the action of PUFA s through GPR120. On ligand binding, GPR120 recruits β arrestin-2 leads to internalization of the receptor/regulatory protein complex.The internalized β arrestin 2 binds to TAB1 and inhibits its binding to TAK1 which is a point of convergence for TNFα and TLR4 signal transduction and its inhibition impairs the progression of the signal towards JNK and IKK activation which leads to inhibition of inflammation.[123] Beneficial effects of a small molecule which acts as a specific agent for GPR120 was also shown by Oh's group.[127] Obese mice treated with this molecule showed improved glucose tolerance and decreased hepatic steatosis

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which is accompanied by a decrease of metabolically inflammatory phenotype which shows GPR120 is an attractive potential target for treatment of obesity-associated metabolic disorders. A beneficial effect of GPR 40 activation has also been seen.[125,129,130] GPR40 is expressed in pancreatic β cells on activation of PUFA's it increases glucose-induced insulin secretion.[125] Also, GPR40 is expressed in intestinal L&K cells, induces GLP1 and GIP secretion which provides another stimulus for insulin secretion.[131] For mechanism of action of GPR120 it is shown that the induction of Ca^{2+} mobilization and activation of CREB may play important roles in some of the effects of this pathway.[132] Hence, the potential therapeutic usefulness of agonists for GPR40 is considered important.[128] Therefore, Dragano et al evaluated the expression and potential role of hypothalamic GPR120 and GPR 40 as targets for treatment of obesity. Male Swiss rats (6 weeks old), were fed with a high-fat diet (HFD, 60% of kcal from fat) for 4 weeks. This was followed by stereotactic surgery to place an indwelling cannula into the right lateral ventricle. Intracerebroventricular (ICV) cannulated mice were treated twice a day for 6 days with 2.0 µl saline or GPR40 and GPR120 agonists, GW9508, TUG 905 (2 µL,10 mM). Food intake and body mass were measured during the treatment period. At the end of the experiment, the hypothalamus was collected for real-time PCR analysis. It was shown that both receptors are expressed in the hypothalamus, GPR120 is primarily present in microglia while GPR 40 was expressed in neurons. Upon ICV treatment GW9508, a nonspecific agonist for both receptors, decreased energy efficiency and the expression of inflammatory genes in the hypothalamus. Reducing GPR120 hypothalamic expression using a lentivirus-based approach resulted in the loss of the anti-inflammatory effect of GW9508 and increased energy efficiency. ICV treatment with the GPR120 and GPR40 specific agonists TUG 1197 and TUG 905 respectively, resulted in milder effects than those produced by GW9508. Thus, it was concluded that GPR120 and GPR40 act in concert in the hypothalamus to reduce energy efficiency and regulate the inflammation associated with obesity. The combined activation of both receptors in the hypothalamus results in better metabolic outcomes than isolated activation of either receptor alone.[133]

ROLE OF ABSCICIC ACID

The thiazolidinediones (TZD) belong to a family of synthetic insulin sensitizer molecules; however, there are adverse effects of some of them. Hence, other compounds having similar properties but fewer side effects are needed. The phytohormone abscisic acid (ABA) was found in mammalian cells over 25 yrs back.[134] Various studies have proposed it to be a universal signaling molecule.[135,136] Structurally, ABA is very similar to TZD's. ABA can improve glucose tolerance,[137] decreases the levels of TNFα and reduce the adipocyte cell size in an *in vivo* model of obesity induced by HFD.[138] Further in human and pancreatic cell lines (RIN m and INS2 cells), ABA can increase glucose-stimulated insulin secretion.[139] This effect can be suppressed using pertussis toxin and PKA inhibitors.[140] Dietary ABA further stimulates granulocyte function and macrophage infiltration in the adipose tissue.[141] In mammalian cells the lanthionine synthetase C Like protein 2 (LANCL2) shows high homology with the ABA receptor in plants, the Arabidopsis GCP2. Blocking the expression of endogenous LANCL2 in granulocyte cells can stop ABA induction of Ca^{2+} response while overexpression of LANCL2 increases the ABA-mediated effects.[142] Because of its role in the mediation of ABA effects, LANCL2 has been proposed as therapeutic targets for the treatment of inflammatory disease and DM.[143]

Also, ABA shows some molecular structural similarities to retinoic acid (RA). RA has useful effects in cognition, improving memory deficits in rodent models of Alzheimer's disease. But both clinical and animal model data show an association between RA administration and the symptoms of depression.[144] ABA given chronically has been shown to be a useful antidepressant as shown by increased sucrose intake, increased swimming in the forced swim test and decreased expression of CRH and RARα mRNA in the rat hypothalamus in control rats with no reported side effects.[145] Thus Sanchez–Sarua et al tried to show if dietary ABA could improve cognitive defects resulting from a HFD induced neuroinflammation. HFD increases the levels of neuroinflammation markers in the brain[146] and may be a link between obesity and degenerative disorders *via* IR.[147] Also HFD has been shown to cause memory loss by increasing inflammatory markers in the hippocampus.[148] Male Wistar rats were fed with standard diet or HFD, with or without ABA (20 ng/ml) in drinking water for 12 weeks. After 11 weeks of treatment they compared the behavior of 4 groups using 2 memory paradigms; the novel object recognition (NOR) and the T maze. Also, they measured ABA levels in the blood and cerebellum of all 4 groups using HPLC. The microglia proliferation using IHC was also analyzed. It was demonstrated that ABA administered in drinking water improved glucose tolerance and cognitive performance and decreased the levels of inflammatory markers in the hypothalamic areas. Their results confirmed a therapeutic potential of this phytohormone in the peripheral metabolic alterations. The data also strongly suggest that the potential beneficial effects of ABA in disorders of neuroinflammatory etiology, not shown earlier.[149]

HEPATIC CLOCK AND OBESITY

To adapt to the physiology of 24 hour rhythm of day and night most species have evolved endogenous circadian clocks in response to piles of earth rotation around its axis.[150,151] These clocks are based on transcriptional-translational feedback loops built from a set of clock gene proteins which includes the 2 transcriptional factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle ANRT like 1 (BMAL1 or ARNTL) which in synergy drive rhythmic expressions of three period and two cryptochrome genes through binding to E box enhancer motif BMAL 1 and CLOCK regulate other E box controlled genes in a tissue-specific manner; thus, translating the circadian clock

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rhythm into physiologically meaningful signals.[152,153] All body tissues have clocks which are synchronized by a master pacemaker located in the hypothalamic SCN[154,155] which is controlled by the external light rhythm. Peripheral clocks and SCN controlled sleep-wake and food intake rhythms regulate the expression of many metabolically relevant genes.[156] Peripheral clocks not only respond to SCN signaling but also get reset by the timing of food intake. Because of mistimed feeding rhythms which occur commonly in modern industrialized societies can promote internal clock desynchrony and the development of metabolic disorders.[157-162] In liver transcriptomic analyses have shown more than 3000 rhythm transcripts[163] and chromatin immunoprecipitation/DNA sequencing experiments showed more than 2000 DNA binding sites for BMAL1 in the murine liver.[164] Circadian regulation has been shown for several metabolic processes like xenobiotic detoxification,[165,166] mitochondrion function and lipid and glucose metabolism.[163,167,168] Mice with hepatocyte-specific abrogation of clock function through deletion of BMAL1 display impaired glucose homeostasis but normal body weight regulation.[162] Relatively, mice carrying a dominant negative mutation in the gene encoding the BMAL partner CLOCK$^{\Delta 19}$ are overweight and under HFD conditions develop symptoms of the metabolic syndrome.[169] This obesogenic phenotype is associated with dysregulated feeding rhythms and overeating during the normal rest phase. Also mistimed feeding is associated with the development of obesity in mice and humans.[170-172] In wild-type mice restricting access to an HFD to the night-time improves clock gene rhythms with normalized weight regulation.[170,173] Appetite control and energy expenditure control are centrally controlled and therefore become difficult targets for clinical intervention.[174-176] Metabolic feedback signals from the periphery like leptin and ghrelin, liver-derived factors such as FGF21,[177] and ketone bodies,[178] reach the brain and modulate neuronal circuits to adjust energy metabolism.[179] This bottom-up communication from peripheral metabolic tissue to control regulatory circuits is impaired during obesity.[114,180] Thus Meyer–Kovac investigated metabolic parameters of wild-type (WT) and CLOCK$^{\Delta 19}$ mutant mice (MT) under ad libitum and night time-restricted HFD feeding. Liver circadian clock function was partially rescued by hydrodynamic tail vein delivery of WT clock DNA vectors in mutant mice and transcriptional, metabolic, endocrine and behavioral rhythms studied. They found night time-restricted feeding restored food intake but not body weight regulation in MT mice under HFD, suggesting clock dependent metabolic dysregulation downstream of circadian appetite control. Liver directed clock gene therapy partially restored liver circadian oscillation function and transcriptome regulation without affecting centrally controlled circadian behavior. Under HFD, MT mice with partially restored liver clock function (MT-LR) showed normalized body weight gain, rescued 24 h food intake rhythms and WT like energy expenditure. This was associated with decreased night time leptin and daytime ghrelin levels, decreased hepatic lipid accumulation and improved glucose tolerance. Transcriptomic analyses revealed the hepatic clock rescue in MT mice affecting a range of metabolic pathways. Thus they concluded that liver clock gene therapy improves resistance against HFD induced metabolic impairments in mice with circadian clock disruption. Restoring or stabilizing liver clock function might be a promising target for therapeutic interventions in obesity and metabolic disorders.[181]

ROLE OF KBH1

KBH1 is a novel herbal mixture which consists of Chinese lizards tail (*Saururus chinensis*), turmeric (*Curcuma longa L.*) and Chinese sonega (*Polygala tenuifolia*). Traditionally, in Korea and other countries like China, these herbal medicines have been used for different anti-inflammatory effects, antioxidative effects, neuroprotective effects and the prevention of hypercholesteremia.[182-188] *Saururus chinensis* has been used in folk medicine for the treatment of various inflammatory diseases, gonorrhea, and edema in Korea[189] and exhibits antiasthmatic and anti-inflammatory activities.[190] Also, previous biological studies of *S. chinensis* have established its effects in metabolic diseases including hyperlipidemia, hyperglycemia, neuroprotective and hepatoprotective effects.[191-195] *Curcuma longa* has been used in traditional medicine in China, Korea, India for ages as the main ingredient in prescriptions like *Xia oyao-san* for mental disorders.[196] Also it has been used for the treatment of blood stasis in traditional Korean medicine.[197] *C. longa* is the main ingredient in Gambigyeong sinhwan, which exerts its antiobesity effects through lipid accumulation and adipose PPARα activation[198] and prevents high-fat diet-induced hyperlipidemia as the main ingredient in Artemesia iwayomaga.[199] *Polygala tenifolia* has been used as a traditional Chinese medicine for the treatment of anxiety and dementia[200,201] along with the preventive effect of this on behavioral disorders and inflammatory diseases.[202,203] Lee et al studied the synergistic effect of the herbal mixture of *S. chinensis*, *C. longa* and *P. tenifolia* (KBH1) in obesity and its possible molecular mechanism in obesity-induced hepatic steatosis and leptin resistance in the hypothalamus. They used Hep G2 cells, primary neuronal cells and an HFD induced obesity rat model to determine the effect of KBH1 *in vitro* and *in vivo* on hepatic steatosis and leptin resistance accompanied by obesity. To identify the alleviation effect on lipid accumulation, Hep G2 cells stimulated by FFA were stained with Oilred O, in addition, immunoblotting and qPCR were done to determine the effects of KBH1 on the activation of proteins and nuclear enzymes in Hep G2 cells and the steatotic liver of HFD induced obesity rats. For studying the effect of KBH1 on leptin resistance of hypothalamus and its possible molecular mechanisms they examined the effects of KBH1 on the activation of the leptin resistance related protein in primary cultured cortical neuron cells and the hypothalamus of an HFD induced obesity rat model. In addition, they used HPLC analysis to identify the standard compound of KBH1. KBH1 besides suppressing lipid deposition in Hep G2 cells exposed to FFA, downregulated major factors in lipogenesis and upregulated major factors in lipolysis. Similarly, in an HFD induced obesity model, KBH1 improved hepatic steatosis by alleviating the effects on lipogenic genes and kinases. Additionally, KBH1 markedly improved the leptin-mediated signals impaired by obesity or FFA in the obesity model and primary cultured cortical neuron cells. In addition, KBH1 was analyzed to include 6 standard compounds using HPLG analysis, among

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these compounds, onjisaponin B, and curcumin potently suppressed the levels of triglycerides. Thus, they concluded that KBH1 inhibits alleviating effects by improving hepatic steatosis and leptin resistance by upregulating the activation of AMPK and suppressing the expression of PPARγ. These findings show the potential of KBH1 as a functional food supplement or preventive agent in the treatment of obesity.[204]

ROLE OF AUTOPHAGY DYSFUNCTION IN OBESITY

In animals, chronic intake of HFD causes DIO which leads to insulin and leptin resistance in hypothalamic neurons.[114,205,206] Increased inflammation in the hypothalamus was identified to mediate the development of obesity and the pathways which include IKKB/NFκB pathway[101,207] and upstream inputs such as MYD88,[208,209] endoplasmic reticulum stress[101,207,208] and JNK signaling.[102,210-212] Chronic inflammatory stimuli can also lead to neuronal apoptosis which is important for the anorexigenic response.[213-214] Recently, neuroimaging studies revealed that dysfunctional and neuronal loss were associated with obesity in the hypothalamus of humans and rodents.[215-217] Besides having effects on food intake and energy expenditure HI seems to impair systemic glucose metabolism.Genetic and pharmacological modulation of the ER stress and inflammatory pathways in the hypothalamus affected liver gluconeogenesis.[208,218-219] Inflammatory inhibition of TLR4 or TNFα signaling in the hypothalamus impaired improved insulin signal transduction in the liver and reduced hepatic glucose production.[208] These studies suggest that HI plays a role in weight gain and systemic dysfunction of glycaemic control. Meng and Cai have shown that neuronal autophagy is compromised under conditions of chronic excess fatty acids in the diet. In chow feeding mice, the site-specific inhibition of ATG7 in the MBH lead to autophagy inhibition, impairment of hypothalamic control of energy balance, obesity and HI through IκB activation. In HFD, these metabolic changes got increased along with the progression of insulin and leptin resistance.[220] Normally autophagy is a homeostatic process that occurs in all eukaryotic cells and is needed for degrading damaged proteins as well as organelles.It also sequesters the cytoplasmic components in the double membrane vesicles known as autophagosome.[221] These autophagosomes thus fuse with lysosomes where the damaged proteins and organelles are degraded by lysosomal proteases and recycled.[221-223] If this autophagy is impaired, it may cause inflammation suggesting that autophagy helps in inhibition of inflammatory response[220,224,225] Portovedo hypothesized that obesity may lead to impairment in hypothalamic autophagy in mice. They examined the hypothalamic distribution and content of autophagic proteins in animals with obesity induced by 8 or 16 weeks HFD to induced obesity and in response to ICV injection of palmitic acid. They showed that chronic exposure to an HFD leads to an increased expression of inflammatory markers and downregulation of autophagic proteins. In obese mice autophagic induction leads to the downregulation of proteins like JNK and Bax which are involved in the stress pathways. In neuron cell lines palmitate has a direct effect on autophagy even without inflammation activity. Thus, understanding the cellular and molecular basis of autophagy is important in finding new diagnostic and therapeutic targets for obesity.[226]

CONCLUSIONS

In this review, we have discussed how HI and glioses precede the development of obesity and gradually is associated with loss of anorexigenic POMC neurons tilting the balance towards higher orexigenic AgRP:POMC neuron ratio. During HFD feeding these neurons may be injured by an unknown mechanism and that this injury triggers activation of local glial cell populations (astrocyte and microglia). The neuron injury and reactive glioses can, in turn, impair homeostatic control of body fat stores leading to increased body weight. Further, we discussed the role of HAM-RS2, abscisic acid, KBH1, polyunsaturated fatty acid receptors GPR120 and GPR40 as potential targets for therapeutic interventions in preventing this HI and obesity and future targets for obesity treatment.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Kochar Kaur K, Allahabadia GN, Singh M. An update on Aetiopathogenesis and management of obesity. *Obes Control Ther*. 2016; 3(1): 1-17. doi: 10.15226/2374-8354/2/2/00123

2. Kochar Kaur K, Allahabadia GN, Singh M. Current management of obesity in an infertile female. Recent Advances and Future Prospectives. *Drugs J Pharm Nutr Soc*. 2013; 3: 1-13.

3. Kochar Kaur K, Allahabadia GN, Singh M. Further update on the management of obesity with emphasis on genetic perspective. *BAOJ Obe Weigh Manage*. 2016; 3(1): 1-17.

4. Kochar Kaur K, Allahabadia GN, Singh M. A review on Nutrient Metabolism with special emphasis on fatty acid metabolism. *BAOJ Food Sci Tec*. 2017; 1: 1: 001.

5. Kochar Kaur K, Allahabadia GN, Singh M. Therapeutic implications of the recent understanding of brown or beige adipocyte physiology. *Adv Tech Biol Med*. 2016; 3: 128. doi: 10.4172/2379-1764.1000128

6. Kochar Kaur K, Allahabadia GN, Singh M. Recent advances in BAT/beige physiology-current therapeutic applications. *J Diab and Metab Control*. 2016.

7. Kochar Kaur K, Allahabadia GN, Singh M. An update on miR's in obesity and metabolic dieases-A review. *Metabolomics*. 2014.

8. Kochar Kaur K, Allahabadia GN, Singh M. Hypothalamic in-

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

flammation and gliosis in obesity a etiopathogenesis specially with high fat diet. Proceedings of the World Congress on and Obesity Diabetes and cardiology; 10-12th July, 2017; Dubai, UAE.

9. Thaler JP, Yi CX, Schur EA, et al. Obesity is accociated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012; 122(1): 153-162. doi: 10.1172/JCI59660

10. Lee D, Thaler JP, Berseth KE, Melhorn SJ, Schwartz MW, Schur EA. Longer T2 relaxation timeis a marker of hypothalamic gliosis in mice with diet induced obesity. *Am J Physiol Endocrinol Metab*. 2013; 304(11): E1245-E1250. doi: 10.1152/ajpendo.00020.2013

11. Gyenet SJ, Nguyen HT, Hwang BH, Schwartz MW, Baskin DG, Thaler JP. High fat diet feeding causes rapid, non apoptotic cleavage of caspase 3 in astrocytes. *Brain Res*. 2013; 1512: 97-105. doi: 10.1016/j.brainres.2013.03.033

12. Garcia-Caceres C,Yi CX, Tschop MH. Hypothalamic astrocytes in obesity. *Endocrinol Metab Clin North Am*. 2013; 42(1): 57-66. doi: 10.1016/j.ecl.2012.11.003

13. Morari J, Anhe GF, Nascimento LF, et al. Fractalkaline (CX-3CL1) is involved in the early activation of experimental obesity. *Diabetes*. 2014; 63(11): 3770-3784. doi: 10.2337/db13-1495

14. Valdearcos M, Xu AW, Koliwad SK. Hypothalamic inflammation in the control of metabolic function. *Annu Rev Physiol* 2015; 77: 131-160. doi: 10.1146/annurev-physiol-021014-071656

15. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and insulin resistance: Disringuishing cause from effect. *Trends Endocrinol Metab*. 2010; 2(11): 643-651. doi: 10.1016/j.tem.2010.08.002

16. Parton LE, Ye CP, Coppari R, et al. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. *Nature*. 2007; 449(7159): 228-232. doi: 10.1038/nature06098

17. Kumar RB, Arrone LJ. Hypothalamic inflammation: Is there evidence for human obesity? *Curr Obes Rep*. 2014; 3(2): 242-247. doi: 10.1007/s13679-014-0104-0

18. Briellmann RS, Kalnis RM, Berkovic SF, Jackson GD. Hippocampal pathology in refractory temporal lobe epilepsy: T2 weighted signal changes reflect dentate gliosis. *Neurology*. 2002; 58(2): 265-271.

19. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonates NK, Hickey WF, Schlapfer WW. Brain MR: Pathologic coorelations with gross and histopathology. 2. Hyperintense white matter foci in the elderly. *AJR Am J Roentgenol*. 1988; 151(3): 559-566. doi: 10.2214/ajr.151.3.559

20. Marshall VG, Bradley WG Jr, Marshal CE, Bhoopat T, Rhodes RH. Deep white matter infarction: Correlation of MR imaging and histopathologic findings. *Radiology*. 1988; 167(2): 517-522. doi: 10.1148/radiology.167.2.3357964

21. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the Mcdonald Criteria. *Ann Neurol*. 2005; 58(6): 840-846. doi: 10.1002/ana.20703

22. Third report of the National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation and treatment of high blood cholesterol in adults (Adult treatment Panel III) final report. *Circulation*. 2002; 106(25): 3143-3421.

23. Schur EA, Melhorn SJ, Oh SK, et al. Radiologic evidence that hypothalamic gliosis is associated with obesity and insulin resistance in humans. *Obesity (Silver Spring)*. 2015; 23(11): 2142-2148. doi: 10.1002/oby.21248

24. Douglass JD, Dorfman MD, Thaler JP. Glia: Silent partners in energy homeosrasis and obesity pathogenesis. *Diabetolgia*. 2017; 60(2): 226-236. doi: 10.1007/s00125-016-4181-3

25. Buckman LB, Thomson MM, Moreno HN, Ellacott KLJ. Regional astrogliosis in the mouse hypothalamus in response to obesity. *J Comp Neurol*. 2013; 521(6): 1322-1333. doi: 10.1002/cne.23233

26. Buckman LB, Hasty AH, Flaherty DK, et al. Obesity induced by a high fat dirt is associated with increased immune cellentry into the central nervous system. *Brain Behav Immun*. 2014; 35: 33-42. doi: 10.1016/j.bbi.2013.06.007

27. Berkseth KE, Guyenet SJ, Melhorn SJ, et al. Hypothalamic glioses associated with high fat diet feeding is reversible in mice: A combined immunohistochmical and magnetic resonance imaging study. *Endocrinology*. 2014; 155(8): 2858-2867. doi: 10.1210/en.2014-1121

28. Andre C, Guzman-Quevedo O, Rey C, et al. Inhibiting the microglia expansion prevents diet induced hypothalamic and peripheral inflammation. *Diabetes*. 2017; 66(4): 908-919. doi: 10.2337/db16-0586

29. Buckman LB,Thomson MM, Lippert RN, Blackwell TS, Yuli FE, Ellacott KLJ. Evidence for a novel functional role of astrocytes in the acute homeostatic response to high fat diet intake in mice. *Molecular Metab*. 2015; 4(1): 58-63. doi: 10.1016/j.molmet.2014.10.001

30. Sofroniew MV, Vinters HV. Astrocytes: Biologyand pathology. *Acta Neuropathologia*. 2010; 119(1): 7-35. doi: 10.1007/s00401-009-0619-8

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

31. Yamanaka K, Chun SJ, Bollee S, et al. Astrocytesasdeterminants of disease progression in inherited amyotrophic lateral sclerosis. *Nat Neurosci*. 2008; 11(3): 251-253. doi: 10.1038/nn2047

32. Osborn LM, Kamphuis W, Wadman WJ, Hol EM. Asitrogliosis: An integral player in the pathogenesis of Alzheimers disease. *Prog Neurobiol*. 2016; 144: 121-141. doi: 10.1016/j.pneurobio.2016.01.001

33. Yang L, Qi Y, Yang Y. Astrocyes controlfood intake by inhibiting AgRP neuron activity via adehisine A1 receptors. *Cell Reports*. 2015; 11(5): 798-807. doi: 10.1016/j.celrep.2015.04.002

34. Chen N, Sugihara H, KimJJJ, et al. Direct modulation of GFAP expressing glia in the arxuate nucleus biderectionally regulatesfeeding. *eLife*. 2016; 5: 5599-5609. doi: 10.7554/eLife.18716

35. Kim JG, Suyama S, Koch M, et al. Leptin signaling in astrocytes regulates hypothalamic neuronal circuitsand feeding. *Nature Neurosci*. 2014; 17(7): 908-910. doi: 10.1038/nn.3725

36. Fuente-Martin E, Garcia-Ciceres C, Argentine-Arizon P, et al. Ghrelin regulates glucose and glutamate transporters in hypothalamic astrocytes. *Science Reports*. 2016; 6: 23673. doi: 10.1038/srep23673

37. Reiner DJ, Mietlicki Baase EG, Mcgrath LE, et al. Astrocytes regulate GLP1 receptor mediated effects on energy balance. *J Neuroscience*. 2016; 36(12): 3531-3540. doi: 10.1523/JNEUROSCI.3579-15.2016

38. Garcia-Ciceres C, Quarta C, Varela L, et al. Astrocytic insulin signaling couples brain glucose uptake with nutrient availability. *Cell*. 2016; 166(4): 867-880. doi: 10.1016/j.cell.2016.07.028

39. Douglass JD, Dorfman MD, Fasnacht R, Schaffer LD, Thaler JP. Astrocyte IKKβ/NFκB signaling is required for diet induced obesity and hypothalamic inflammation. *Molecular Metab*. 2017; 6(4): 366-373. doi: 10.1016/j.molmet.2017.01.010

40. Yang Y, Zhou IG, Wu QJ, Ma X, Xiang YB. Association between dietary fiber and lower risk of all cause mortality: A meta-analysis of cohort studies. *Am J Epidemiol*. 2015; 181(2): 83-91. doi: 10.1093/aje/kwu257

41. Slavin R. Dietary fiberand body weight. *Nutrition*. 2005; 21(3): 411-418. doi: 10.1016/j.nut.2004.08.018

42. Wanders AJ, Van den Borne JJ, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: A systematic review of randomized controlled trials. *Obes Rev*. 2011; 12(9): 724-739. doi: 10.1111/j.1467-789X.2011.00895.x

43. Lattimer JM, Haulo MD. Effect of dietary fiber and its components on metabolic health. *Nutrients*. 2010; 2(12): 1266-1289. doi: 10.3390/nu2121266

44. Guynet SJ, Schwatz MJ. Regulation of food intake energy balance and body fat mass: Implications for the pathogenesis and treatment of obesity. *J Clin Endocrinol Metab*. 2012; 97(3): 745-755. doi: 10.1210/jc.2011-2525

45. Malijaars P, Peters H, Mela D, Masclee A. A ilieal break: A sensible food target for appetite control.A review. *Physiol Behav*. 2008; 95(3): 271-281. doi: 10.1016/j.physbeh.2008.07.018

46. Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. *Nature*. 2006; 444(7121): 854-859. doi: 10.1038/nature05484

47. Nilsson AC, Johanson–Boll EV, Bjorck IME. Increased gut hormones and insulin sensitivityindex following a 3-d ntervention with barleykernel based product: A randomized cross over study inhealth middle aged subjects. *Br J Nutr*. 2015; 114(6): 899-907. doi: 10.1017/S0007114515002524

48. Ye Z, Arumugam V, Haugabrooks E, Williamson P, Hendrich S. Soluble dietary fibre (Fibersol-2) decreases hungerand increases satiety hormonesin humans when ingested with a meal. *Nutr Res*. 2015; 35(5): 393-400. doi: 10.1016/j.nutres.2015.03.004

49. Sarda FAH, Giuntini FB, Gomez ML, et al. Impact of resistant starch from unripe banana flour on hunger, satiety and glucose homeostasis in healthy volunteers. *J Func Foods*. 2016; 24: 63-74. doi: 10.1016/j.jff.2016.04.001

50. Vasselli JR, Scarpace PJ, Harris RBS, Banks WA. Dietary components in the development of insulin resistance. *Adv Nutr*. 2013; 4: 164-175. doi: 10.3945/an.112.003152

51. Robertson MD, Bickerton AS, Dennis AI, Vidal H, Frayn KN. Insulin sensitizing effect of dietary resistant starch and effects on skeletal muscleand adipose tissue metabolism. *Am J Clin Nutr*. 2005; 82(3): 559-567.

52. Maki KC, Pelkman CL, Finocchiaro ET, et al. Resistant starch from high amylase maize increases insulin sensitivity in overweight and obese men. *J Nutr*. 2012; 42(4): 717-723. doi: 10.3945/jn.111.152975

53. Robertson MD, Wright JW, Loizon E, et al. Insulin sensitizing effects on muscle and adipose tissue after dietary fiber intake in men and women with metabolis syndrome. *J Clin Endocrinol Metab*. 2012; 297(9): 3326-3332. doi: 10.1210/jc.2012-1513

54. Johnston K, Thomas E, Bell J, Frost G, Robertson M. Resistant starch improves insulin sensitivity in metabolic syndrome.*Diab Med*. 2010; 27(4): 391-397. doi: 10.1111/j.1464-5491.2010.02923.x

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

55. Higgins JA, Higbee DR, Donahoo WT, Brown IL, Bell ML, Bessett DH. Resistant starch consumption promotes lipid oxidation. *Nutr Met*. 2004; 1(1): 8. doi: 10.1186/1743-7075-1-8

56. Ebhihara K, Shiraishi R, Okuma K. Hydroxy propyl-modified potato starch increases fecalbile acid excretion in rats. *J Nutr*. 1998; 128: 848-854.

57. Venkatraman A, Sieber JR, Schmidt AW, et al. Variable responses of human microbiomes to dietary supplementation with resistant starch. *Microbiome*. 2016; 4: 33. doi: 10.1186/s40168-016-0178-x

58. Maziarz MP, Preisendanz S, Juma S, Imrhan V, Prasad C, Vijayagopal P. Resitant starch lowers postprandial glucose and leptin in overweight adults consuming a moderate to high fat diet: A randomized controlled trial. *Nutr Journal*. 2017; 16: 14. doi: 10.1186/s12937-017-0235-8

59. Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPAR alpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab*. 2007; 5(6): 426-437. doi: 10.1016/j.cmet.2007.05.002

60. Inagaki T, Dutchak P, Zhao G, et al. Endocrine regulation of the fasting response by PPAR alpha mediated induction of fibroblast growth factor 21. *Cell Metab*. 2007; 5: 415-425. doi: 10.1016/j.cmet.2007.05.003

61. Potthoff MJ, Inagaki T, Satapati S, et al. FGF21 induces PGC-1 alpha and regulates carbohydratesand fatty acid metabolism during the adaptive starvation response. *Proc Natl Acad Sci USA*. 2009; 106: 10853-10858. doi: 10.1073/pnas.0904187106

62. Potthoff MJ, Kliewer SA, Mangelsdorf DJ. Endocrine fibroblast growth factor 15/19 and 21 from feast to famine. *Genes Dev*. 2012; 26: 312-324. doi: 10.1101/gad.184788.111

63. Laeger T, Henagan TM, Albarado DC, et al. FGF21 is an endocrine signal of protein restriction. *J Clin Invest*. 2014; 124: 3913-3922. doi: 10.1172/JCI74915

64. DeSouza–Coelho AL, Marrero PF, Haro D. Activating transcription factor4 dependent induction of FGF21 during amino acid deprivation. *Biochem J.* 2012; 443: 165-171. doi: 10.1042/BJ20111748

65. Wek SA, Zhu S, Wek RC. The histidyl-tRNA synthetaserelated sequencein the Eif2alpha protein kinase GCN2 interacts with Trna and is required foractivation in response to starvation for different amino acids. *Mol Cell Biol*. 1995; 15: 4497-4506. doi: 10.1128/MCB.15.8.4497

66. Xiao F, Huang Z, Li H, et al. Leucine deprivation increases hepatic insulin sensitivity via GCN2/Mtor/S6K1 and AMPK pathways. *Diabetes*. 2011; 60: 746-756. doi: 10.2337/db10-1246

67. Zhang P, McGrath BC, Reinert J, et al. The GCN2Eif2 alpha kinase is required for adaptation to amino acid deprivationin mice. *Mol Cell Biol*. 2002; 22: 6681-6688. doi: 10.1128/MCB.22.19.6681-6688.2002

68. Kim KH, Jeong YT, Kim SH. Metformin induced inhibition of the mitochondrial respiratory chain increases FGF21 expression via ATF4 activation. *Biochem Biophys Res Commun*. 2013; 440: 76-81. doi: 10.1016/j.bbrc.2013.09.026

69. Schaap HG, Kremer AE, Lamers WH, Jansen PL, Gaemers IC. Fibroblast growth factor 21 is induced by endoplasmic reticulum stress. *Biochimie*. 2013; 95: 692-699. doi: 10.1016/j.biochi.2012.10.019

70. Wilson GJ, Lennox BA, She P, et al. GCN2 is required to increase fibroblast growth factor 21 and maintain hepatic triglyceride homeostasis during asparaginase treatment. *Am J Physiol Endocrinol Metab*. 2015; 308(4): E283-E293. doi: 10.1152/ajpendo.00361.2014

71. Laegar T, Albarado DC, Burke SJ, et al. Metabolic responses to dietary protein restriction require an increasein FGF21 that is delayed in absence of GCN2. *Cell Rep*. 2016; 16(3): 707-716. doi: 10.1016/j.celrep.2016.06.044

72. Hartmann P, Ramseier A, Gundat F, Mihatsch MJ, Polasek W. Normal weight of the brain in adults in relation to age, sex body height and weight. *Pathologie*. 1994; 15: 165-170.

73. Peters A, Schweiger U, Pellerin L, et al. The selfish brain: Competition for energy resources. *Neurosci Behav Rev*. 2004; 28: 143-180. doi: 10.1016/j.neubiorev.2004.03.002

74. Sokoloff L, Reivich M, Kennedy C, et al. The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anaesthetized albino rat. *J Neurochem*. 1977; 23: 897-916. doi: 10.1111/j.1471-4159.1977.tb10649.x

75. Edmond J. Energy metabolism in developing brain cells. *Can J Physiol Pharmacol.* 1992; 70(S1): S118-S129. doi: 10.1139/y92-253

76. Yi CX, Habegger KM, Chowen JA, Stern J, Tscop MH. Arole for astrocytes in the central control of metabolism. *Neuroendocrinology*. 2011; 93: 143-149. doi: 10.1159/000324888

77. Abbott NJ, Revest PA, Romero IA. Astrocyte oendothelial interaction: Physiology and pathology. *Neuropathol Appl Neurobiol*. 1992; 18: 424-433. doi: 10.1111/j.1365-2990.1992.tb00808.x

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

78. Tsacopolous M, Magistretti PJ. Metabolic coupling between glia and neurons. *J Neurosci*. 1996; 16: 877-885.

79. Liu B, Niu L, Shen MZ, et al. Decreased astroglial monocarboxylate transporter 4 expression in temporal lobe epilepsy. *Mol Neurobiol*. 2014; 50: 327-338.

80. Pellerin L, Magistretti PJ. Glutamate uptake into astrocytes stimulates aerobic glycolysis: A mechanism coupling neuronal activity to glucose utilization. *Proc Natl Acad Sci U S A*; 91: 10625-10629.

81. Perea G, Navarette M, Araque A. Tripartite synapses: Astrocytes process and control synaptic information. *Trends Neurosci*; 32(8): 421-431. doi: 10.1016/j.tins.2009.05.001

82. Pellerin L, Magistretti PJ. Sweet sixteen for ANLS. *J Cereb Blood Flow Metab*. 2012; 32: 1152-1166. doi: 10.1038/jcbfm.2011.149

83. Pellerin L, Pellegri G, Bittar PG, et al. Evidence supporting the existence of an activity dependent astrocyte–neuron lactate shuttle. *Dev Neurosci*. 1998; 20: 291-299.

84. Blanger M, Allaman I, Magistretti PJ. Brain energy metabolism: Focus on astrocyte–neuron metabolic cooperation. *Cell Metab*. 2011; 14: 724-738. doi: 10.1016/j.cmet.2011.08.016

85. LeFoll C, Dunn Meynell AA, Miziorko HM, Levin BE. Regulation of hypothalamic neuronal sensing and food intake by ketone bodies and fatty acids. *Diabetes*. 2014; 63: 1259-1269. doi: 10.2337/db13-1090

86. LeFoll C, Dunn Meynell AA, Miziorko HM, Levin BE. Role of VMH ketone bodiesin adjusting caloric intaketo increased dietary fat content in DIO and DR rats. *Am J Physiol Regul Integr Comp Physiol*. 2015; 308: R872-R878. doi: 10.1152/ajpregu.00015.2015

87. Belanger M, Allaman I, Magistretti PJ. Brain energy metabolism: Focus on astrocyte neuron metabolic cooperation. Ce*ll Metab*. 2011; 14: 724-738. doi: 10.1016/j.cmet.2011.08.016

88. LeFoll C, Levin BE. Fatty acid-induced astrocyte ketone production and the control of food intake. *Am J Physiol Regul Integr Comp Physiol*. 2016; 310(11): R1186-R1192. doi: 10.1152/ajpregu.00113.2016

89. Serhari CN, Savill J. Resilution of inflammation: The beginning programs the end. *Nat Immunol*. 2005; 6: 191-197. doi: 10.1038/ni1276

90. Takano T, Clish CB, Gronert K, Pertasis N, Serhan CN. Neutrophil mediated changes in vascular permeabilityare inhibited by topical applications of asprin triggered 15-epi-lipoxin A4 and novel lipoxin B4 stable analogues. *J Clin Invest*. 1998; 101: 819-826. doi: 10.1172/JCI1578

91. Serhan CN, Hong S, Gronert K, et al. Resolvins: A family of bioactive products of omega-3 fatty acid transformation circuits initiated by asprin treatment that counter proinflammatory signals. *J Exp Med*. 2002; 106: 1025-1037.

92. Arita M, Bianchini J, Alberti J, et al. Stereochemical assignment ,anti-inflammatory properties and receptor for omega3 lipid mediator resolvin E1. *J Exp Med*. 2005; 201: 713-722. doi: 10.1084/jem.20042031

93. Serhan CN, Gotlinger K, Hong S, et al. Resolving inflammation: Dual antiinflammatory actions of neuroprotectin D1/Protectin D1 and its natural stereoisomer assignments of dihydroxy containing docosatrienes. *J Immunol*. 2006; 176: 1848-1859.

94. Serhan CN, Chang N, Van Dyke TE. Resolving inflammation: Dual antiinflammatory and proresolution lipid mediators. *Nat Rev Immunol*. 2008; 8: 349-361. doi: 10.1038/nri2294

95. Chung H, Fredman G, Backhed F, et al. Infection regulates proresolving mediators that lower antibiotic requirements. *Nature*. 2012; 484: 524-528.

96. Norling IV, Dalli J, Flower RJ, Serhan CN, Perretti M. Resolvin D1 limits polymorphonuclear leukocytes-recruitment to inflammatory loci: Receptor dependent actions. *Arterioscler Thromb Vasc Biol*. 2012; 232: 1970-1978. doi: 10.1161/ATVBAHA.112.249508

97. Claria J, Dalli J, Yacoubian S, Gao F, Serhan CN. Resolvin D1 and resolvin D2 govern local inflammatory tone in obese fat. *J Immunol*. 2012; 189: 2597-2605. doi: 10.4049/jimmunol.1201272

98. Neunofer A, Zeyda M, Mascher D, et al. Impaired local production of proresolving lipid mediators in obesity and 17HDHA as a potential treatment for obesity associated inflammation. *Diabetes*. 2013; 62: 1945-1956. doi: 10.2337/db12-0828

99. Moraes JC, Coope A, Morari J, et al. High fat diet induces apoptosis of hypothalamic neurons. *PLoS One*. 2009; 4: e5045. doi: 10.1371/journal.pone.0005045

100. Milanski M, Dejasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: Implications for the pathogenesis of obesity. *J Neurosci*. 2009; 29: 359-370. doi: 10.1523/JNEUROSCI.2760-08.2009

101. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKK beta /NF kappa B and ER stress links overnutrition to energy balancend obesity. *Cell*. 2008; 13561-13573. doi: 10.1016/j.cell.2008.07.043

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

102. DeSouza-CT, Araujo EP, Bordin S, et al. Consumption of a fat rich diet activates a proinflammatory response and induces insulin resistancein the hypothalamus. *Endocrinology*. 2005; 146: 4192-4199. doi: 10.1210/en.2004-1520

103. Velloso LA, Folli F, Saad MJ. TLR4 at the crossroads of nutrients, gut microbiotaand metabolic inflammation. *Endocr Rev.* 2015; 36: 245-271. doi: 10.1210/er.2014-1100

104. Ignacio-Souza LM, Bonbassaro B, Pascol LB, et al. Defective regulation of the ubiquitin/proteasome system in the hypothalamus of obese male mice. *Endocrinology*. 2014; 155: 2831-2844. doi: 10.1210/en.2014-1090

105. Romanatto T, Roman EA, Arruda AP, et al. Deletion of tumor necrosis factor alpha receptor (TNFR1) protects against diet induced obesity by means of increased thermogenesis. *J Biol Chem*. 2009; 284: 36213-36222. doi: 10.1074/jbc.M109.030874

106. Cintra DE, Ropelle ER, Moraes JC, et al. Unsaturated fatty acids reverse diet induced hypothalamic inflammation in obesity. *PLoS One*. 2012; 7: e30571. doi: 10.1371/journal.pone.0030571

107. Nascimento LF, Souza GF, Morari J, et al. Omega 3 fatty acids induce neurogenesis of predominantly POMC expressing cells in the hypothalamus. *Diabetes*. 2016; 65: 673-686. doi: 10.2337/db15-0008

108. Pascoal LB, Bombasarro B, Ramalho AF, et al. Resolvin RvD2 reduces hypothalamic inflammation and rescues mice from diet induced obesity. *J Neuroinflammation*. 2015; 14: 5. doi: 10.1186/s12974-016-0777-2

109. Hotamisligil GS. Inflammation and endoplasmic reticulum stress in obesity and diabetes. *Int J obese (Lond)*. 2008; 32(Suppl 7): 552-554. doi: 10.1038/ijo.2008.238

110. Hill JQ, Peters JC. Environmental contributions to the obesity epidemic. *Science*. 1998; 280: 1371-1374. doi: 10.1126/science.280.5368.1371

111. Flier JS. Obesity wars: Molecular progress confronts an expanding epidemic. *Cell*. 2004; 116: 337-350. doi: 10.1016/S0092-8674(03)01081-X

112. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunityand fatty acid induced insulin resistance. *J Clin Invest*. 2006; 116: 3015-3025. doi: 10.1172/JCI28898

113. Velloso LA, Fiznick DL, Croop M. Type2 diabetes mellitus-An autoimmune disease? *Nat Rev Endocrinol*. 2013; 9: 750-755. doi: 10.1038/nrendo.2013.131

114. Osborn O, Olefsky JM. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat Med*. 2012; 18: 363-374. doi: 10.1038/nm.2627

115. Velloso LA, Shwartz MW. Altered hypothalamic function in diet induced obesity. *Int J obese(Lond)*. 2011; 35: 1455-1465. doi: 10.1038/ijo.2011.56

116. Fiznick DE, Cardozo AK, Crop M. The role for endoplasmic reticulum stressin diabetes mellitus. *Endocr Rev*. 2008; 29: 42-61.

117. Crop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesityand diabetes. *Trends Mol Med*. 2012; 18: 59-68. doi: 10.1016/j.molmed.2011.07.010

118. Samuel VT, Schulmn GI. Mechanisms for insulin resistance: Common threads and missing links. *Cell*. 2012; 148: 852-871. doi: 10.1016/j.cell.2012.02.017

119. Donathan MY, Shoelson SE. Type 2 diabetes mellitus as an inflammatory disease. *Nat Rev Immunol*. 2011; 11: 98-107. doi: 10.1016/j.diabres.2006.06.007

120. Cregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol*. 2011; 29: 415-445. doi: 10.1146/annurev-immunol-031210-101322

121. McNeils JC, Olefsky JM. Macrophages, immunity and metabolic disease. *Immunity*. 2014; 41: 36-48. doi: 10.1016/j.immuni.2014.05.010

122. Goldfine AB, Fonseca V, Jablonski KA, et al. Targeting inflammation using salsalate in patients with type 2 diabetes: A randomized trial. *Annu Intern Med*. 2013; 159: 1-12. doi: 10.2337/dc13-0859

123. Nagasumi K, Esaki R, Iwachidow K, et al. Overexpression of GPR40 in pancreatic beta cells, augments glucose –stimulated insulin secretion and improves glucose tolerance in normal and diabetic mice. *Diabetes*. 2009; 58: 1067-1076. doi: 10.2337/db08-1233

124. Oh DY, Takukdar S, Kae EJ, et al. GPR120 ia an omega 3 fatty acid receptor mediating potent anti-inflammatory and insulin sensitizing effects. *Cell*. 2010; 142: 687-698. doi: 10.1016/j.cell.2010.07.041

125. Cinitra DE, Ropelle ER, Moraes JC, et al. Unsaturated fatty acidsrevert diet induced hypothalamic inflammation in obesity. *PLoS One*. 2012; 7: e30571. doi: 10.1371/journal.pone.0030571

126. Itoh Y, Kuwamata Y, Harada M, et al. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature*. 2003; 422: 173-176. doi: 10.1038/nature01478

127. Oh DY, Olefsky JM. Omega 3 fatty acids and GPR120. *Cell Metab*. 2012; 15: 564-565. doi: 10.1016/j.cmet.2012.04.009

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

128. Da Oh Y, Walenta I, Akiyama TE, et al. GPR120 selective agonists improves insulin resistance and chronic inflammation in obese mice. *Nat Med*. 2014; 20: 942-947. doi: 10.1038/nm.3614

129. Burant CF. Activation of GPR40 as a therapeutic target for the treatment of diabetes. *Diabetes Care*. 2013; 36 (Suppl 2): 5175-5179. doi: 10.2337/dcS13-2037

130. Briscoe CP, Tadayyon M, Andrews JL, et al. The orphan G protein coupled receptor GPR40 is activated by median and long chain fatty acids. *J Biol Chem*. 2003; 278: 11303-11311.

131. Briscoe CP, Peat AJ, Mckeown SC, et al. Pharmacological regulation of insulin secretion in MIN 6 cells through the fatty acid eceptor GPR40: Identification of agonist and antagonist small molecules. *Br J Pharmacol*. 2006; 148: 619-628. doi: 10.1038/sj.bjp.0706770

132. Fdfalk S, Steneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acidsstimulation of incretin secretion. *Diabetes*. 2008; 57(9): 2280-2287. doi: 10.2337/db08-0307

133. Boneva NB, Yamashima T. New insights into GPR40-CREB interactions in adult neurogenesis specific for primates. *Hippocampus*. 2012; 22(4): 296-305. doi: 10.1002/hipo.20951

134. Dragano NRV, Solon C, Ramalho AF, et al. Polyunsaturated fatty acids receptors, GPR40 and GPR120, are expressed in the hypothalamus and control energy homeostasis and inflammation. *J Neuroinflammation*. 2017; 14: 91. doi: 10.1186/s12974-017-0869-7

135. Le-Page-Devigry MT, Bidard JN, Rouvier F, Bulari C, Lazdunski M. Presence of abscicic acid, a phytohormonein the mammalian brain. *Proc Natl Acad Sci U S A*. 1986; 83: 1155-1158.

136. Minorsky PV. Abscicic acid, a universal signaling factor? *Plant Physiol*. 2007; 128: 788-789.

137. Gomez-Cadenas A, Vives V, Zandalinas SI, et al. Abscisic acid and a versatile phytohormone in plant signaling and beyond. *Curr Prot Papt Sci*. 2015; 16(5): 13-34. doi: 10.2174/1389203716666150330130102

138. Magnone M, Ameri P, Salis A, et al. Microgram amounts of abscicic acid in fruit extract improves glucose tolerance and reduces insulin secretionin rats and in human. *FASEB J*. 2015; 29: 4783-4793. doi: 10.1096/fj.15-277731

139. Fuce S, Barsile G, Bavestrello G, et al. Abscicic acid signaling through cyclic ADP-ribose in hydroid regeneration. *J Biol Chem*. 2004; 279: 39783-39788. doi: 10.1074/jbc.M405348200

140. Bassanganya-Rera J, Shoneckza J, Kingston DG, et al. Mechanism of action and medicinal application of abscicic acid. *Curr Med Chem*. 2010; 17: 457-478. doi: 10.2174/092986710790226110

141. Bruzzone S, Rodato N, Usai C, et al. Abscicic acid is an endogenous stimulator of insulin release from human pancreatic islets with cyclic ADP-ribose as second messenger. *J Biol Chem*. 2008; 283: 32188-32197. doi: 10.1074/jbc.M802603200

142. Gun AJ, Evans NP, Honterollas R, Bassanganya-Rera J. T cell PPAR γ is required for the anti-inflammatory effecicacy of abscicic acidagainst experimental IBD. *J Nutr Biochem*. 2011; 22: 812-819. doi: 10.1016/j.jnutbio.2010.06.011

143. Sturla L, Fresia C, Guida I, et al. LANCL2 is necessary forabscicic acid binding and signaling in human granulocytes and in rat insulinoma cells. *J Biol Chem*. 2009; 284: 28045-28057. doi: 10.1074/jbc.M109.035329

144. Lu P, Hontecillas R, Philipson CW, Bassanganya-Rera J. Lanthionine synthetase components C like protein 2 a new drug target forinflammatory diseases and diabetes. *Curr Drug Targets*. 2014; 15(6): 565-572. doi: 10.2174/1389450115666140313123714

145. Brenner JD, Shearer KD, McCaffery PJ. Retinoic acid and affective disorders:the evidence for an association. *J Clin Psychiatry*. 2012; 73: 37-50. doi: 10.4088/JCP.10r05993

146. Qi CC, Zhang Z, Fang H, et al. Antidepressant effects of abscicic acid mediated by the downregulation of corticotrophic realeasing hormone gene expression in rats. *Int J Neuropsychopharmacol*. 2014; 18(4): pyu006. doi: 10.1093/ijnp/pyu006

147. Gao Y, Ottaway N, Shriever SC, et al. Hormones and diet but not body weight controlypothalamic microglial circuitry. *Glia*. 2014; 62: 17-25. doi: 10.1002/glia.22580

148. Spielman LL, Little JP, Klegeris A. Inflammation and insulin/IGF1 resistance as the possible link between obesity and neurodegeneration. *J Neuroimmuol*. 2014; 273: 8-21. doi: 10.1016/j.jneuroim.2014.06.004

149. Sobesky JL, Barrientos RM, De May HS, et al. High fat diet consumption disrupts memory and primes elevations in hippocampal IL-1β an effect that can be prevented by dietary reversal or IL1 receptor antagonist. *Brain Behav Immun*. 2014; 20: 142: 22-32. doi: 10.1016/j.bbi.2014.06.017

150. Sanchez-Sarua S, Moustafa S, Garcia-A.viles A, et al. The effect of acscicic acid chronic treatment on neuroinflammatory markers and memory in a rat model of high fat diet induced neuroinflammation. *Nutr Metab*. 2016; 13: 73. doi: 10.1186/s12986-016-0137-3

151. Tseng AH, Barclay JL, Oster H. Interactions between endocrine and circadian systems. J of Mol Endocrinol. 2014; 52: R1-R6. doi: 10.1530/JME-13-0118

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

152. Bass J, Takahashi JS. Circadian integration and energetic. *Science*. 2010; 230: 1349-1354.

153. Ueda HR, Chon W, Adachi A, et al. A Transcription factor response elementfor gene expression during circadian night. *Nature*. 2002; 418: 534-539. doi: 10.1038/nature00906

154. Panda S, Antoch MP, Miller RH, et al. Coordinated transcription of key pathways in the mouse by circadian clock. *Cell*. 2002; 109: 307-320. doi: 10.1016/S0092-8674(02)00722-5

155. Golombek DA, Rosenstein RE. Physiology of circadian entrainment. *Physiol Rev*. 2010; 90: 1063-1102.

156. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: Organization and coordination of central and peripheral clocks. Annual Reviews of Physiology. 2010; 72: 517-549. doi: 10.1146/annurev-physiol-021909-135821

157. Vollmers C, Gill S, Di Tacchio I, Pulivarthy SR, Le HD, Panda S. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *Proc Natl Acad Sci U S A*. 2009; 106: 21453-21458. doi: 10.1073/pnas.0909591106

158. Li Y, Sato Y, Yamaguchi N. Shift work and the risk of metabolic syndrome: A nested case control study. *Int J Occup Environ Health*. 2011; 17: 154-160. doi: 10.1179/107735211799030960

159. Karisson B, Knulsson A, Lindani B. Is there an association between shiftwork and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup Environ Med*. 2001; 58: 747-752. doi: 10.1136/oem.58.11.747

160. Barclay JL, Husse J, Bode B, et al. Circadian desynchrony promotesmetabolic disruption in a mouse model of shift work. *PLoS One*. 2012; 7: e37150. doi: 10.1371/journal.pone.0037150

161. Foster RG, Kretzman L. The rhythms of life: What your body clock means to you! *Exp Physiol*. 2014; 99: 599-606. doi: 10.1113/expphysiol.2012.071118

162. Jones SG, Benca RM. Circadian disruption in psychiatric disorders. *Sleep Medicine Clinics*. 2015; 10: 481-493. doi: 10.1016/j.jsmc.2015.07.004

163. Lamia KA, Storch KF, Weitz CJ. Physiological significance of a peripheraltissue circadian clock. *Proc Natl Acad Sci U S A*. 2008; 105: 15172-15177. doi: 10.1073/pnas.0806717105

164. Zhang D, Tong X, Arthurs B, et al. Liver clock protein BMAL1 promotes de novo lipogenesis through insulin Mtorc-AKT signaling. *J Biol Chem*. 2014; 289(37): 25925-25935; doi: 10.1074/jbc.M114.567628

165. Rey G, Cesbron F, Rougemont J, Reinke H, Brunner M, Naef F. Genome wide and phase specific DNA binding rhythms of BMAL1 controlcircadian output functions in mouse liver.*PLoS Biology*. 2011; 9: e1000595. doi: 10.1371/journal.pbio.1000595

166. Gachon F, Oiela FF, Schaad O, Descombes P, Scabier U. The circadian PAR- domain basic leucinezipper transcription factors DBP, TEF and HLF modulate basal and inducible xenobiotic detoxification. *Cell Metb*. 2006; 4: 25-36. doi: 10.1016/j.cmet.2006.04.015

167. De Boyne JP, Weaver DR, Dallman R. The hepatic circadian clock modulates xenobiotic metabolism in mice. *J Biol Rhythms*. 2014; 29: 277-287. doi: 10.1177/0748730414544740

168. Fuku K, Ferris HA, Kahn CR. Effect of cholesterol reduction on receptor signaling in neurons. *J Biol Chem*. 2015; 290: 26383-26392. doi: 10.1074/jbc.M115.664367

169. Grechez-Cassau A, Rayet B, Guillamond F, Teboui M, Delaumay F. The circadian clock component BMAL1 ia a critical regulator of p21WAF1/CIP1 expression and hepatocyte proliferation. *J Biol Chem*. 2008; 283: 4535-4542. doi: 10.1074/jbc.M705576200

170. Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian clock mutant mice. *Science*. 2005; 308: 1043-1045. doi: 10.1126/science.1108750

171. Arble DM, Sandova DA. CNS controlof glucose metabolism response to environmental challenges. *Front Neurosci*. 2013; 7: 20. doi: 10.3389/fnins.2013.00020

172. Rubic RD, McNamara P, Curtis AM, et al. BMAL1 and CLOCK-two established components of the circadian clock, are involved in glucose homeostasis. *PLoS Biology*. 2004; 2: e377. doi: 10.1371/journal.pbio.0020377

173. Barclay JL, Shostak A, Lelavski A, et al. High fat diet induced hyperinsulinemia and tissue specific insulin resistance in cry deficient mice. *Am J Physiol Endocrinol Metab*. 2013; 104: E1053-E1063. doi: 10.1152/ajpendo.00512.2012

174. Sherman H, Genzer Y, Cohen R, Channik N, Madat Z, Froy O. Timed high fat diet resets circadian metabolism and prevents obesity. *FASEB J*. 2012; 26: 3493-3502. doi: 10.1096/fj.12-208868

175. Cornejo MP, Hentges ST, Maliqueo M, Corini H, Racu-Wilacbos D, Elias CF. Neuroendocrine regulation of metabolism. *J Neuroendocrinol*. 2016; 28(7): doi: 10.1111/jne.12395

176. Waterson MJ, Horvath TL. Neuronal regulation of energy homeostasis. *Cell Metab*. 2015; 22: 962-970. doi: 10.1016/j.cmet.2015.09.026

177. Horvath TL, Diano S, Tschop M. Brain circuits regulating energy homeostasis. *Neuroscientist*. 2004; 10: 235-246. doi: 10.1016/j.regpep.2007.10.006

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

178. Xu J, Lloyd DJ, Hale C, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure and improves insulin sensitivity in diet induced obese mice. *Diabetes*. 2009; 58: 250-258. doi: 10.2337/db08-0392

179. Dhawan R, Fellet C, Costa SS, et al. Liver derived ketone bodies are necessary for food anticipation. *Nat Commun*. 2016; 7: 10580. doi: 10.1038/ncomms10580

180. Schwartz MW, Woods SC, Porte Jr C, Seeley BJ, Baskin DG. Central nervous system control of food intake. *Nature*. 2000; 404: 661-671. doi: 10.1038/35007534

181. Yi CX, Tschop MH. Brain-gut-adipose tissue communication pathways at a glance. *Dis Model Mech*. 2012; 5: 583-587. doi: 10.1242/dmm.009902

182. Meyer-Kovac J, Kolbe I, Ehrhardt L, et al. Hepatic gene therapy rescues high fat diet responses in circadian Clock mutant mice. *Molecular Metab*. 2017; 6: 512-523. doi: 10.1016/j.molmet.2017.03.008

183. Li C, Yang J, Yu S, et al. Triterperiod sapponins with neuroprotective effects from the roots of Polygala Tenuifolia. *Planta Med*. 2008; 74(2): 133-141.

184. Jiang Y, Zhang W, Tu F, Xu X. Polygala Tenuifolia. And their conformational analysis. *J Nat Prod*. 2005; 68(6): 875-879.

185. Le TK, Jeong JJ, Kim DH. Clionosterol and ethyl cholestan-22-enolisolated from the rhizome of Polygala Tenuifolia inhibit phosphatidylinositol-3kinase'/Akt pathway. *Mol Pharm Bull*. 2012; 35(8): 1379-1383. doi: 10.1248/bpb.b12-00426

186. Pari L, Tewas D, Eckel J. Role of curcumin in health and disease. *Arch Physiol Biochem*. 2008; 114(2): 127-149. doi: 10.1080/13813450802033958

187. Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway indiabetic albino rats. *Plants Foods Hum Nutr*. 2002; 57(1): 41-52. doi: 10.1023/A:1013106527829

188. Ramadan G, Al-Kahtani M, El Sayed WM. Antiinflammatory ans antioxidant properties of Curcuma longa (turmeric) versus Zingiber officinale (ginger) rhizomes in rat adjuvant induced arthritis. *Inflammation*. 2011; 34(4): 291-301. doi: 10.1007/s10753-010-9278-0

189. YuWF, Kwan PL, Wong CY, et al. Attenuation of fatty liverand prevention of hypercholesterolemia by extreact of curcumina longa through regulating the expression of CYP7A1, LDL-receptor HO-1 and HMG-COA reductase. *J Food Sci*. 2011; 76(3): 1180-1189. doi: 10.1111/j.1750-3841.2011.02042.x

190. Chung BS, Chin MG. *Dictionary of Korean Folk Medicine*. Incheon, South Korea: Young Lim Publishing Co Ltd; 1990: 813-914.

191. Wang ES, Zhao DQ, Cheng DY, Liu YH. Ent-Sauchinone from Saurus chinensis. *Heterocytes*. 2008; 75(5): 1241-1246.

192. Yu MH, Im HG, Lee JW, et al. Effects of ehanol extract from Saurus chinensis (Bour) Baill on lipid and antioxidantmetabolism in rats fed a high fat diet. *Nat Prod Res*. 2008; 22(3): 275-283. doi: 10.1080/14786410701590657

193. Yun YR, Kim MJ, Kwon MJ, Kim HA, Song KB, Song YO. Lipid lowering effect of hot water soluble extracts of Saurus chinensis Bail on rats fed high fat diet. *J Med Food*. 2007; 10(2): 316-322. doi: 10.1089/jmf.2006.149

194. Joo HJ, Kang MJ, Seo TJ, et al. The hypoglycaemic effect of Saurus chinensis Bail in animal models of diabetes mellitus.*Food Sci Biotechnol*. 2006; 15(3): 413-417. doi: 10.1017/S0022029914000582

195. Kim SR, Sung SH, Kang SY, et al. Aristolactam Bill OF Saurus chinensis attenuates glutamate induced neurotoxicityin rat cortical cultures probably by inhibiting nitric oxide production. *Plant Med*. 2004; 70(5): 391-396.

196. Sung SH, Kim YC. Hepatoprotective diasteromeric lignanas from Saurus chinensis herbs. *J Natl Prod*. 2000; 63(7): 1019-1021. doi: 10.1021/np990499e

197. Zhu X, Jing I, Chen C, et al. Danzhi Xiaoyao San amelioratesdepressive–like behavior by shifting toward serotonin via the downregulation of hippocampal indoleamin e2,3 dioxygenase. *J Ethnopharmacol*. 2015; 160: 86-93. doi: 10.1016/j.jep.2014.11.031

198. Oh HI, Park HB, Ju MS. Comparitive study of antioxidant and antiinflammatoryactivities between curcumin longae radix and curcumin longae rhizona. *Korea J Herbology*. 2010; 25(1): 83-91.

199. Roh JS, Lee H, Woo S, et al. Herbal composition Gambigyeeongsihwan (4) from curcumin longa Alnusjaponica, and Massa Medicata fermentata inhibits lipid accumulation in 3T3L1 cells and regulates obesity in Otsuka long Evans Tokushima fatty rats. *J Ethno Pharmacol*. 2015; 171: 287-294. doi: 10.1016/j.jep.2015.05.056

200. Has JM, Lee JS, Kim HG, et al. Synergistic effects Artermisia Imayomogi and curcumin longae radix on high fat dietinduced hyperlipidemia in a mouse model. *J Ethno pharmacol*. 2015; 173: 217-224. doi: 10.1016/j.jep.2015.07.021

201. Huang KC. *The Pharmacology of Chinese Herbs*. Boca Ratnon, FL, USA: CRC Press; 1991.

202. College JNM. *Dictionary of Chinese Drugs Shanghai*. HongKong Island, Hong Kong: Shanghai Scientific Technologic Publisher; 1997

ISSN 2377-8385 http://dx.doi.org/10.17140/OROJ-4-132

203. Chen YL, Hsieh CL, Wu PH, Lin JC. Effect of polygala tenuifolia on behavioral disorders of lesioning nucleus basalis magnocellularis in rat. *J Ethno pharmacol*. 2004; 95(1): 47-55. doi: 10.1016/j.jep.2004.06.015

204. Spelman K, Burns J, Nichols D, Winters N, Offersberg N, Fenninnorg M. Modulation of cytokine expression by traditional medicines: A review of herbal immunomoodulators. *Alter Med Rev.* 2006; 11(2): 128-150. doi: 10.1016/j.jep.2015.07.021

205. Lee JH, Lee JJ, Cho WK, et al. KBH1, an herbal composition, improves hepatic steatosis and leptin resistance in high fat diet induced obese mice. *BMC Complement Altern Med*. 2016; 16: 355. doi: 10.1186/s12906-016-1265-z

206. Milanski M, Degasperi G, Coope A, et al. Satturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamic implications for the pathogenesis of obesity. *J Neurosci*. 2004; 29(2): 359-370. doi: 10.1523/JNEUROSCI.2760-08.2009

207. Schwartz MW, Porte D Jr. Diabetes, obesity and the brain. *Science*. 2005; 21: 307(5708): 375-379. doi: 10.1126/science.1104344

208. Williams KW, Elmquist JK. From neuroanatomy to behavior: Central integration of peripheral signals regulating feeding behavior. *Nat Neurosci*. 2012; 15(10): 1350-1355. doi: 10.1038/nn.3217

209. Purkayastha S, Zhang H, Zhang G, Ahmed Z, Wang Y, Cai D. Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. *Proc Natl Acad Sci U S A*. 2011; 108: 2939-2944. doi: 10.1073/pnas.1006875108

210. Kleinridders A, Schenlen D, Konner AC, et al. MyD88 signaling in the CNS is required for development of fatty acid induced leptin resistance and diet induced obesity. *Cell*. 2009; 10: 249-259. doi: 10.1016/j.cmet.2009.08.013

211. Belgardt BF, Mauer J, Wunderlich FT, et al. Hypothalamic and pituitary c-jun N terminal kinase 1 signaling coordinately regulates glucose metabolism. *Proc Nat Acad Sci U S A*. 2010; 107: 6028-6033. doi: 10.1073/pnas.1001796107

212. Sabio G, Cavanagh-Kyros J, Barett T, et al. Role of the hypothalamic-pituitary-thyroid axis in metabolic regulationby JNK1. *Genes Dev*. 2010; 24: 256-264. doi: 10.1101/gad.1878510

213. Unger EK, Piper ML, Olofsson LE, Xu AW. Functional role of c-jun-N terminal kinase in feeding regulation. *Endocrinology*. 2010; 151: 671-682. doi: 10.1210/en.2009-0711

214. Moraes JC, Coope A, Morari J, et al. High fat diet induces apoptosis of hypothalamic neurons. *PLoS One*. 2009; 4(4): 5045. doi: 10.1371/journal.pone.0005045

215. McNay DE, Briancon N, Kokoeva MV, Maralos-Flier E, Flier JS. Remodeling of the arcuate nucleus o energy balance circuit is inhibited in obese mice. *J Clin Invest*. 2012; 122(1): 153-162. doi: 10.1172/JCI43134

216. Van de Sande-Lee S, Pereira FR, Cintra DE, et al. Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. *Diabetes*. 2011; 60(6): 1699-1704. doi: 10.2337/db10-1614

217. Li J, Tang Y, Cai D. IKK beta/NF kappa B disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and prediabetes. *Nat Cell Biol*. 2012; 14: 999-1012. doi: 10.1038/ncb2562

218. Steinberg GR, Kemp BE. AMPK in healthand disease. *Physiol Rev*. 2009; 89: 1025-1078. doi: 10.1152/physrev.00011.2008

219. Kalsbeek A, Bruinstroop E, Yi CX, Khoverick LP, La-Fleur SE, Fliers E. Hypothalamic control of energy metabolism via the autonomic nevous system. *Ann NY Acad Sci*. 2010; 1212: 114-129. doi: 10.1111/j.1749-6632.2010.05800.x

220. Mong Q, Cai D. Defective hypothalamic autophagy directs the central pathogenesis of obesity via the I kappa B kinase beta(IKKbeta)/NF-kappa B pathway. *J Biol Chem*. 2011; 286(37): 32324-32332. doi: 10.1074/jbc.M111.254417

221. Ravikumar B, Sarkar S, Davies JE, et al. Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol Rev*. 2010; 90(4): 1383-1435. doi: 10.1152/physrev.00030.2009

222. Yang Z, Kilonsky D. An overview of the molecular mechanism of autophagy. *Curr Top Microbiol Immunol*. 2009; 335: 1-32. doi: 10.1007/978-3-642-00302-8_1

223. Glick D, Barth S, Macleod KF. Autophagy, cellular and molecular mechanisms. *J Pathol*. 2010; 221(1): 3-12. doi: 10.1002/path.2697

224. Shi CS, Shendrov K, Huang NN, et al. Activation of autophagy by inflammatory signals limits IL-1β Production by targeting ubiquitinated inflammasomes for destruction. *Nat Immunol*. 2012; 13(3): 255-263. doi: 10.1038/ni.2215

225. Harris J, Hartman M, Roche C, et al. Autophagy controls IL-1beta secretion by targeting pro-IL-1beta secretion by targeting pro-IL-1beta for degradation. *J Biol Chem*. 2011; 286(11): 9587-9597.

226. Portovedo M, Ignacio-Souza LM, Bombassaro B, et al. Saturated fatty acids modulate autophagy's proteins in the hypothalamus. *PLoS One*. 2015; 10(3): e0119850. doi: 10.1371/journal.pone.0119850