Nutrient And Immune Sensing Are Obligate Pathways In Metabolism, Immunity And Disease

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**Abbreviations**

**CNS** – Central Nervous System; **PKC** – Protein Kinase C; **CoA** – Coenzyme A; **TLRs** - Toll-like Receptors; **NODs** – Nucleotide-binding Oligomerisation Domain proteins; **RAGE** – Receptor for Advanced Glycation Endproducts; **SOCS** – Suppressor Of Cytokine Signaling; **NFκB** – Nuclear Factor κB; **MYD** – Myeloid Differentiation; **TNF** – Tumour Necrosis Factor; **IL** - Interleukin; **GPCRs** – G-protein Coupled Receptors; **PAR2** – Protease Activated Receptor 2; **C3aR** – Complement factor 3a Receptor; **C5aR** - Complement factor 5a Receptor; **EP3** – Prostaglandin E 3 receptor; **LPS** - Lipopolysaccharide; **Treg** – T regulatory cells; **iNOS** – inducible Nitric Oxide Synthase; **PGI** - Prostacyclin; **PPAR** – Peroxisome Proliferator-Activated Receptor; **PGE2** – Prostaglandin E2; **cAMP** – cyclic Adenosine Mono Phosphate.
Abstract
The growth and survival of multi-cellular organisms depends upon their abilities to acquire and metabolize nutrients, efficiently store and harness energy, and sense and fight infection. Systems for sensing and using nutrients have consequently co-evolved alongside systems for sensing and responding to pathogens and other danger signals, and share many of the same cell signaling proteins and networks. Hypercaloric diets high in fats and carbohydrates can overload these systems, leading to obesity, metabolic dysfunction, impaired immunity, and cardiovascular disease. Excessive nutrient intake promotes adiposity, typically altering adipocyte function and immune cell distribution, both of which trigger metabolic dysfunction. Here we discuss novel mechanistic links between metabolism and immunity that underlie metabolic dysfunction in obesity. We aim to stimulate debate about how the endocrine and immune systems are connected through autocrine, paracrine and neuroendocrine signaling in sophisticated networks that are only now beginning to be resolved. Understanding the expression and action of signaling proteins, and modulating their receptors or pattern recognition by agonists or antagonists, may resolve whether intervention in immunometabolism can lead to novel treatments for obesity and metabolic dysfunction.

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**Obesity, inflammation, and metabolic dysfunction**

Obesity is defined as abnormal or excessive fat accumulation and is increasingly a major cause of human morbidity and mortality in most societies (1-3). Clinical features of obesity combined with hyperglycemia, hyperlipidemia, and hypertension are now collectively termed the ‘metabolic syndrome’. The resulting abnormalities in glucose, lipid, and fluid homeostasis increase the risk of Type 2 diabetes and cardiovascular disease (4,5). Obesity is considered to be a low-grade chronic inflammatory condition (3), and involves sophisticated interplay between metabolic and immune systems. This concept is highlighted by observational links between healthy diet and successful protective immunity, and between chronic malnutrition and low immunity (1,3). However, many key issues remain unresolved. An important question is whether inflammatory stress leads to adiposity and metabolic disease, or whether adiposity leads to inflammatory responses that initiate or exacerbate metabolic dysfunction, or whether they stimulate each other. Metabolic dysfunction can result from inflammation-induced cellular damage (3,6,7), but conversely inflammation can also be initiated and sustained by chronic energy overload inducing cellular stress such as mitochondrial dysfunction, endoplasmic reticulum stress and increased production of reactive free radicals (8-10). Metabolic disease, which initiates inflammation and lipid accumulation in the liver, may occur in pre-obese states without evident systemic inflammation (11). Inflammation in metabolic dysfunction appears to be initiated in the liver, followed by adipocyte dysfunction and then muscle insulin resistance (12). Yet other studies show that high fat diets induce oxidative and inflammatory responses in healthy lean people and some patients with chronic inflammatory diseases develop metabolic disease, supporting the notion that inflammatory stress precedes metabolic disease (7). Furthermore, obesity without metabolic dysfunction (‘fit fat’) is not uncommon and, conversely, some lean people have severe metabolic disease (13). Thus, instead of one initiating the other, these observations hint that energy-demanding processes such as recognition, absorption, storage, and metabolism of host energy supply may be entangled with mechanisms for immune defense and ‘danger sensing’. We speculate that a balanced energy flux and maintenance of favorable metabolic homeostasis is required for the proper functioning of the immune system, since initiation and maintenance of immunity is a metabolically expensive process and cannot function effectively or for very long during energy surplus or deficiency.

Inflammation is succinctly defined as an acute physiological response to infection or injury, involving coordination of many complex signals in distinct cells and organ systems to negate and remove the source of infection and to repair tissue injury (14). When this response does not remove the inflammatory stimulus or resolve the damage, it becomes prolonged and leads to characteristic pathologies. In metabolic disease, the prolonged response becomes a low grade chronic inflammation, sustained by nutritional and metabolic surplus using a similar set of molecules and signaling pathways as inflammatory responses to infection (15). Unlike the inflammatory response to infection, the inflammation in metabolic disease is geared to regulating endogenous nutrient metabolism and exogenous nutrient intake (1). The innate-immune molecules and pathways alter responses in many organ systems that collaborate in the recognition, absorption, storage, and metabolism of surplus energy supply. These differences emphasize that systemic inflammation is not a useful measure of the low-grade inflammation in metabolic disease, and highlight that these organ systems and signaling pathways were co-developed to coordinate metabolism with immunity. The study of this interface is now referred to as ‘immunometabolism’ (16-18) and identifying novel therapeutic opportunities relies on the detailed understanding, usage, and interpretation of this concept.
**Nutrient sensing and energy homeostasis**

Claude Bernard in 1865 and Walter Cannon in 1926 described the essential concept of homeostasis – the body’s ability to achieve and maintain a stable internal environment. They suggested that multiple mechanisms contribute to dynamic equilibria that regulate the balance between nutrient intake and energy use in all living organisms. In general, free energy in multi-cellular organisms is traded in adenosine triphosphate (ATP). Food is converted into nutrients such as glucose, free fatty acids, and amino acids. These nutrients are either directly metabolised to ATP or stored as lipids, glycogen or proteins that are later metabolised to ATP via relatively energy-expensive catabolic processes. When an organism encounters excess energy as food, it conserves the nutrients either as glycogen for short-term storage, or as lipids for longer storage duration and lipid combustion as a higher energy source (3). During evolution, limited or spasmodic nutrient supply forced organisms to manage the need for portable energy with the need to store fatty acids efficiently, and to develop effective transcriptional machineries such as PPARs and NFκB that are activated by fatty acids to regulate cellular responses, physiological processes, and immune defence (3). However, dietary calories are no longer limited for most individuals in the 21st century, and this has led to an epidemic of obesity and associated metabolic disturbances. Energy homeostasis relies upon controlling the balance between glucose and lipid storage with energy usage. When this balance is disrupted or impaired, it can lead to hyperglycemia, hyperlipidemia, and hyperphagia. In obesity, the efficiency of lipid to ATP conversion may become compromised, so that obese individuals have a deficit of energy in the form of ATP with simultaneous over-synthesis and storage of lipids resulting in excess adiposity. In obese patients, the induction of a negative energy balance, that is, consuming fewer calories than expended, improves metabolic abnormalities prior to significant reduction in the excess fat storage.

Energy, lipid, and glucose homeostasis are achieved by a balance between food intake and energy expenditure, as well as fatty acid and glucose production and utilization. In humans, there is a complex nutrient sensing system for balancing hunger and satiety, set against an obvious survival genetic background of opportunistically increasing energy storage. This involves recognising nutrients in the gut and absorbing them, and sensing whether to metabolise or store these nutrients in adipose and other peripheral tissues. Here we describe a working hypothesis whereby a chronic increase in macronutrients disrupts normal nutrient sensing and triggers neuronal negative feedback mechanisms, involving signaling molecules that have traditionally been seen to play immune roles, in order to maintain metabolic homeostasis. In particular, we will discuss how disruption of nutrient sensing in the gut and the brain trigger neuronal and immune networks to regulate nutrient intake, storage, and metabolism in adipose and peripheral tissues such as pancreas, muscle, and liver to alter energy homeostasis in obesity and metabolic dysfunction. This model provides a framework to identify novel therapeutic strategies targeting peripheral neural and immune signaling to restore energy, lipid, and glucose homeostasis in metabolic disease.

The central nervous system (CNS) is critical for mediating the systemic nutrient sensing mechanisms by activating neural networks as negative feedback systems, the gut-brain, gut-pancreas, brain-adipose, and gut-brain-liver axes thereby regulating energy, fatty acid, and glucose homeostasis (*Figure 1*) (19,20). Nutrient or lipid sensing within the intestine, or locally in the brain, triggers the CNS to reduce food intake and hepatic glucose production, and this helps to maintain glucose and energy homeostasis. Further, nutrient sensing within the gut triggers the secretion of incretins, involving the gut-pancreas axis to regulate whole body glucose homeostasis (21). Parallel sensing and metabolism of nutrients within the
hypothesis is that the hypothalamus regulates food intake and circulating fatty acid and glucose concentrations through regulatory hormones, including leptin, insulin, adiponectin, orexin, ghrelin, melanocortins and neuropeptide Y (19-24). This review aims to stimulate discussion by presenting some mechanistic associations and hypotheses on the complex network between the endocrine and the danger sensing systems, and how the endocrine system relies on autocrine, paracrine, and neuroendocrine signaling of the danger sensing system to regulate energy homeostasis in metabolically relevant tissues.

**Nutrient regulation by the CNS**

The ability to adjust food intake in response to changing energy requirements and environmental conditions is essential for an organism to survive and adapt to its conditions (25). The CNS receives and processes complex information from cognitive, visual, and olfactory cues in order to make an overall assessment of food availability and palatability before responding by emitting regulatory signals geared to manage digestion, absorption, nutrient transport, and storage (25). Integration of these signals is important for controlling appetite, so that food consumed does not exceed what can be safely managed and, conversely, that energy demands do not exceed energy supply (25). Many blood-borne and afferent neural regulatory signals communicate with the brain to adjust food intake and fat storage over time (24,25). The motivation to consume food and the amount tends to increase until energy stores are replenished, and disruption of any of the regulatory hormonal signals such as ghrelin, leptin, orexin, or adiponectin induces obesity or appetite suppression in animal models and humans (24). Current evidence indicates that nutrient or lipid sensing within the intestine or locally in the brain triggers the CNS to reduce food intake and hepatic glucose production, which helps to maintain glucose and energy homeostasis. Conversely, appetite and food intake are automatically stimulated by energy losses via the gastrointestinal and/or renal tract or through intense physical activity.

Apart from participating in the hormonal regulation of hunger and satiety, the brain can recognise and detect subtle local changes in nutrient concentrations, resulting in signaling to the periphery to change hepatic glucose production and food intake to maintain homeostasis (19,25). However, the precise non-hormonal mechanisms by which the brain regulates this glucose and energy homeostasis in humans are not currently known. Mechanistic studies in rodent models suggest that hypothalamic fatty acid metabolism helps to mediate actions of leptin and ghrelin that regulate hunger and satiety, with involvement of protein kinase C (PKC) isoforms together with fatty acids and enzymes, involved in inflammation and fatty acid metabolism, known to impair insulin signaling in liver and muscle (19,26,27). Hypothalamic PKC-θ activated by palmitic acid impairs central actions of regulators of energy homeostasis such as leptin and insulin (19,28). Knocking down hypothalamic PKC-θ restores otherwise impaired insulin action and glucose intolerance in diet-induced obesity (19,28). Hypothalamic PKC-δ activation by lipids (23) decreases hepatic glucose production, but no studies have evaluated the lowering of hepatic glucose production or food intake by direct activation of PKC isoforms in the hypothalamus (19). High-fat feeding impairs the ability of long-chain fatty acid-CoA in the hypothalamus to lower hepatic glucose production (29-32). Inhibition of hypothalamic enzymes involved in fatty acid metabolism such as carnitine palmitoyltransferase-1 restores long-chain fatty acid-CoA, thereby improving glucose homeostasis impaired by high-fat feeding (19,29,30). Genetic deletion of hypothalamic fatty acid synthase also lowers hepatic glucose production and restores hypothalamic lipid sensing mechanisms in high-fat fed mice (19). Hypothalamic fatty acid metabolism plays an important role in mediating the actions of leptin (31) and ghrelin (32) to regulate hunger and satiety. The ability of ghrelin or leptin to regulate glucose homeostasis...
may be regulated through the central fatty acid metabolic network, given that fatty acid metabolism in the hypothalamus is important in peripheral glucose regulation (19). Thus, both local sensing and direct metabolism of certain nutrients such as fatty acids within the hypothalamus together may regulate food intake and blood glucose concentration. Since fatty acids can play immune roles, further studies into whether fatty acid metabolism is dysregulated due to altered immune sensing is necessary to tease out non-hormonal mechanisms by which the brain regulates this glucose and energy homeostasis (33).

**Nutrient sensing, recognition and absorption by the gut**

Similar to the brain, local sensing of nutrients in the intestine activates a gut-brain signaling axis to regulate energy homeostasis, and a gut-brain-liver and gut-pancreas signaling axis to regulate glucose homeostasis (19). Lipid sensing in the intestine activates neuronal negative feedback systems to regulate peripheral glucose homeostasis, whereas it triggers a more central mechanism to regulate energy homeostasis (19). In general, food is broken down into nutrients that are then transported through the cells of the intestine and passed on to the circulation. However, lipids inside the gut can inhibit food intake in rats and humans (34,35). Lipids synthesized in the intestine, such as oleylethanolamide and N-acetylphosphatidylethanolamine, act on the CNS to reduce food intake (36,37). Further, dietary lipids modulate ghrelin activation and acylation to increase food intake through neural networks (38,39). Intestinal lipids stimulate the release of cholecystokinin from intestinal cells while activation of cholecystokinin-A receptors triggers a gut-brain signaling axis to lower food intake (40). Further, cholecystokinin and other enterohormones such as incretins trigger a gut-pancreas axis to control glucose homeostasis and appetite via both neural and direct hormonal mechanisms (41). Intestinal lipid sensing regulates glucose homeostasis, shown by improved glucose metabolism in diabetic patients following gastric bypass surgery before substantial weight loss (19,42,43). However, this is still debatable as gastric bypass surgery suppresses appetite and similar effects could be mimicked by caloric restriction (44). Nonetheless, nutrient sensing in the intestine could be enhanced after gastric bypass surgery or caloric restriction to lower hepatic glucose production by triggering a portal vein-brain-liver axis (45) and a portal vein-brain-muscle axis to regulate glucose uptake in the muscle under hyperinsulinemic conditions (46,47). A further example of multi-tissue integration of energy handling is the recent recognition of free fatty acids and bile acids as signaling molecules, acting via TGR5 and GPR40 receptors respectively, to promote post-prandial energy management.

Clearly, a better understanding will be gained by identifying the underlying mechanisms that define how intestinal nutrient sensing and caloric restriction trigger neural networks to communicate with the brain and peripheral tissues. Recent evidence from animal studies suggests that dysfunction or disruption of the body’s danger sensing system including Toll-like receptor (TLR) signaling and gut microflora can increase food intake and induce insulin resistance, metabolic dysfunction, and obesity in mice (6,48-50). There are some obvious questions to be asked, including whether the increase in food intake occurs through a gut-brain axis; if so, the role of TLR signaling, as the major danger sensor, to regulate this gut-brain axis in order to maintain energy homeostasis needs to be clarified. The CNS and the immune system have traditionally been considered as separate entities and their interaction and communication has been thought to occur as a result of dysfunctional systems. However, emerging evidence suggests that TLRs are likely to be an integral component in the communication between the CNS and the periphery in neurodegenerative diseases (49,50). Since these pattern recognition receptors are also involved in initiation and progression of
metabolic disease (10), they may facilitate communication between the CNS and the periphery to regulate metabolism.

Pathogen and danger sensing
The origin of inflammation in obesity and metabolic disease, either infectious or non-infectious or both, is still debatable. Nutrient intake continuously exposes the GI tract to new and potentially harmful microbes, although many microbiota already cohabit peacefully in the gut and contribute beneficially to immunity and homeostasis. Perturbations in these symbiotic relationships can distort both immune and nutrient sensing mechanisms. Immune defence against infection in the gut is similar to immune mechanisms elsewhere. In mammals, the danger sensing system is equipped with pattern recognition receptors such as the TLRs as well as the nucleotide-binding oligomerisation domain proteins (NODs) (51). These receptors initiate downstream signaling pathways to express proinflammatory cytokines required for host defence (51). An active danger sensing system in metabolically relevant tissues including the intestine, adipose, brain, and immune cells suggests a much more complex and intertwined relationship between sensing systems (Figure 2). The innate immune system reacts to pathogen-associated molecular patterns during infection, as well as other sets of conserved endogenous molecules released after cellular stress referred to as damage-associated molecular patterns. The latter compounds signal through the same pattern sensing receptors to initiate a response even in the absence of pathogens (52). Circulating mitochondrial damage-associated molecular patterns, including formyl peptides and mitochondrial DNA, induce inflammatory responses to injury (9). The immune response is perpetuated by advanced glycation end products acting on the Receptor for Advanced Glycation Endproducts (RAGE) (53). Whether metabolic dysfunction is induced via these molecules through mitochondrial dysfunction is not known. Furthermore, complex communication between gut microbiota and the innate immune system through TLRs may help maintain metabolic homeostasis (6,48,54). These observations further substantiate the idea that metabolic and immune regulatory mechanisms interact in human metabolic disease and metabolic dysfunction possibly as a result of both external and internal triggers, both pathogen-associated and damage-associated molecular patterns, signaling through the body’s danger sensing mechanisms to induce a chronic inflammatory state. TLRs are key suspects given their precursor status to both infection-induced (microbiota) and non-infectious sterile inflammatory pathways by endogenous molecules produced during tissue/cellular stress, and also saturated fatty acids such as lauric and palmitic acids from modern diets (51).

Nutrient and danger sensing cooperate in energy homeostasis and immunity
Nutrient and danger sensing mechanisms influence one another in contributing to regulation of energy homeostasis. Nutrients such as lipids and carbohydrates regulate both energy requirements and danger sensing signaling. A balanced energy flux and maintenance of metabolic homeostasis is clearly required for effective functioning of the immune system (1). The gastrointestinal tract plays important roles in immunity, with its large surface area continuously exposed to many microbes and food making it a unique interface between nutrient sensing, absorption, and the danger sensing system (55,56). The Bacteroidetes and the Firmicutes constitute over 90% of the microbes present in the distal gut (56). Gut microbes contribute towards breakdown and energy extraction from food. The gut microbiota are also involved in the development of obesity, metabolic disease, and associated inflammation. Changes in the gut microbiome have been implicated in diseases such as colon cancer, inflammatory bowel diseases, Type 1 diabetes (56-58) and obesity, since such changes may enhance energy extraction from the diet (58). Further, damage to gut barrier function following changes to the microbiota may increase blood concentrations of
endotoxins such as lipopolysaccharide (LPS) from gut bacteria that trigger obesity-associated inflammation (59). These endotoxins could supply the infectious sources of low-grade inflammation in obesity, acting together with dietary saturated fatty acids to initiate innate immune responses. This concept has been supported by studies in human patients and knockout mice, such as those described below.

Some human studies in lean, obese and Type 2 diabetic patients report that high fat meals can induce postprandial increases in plasma LPS concentrations leading to low grade inflammation (7, 60-62). In rodent models of diet-induced obesity, TLR4 knockout prevents saturated fat-induced weight gain and obesity-related inflammation (63). Selective knockdown of TLR4 in hepatocytes prevents obesity-induced inflammation and insulin resistance without affecting body weight in diet-induced obese mice (64). Furthermore, intracerebroventricular administration of TLR4 neutralising antibody prevents hypothalamic inflammation, defective liver gluconeogenesis and hyperglycemia, validating a TLR4-mediated brain-liver axis in regulating glucose homeostasis (65). Pharmacological antagonism of TLR4 also prevents the progression of kidney disease in diet-induced obese mice (66). Other TLRs may also be activated by dietary lipids, as specific knockdown of hypothalamic neural TLR2 protects also against both mature-onset age-induced and high fat-induced obesity in mice (67). Taken together, these studies suggest that diet-induced obesity, insulin and leptin resistance may be mediated by TLRs (7,63-67). Cytoplasmic danger sensing signals such as NODs are also involved in initiating inflammasome-mediated responses (68). For example, lipid molecules such as cholesterol crystals activate NLRP3 inflammasome after TLR4 stimulation (69). Peptidoglycan released from gut microbiota could influence the innate immune system through NOD1 (6,69,70). Further, short-chain fatty acids produced by the gut modulate immune responses through G-protein coupled receptors such as GPR43 (6,69,70). These studies leave open the roles of other TLRs, and whether components of microbiota or metabolised nutrients are ligands for these receptors (6). Disruption of the normal interactions between gut microbiota and innate immune cells could alter the microbiota, promoting inflammation by signaling back to the innate immune system probably via pattern-recognition receptors such as TLRs resulting in metabolic dysfunction (6,48,63-67).

In contrast to TLR2 & 4, mice lacking TLR5 exhibited increased adipose tissue mass combined with mild inflammation, reduced insulin sensitivity, elevated blood pressure, and increased circulating lipids compared to normal mice (48). Moreover, in TLR5 knockout mice, a high-fat diet accentuated metabolic dysfunction giving rise to fatty liver disease and Type 2 diabetes (48). Furthermore, transplanting gut microbiota from TLR5 knockout mice to normal germ-free mice induced the metabolic syndrome (48). TLR5 knockout mice also have increased food intake compared to normal mice (48). Crossing these mice with strains lacking other key immune system signaling did not change the phenotype of TLR5 knockout mice, suggesting that the metabolic dysfunction did not involve direct interactions between TLRs and other immune system signaling molecules (48,54). Which other signaling cascades could account for the metabolic dysfunction? In metabolic disease, redundant mechanisms may be initiated in order to limit exogenous nutrient intake and endogenous nutrient output, utilizing similar signaling molecules and pathways as in innate immunity. These changes may alter direct nutrient sensing in the brain probably through a gut-brain or gut-brain-liver axis via danger sensing signaling pathways. Saturated fatty acids may regulate hypothalamic function and hormone homeostasis in obesity through TLR/IlkxB/NFkB signalling and endoplasmic reticulum stress (51,71). IlkxB/NFkB activation in the hypothalamus increases food intake with impaired insulin and leptin signaling in mice fed a high-fat diet (51,71). Fatty acids such
as arachidonic acid induce TLR2 and 4 activation, initiating endoplasmic reticulum stress in the hypothalamus in rats (51,72). High-fat diet-induced anti-anorexigenic responses to leptin are reversed by TLR4 inhibiting antibody (51,72). Studies on neurodegenerative diseases also suggest that TLRs form an integral component in the communication between the CNS and the periphery (50).

As mentioned, the CNS and immune system have been considered discrete entities with interaction between the two thought to be the result of dysfunctional systems (50). The brain, with a higher glucose demand but a lower minimal threshold for nutrient supply, engages mechanisms to respond to stress or nutritional starvation (19,25,50). These mechanisms could become dysfunctional during nutritional surplus as in obesity. In the brain, the TLRs are differentially expressed in neurons, astrocytes and microglial cells, at least at mRNA levels (50), with TLR2 and TLR4 being highly expressed (50,73,74). Microglia are the resident macrophages of the brain and express different TLRs (50), while astrocytes provide structural and metabolic support to neural tissue and express only TLR3 mRNA in humans and TLR 2, 4, 5, and 9 mRNAs in mice (50,75). The mRNA for all TLRs has been detected in neurons in mice (76) but, as yet, only TLR3 (77) and TLR8 (78) mRNAs have been detected in humans. Schwann cells show relatively high expression of TLRs, especially 3, 4 and 7, suggesting they might act as sentinel cells in the peripheral nervous system (79). Bacterial lipoprotein ligands for TLR1 and TLR2 yield the strongest response in Schwann cells (79). Similar to Schwann cells, sciatic nerves express TLRs 3, 4, and 7 at basal levels, but upon axotomy, TLR1 becomes strongly induced compared to other TLRs, suggesting specialized receptor functions in basal and activated conditions of the peripheral nerve (79). mRNA expression was observed for TLRs 1-6 and 9, adapter proteins Md-1 and 2, and MYD88 in a study examining whether bacterial endotoxins that enter the intestinal interstitium could activate mouse colonic nociceptive dorsal root ganglion neurons (80). LPS induction increased neuronal excitability and expression and secretion of TNFα and IL1β from neurons (80). Further, systemic LPS administration induced inflammation in various regions of the brain (81). However, radiolabeling studies suggest that systemic administration of LPS gives rise to only limited LPS within the brain due to the blood-brain barrier prompting the suggestion that activation of the innate immune response in the brain may occur via peripheral activation of neural or endocrine networks that involve TLR4 (82). Thus, TLR signaling is an important component of the communication between the CNS and the periphery, including the intestine. More studies are required to address the unique roles of these receptors in regulating energy metabolism through neuronal feedback networks.

Another class of cell-surface pattern-recogznising receptors are G protein coupled receptors (GPCRs), which are involved in host immunity and many inflammatory diseases (83-85). Chemokines, complement products, and some cytokines act via GPCRs to trigger immune cell antimicrobial and/or inflammatory responses, but dysregulated GPCR expression or activation promotes disease (83-85). In obesity and metabolic disease, adipocyte stress and other functions such as lipolysis, fatty acid, and glucose uptake are modulated by inflammatory GPCRs and play a major role in inducing adiposity, chronic inflammation, and metabolic disease (3,86). We have identified a number of inflammatory GPCRs, including PAR2, C3aR, C5aR, and EP3 that play important functional roles in adipose biology, with their pharmacological inhibition preventing or treating diet-induced obesity and metabolic dysfunction in rats (87-89). Moreover, signaling through inflammatory GPCRs influences other innate immune signaling pathways through crosstalk with other receptors, including TLRs. For example, we recently characterised differential expression of about 100 GPCRs with LPS/TLR4 stimulation in human macrophages (90). Functionally, we showed
differential immune responses with co-activation of a GPCR, C5aR, and TLR4 in human monocytes and macrophages (91). Free fatty acids are ligands for some low-affinity GPCRs. We recently identified that dietary saturated fatty acids influence the expression of inflammatory GPCRs in both the mRNA and protein levels in immune cells such as macrophages (87). More detailed studies on the influence of dietary fats and crosstalk mechanisms are required as immune cells such as macrophages are highly motile and their activation state and their movement to specific organ types such as the adipose and liver could trigger an inflammatory state associated with obesity and metabolic disease.

**Energy storage, metabolism, immune cells and disease**

Many organ systems collaborate in recognition, absorption, storage, and metabolism of energy supply. The brain, brown and white adipose tissue, liver, skeletal muscle, and pancreas communicate to maintain energy homeostasis, regulating the balance between energy storage and metabolism when surplus energy is available. Once the food is recognized and absorbed in the intestine, the body initiates mechanisms to store or metabolize the nutrients in line with normal physiological needs. This process involves the body making a decision to store the nutrients, either as glycogen in tissues such as liver and muscle or as lipids in adipose tissue. Lipid-sensing processes such as fat synthesis, beta-oxidation, lipid transportation and distribution may be disturbed in obesity and metabolic dysfunction. In general, free fatty acids, lipoproteins, and chylomicrons determine which cells absorb lipids through specific membrane receptors for metabolism and storage.

The activation of pattern recognition receptors can be dynamically modulated by metabolic products, by sensing the balance between saturated and unsaturated fatty acids in cellular and circulating lipids (51). For example, oxidized low-density lipoproteins and high blood glucose concentrations in diabetes enhance the expression and activation of TLR4 (51,92,93). In obesity, this disrupted lipid sensing can enhance the activation of these pattern recognition receptors in circulating leukocytes, particularly monocytes and macrophages, promoting tissue infiltration and a proinflammatory state (51). Both mammalian liver and adipose tissue, the major organs of storage and metabolism, have comparable structural blueprints in which metabolic cells such as hepatocytes and adipocytes are in close proximity to immunoregulatory cells such as Kupffer cells, macrophages, and T cells, with immediate access to a vast network of blood vessels (1,3). In the brain, neural tissues are in close proximity to microglial cells, which serve as resident macrophages (50). Such cellular proximity facilitates a continuous dynamic interaction between the immune and metabolic networks and affords the coordination of more distal sites such as the pancreatic islets and skeletal muscle (3). Thus, the immune system and the danger sensing system may integrate and process the signaling of these common biochemical and molecular nutrient and lipid-sensing mechanisms at these sites to maintain or restore homeostasis.

**Adipose tissue**

Adipocytes are key cells in mammalian energy storage and metabolism. The central and autonomic nervous systems regulate whole body energy homeostasis, at least in part by modulating the metabolic and secretory activity of adipose tissue (94,95). Mammals have two main types of adipose tissue, white and brown, which store energy in the form of triglycerides and metabolize them to fatty acids. White adipose tissue provides these fatty acids to other tissues for normal physiological function. Brown adipose tissue plays a pivotal role in maintenance of body temperature by thermogenesis, and in protection against detrimental effects of surplus energy intake, which is regulated by the sympathetic nervous system (94,95). Neural feedback mechanisms, and possibly also the danger sensing system,
connect these adipose tissues to the brain which plays a major role in regulating energy homeostasis (94).

**White adipose tissue**

White adipocytes provide an important reversible storage depot for saving excess energy as lipids (3). In obesity, excessive white adipose tissue growth is associated with hypertrophy and hyperplasia of adipocytes (3). Excess energy intake or decreased expenditure results in excess triglyceride accumulation in white adipose tissue, which results in hypertrophy (3). Adipocyte tissue mass expands and redistributes throughout adult life, with proliferative adipocyte precursor cells standing ready to respond to increased demands for energy storage (3). Thus, hyperplasia results from recruitment of new adipocytes, involving proliferation and differentiation of pre-adipocytes (adipogenesis) (3). Adipocyte function can become compromised during storage of excess energy as fat (3) even though white adipocytes have an additional role to protect non-adipocytes from excessive fat intake and lipotoxicity (96). When there is continued nutritional surplus, the altered production of various endocrine, paracrine, and autocrine factors by mature white adipocytes is thought to play important roles in processes governing recruitment of new adipocytes as well as inflammatory cells such as macrophages. These processes may give rise to obesity together with ectopic fat deposition in liver, heart, muscle, and pancreatic beta cells that, in turn, leads to lipotoxicity and insulin resistance (3,96). The interactions between the systems regulating energy storage in adipocytes and adipose tissue with the danger sensing systems, most notably the macrophages, T cells, and mast cells that reside in or infiltrate the adipose tissue, are being investigated in a variety of rodent models of disease. These studies suggest that the signaling proteins secreted during energy storage and danger sensing can profoundly affect insulin sensitivity, triglyceride synthesis, and cardiovascular structure and function (3,5).

White adipose tissue contains a resident population of innate immune cells, in particular macrophages and T lymphocytes that could sustain adipocyte dysfunction (3,97). These inflammatory cells are spatially and temporally associated with adiposity and may alter adipocyte secretory profiles (3,97). Alterations in both population and function of white adipose tissue T cells occur during early development of obesity but the triggers for this immune cell activation remain unknown (3,97). Most resident T cells in white adipose tissue of lean individuals are T regulatory (Treg) cells and T helper2 cells that, together with resident macrophages, produce IL10 and impede inflammation (3,97). Treg cells regulate innate immunity and express chemokine receptors that respond to cytokines produced by adipocytes (3,97). Conversely, the predominant resident T cells in white adipose tissue of obese individuals are T helper1 and CD8+ effector T cells (3,97). Similarly, the major resident macrophages in obese white adipose tissue are the classically activated proinflammatory M1 macrophages, which express F4/80, CD11c, and iNOS. However, adipose tissue in lean animals contains alternatively activated anti-inflammatory M2 macrophages, which express F4/80, CD301, and Arg1 (98). In white adipose tissue of obese individuals, decreases in the number of Treg cells and the early appearance of CD8+ effector T cells, which assist infiltration of proinflammatory macrophages, together may disrupt adipocyte homeostasis and trigger an immune response that leads to further recruitment of circulating proinflammatory macrophages (3,97). This recruitment is then followed by macrophage activation, chemoattraction, and induction of the expression and release of cytokines and adhesion molecules (3,97). These inflammatory effectors from macrophages can act in a paracrine manner on adipocytes to stimulate other proinflammatory cytokines, macrophages, and adipokines and hence link inflammation to adipocyte dysfunction (3,97).
In a macrophage environment, pre-adipocytes can be effectively converted into macrophages, which suggests substantial cellular plasticity in adipocyte precursors (99).

Macrophage infiltration of white adipose tissue during obesity alters expression of genes associated with danger sensing, including TLRs and complement components (3,98). The infiltration of macrophages to white adipose tissue was first reported in 2003, yet it is still not known whether a specific immune cell is chiefly responsible for metabolic dysfunction following macrophage infiltration in WAT in humans (97,100). Genetic knockout and DIO rodent studies suggest that macrophages, monocytes, leukocytes, platelets, T cells, Treg cells, and mast cells may contribute to development of metabolic diseases, particularly obesity and type 2 diabetes (3). Elevated free fatty acids in obesity can enhance activation of TLRs in adipocytes and immune cells (3,51). Human and animal studies show increased expression of TLR4 target genes, such as monocyte chemoattractant protein-1, TNFα, and IL6, in adipose and immune cells associated with obesity and insulin resistance (51). Further studies are necessary to tease out roles of individual immunoinflammatory cells in human metabolic dysfunction and to determine whether induced TLR signaling is local or systemic in origin.

Further, in mice, weight loss induced by calorie restriction is associated with a rapid, temporary recruitment of macrophages to white adipose tissue, with remarkable similarities between the infiltrating macrophages found during weight loss and the cholesterol-laden macrophages found in atheromatous plaques (101). These observations lead to the prediction that the infiltrating macrophages may facilitate trafficking of lipids from the white adipose tissue to the liver for subsequent metabolism, a postulate that was supported by the transient recruitment patterns and the expression of scavenger receptors and lipid-handling genes (101). Mechanisms of macrophage regulation of white adipose tissue lipolysis in both rodents and humans remain unknown (101); further, whether macrophages exert endocrine or paracrine functions by transfer from macrophages to adipocytes is yet to be elucidated. However, it is clear that the sympathetic nervous system plays a major role as primary initiator of lipolysis in rodents and humans (102-104) and that immune cells and microglia interact with neurons, at least in many neurological disorders (49). Macrophages and mast cells are increased at the site of nerve injury, found close to primary nociceptive neurons, and contribute to nociceceptor sensitization (49). Degranulation of mast cells also requires direct interaction between mast cells and peripheral nerve terminals (49). These immune cells are elevated in white adipose tissue in obese humans and may communicate with the brain to regulate lipolysis, thereby utilizing stored lipids for metabolism. Suppression or absence of mast cells by pharmacological inhibition, stabilization or genetic deficiency also prevents or treats diet-induced obesity in rodent models (105-107). Taken together, these studies suggest that, in addition to inducing local adipocyte inflammation, these immune cells may have distinct roles in regulating metabolism by communicating with the brain and peripheral tissues, but precisely how they communicate and alter metabolism still needs to be fully elucidated.

Brown adipose tissue
Brown adipose tissue plays a pivotal role in maintaining body temperature and protecting against detrimental effects of surplus energy intake (108). Brown adipose tissue uses fatty acids to produce heat, a process known as thermogenesis. Brown adipose tissue has been known for 500 years and it regulates cold-induced thermogenesis (109), but until recently other consequences of adaptive or diet-induced thermogenesis were unknown. Animal studies have shown that activation or expansion of brown adipose tissue prevents diet-induced weight gain and associated metabolic disorders (108). Diet-induced thermogenesis is the
physiological mechanism for dissipating excessive calorific intake as heat via brown adipose tissue and is regulated by the sympathetic nervous system (109,110). In obesity, varied susceptibility to diet-induced thermogenesis may account for differences in body weight gain by individuals in response to surplus energy (110). Human therapeutics targeting the brown adipose tissue in metabolic disease have so far failed (111). However, an important question relevant to this review is whether brown adipose tissue regulates energy homeostasis and metabolism in obesity by communicating through nutrient and danger sensing systems.

In other endocrine disorders such as hyperthyroidism, brown adipose tissue communicates with the hypothalamus using nutrient sensing enzymes, including AMP kinase, to regulate energy expenditure and body weight in rats (112,113). There is circumstantial evidence for involvement of the danger sensing system. Fatty acids mediate diet-induced thermogenesis (51), with polyunsaturated fatty acids causing greater induction than saturated fatty acids (110). Since danger sensing receptors can sense the balance between saturated and unsaturated fatty acids (51), it is possible that TLRs or their downstream components may modulate this change. Indeed, other traditional inflammatory components such as cyclooxygenase II, an important intermediate between lipids and inflammation, control energy homeostasis in mice by de novo recruitment of brown adipose tissue in white adipose tissue (114). Cyclooxygenase II is a downstream effector of beta-adrenocceptor signaling in white adipose and is required for induction of brown adipose in white adipose tissue depots (114). Noradrenaline from sympathetic nerves may induce cyclooxygenase II activity in white adipose and signaling downstream of PGI2/Ptgir/PPARγ shifts the differentiation of mesenchymal progenitors from the stromovascular cells towards a brown adipose phenotype in white adipose tissue (114). This reinforces the idea that danger sensing mechanisms in an organism are interrelated with other energy-demanding processes, such as control of cellular energy supply. Of the prostanoids, PGI2 activates PPARδ and γ and induces adipogenesis and adipocyte differentiation, whereas PGE2 acts on EP3 receptors to decrease lipolysis by decreasing cAMP concentrations, thereby contributing to storage of fat in white adipocytes (3). This exemplifies at least two components of the traditional immune system playing opposing roles to regulate energy homeostasis, with PGI2 inducing brown adipose for energy consumption and PGE2 inducing white adipose tissue to store fat or energy. A more detailed understanding is needed of the communication between the danger sensing system and the sympathetic nervous system in brown adipose tissue.

**Other metabolic tissues**

Adipose tissue communicates with other organ systems such as liver, skeletal muscle, and pancreas to maintain energy homeostasis, regulating the balance between nutrient intake, storage and metabolism. Hormonal feedback loops such as glucagon, insulin, and incretins are well studied and enable communication between organ systems to regulate blood glucose and fatty acid concentrations. An important question is whether the danger sensing system plays similar regulatory roles via autocrine, paracrine, and neuroendocrine signaling networks. The presence and signaling of the danger sensing system in these metabolically relevant tissues suggests a more diverse role in regulating metabolism (51). Although inflammatory signaling in the liver during insulin resistance, obesity and fatty liver disease is well established (115-117), recent evidence suggests the presence of inflammatory signaling in skeletal muscle and pancreas (118-120). Studies on the underlying mechanisms that link metabolic dysfunction in obesity to the danger sensing system are still in their infancy. Until now, relatively few studies have focused on the roles of these receptors in the muscle and pancreas while the role of inflammatory mediators in liver disease is a rapidly expanding
field of research. This section will summarise the emerging roles for the danger sensing system in the liver, pancreas, and skeletal muscle.

Liver
The liver is the largest visceral organ in the body and is primarily responsible for metabolic regulation. Most of the blood leaving the absorptive surfaces of the digestive tract enters the hepatic portal system and flows into the liver, where liver cells extract the nutrients before the blood reaches the systemic circulation. Induction of immune cells and activation of inflammatory pathways during obesity leading to liver complications have been well-studied (115-117). Although lipid accumulation in liver may occur in pre-obese states without detectable systemic inflammation (11), obese patients without histopathological abnormalities in the liver display a low-grade expression signature of inflammatory genes; these livers could be more responsive to the TLR pathway (121). This study suggests that genes encoding chemokines and their respective receptors and cytokines involved in T-cell activation are increased and specific to the liver compared to visceral adipose tissue from these patients (121). Further, selective knockdown of TLR4 in hepatocytes prevents obesity-induced inflammation and insulin resistance without affecting body weight in diet-induced obese mice (64). These findings support a hypothesis that inflammation, adiposity, and metabolic dysfunction do not necessarily initiate and perpetuate one another. Instead, energy-regulatory processes (such as recognition, absorption, storage, and metabolism of host energy supply) utilize similar sets of signaling molecules and signaling pathways as in innate immune responses in order to maintain energy homeostasis.

Pancreas
Glucose is a major source of energy for all cells, particularly when stressed (e.g. ischaemia), so precise control over blood glucose concentrations by insulin, other hormones such as the incretins, and free fatty acids is essential. Impaired glucose tolerance is a delayed normalization of blood glucose concentrations after glucose intake, due to insufficiency of insulin or sometimes despite adequate insulin concentrations. Depending on systemic glucose and fatty acid concentrations, pancreatic beta cells are thought to regulate insulin secretion via the regulatory hormones. More recently, different fatty acids and inflammatory cytokines have been shown to regulate insulin secretion directly via endocrine, paracrine, and potentially autocrine mechanisms (122,123). Interleukin-22 was identified as a key anti-inflammatory cytokine able to restore glucose homeostasis in mouse models of type 2 diabetes by restoring insulin secretion from the pancreatic beta cells concomitant with reduced oxidative and endoplasmic reticulum stress (122). Increases in free fatty acids for 24 to 48 hours also alter insulin gene expression and induce apoptosis in beta cells both in vitro and in vivo (124-126). Inflammatory signaling and mediators such as IL1β, TLRs, macrophages, and chemokines are elevated in pancreatic islets from patients with type 2 diabetes (127). Increased glucose concentrations enhance free fatty acid-induced expression of inflammatory mediators in both human and mouse islets, suggesting that these responses are probably through an IL-1R/TLR dependent pathway (127). Activation of TLR4 in pancreatic beta cells affects insulin secretion in response to glucose in both humans and rodents (127). Although the expression and roles of TLR pathways in type 1 diabetes have been well characterized, details about their specialized roles in type 2 diabetes are not well understood.

Skeletal muscle
Recent studies reveal that skeletal muscle is not a passive organ, but rather drives tolerance and elicits inflammatory signaling to foreign DNA and proteins (128). Similarly, in metabolic dysfunction, fatty acids can elicit inflammatory signaling to induce insulin resistance in muscle (118-120). Further, important roles have been proposed for resident skeletal muscle macrophages in muscle insulin resistance (118-120). In cultured muscle cells, conditioned media from palmitate-stimulated macrophages and other pro-inflammatory cytokines induce insulin resistance (128-130). This suggests that increased pro-inflammatory cytokines and saturated fatty acids in obesity can act on TLRs on muscle cells to regulate insulin responsiveness (128-131). Cytoplasmic danger sensing signaling such as NOD1 and NOD2 are also expressed in muscle cells and activation of these receptors by saturated fatty acids induces insulin resistance in muscle (132). Taken together, these studies support roles for danger sensing signaling in regulating insulin sensitivity at the major sites of postprandial glucose utilization in the body.

**Human perspectives and concluding remarks**

Approaches to the treatment of Type 2 diabetes and obesity have provided significant insights into mechanisms of energy homeostasis. Current treatments to restore blood glucose concentrations and insulin sensitivity include insulin, metformin, sulphonylureas, thiazolidinediones, α-glucosidase inhibitors, incretin hormone-based therapies, and sodium-dependent glucose co-transporter (SGLT) inhibitors (133). All of the above strategies improve glycemia and some even delay the onset of Type 2 diabetes. However, unfortunately none of the current therapeutic approaches seems to have disease-modifying characteristics that might result in slowing the progressive decline in insulin secretion (133). Furthermore, aggressive glucose control alone has not been shown to improve mortality from macrovascular causes, suggesting that the picture is more complex, likely involving elevated blood pressure, lipids, and inflammation. This hypothesis is supported by the significant impact on mortality of statin therapy, with some proportion of this benefit attributable to the off-target, anti-inflammatory actions of these widely used drugs.

Nonetheless, a major observation from past and existing human therapies is the resilience of the human system to significant manipulation of body weight. A common feature of pharmacological approaches used to date, which include appetite suppression, reduction in gut nutrient intake, and renal glucose loss, is the consistent stabilization of weight after ~5% loss. Indeed, recent studies on the SGLT-2 inhibitors elegantly demonstrate that renal glucose loss is quickly matched by an increase in hepatic glucose intake (134), supporting our discussion above on multi-organ communication and sensing. Thiazolidinediones as a class also induce weight gain while improving glucose and insulin sensitivity (133). On the other hand, GLP1 and other incretins improve glycemia together with some reduction in body weight (133).

Furthermore, achieving and maintaining weight loss is not necessarily the Holy Grail of therapeutic strategies for metabolic disease. Indeed, cardiovascular risk reduction in response to therapy can be explained and/or predicted using recognized risk factors such as BP and lipids, without weight. A central issue is to understand whether metabolic improvement with very little or no weight loss is achievable or desirable from a clinical perspective. Obesity without overt metabolic dysfunction (‘fit fat’) is not uncommon and, conversely, some lean people have severe metabolic disease (13). Some clinical studies suggest that systemic inflammation could determine the metabolic health status in obese and non-obese human patients (135). Decreased concentrations of many inflammatory mediators such as complement C3, CRP, TNF, IL6, PAI-1, and leukocytes numbers together with higher
adiponectin concentrations correlate directly with metabolically healthy, but obese, individuals versus their metabolically unhealthy obese counterparts (135). Mechanistic evidence to date suggests that a minority (10-20%) of people are able to accommodate excess nutrients in adipose tissue by a process that relies mainly on generation of new fat cells as opposed to hypertrophy of existing fat cells (136). The former correlates with reduced adipose tissue inflammation and decreased ectopic fat in liver and muscle (136). It is unclear what the real drivers are in this compensatory process. Does early infiltration of inflammatory cells compromise adipogenesis, leading to defects in metabolic flexibility of adipose tissue and excess lipids entering other tissues such as liver, muscle and fat making them defective? Or, do intrinsic differences in differentiation capacity of preadipocytes initiate inflammatory and metabolic complications? In favour of the latter notion is the fact that isolation and long-term culturing of preadipocytes from healthy obese versus unhealthy obese has revealed ‘hard-wired’ changes in gene expression profiles consistent with the respective metabolic phenotypes (136).

Thus, an ideal therapeutic strategy for human patients with Type 2 diabetes would not only restore glycemia, but would also prevent the progression of disease and the associated comorbidities such as cardiovascular, liver, and kidney diseases. As inflammation underlines most of these comorbidities, the aim of this review has been to highlight how targeting the immune system can not only restore glycemia but also prevent the progression of disease and the associated comorbidities. Finding new links between inflammation and metabolism promises a new and more detailed understanding of the interplay between immunity, nutrition, and energy homeostasis. Nutrient sensing and danger sensing systems in different organ systems share biochemical mediators and molecular mechanisms that maintain energy homeostasis and mediate immune responses. There is increasing evidence that dysfunctional autocrine, paracrine, and neuroendocrine signaling in these systems can lead to human obesity and metabolic dysfunction. Since both danger signaling and nutrient sensing modify metabolic function, some anti-inflammatory drugs, controlled dietary intake, and ‘smart’ designer foods might be expected to augment the immune system and peripheral neuroendocrine signaling thereby improving tolerance to surplus nutrients in obesity and restoring energy homeostasis. New studies designed to identify roles for specific signaling molecules shared by danger sensing and nutrient sensing pathways should aid the understanding of ways to modulate metabolism and immunity under either nutritional or immunological stress. Greater knowledge about how intersecting molecular signatures determine either good health or disease progression could lead to more rational choices of the most effective targets for therapeutic intervention in obesity, diabetes, inflammation, and cardiovascular diseases.
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Figures

Figure 1 – Communication between the brain, liver, adipose tissue, and gut in controlling appetite and energy homeostasis. The central nervous system processes complex information, including cognitive, visual, and olfactory cues to assess food palatability and both short- and long-term signals relating to changing nutritional status. Blood-borne and afferent neural regulatory signals including leptin, insulin, orexin, ghrelin, melanocortins, and neuropeptide Y communicate with the brain, liver, adipose tissue, and gut to adjust food intake and fat storage over time. The brain also communicates with adipose tissue in regulating storage and release of fatty acids – lipolysis. These organ systems may communicate with each other using non-hormonal mechanisms to regulate energy homeostasis, for example with the involvement of autocrine, paracrine, and neuroendocrine signaling of the danger sensing system. The working hypothesis is that disruption of this communication leads to the chronic inflammatory state seen in obesity and metabolic dysfunction.
Figure 2 – Role of immune sensing system in initiating metabolic dysfunction. The origin of inflammation in obesity and metabolic disease, either infectious or non-infectious or both, is still debatable. Activation of damage associated molecular patterns (DAMPs) due to tissue injury or pathogen associated molecular patterns (PAMPs) from the gut microbiota could lead to activation pattern recognizing receptors (PRRs) in other metabolic organs driving inflammation that underpins obesity and associated metabolic disease.