Cellular and Molecular Neurobiology (2019) 39:11–29
https://doi.org/10.1007/s10571-018-0631-4

REVIEW PAPER

Hypothalamic Inflammation at a Crossroad of Somatic Diseases

Boris Mravec[1,2] · **Lubica Horvathova**[2] · **Alena Cernackova**[1,2]

Received: 15 May 2018 / Accepted: 24 October 2018 / Published online: 30 October 2018

Abstract

Various hypothalamic nuclei function as central parts of regulators that maintain homeostasis of the organism. Recently, findings have shown that inflammation in the hypothalamus may significantly affect activity of these homeostats and consequently participate in the development of various somatic diseases such as obesity, diabetes, hypertension, and cachexia. In addition, hypothalamic inflammation may also affect aging and lifespan. Identification of the causes and mechanisms involved in the development of hypothalamic inflammation creates not only a basis for better understanding of the etiopathogenesis of somatic diseases, but for the development of new therapeutic approaches for their treatment, as well.

Keywords Aging · Cachexia · Cytokines · Diabetes mellitus · Hypertension · Hypothalamus · Inflammation · Obesity

Introduction

Homeostasis maintenance is essential for the preservation of health (Huber et al. 2011). Homeostasis is preserved at the cellular (e.g., regulation of proteosynthesis, cell volume, and electric potential across the plasma membrane), tissue (e.g., regulation of the number of cells in tissue, ratio between different cells, and composition of the extracellular matrix), and systemic levels (e.g., regulation of energy balance, blood pressure, glycemia, plasma osmolality, and pH) (Chovatiya and Medzhitov 2014). Here we are focusing on systemic homeostasis, which depends on the activity of complex regulatory systems known as homeostats (Fig. 1) (Goldstein 2008). Whereas some systemic homeostats are localized in the peripheral tissues (e.g., glucostat in pancreas, homeostat regulating calcemia in parathyroid glands), the central components (comparators and regulators) of the majority of systemic homeostats are located in the brain, mainly within the hypothalamus and medulla (Fig. 1) (Goldstein and Kopin 2017).

Dysfunction of these central comparators and regulators leads to disruption of homeostatic regulation and plays a crucial role in disease development. There have been various studies showing that inflammation within the hypothalamus represents an important factor that compromises functions of the central parts of homeostats localized in this brain structure and participates in the development of diseases such as obesity, diabetes, and hypertension (Valdearcos et al. 2015; Araujo et al. 2016).

The Hypothalamus Contains Central Components of Various Homeostats

Hypothalamic nuclei represent central components of systemic homeostats that are involved in the regulation of various physiological variables. These nuclei include the paraventricular, suprachiasmatic, medial preoptic, arcuate, ventromedial, and dorsomedial nuclei (Table 1). Of these, the paraventricular hypothalamic nucleus occupies a prominent position, coordinating the activity of autonomic, neuroendocrine, and immune systems. Interaction between hypothalamic nuclei allows for the orchestration of different homeostatic regulations to maintain homeostasis of an organism (Graebner et al. 2015; Watts 2015).

Besides the hypothalamus, central components of homeostats are also localized in the lower part of the brain stem, specifically in the medulla. These homeostats are involved in the regulation of blood pressure, partial pressure of O_2

✉ Boris Mravec
boris.mravec@fmed.uniba.sk

[1] Institute of Physiology, Faculty of Medicine, Comenius University in Bratislava, Sasinkova 2, 813 72 Bratislava, Slovakia

[2] Biomedical Research Center, Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia

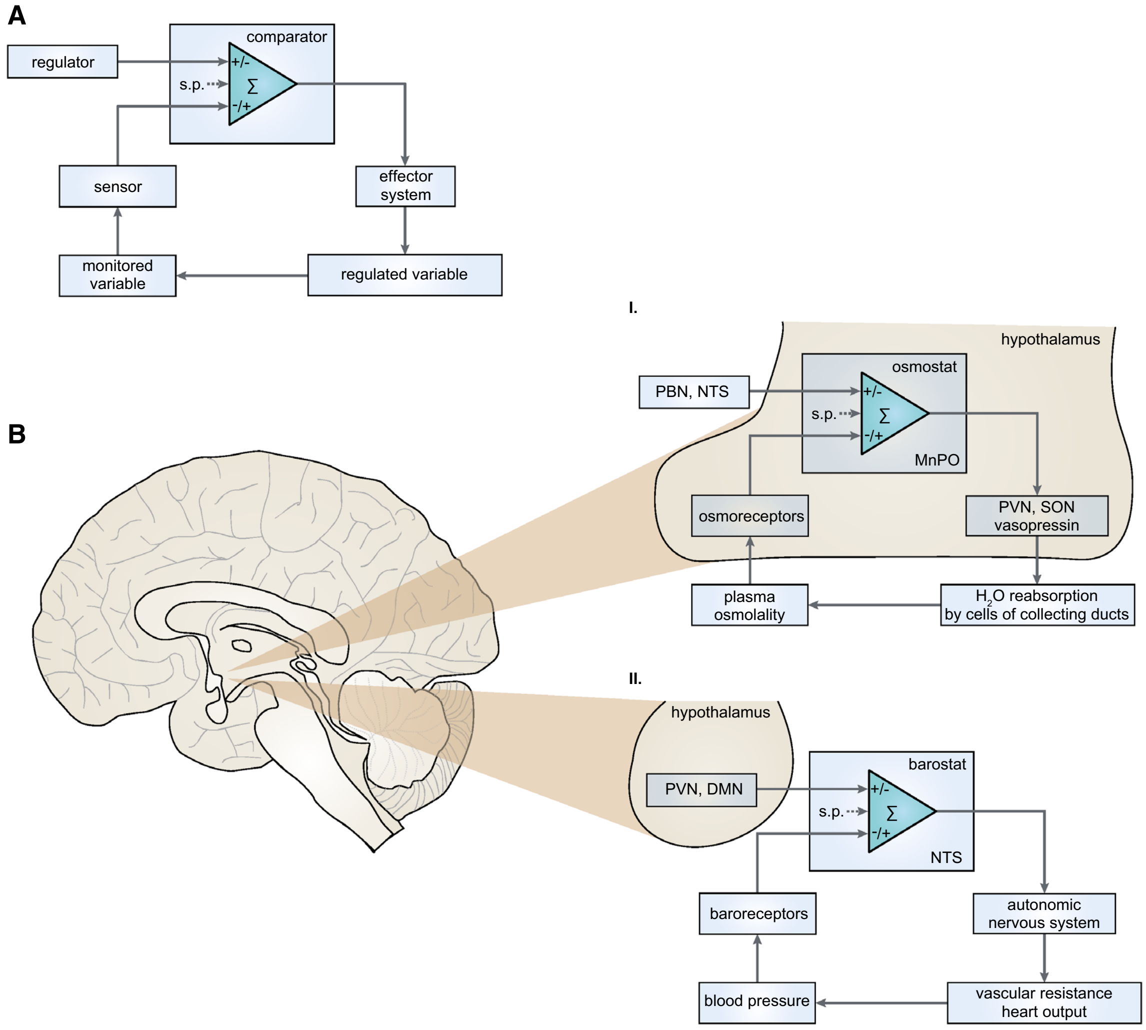

Fig. 1 **a** Schematic diagram of the basic components of a homeostat (modified from Goldstein 2010). **b** Schematic diagram of the hypothalamic homeostats regulating plasma osmolarity (I) and blood pressure (II). Whereas the hypothalamus contains a receptor, comparator, and effector of the osmostat, it only contains a regulator of the barostat. *DMN* hypothalamic dorsomedial nucleus, *MnPO* median preoptic nucleus, *NTS* nucleus of the solitary tract, *PBN* parabrachial nucleus, *PVN* hypothalamic paraventricular nucleus, *s.p.* set-point (physiological value) of the monitored variable

and CO_2, pH, and energy intake and expenditure (Goldstein and Kopin 2017). Because the majority of papers describing the role of neuroinflammation in the disruption of systemic homeostatic regulation is focused on the hypothalamus, the next chapters describe mechanisms underlying the relationship between hypothalamic inflammation and the development of somatic diseases.

Hypothalamic Inflammation Disrupts the Function of the Central Components of Homeostats: Central Role of Glial Cells

Whereas neurons in the hypothalamic nuclei are the basic functional units of central components of homeostats (Goldstein and Kopin 2017), glial cells are crucial for maintenance of tissue homeostasis in the hypothalamus by regulating nutrient delivery, the removal of waste products, and the modulation of processes related to synaptic transmission between neurons (Allen and Barres 2009). Therefore, glial cells significantly contribute to the maintenance of a highly stable brain *milieu* that ensures proper functioning of the central components of hypothalamic

Table 1 List of selected hypothalamic nuclei that significantly contribute to systemic homeostatic regulation

Nucleus	Regulated biological variables	Mechanism of biological variables regulation
Paraventricular nucleus	Plasma osmolality	AVP secretion into systemic circulation
	Blood pressure	Oxytocin and vasopressin released by premotor neurons in synapses with autonomous preganglionic neurons
	Immune system activity	CRH secretion into hypothalamic-pituitary portal circulation (regulation of plasma glucocorticoid levels)
Suprachiasmatic nucleus	Circadian rhythms	Synchronizing action of melatonin
	Reactive oxygen species production	Antioxidant action of melatonin
Supraoptic nucleus	Plasma osmolality	AVP secretion into systemic circulation
	Blood pressure	
Medial preoptic nucleus	Core body temperature	Regulation of the generation and loss of heat
	Aging	GnRH released into circulation regulates aging
Arcuate nucleus	Energy metabolism	Modulation of activity of central circuits regulating food intake and energy metabolism (neuromodulators released: AgRP, NPY, POMC, CART, galanin)
	Aging	GnRH released into circulation regulates aging
Ventromedial nucleus	Energy metabolism	Modulation of activity of central circuits regulating food intake and energy metabolism (neuromodulators released: cholecystokinin)
Dorsomedial nucleus	Energy metabolism	Modulation of activity of central circuits regulating food intake and energy metabolism (neuromodulators released: CART, galanin, cholecystokinin)

AVP arginine vasopressin, *AgRP* agouti-related peptide, *CART* cocaine- and amphetamine-regulated transcript, *CRH* corticoliberin, *NPY* neuropeptide Y, *POMC* proopiomelanocortin, *GnRH* gonadotropin-releasing hormone

homeostats, even in conditions of changing internal and/or external environments. As such, glial cells are sensitive to alterations in the chemical composition of extracellular fluid that surrounds them. However, if these alterations are significant and long-lasting, glial cells become activated, which in turn leads to the development of hypothalamic inflammation (de Git and Adan 2015; Burfeind et al. 2016; Rahman et al. 2018). The subpopulations of glial cells that contribute the most to hypothalamic inflammation are microglia and astrocytes (Le Thuc et al. 2017; Rahman et al. 2018). Microglia represent a subpopulation of macrophages localized in the central nervous system (CNS) and are involved primarily with immune functions. When activated, microglia release pro-inflammatory molecules, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) (Smith et al. 2012; Valdearcos et al. 2017). Astrocytes on the other hand, are especially important due to their role in regulating neuronal metabolism. However, they also contribute to neuronal proliferation, synaptogenesis, and neurotransmission (Nedergaard et al. 2003). Like microglia, activated astrocytes also produce inflammatory cytokines (Choi et al. 2014). Moreover, they contribute to hypothalamic inflammation by morphological changes known as astrocytosis. Astrocytosis, the most prevalent type of gliosis, may significantly influence signaling in the affected area and thus contribute to neuroinflammation (Garcia-Caceres et al. 2013; Buckman et al. 2015).

Activated glia-driven inflammatory processes in the hypothalamus alter the tissue *milieu* and thereby disrupt the functionality of the central components of hypothalamic homeostats (Burfeind et al. 2016; Rahman et al. 2018). Alterations in homeostatic control mechanisms may lead to the development of somatic diseases, or have a negative effect on the course of already present somatic diseases (Valdearcos et al. 2015). Importantly, as the activity of microglia in the brain increases with age (Koellhoffer et al. 2017), hypothalamic inflammation may represent a factor interconnecting aging with disturbance of homeostatic regulations, thereby participating in the increased incidence of somatic co-morbidities in the elderly.

Intracellular Signaling Pathways Triggering Inflammatory Processes in the Hypothalamus

Various factors may induce hypothalamic inflammation (Fig. 2) via activation of several different intracellular processes in hypothalamic glial cells. These processes include oxidative stress, endoplasmic reticulum stress, RNA stress, autophagy defects, or activation of Toll-like (TLR) and cytokine receptors (Fig. 2). The majority of these intracellular processes converge on the activation of c-Jun N-terminal kinase (JNK) and pathway IκB kinase/nuclear factor kappa B (IKK/NF-κB) (Fig. 3) (Cai and Liu 2011; Han et al. 2016).

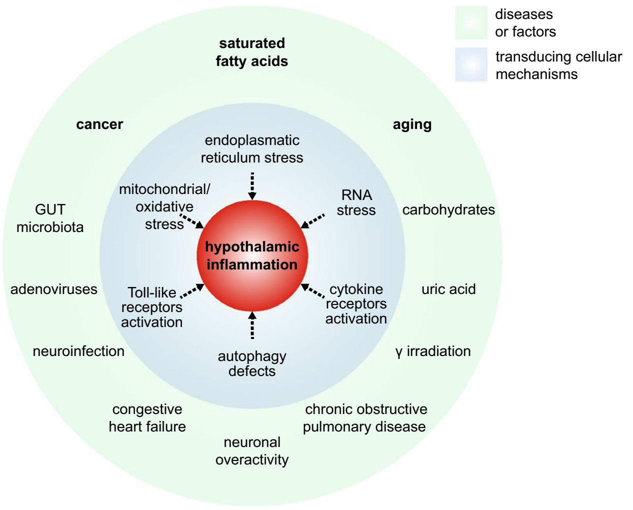

Fig. 2 Hypothalamic inflammation may be induced by several systemic factors, including overnutrition (excessive intake of fatty acids; (de Git and Adan 2015)), neuroinfection (caused by neurotrophic viruses, bacteria, parasites (Swaab 2004)), aging-associated changes (e.g., reduced anti-oxidative capacity), chronic diseases accompanied by cachexia (e.g., congestive heart failure, cancer, chronic obstructive pulmonary disease, and chronic kidney disease (Burfeind et al. 2016)), neuronal overactivity (Xanthos and Sandkuhler 2014), or γ irradiation of the hypothalamus (Velickovic et al. 2012; Ballesteros-Zebadua et al. 2014). Other factors such as increased intake of carbohydrates (Gao et al. 2017), elevated plasma levels of uric acid (Lu et al. 2015), alterations in gut microbiota (Moreira et al. 2012; Rocha et al. 2016), and somatic infection by adenoviruses (Wierucka-Rybak and Bojanowska 2014) may also induce hypothalamic inflammation. All these factors trigger inflammation of the hypothalamus by activation of several different cellular processes

JNK belongs to the family of mitogen-activated protein kinases (MAPK). It is assumed that activation of JNK is associated with oxidative and endoplasmic reticulum stress in hypothalamic glial cells and neurons (Zhang and Kaufman 2008). JNK may activate inflammation-inducing processes in the hypothalamus and additionally, hypothalamic inflammation may itself activate JNK. Activated JNK modulates the function of multiple transcription factors (such as activator protein 1—AP1), nuclear receptors, and other signaling pathways thereby affecting a wide spectrum of cellular processes (Cai and Liu 2011).

NF-κB is the key mediator of the immune response at the subcellular level and is activated by various biological factors, including immune stimuli (e.g., bacteria and their products, viruses, eukaryotic parasites), cytokines, and chemokines (Pahl 1999). There are several types of NF-κB. In its inactive form, NF-κB is a dimer associated with the IκB inhibitory molecule. The IKK is activated as the first step in the canonical activation of the IKK/NF-κB pathway (e.g., via the TLR). IKK in turn, phosphorylates IκB on two serine residues, which results in dissociation of IκB from NF-κB and to the ubiquitination and subsequent degradation of IκB. The released NF-κB complex is then transferred to the nucleus where it switches expression of target genes (Gilmore 2006), which include cytokines, chemokines and their modulators, immunoreceptors, acute phase proteins, and many others (Pahl 1999).

Hypothalamic Inflammation Alters Functions of Several Homeostats

Inflammation-induced dysfunction of hypothalamic homeostats leads to alteration of the activity of many effectors regulated by hypothalamic neurons:

- orexigenic and anorexinergic neuronal brain circuits modulating satiety (energy intake) (de Git and Adan 2015);
- sympathetic nerves innervating fat tissue to regulate metabolism (release of fatty acids and glycerol into circulation from white fat tissue) and energy expenditure (uncoupling mechanisms in brown fat tissue) (Bartness and Song 2007);
- autonomic nerves innervating the liver and regulating glucose storage and its release into circulation (Purkayastha et al. 2011b);
- sympathetic nerves innervating skeletal muscles and regulating metabolism (glucose reuptake) (Roatta and Farina 2010);
- autonomic nerves innervating the cardiovascular system to regulate vascular resistance, heart rate, and contractility (blood pressure regulation and thermoregulation) (Purkayastha et al. 2011a, b);
- autonomic innervation of endocrine glands, regulating their mass and hormone release (Wilson et al. 1998);
- release of liberins (corticotropin-releasing hormone—CRH, thyrotropin-releasing hormone—TRH, growth hormone–releasing hormone—GHRH, gonadotropin-releasing hormone—GnRH), and statins (growth hormone-inhibiting hormone—GHIH) that regulate secretion of hormones from endocrine glands (Zhang et al. 2013; Valdearcos et al. 2015; Rahman et al. 2018).

In the next chapters, we discuss the connection between hypothalamic inflammation and the development and progression of certain somatic diseases.

Hypothalamic Inflammation and Metabolic Syndrome

Metabolic syndrome is characterized by several metabolic abnormalities, including insulin resistance followed by impaired glucose tolerance (type 2 diabetes mellitus), central

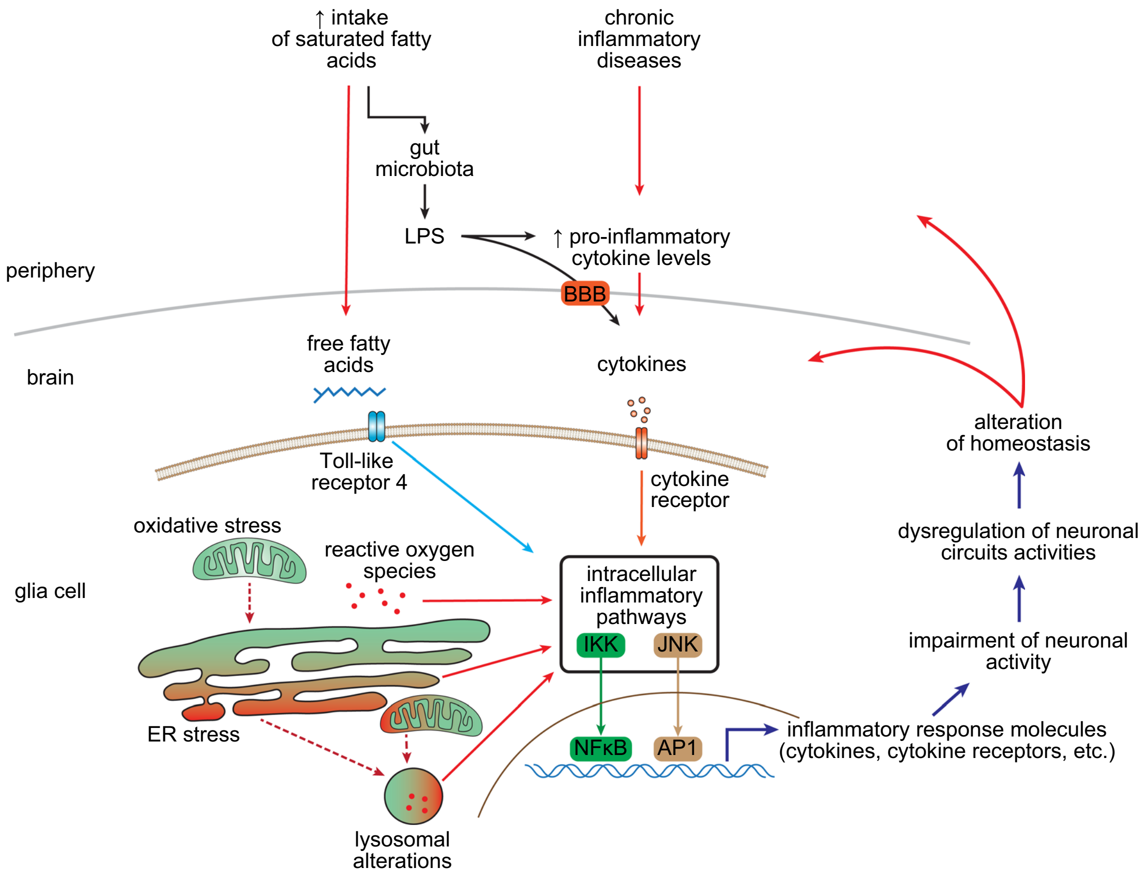

Fig. 3 Schematic depiction of the factors and molecular pathways participating in the development of hypothalamic inflammation. *AP1* activator protein 1, *BBB* blood–brain barrier, *ER* endoplasmic reticulum, *IKK* IκB kinase, *JNK* c-Jun N-terminal kinases, *NF-kB* nuclear factor kappa B. Modified from Cai and Liu (2011)

obesity, dyslipidemia, and hypertension (Kaur 2014). Investigation of the etiopathogenesis of metabolic syndrome is classically focused on peripheral factors participating in the development of insulin resistance that may lead to alteration of homeostatic regulations of metabolically active tissues, including the liver, skeletal muscles, and adipose tissue (Eckel et al. 2005). However, data published in the last decades have clearly shown that hypothalamic inflammation alters insulin sensitivity in peripheral tissues, increases food intake participating in obesity development, and alters blood pressure regulation. Moreover, hypothalamic inflammation is associated with central leptin resistance, another factor related to metabolic syndrome. Therefore, hypothalamic inflammation may represent a crucial factor in development of metabolic syndrome (Valdearcos et al. 2015; Rahman et al. 2018) (Fig. 4).

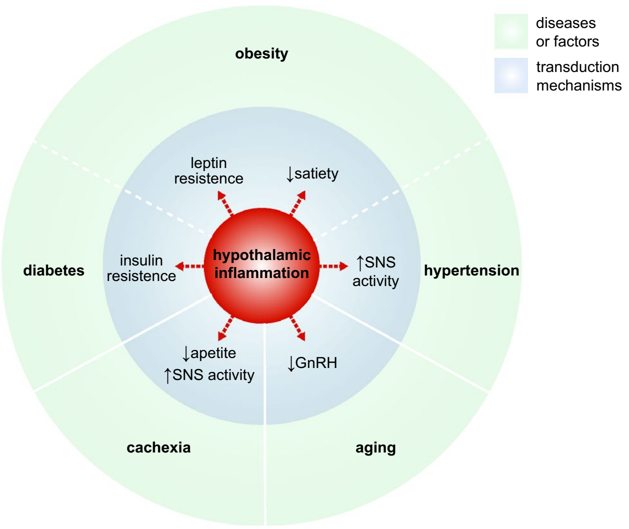

Fig. 4 Hypothalamic inflammation participates in the development of metabolic syndrome (obesity, diabetes, and hypertension) and cachexia, as well as contributes to aging. *SNS* sympathetic nervous system, *GnRH* gonadotropin-releasing hormone

Hypothalamic Inflammation and Obesity

The hypothalamus represents a key structure maintaining balance of energy intake and expenditure. The hypothalamus monitors glycemia, is informed about fat stores by adipokines, and receives hormonal signals related to food intake and nutrient absorption from the gastrointestinal system. Based on these signals, the hypothalamus regulates food intake-related behavior, as well as digestion, absorption, and storage of nutrients in metabolically active tissues. Regulators, comparators, and sensors of homeostats maintaining energy homeostasis are localized in the arcuate, paraventricular, ventromedial, and dorsomedial nucleus, along with the lateral hypothalamic area (Gao and Horvath 2008; Seoane-Collazo et al. 2015).

Subclinical inflammation, frequently found in obese individuals, is characterized by a slightly increased concentration of pro-inflammatory cytokines in fat tissue, skeletal muscles, and liver (Gregor and Hotamisligil 2011). Recent findings also indicate that in obese individuals subclinical inflammation is present in the hypothalamus and alters the functions of the above-mentioned hypothalamic nuclei (Zhang et al. 2008; Posey et al. 2009; Purkayastha et al. 2011a). Hypothalamic inflammation also affects the activity of homeostats regulating food intake, energy expenditure, insulin secretion, glucose production in the liver, and fatty acid metabolism. Thus, inflammatory changes in the hypothalamus may be an important component in the etiopathogenesis of obesity, diabetes mellitus, and metabolic syndrome (Rahman et al. 2018). Even if some data indicate that dietary sugars are an important factor in triggering hypothalamic inflammation (Gao et al. 2017), the majority of published data related to hypothalamic inflammation and overnutrition support a key role for the excessive intake of saturated fatty acids in the development of hypothalamic inflammation (Posey et al. 2009). Several experiments have shown that excessive intake of saturated fatty acids can cause hypothalamic inflammation directly through the induction of oxidative and endoplasmic reticulum stress, as well as through TLR4 activation (Kleinridders et al. 2009; Milanski et al. 2009; Posey et al. 2009). Moreover, increased levels of circulating pro-inflammatory cytokines in obese individuals may be involved in the maintenance of hypothalamic inflammation. Therefore, the following vicious circle may be proposed: (a) increased intake of saturated fatty acids induces hypothalamic inflammation in lean individuals; (b) hypothalamic inflammation leads to altered regulation of metabolism, reduced satiety signaling with subsequent increased food intake, and adiposity; (c) fat tissue enlarges, and pro-inflammatory activity in this tissue predominates, which in turn leads to development of subclinical inflammation characterized by increased plasma levels of pro-inflammatory cytokines; (d) circulating pro-inflammatory cytokines participate in the maintenance of hypothalamic inflammation, even if intake of saturated fatty acids is reduced; (e) prolonged hypothalamic inflammation participates in obesity maintenance and alters activity of central components of other homeostats in the hypothalamus. Additionally, these disturbances may lead to other alterations (e.g., reduced insulin sensitivity, increased blood pressure) followed by development of metabolic syndrome (Castanon et al. 2014) (Fig. 5).

Recently, experimental findings have elucidated the molecular mechanisms responsible for induction of hypothalamic inflammation by increased intake of saturated fatty acids using animals fed a high-fat diet (HFD) (Tang et al. 2015; Jais and Bruning 2017). Although it is still not clear whether neurons or glial cells are primarily affected in HFD-induced inflammatory changes in the hypothalamus, interaction of both cell types appears to be essential for induction

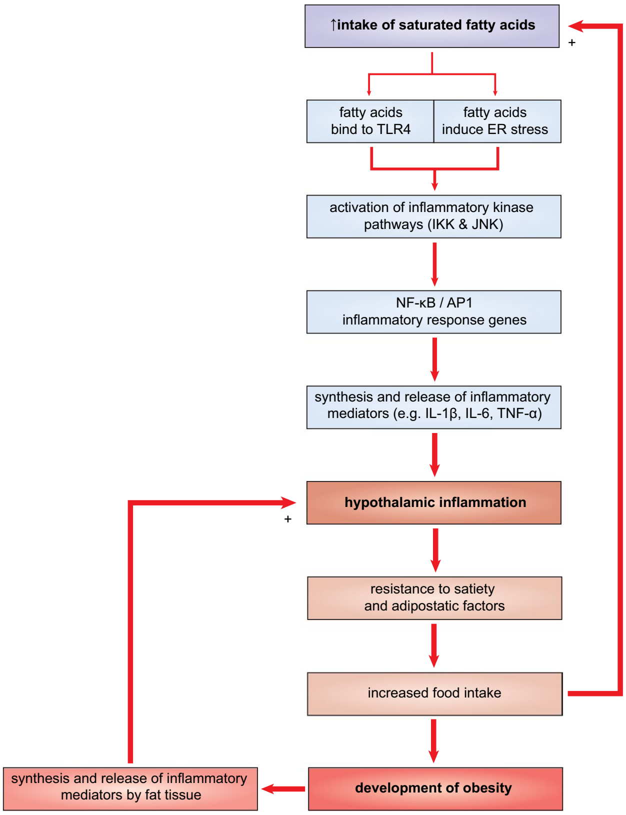

Fig. 5 Proposed cascade of pathological events that connect increased intake of saturated fatty acids with the development of obesity. Possible positive feedback loops are also shown. *TLR4* toll-like receptor 4, *ER* endoplasmic reticulum, *IKK* I kappa B kinase, *JNK* c-Jun N-terminal kinase, *NF-κB* nuclear factor kappa B, *AP1* activator protein 1, *IL-1β* interleukin-1 beta, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor alpha

and maintenance of hypothalamic inflammation (Thaler et al. 2010; de Git and Adan 2015).

Activation of the TLRs, in particular the TLR4 subtype, plays a key role in the development of HFD-induced hypothalamic inflammation (Milanski et al. 2009; Posey et al. 2009). TLRs represent a group of membrane receptors whose function is associated with innate immunity. Activation of these receptors by lipopolysaccharides and other microbial components triggers an intracellular signaling cascade resulting in the synthesis of pro-inflammatory molecules (Fresno et al. 2011). In rodents, saturated fatty acids bind to TLR4 and trigger an interaction between TLR4 and the myeloid differentiation primary response gene 88 (MyD88) (Milanski et al. 2009), an adapter molecule connecting TLR4 with intracellular signaling cascades including JNK and IKK/NF-κB (Velloso and Schwartz 2011). In support of this, knockout of either TLR4 or MyD88 prevents HFD-induced obesity (Kleinridders et al. 2009; Milanski et al. 2009). Moreover, recent data indicate that stimulation of TLR4 by saturated fatty acids also leads to activation of a MyD88 independent signaling pathway through induction of endoplasmic reticulum stress. This is supported by the fact that MyD88 gene knockout does not affect the expression of inflammatory markers or markers of endoplasmic reticulum stress in mice fed HFD (Kleinridders et al. 2009).

In the brain, expression of TLR4 is found in glial cells, including microglia and astrocytes, as well as in neurons (Trudler et al. 2010). However, published data indicate that glial cells play a primary role in the inflammation induced by interactions between saturated fatty acids and TLR4. Studies using cell culture have shown that administration of saturated fatty acids to astrocytes induces the expression of pro-inflammatory cytokines in these cells (Gorina et al. 2011; Gupta et al. 2012), while saturated fatty acids do not induce this effect if added to a culture of hypothalamic neurons (Choi et al. 2010). While fatty acids can cross the blood–brain barrier by several mechanisms and directly activate TLR4, the specific mechanism of transport depends on the structure of the particular acid (Spector 1988; Hamilton and Brunaldi 2007). Moreover, TLR4 are also found on the endothelial cells of the blood–brain barrier. Their activation can therefore induce changes in the central expression of cytokines even if their agonists do not cross the blood–brain barrier themselves (Quan et al. 1998). However, it is necessary to note that several recent papers question the role of saturated fatty acids as agonists of TLR4 (Erridge and Samani 2009; Lancaster et al. 2018). It is possible that the major agents triggering the TLR signaling cascade are not fatty acids, but bacterial lipopolysaccharides and lipopeptides, which often occur as contaminants in complexes of chemicals containing fatty acids administered to cell cultures (Erridge and Samani 2009). In addition, HFD can modify intestinal microflora and induce production of lipopolysaccharides. These lipopolysaccharides subsequently activate the TLRs, which may ultimately lead to neuroinflammation (Moreira et al. 2012; Rocha et al. 2016). Although the precise mechanism by which increased intake of saturated fatty acids causes neuroinflammation has not been fully explained, it is known that the final pathway involves TLR4 activation and production of pro-inflammatory cytokines.

Hypothalamic inflammation induced by HFD is associated with increased levels of several pro-inflammatory cytokines in hypothalamic tissue. These cytokines include TNF-α, IL-1β, and IL-6 (Wang et al. 2012). TNF-α seems to have an important role in the hypothalamic inflammation associated with a positive energy balance, as its intracerebroventricular administration leads to increased expression of suppressor of cytokine signaling 3 (SOCS3), even at low doses. SOCS3 is a negative regulator of leptin signaling and its increase results in reduction of the leptin effect in the hypothalamus. Furthermore, central administration of low doses of TNF-α is associated with increase in basal plasma insulin levels, as well decrease in the expression of thermogenic proteins in brown fat tissue of rats (Arruda et al. 2011).

Various studies have indicated that interactions between neurons and glial cells via cytokine signaling are involved in induction and maintenance of hypothalamic inflammation (de Git and Adan 2015; Burfeind et al. 2016). In addition to cytokine signaling, interactions between neurons and glial cells may also include other mechanisms. For example, Thaler et al. (2012) found that rodents fed a HFD developed reactive gliosis in the arcuate nucleus within a week of feeding. Gliosis in the arcuate nucleus influences both microglia and astrocytes and significantly affects signal transmission in this brain structure. Conversely, administration of the antimitotic drug arabinofuranosyl cytidine reduces the number of activated microglia in the arcuate nucleus. Arabinofuranosyl cytidine also prevents the activation of NF-κB and reduces the expression of TNF-α in arcuate nucleus microglia. Finally, arabinofuranosyl cytidine reduces food intake, weight gain, and restores central leptin signaling in mice fed an HFD (Andre et al. 2017).

The effect of hypothalamic inflammation on the development of obesity is mediated by altering the activity of hypothalamic orexinergic and anorexinergic neurons. For example, the dietary-induced pro-inflammatory milieu of the arcuate nucleus impairs both insulin and leptin signaling (Munzberg et al. 2004; Zabolotny et al. 2008; Zhang et al. 2008). This leads to inhibition of catabolic processes via reduction of the activity of anorexinergic neurons synthesizing proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), along with the potentiation of anabolic processes via exaggeration of activity of orexinergic neurons synthesizing agouti-related peptide (AgRP) and neuropeptide Y (NPY). Furthermore, activation of orexinergic neurons in the arcuate nucleus inhibits the activity of anorexigenic neurons in the hypothalamic paraventricular nucleus, promoting feeding behavior by reducing satiety (Rahman et al. 2018). This effect may be partially explained by the different roles of NF-κB in orexinergic and anorexinergic neurons. Under physiological conditions, NF-κB is a component of signaling pathways that are involved in the regulation of energy metabolism in POMC/CART neurons. When activated, NF-κB interacts with a POMC promoter, triggering POMC expression (Jang et al. 2010). In mice fed by HFD for a long period of time, increased NF-κB activation in the POMC/CART neurons of the arcuate nucleus was detected. Yet, NF-κB was not able to bind the POMC promoter because of the hypermethylation caused by chronic HFD feeding (Shi et al. 2013). Taken together, hypothalamic inflammation induced by excessive food intake is on one hand, associated with increased activation of NF-κB in AgRP/NPY neurons; while on the other hand, it disrupts POMC gene expression (de Git and Adan 2015). The differing responses of POMC/CART and AgRP/NPY neurons in hypothalamic inflammation associated with HFD feeding were also confirmed by a study using a gene knockout for IKK. While AgRP/NPY neuron-specific knockout of IKK partially prevented obesity development in mice receiving HFD (Zhang et al. 2008), IKK knockout in POMC/CART neurons had no such effect (Purkayastha et al. 2011a). These data indicate the primary role of AgRP/NPY neurons in inflammation-related mechanisms participating in the development of obesity.

A possible explanation of mechanisms related to HFD-induced, positive energy balance is found in a study by Thaler et al. (2012). This study detected an increase in the synthesis of heat shock protein 72 (hsp72), a marker of subcellular stress responses in POMC/CART neurons, in mice after one week of HFD. After 8 months, a significant reduction in the number of POMC/CART neurons was observed in the arcuate nucleus of these animals. If neuronal damage due to hypothalamic inflammation induced by excessive intake of saturated fatty acids involves predominantly anorexinergic rather than orexinergic neurons, the loss of POMC/CART neurons could possibly explain the shift in energy metabolism in favor of the positive energy balance (Thaler et al. 2012).

Hypothalamic Inflammation and Diabetes Mellitus

Type 2 diabetes mellitus is characterized by impaired regulation of glucose homeostasis resulting from insulin resistance in metabolically active tissues (liver, skeletal muscles, and adipose tissue) (Blair 2016). The homeostat regulating glycemia (glycostat) is localized in the pancreas and is represented by pancreatic β-cells. These cells comprise a sensor, comparator, as well as an effector of glycostat that regulates plasma glucose levels through secretion of insulin. In the last decades, it was confirmed that besides the pancreas, the hypothalamus also represents an important regulator of glycemia. Furthermore, the hypothalamus contains not only central components of homeostats regulating glycemia, but also sensory components of these homeostats as well (Schwartz et al. 2013).

Hypothalamic inflammation may participate in the development of peripheral insulin resistance and type 2 diabetes mellitus through alteration of the activity of autonomic nerves innervating the liver, muscles, adipose tissue, and pancreas (Han et al. 2016). In addition, the reduced hypothalamic insulin and glucose sensitivity seen as a consequence of hypothalamic inflammation, along with the subsequently altered neuroendocrine regulatory mechanisms (including hypothalamo-pituitary-adrenocortical axis and glucocorticoids release) may also participate in the development of insulin resistance.

In support of above-mentioned assumptions, it has been found that the feeding of laboratory animals with HFD induces development of central insulin resistance (for review see Pimentel et al. 2014). In addition, induction of hypothalamic inflammation in laboratory animals increases base-line plasma insulin levels and impairs insulin signal transduction in liver and skeletal muscles (Arruda et al. 2011).

Hypothalamic Inflammation and Central Leptin Resistance

It has been suggested that leptin signaling dysfunction (leptin resistance) represents one of the central components of the etiopathogenesis of metabolic syndrome (for review see (Eckel et al. 2005)). Hypothalamic neurons detecting plasma leptin concentrations represent a sensory component of homeostats regulating the balance between energy intake and expenditure (Gao and Horvath 2008; Seoane-Collazo et al. 2015). Leptin resistance in these neurons disrupts hypothalamic homeostatic regulation and participates in the development of obesity and associated metabolic disorders (de Git and Adan 2015). Several data indicate that hypothalamic leptin resistance is caused by inflammation of hypothalamic tissue. In support of this, it has been found that found that a HFD can induce leptin resistance (Munzberg et al. 2004).

If hypothalamic inflammation is present, the leptin signalization is disturbed at several levels. Under physiological conditions, leptin regulates its own effect by inducing expression of protein tyrosine phosphatase 1B (PTP1B) and SOCS3 via signal transducer and activator of transcription 3 (STAT3). Furthermore, PTP1B and SOCS3 act as negative regulators of leptin signaling by inhibiting the Janus kinase

2-STAT3 (JAK2-STAT3) signaling cascade via an ultrashort loop negative feedback (Velloso and Schwartz 2011). However, excessive intake of saturated fatty acids activates the IKK/NF-κB pathway and attenuates leptin sensitivity by increasing the expression of SOCS3 and PTP1B in hypothalamic cells (Zabolotny et al. 2008; Zhang et al. 2008). Moreover, it is thought that one of the NF-κB subunits may bind to STAT3 and block its promoter activity in POMC neurons (Shi et al. 2013). In addition, centrally administered palmitic acid suppresses leptin's attenuating effect on gene expression of molecules associated with glucose transport, gluconeogenesis, and lipogenesis in the liver, thereby altering processes related to energy homeostasis in the liver of laboratory mice (Cheng et al. 2015).

Hypothalamic Inflammation and Hypertension

A central component of the barostat (a homeostat regulating blood pressure) is localized in the lower brain stem, specifically in the nucleus of the solitary tract. However, hypothalamic nuclei, namely the paraventricular and dorsomedial, are also regulators of the barostat. These nuclei, especially the paraventricular nucleus, exert their regulatory influence on blood pressure via several mechanisms, including modulating the activity of the sympathetic nervous system (SNS) (Ulrich-Lai and Herman 2009) (Fig. 1). In this way, hypothalamic inflammation may disrupt activity of these regulators and participate in the development of hypertension.

Published data indicate that the renin-angiotensin-aldosterone system (RAAS) represents a link between hypothalamic inflammation and hypertension. It is believed that increased levels of plasma angiotensin II (Ang II) may lead to resetting of the barostat by induction of hypothalamic inflammation thereby causing a maintenance of blood pressure at higher levels (Khor and Cai 2017). Ang II binding to AT1 receptors promotes inflammation by several mechanisms, including free radical generation and activation of TLR4 expression and immune cells, followed by increased secretion of pro-inflammatory cytokines (Benigni et al. 2010). In addition, hypothalamic inflammation may be indirectly induced by increased activity of peripheral RAAS by activation of central RAAS. This way, Ang II synthesized by neuronal cells may then induce pro-inflammatory processes in the hypothalamus. Finally, Ang II may also induce inflammation by activation of pro-inflammatory processes in hypothalamic vessels (Erdos et al. 2006; Braga 2010; Cardinale et al. 2012).

Cardinale et al. (2012) found that Ang II administration, in addition to increasing the formation of reactive oxygen species (ROS), also increases in the paraventricular hypothalamic nucleus the expression of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α thereby inducing inflammatory process in this hypothalamic nucleus. In support of this, several studies have detected elevated expression of pro-inflammatory cytokines in the paraventricular nucleus of the hypothalamus in animal models of hypertension (Sriramula et al. 2008; Kang et al. 2009). Importantly, stimulation of this nucleus by IL-1β and TNF-α increases adrenocorticotropic hormone secretion as well as sympathetic nervous system activity (Han et al. 2016). Moreover, the presence of pro-inflammatory cytokines and ROS in the paraventricular nucleus of the hypothalamus leads to activation of NF-κB (Cardinale et al. 2012). NF-κB activation in turn increases concentrations of both ROS and pro-inflammatory substances via a positive feedback loop, thereby contributing to further disruption of central blood pressure regulation (Bubici et al. 2006; Kang et al. 2009). At the cellular level, NF-κB activation triggers several molecular pathways (including SOCS3 and PTP1B) that participate in SNS activation, resulting in increased blood pressure. In addition, activation of perivascular macrophages by IL-1β and TNF-α increases production of prostaglandin E_2, which leads to activation of the paraventricular hypothalamic nucleus, followed by increased activity of SNS, and subsequently increased blood pressure (Khor and Cai 2017).

Finally, Ang II may be involved in disrupting the functionality of homeostats regulating blood pressure by various different mechanisms. For example, oxidative stress caused by Ang II induces inflammatory changes in the blood–brain barrier microvasculature that increase its permeability, which further enhances hypertension related neuroinflammation (Zhang et al. 2010). In addition, modified leptin signaling or altered activity of the central melanocortin system may also be involved in the development of hypertension as they are related to hypothalamic inflammation as well. Administration of leptin induces hypertension in laboratory mice, while administration of anti-leptin antibodies reduces blood pressure (Simonds et al. 2014). Similarly, when an agonist of melanocortin receptor type 3 and 4 (MC3R/MC4R) is centrally administrated, it induces an increase of SNS activity, as well as blood pressure (Li et al. 2013); while central administration of an antagonist of these receptors has the opposite effect (da Silva et al. 2008). Considering that changes in leptin and central melanocortin system signaling are present in patients with obesity and metabolic syndrome, it is possible that some of these mechanisms may also contribute to the development of hypertension. In addition, in metabolic syndrome, the patients' hypertension may be associated with an already existing hypothalamic inflammation that occurs in response to other factors, such as a chronically elevated intake of saturated fatty acids. Thus in patients with obesity, hypertension may be induced by pre-existing inflammation in the hypothalamus associated with the production of pro-inflammatory cytokines, NF-κB activation in POMC neurons, as well as altered central leptin and melanocortin signaling; all of which converge to induce sympathetic nervous system activation and elevate blood pressure (Purkayastha et al. 2011). Inflammatory changes in the hypothalamus may also lead to increased hypothalamic synthesis of Ang II, thereby creating a vicious circle maintaining elevated blood pressure, which can lead to the progression of hypertension (Khor and Cai 2017).

Plenty of data have shown that the incidence of hypertension is increased in obese individuals, with estimations that 60–70% of arterial hypertension in adults is attributed to adiposity. Also, available data indicate that obesity-related hypertension represents a distinct hypertensive phenotype (Kotchen 2010). The findings discussed above and in previous chapters indicate that hypothalamic inflammation represents a crucial factor interconnecting etiopathogenetic mechanisms that lead to the development of hypertension in obese individuals.

Hypothalamic Inflammation and Cachexia

Whereas the majority of data related to hypothalamic inflammation indicate that this pathological process is connected to a positive energy balance followed by development of obesity, published data show that hypothalamic inflammation is also present in patients with the opposite condition, cachexia (Pimentel et al. 2014).

Cachexia represents a life-threatening condition characterized by a significant decrease in body weight due to muscle protein catabolism (Evans et al. 2008). This maladaptive syndrome is present in a number of chronic diseases, including cancer (Vaughan et al. 2013), infections (Vonroenn et al. 1992), cardiovascular (e.g., heart) failure, (Okoshi et al. 2013), and respiratory diseases (e.g., chronic obstructive pulmonary disease) (Sanders et al. 2016). These diseases are all characterized by a prolonged inflammatory response accompanied by significantly increased levels of circulating pro-inflammatory cytokines, particularly IL-1β, IL-6, and TNF-α (Moldawer et al. 1987; Levine et al. 1990; Anker et al. 1999; Borges et al. 2015).

Whereas the majority of cachexia-related studies are focused on investigating factors that disrupt the anabolic/catabolic balance in muscles and other peripheral tissues, it is suggested that the catabolic changes in soft tissues induced by the direct action of pro-inflammatory cytokines are not sufficient for full development of cachectic syndrome. In support of this, recent studies indicate that cachexia is also connected with hypothalamic inflammation triggered by increased plasma levels of pro-inflammatory cytokines. This assumption is supported by the observation that centrally administered IL-1β enhances expression of muscle ring-finger protein-1 (also known as tripartite motif containing 63, MurF1), which mediates muscular atrophy in skeletal muscles. Furthermore, central administration of IL-1β reduces food intake in rats, whereas intraperitoneal administration of IL-1β has no such effect (Braun et al. 2011). In summary, recent data indicate that chronic, significantly elevated levels of pro-inflammatory cytokines in the circulation induce a negative energy balance in the organism by altering the function of central components of homeostats regulating energy intake and expenditure (Wisse et al. 2007; Braun et al. 2011).

Importantly, hypothalamic inflammation may represent a factor that perpetuates development of cachexia. In this way, increased plasma levels of pro-inflammatory cytokines in chronic diseases, such as oncologic, cardiovascular, or respiratory diseases may lead to development of hypothalamic inflammation followed by dysregulation of homeostatic regulation of autonomic nerves (innervation of muscles, liver and other organs) that may further potentiate dysregulation of metabolism and enhance peripheral, pro-inflammatory reactions. In this way, neuro-inflammatory processes in the hypothalamus induced by peripheral inflammation may play a key role in the development of cachexia in several chronic diseases (Wisse et al. 2007; Braun et al. 2011; Burfeind et al. 2016).

Inflammation in the hypothalamus may participate in the development of cachexia by altering activity of the central melanocortin system. For example, intraperitoneal injection of lipopolysaccharide in rats results in a significant increase in the expression of POMC and CART mRNA in the arcuate nucleus within four hours after administration (Sergeyev et al. 2001), implicating the involvement of NF-κB as it is required for increased expression of POMC (Jang et al. 2010; Shi et al. 2013; Burfeind et al. 2016). Additionally, changes in POMC and CART expression are accompanied by decreased food intake (Sergeyev et al. 2001). In addition to changes in anorexinergic neurons, changes in orexinergic neurons also occur in response to peripheral inflammation. After intraperitoneal administration of lipopolysaccharide, a decrease in AgRP protein release was detected despite increased levels of AgRP mRNA (Scarlett et al. 2008). The presence of cytokine receptors in the arcuate nucleus (Utsuyama and Hirokawa 2002) suggests that direct action of pro-inflammatory cytokines on subpopulations of orexinergic and anorexinergic neurons plays a role in the initiation of hypothalamic inflammation in the presence of peripheral inflammation. This is also supported by studies employing central administration of pro-inflammatory cytokines. For example, intracerebroventricular administration of TNF-α decreases food intake in rats (Romanatto et al. 2007). Similarly, centrally administrated IL-1β also decreases food intake (Gonzalez et al. 2006), probably due to the reduced expression of NPY in the hypothalamus (Gayle et al. 1997) and activation of POMC neurons in the arcuate nucleus

(Scarlett et al. 2007). Furthermore, central administration of IL-1β also triggers catabolism in muscle tissues (Braun et al. 2011).

In addition to changes in the central melanocortin system, inflammatory changes in the hypothalamus are also associated with activation of the neuroendocrine stress reaction, specifically those involving the hypothalamic–pituitary–adrenocortical (HPA) axis. Recent data indicate that IL-1β plays an important role in these processes as it can activate the HPA axis. Moreover, previous studies using animal models of cachexia detected an increase in IL-1β mRNA expression within the hypothalamus (Berkenbosch et al. 1987; Sapolsky et al. 1987; Braun et al. 2011). It is thought that HPA axis activation results in elevated circulating glucocorticoid levels that may lead to an increased expression of genes playing a role in skeletal muscle proteostasis (Braun et al. 2011). In support of this, a recently published study has shown that glucocorticoids activate NF-κB in skeletal muscles, which in turn leads to increased expression of muscle atrophy mediators such as MuRF1 (Fry et al. 2016). Additionally, activation of the HPA axis leads to the release of amino acids from skeletal muscles into the circulation (Burfeind et al. 2016).

The acute phase of hypothalamic inflammation associated with a negative energy balance has an adaptive function as it promotes survival of an organism through behavioral changes and shifting anabolic/catabolic balance during acute diseases. It becomes detrimental only when transitioned to a chronic stage, as a chronic form of hypothalamic inflammation may subsequently lead to a significant disruption of the energy balance and the development of cachexia (Burfeind et al. 2016). Mechanisms responsible for the transition of acute, time-limited hypothalamic inflammation to the chronic stage have not yet been elucidated in detail. Although pro-inflammatory cytokines such as IL-1β acutely induce a reduction in food intake and lead to the activation of the HPA axis, their long-term administration causes receptor desensitization and is not sufficient for the development of cachexia (Hill et al. 1996). Therefore, it is likely that other mechanisms and signal molecules are necessary. One of these mechanisms may include leukemic inhibitory factor (LIF). Similar to increased expression of other pro-inflammatory cytokines, expression of LIF was also increased following lipopolysaccharide administration (Brown et al. 1994; Daniel et al. 2016). LIF via its receptor, induces POMC expression, increases the release of α-melanocyte-stimulating hormone (α-MSH) from the anorexinergic neurons of the arcuate nucleus (Grossberg et al. 2010), and together with IL-1β can participate in activation of the HPA axis in response to inflammation (Auernhammer et al. 1998; Chesnokova and Melmed 2000). It appears that the effects of LIF overlap with the effects of IL-1β and it is likely that these signal molecules can act synergistically. However, unlike IL-1β, chronic LIF administration does not lead to desensitization, and therefore this cytokine may participate in the transition of hypothalamic inflammation to the chronic stage (Beretta et al. 2002; Prima et al. 2004). Another potential mechanism of transitioning acute hypothalamic inflammation into the chronic stage was described by Burfeind et al. (2016). They have suggested that increased peripheral levels of pro-inflammatory cytokines can lead to changes in the blood–brain barrier triggering the activation of the hypothalamic endothelium and consequently the expression of pro-inflammatory cytokines and adhesion molecules by endothelial cells. These changes at the blood–brain barrier, together with changes in the central expression of chemokines, could ultimately lead to the entry of leukocytes into the CNS, potentiating neuroinflammation and the transition to chronic stage hypothalamic inflammation (Burfeind et al. 2016).

Interestingly, accumulated findings have shown that hypothalamic inflammation plays a role in two pathological conditions that are completely opposite from the view of homeostasis of energy intake and expenditure, obesity, and cachexia. These counterintuitive findings may be explained based on the differences in plasma cytokine levels found in obese and cachexic individuals. Whereas obese individuals show only a slight increase in plasma pro-inflammatory cytokines, plasma levels of these molecules are much higher in patients with cachexia. Therefore, it is suggested that the degree of inflammation determines whether inflammation-induced alterations of hypothalamic homeostats will result in a positive or negative energy balance (Pimentel et al. 2014) (Fig. 6).

Hypothalamic Inflammation and Aging

Aging is a progressive process accompanied by a gradual disruption of homeostatic regulation at all levels of biological systems, including cellular, tissue, and systemic. Recent data indicate that functional alteration of the central components of hypothalamic homeostats caused by inflammation plays a significant role in aging (Gabuzda and Yankner 2013).

Aging is accompanied by changes at the cellular level when aging cells acquire a so-called senescent secretion phenotype (Ovadya and Krizhanovsky 2014). These changes are related to telomere shortening, genome instability, epigenetic changes, and proteostasis disruption (Lopez-Otin et al. 2013). Since cells with a senescent profile have a pro-inflammatory phenotype, their accumulation is accompanied by chronic subclinical inflammation. Furthermore, increased concentrations of pro-inflammatory cytokines (e.g., IL-6, TNF-α), acute phase proteins, ROS, and antibodies are present in the

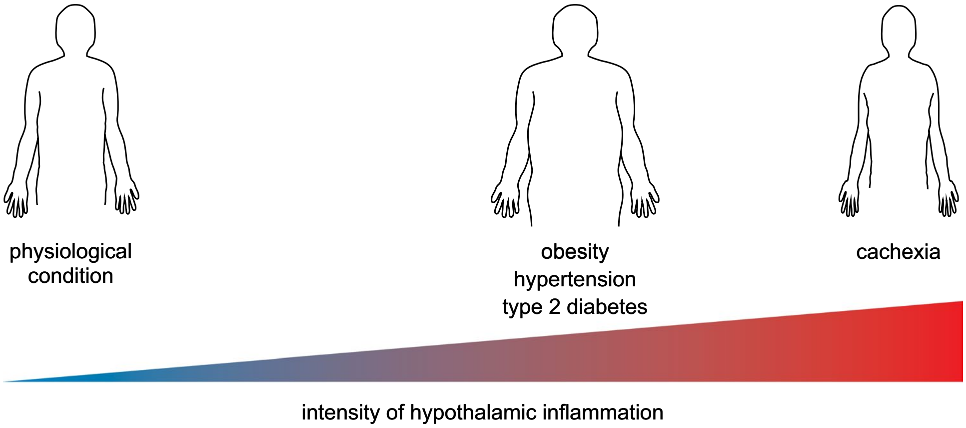

Fig. 6 Hypothalamic inflammation may be found in individuals with different pathological conditions or diseases, such as obesity, hypertension, type 2 diabetes mellitus, or tumor-associated cachexia. The effect of hypothalamic inflammation on an organism's energy balance depends on the intensity of hypothalamic inflammation, which positively correlates with the level of circulating pro-inflammatory cytokines (modified from Pimentel et al. 2014)

peripheral circulation of the aging organism (Franceschi et al. 2000; Deleidi et al. 2015). This peripheral, subclinical inflammation may exaggerate pro-inflammatory activity of microglia, initiate or potentiate microglia aging, and contribute to the development of neuroinflammation in the hypothalamus (Franceschi et al. 2000; Ye and Johnson 2001; von Bernhardi et al. 2010).

In the brain, changes associated with aging are characterized by microglial senescence and hyperactivity (Streit et al. 2004). Moreover, senescent microglia lose phagocytotic ability and are a source of pro-inflammatory cytokines due to their uncontrolled activation (Sheng et al. 1998; Sierra et al. 2007; Njie et al. 2012). Therefore, age-related changes in nervous tissue may participate in the development of hypothalamic inflammation, which may be responsible for the increased incidence of co-morbidities in elderly. Hypothalamic inflammation may also accelerate already present diseases (e.g., hypertension, metabolic syndrome, or atherosclerosis), as well as neurodegenerative and psychiatric ones (Ovadya and Krizhanovsky 2014).

The above-mentioned facts indicate that age-related inflammation in the hypothalamus participates in the development of somatic diseases and therefore potentiates aging-related functional deterioration across the body. However, recent data suggest that hypothalamic inflammation may promote aging-related changes by another mechanism, as well. Mechanistic studies in mice have shown that NF-κB and IKKβ exaggerate aging of the organism by reducing release of GnRH. In support of this, aging is decelerated in mice treated by GnRH. These data indicate that the hypothalamus plays an important role in systemic aging and lifespan control via modulation of GnRH secretion (Zhang et al. 2013). Therefore, reduction of hypothalamic inflammation may represent promising approach for attenuation of systemic aging and prolonging lifespan.

Hypothalamic Inflammation: The Cause or Consequence of Somatic Disease?

The above-mentioned facts suggest that hypothalamic inflammation plays a significant role in the etiopathogenesis of various somatic diseases. On the other hand, inflammatory changes in the hypothalamus may result from pathological processes that accompany already present somatic diseases. Therefore, it may be difficult to assess whether a given somatic disease is a consequence of hypothalamic inflammation and associated alterations of hypothalamic homeostatic regulations, or whether the disease itself induces hypothalamic inflammation, which then perpetuates progression of somatic disease forming a vicious cycle (Castanon et al. 2014; Burfeind et al. 2016; Khor and Cai 2017) (Fig. 7).

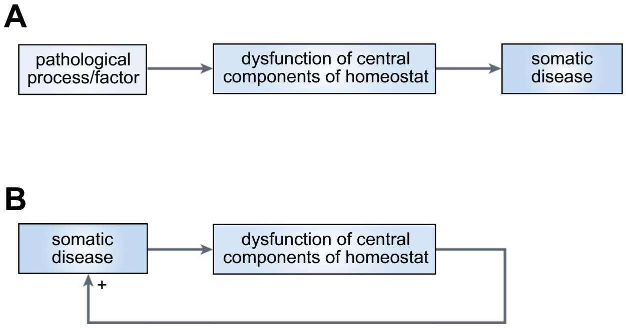

Fig. 7 **a** Long-term increases in plasma concentrations of saturated fatty acids or cytokines may induce the development of hypothalamic inflammation. Inflammatory changes in the hypothalamus then alters activity of central components of homeostats. This disturbance of homeostatic regulation then leads/participates in the development of various somatic diseases (e.g., obesity, diabetes, and hypertension). **b** Somatic disease (e.g., cancer) may also lead to the dysfunction of central components of homeostats localized in the hypothalamus, which results in acceleration of pathological processes. In the case of cancer, there is a change in the homeostat set-point, which regulates the energy balance of the organism. This resetting of the set-point contributes to the development and progression of cachexia

Acute and Chronic Hypothalamic Inflammation

Available data indicate that in the acute phase, hypothalamic inflammation exerts an adaptive response of an organism to a triggering stimulus. In this phase, expression of the inflammatory markers in the hypothalamus is essential for homeostasis maintenance (Sergeyev et al. 2001; Wisse et al. 2007). However, if hypothalamic inflammation lasts long enough, it can lead to further functional alterations of the central components of homeostats (Beretta et al. 2002; Prima et al. 2004; Grossberg et al. 2010), while the development of somatic diseases then participates in the progression of inflammation. This results in the development of a vicious cycle, in which chronic hypothalamic inflammation may significantly contribute to further progression of somatic disease, which can then potentiate inflammatory changes in the hypothalamus. This leads to the exacerbation of pathological changes on multiple levels and the disruption of homeostasis. If compensatory responses fail, such as in tumor cachexia, hypothalamic inflammation may have fatal consequences (Burfeind et al. 2016). However, as there is no clear borderline between acute and chronic hypothalamic inflammation, there is no clear borderline between its adaptive and maladaptive functions. Thus, hypothalamic inflammation should be understood as a dynamic process whose effect on the organism can vary significantly depending on its stage.

Detection of Hypothalamic Inflammation

In animal studies, the presence of hypothalamic inflammation is determined from hypothalamic samples by various in vitro and ex vivo methods. However, in clinical studies it is feasible to detect neuroinflammation in probands using in vivo imaging methods (Jacobs et al. 2012). In this way, the presence and dynamics of hypothalamic inflammation can be investigated through non-invasive imaging methods such as positron emission tomography (PET), single photon-emission computed tomography (SPECT), and magnetic resonance imaging (MRI) (Jacobs et al. 2012). For example, several markers of microglial activation, as well as reactive gliosis, can be detected using radioligands via PET or SPECT (Arlicot et al. 2008; Chauveau et al. 2008; Dolle et al. 2009). Translocator protein 18 kDa (TSPO) is frequently used as a marker of microglial activity. It is particularly useful as it is present on the outer mitochondrial membrane (Rupprecht et al. 2010) and its expression is low under physiological conditions, but it increases significantly in activated microglia (Chauveau et al. 2008). For TSPO detection, radionuclides of carbon (^{11}C) and fluorine (^{18}F) are widely used (Jacobs et al. 2012). Inflammatory changes in the brain may also be detected by determining the activity of enzymes associated with inflammatory reactions such as metalloproteinases or cyclooxygenases (Pinas et al. 2009; Shukuri et al. 2011), which can be detected by the use of radioactively labeled substances whose concentration reflects enzymatic activity (Pinas et al. 2009; Shukuri et al. 2011).

Some modern techniques, such as imaging methods using labeled microparticles, allow detection of inflammation-induced changes in the blood–brain barrier endothelium through detection of vascular cell adhesion molecule (VCAM) expression (McAteer et al. 2007). More specifically, VCAM expression can be detected using anti-VCAM antibodies, which are attached to iron oxide-labeled microparticles detectable by MRI (McAteer et al. 2007). Furthermore, labeled nanoparticles are used for the detection of intracellular adhesion molecules (ICAM) (Shao et al. 2011). These nanoparticles can be labeled with radionuclides of iodine (^{125}I) or copper (^{64}Cu) and are conjugated to ICAM antibodies (Rossin et al. 2008; Shao et al. 2011). Moreover, changes in the permeability of the blood–brain barrier can be recorded by other methods, such as MRI using magnetically labeled water molecules in arterial blood (Tiwari et al. 2017). In addition, magnetic resonance spectroscopy (MRS) allows us to investigate various aspects of inflammation by in vitro detection of selected substances. For example, MRS allows monitoring microglial activation by creatinine and myoinositol detection (Quarantelli 2015).

It is necessary to note that the use of in vivo imaging methods in the detection of hypothalamic inflammation in humans is questionable at this point, as there are no available studies dealing with this issue. Regardless, these methods seem to have clinical potential. However, several factors will have to be considered when attempting detection of hypothalamic inflammation via imaging methods. Mostly importantly, hypothalamic inflammation is a subclinical form of inflammation and therefore it would be more appropriate to use more sensitive and specific methods for its detection. For example, MRI can detect changes in blood–brain barrier permeability in stroke, but it is questionable whether it is an appropriate method for detecting hypothalamic inflammation-associated changes in the blood–brain barrier (Tiwari et al. 2017).

Directions for Future Research and Possible Clinical Implications

Hypothalamic inflammation is associated with both physiological adaptation responses and pathological processes. However, as mentioned above, inflammatory changes in the hypothalamus do not have uniform characteristics but differ depending on the stage of inflammation and the inducing stimulus. Recent data suggest that the chronic form of hypothalamic inflammation is an important factor contributing to the development and progression of various somatic diseases (Castanon et al. 2014; Burfeind et al. 2016; Khor and Cai 2017). In addition to obesity, diabetes, hypertension, and cachexia, the recently published data indicate that hypothalamic inflammation plays a role in heart failure, as well (Rigas et al. 2018). Yet, the role of hypothalamic inflammation in other diseases, such as osteoporosis, anemia, and polycystic ovarian syndrome remains questionable (Kawai et al. 2012; Lian et al. 2016). A more detailed understanding of mechanisms participating in the development of hypothalamic inflammation may lead to a better understanding of the etiopathogenesis of various somatic diseases and to the introduction of new therapeutic approaches in their treatment.

However, potential treatments are emerging as a result of rapid advances in research within the field of hypothalamic inflammation. One of the more promising therapeutic approaches, which exerts a significant reduction of hypothalamic inflammation, is regular physical activity (exercising). For example, a study on mice showed a positive effect of physical activity on the reduction of hypothalamic inflammation induced by HFD mediated by increased production of cytokines IL-6 and IL-10 in the hypothalamus (Ropelle et al. 2010). Another potential therapeutic approach is based on the quantitative and qualitative changes of consumed food. For example, hypothalamic inflammation may be attenuated by the administration of unsaturated fatty acids. Intake of linseed oil and olive oil reduces hypothalamic inflammation and is associated with restoration of leptin and insulin signaling and increased expression of POMC and CART in the hypothalamus (Cintra et al. 2012). Another study has shown that activation of polyunsaturated fatty acid receptors (GPR120) and free fatty acid receptor 1 (GPR40) may prevent the development of hypothalamic inflammation as it reduces the expression of the pro-inflammatory cytokines IL-1β and TNF-α while increasing the expression of the anti-inflammatory cytokine IL-10 in the hypothalamus of mice receiving HFD (Dragano et al. 2017). Caloric restriction may also represent another efficient approach attenuating hypothalamic inflammation, especially in connection with aging-associated pro-inflammatory changes in hypothalamic tissue (Sadagurski et al. 2015).

The reduction of hypothalamic inflammation associated with negative energy balance and the development of cachexia seems to be even more important as cachexia represents a life-threatening factor in oncological patients. For example, in mice with cachexia, endurance training has been shown to reduce hypothalamic inflammation (Lira et al. 2011). Another study has demonstrated the positive effect of resistance exercise on the preservation of soft body tissues in mice with colon adenocarcinoma (al-Majid and McCarthy 2001). Unfortunately, although physical activity seems to reduce the devastating consequences of cachexia, its potential use in oncologic patients is limited by the physical condition of these patients.

When life-style changes are not sufficient, hypothalamic inflammation may also be attenuated by drugs that interfere with activation of NF-κB in the brain. Several drugs that suppress inflammation by reducing NF-κB-related signaling are being tested (Bremner and Heinrich 2002; Viatour et al. 2005). In addition, many approved drugs, such as salicylates, derivates of glucocorticoids, disulfiram, and others exert inhibitory effect on NF-κB (Miller et al. 2010). Importantly, some of these drugs are able to pass the blood–brain barrier and therefore may be potentially used for targeted reduction of hypothalamic inflammation.

Conclusion

Mechanisms involved in the development of hypothalamic inflammation and its negative effects on body functioning are only starting to be described in detail. However, recent findings indicate that hypothalamic inflammation may represent an important target in the treatment of many somatic diseases. Life-style change represents a potent, inexpensive, and simple approach to reducing hypothalamic inflammation. For example, regular physical activity and rational diet exert beneficial effects on somatic diseases, not only by affecting pathological processes in peripheral tissues, but also by attenuating hypothalamic inflammation. Physical activity and rational diet thereby participate in the restoration of homeostasis through their effect on the central components of homeostats localized in the hypothalamus. Thus, exercising and rational diet are one of the most accessible, yet the most effective mechanisms to prevent many somatic diseases. Published data also indicate that drugs reducing inflammatory changes in the hypothalamic tissue improve the prognosis of certain somatic diseases.

The view of obesity, hypertension, cachexia, and other somatic diseases and pathological processes as complex disorders associated with hypothalamic inflammation and the consequent disruption of homeostatic regulations, creates a basis for more focused and effective treatment as well as prevention of these diseases that have a high prevalence in modern society.

Acknowledgements This work was supported by the Slovak Research and Development Agency (APVV-17-0090), VEGA Grant 2/0028/16, and EU Grant from cross-border cooperation program Interreg V-A SK-AT V014 - NutriAging. We wish to thank Dr. Ken Goldstein of ScienceDocs (http://www.sciencedocs.com) for the editing of this paper.

Author Contributions All authors contributed to the preparation of manuscript, BM finalized manuscript and prepared figures.

Compliance with Ethical Standards

Conflict of interest We declare that we have no conflict of interest.

References

Allen NJ, Barres BA (2009) Neuroscience: Glia—more than just brain glue. Nature 457:675–677

al-Majid S, McCarthy DO (2001) Resistance exercise training attenuates wasting of the extensor digitorum longus muscle in mice bearing the colon-26 adenocarcinoma. Biol Res Nurs 2:155–166

Andre C, Guzman-Quevedo O, Rey C, Remus-Borel J, Clark S, Castellanos-Jankiewicz A, Ladeveze E, Leste-Lasserre T, Nadjar A, Abrous DN, Laye S, Cota D (2017) Inhibiting microglia expansion prevents diet-induced hypothalamic and peripheral inflammation. Diabetes 66:908–919

Anker SD, Ponikowski PP, Clark AL, Leyva F, Rauchhaus M, Kemp M, Teixeira MM, Hellewell PG, Hooper J, Poole-Wilson PA, Coats AJS (1999) Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. Eur Heart J 20:683–693

Araujo EP, Moraes JC, Cintra DE, Velloso LA (2016) MECHANISMS IN ENDOCRINOLOGY: hypothalamic inflammation and nutrition. Eur J Endocrinol 175:R97–R105

Arlicot N, Katsifis A, Garreau L, Mattner F, Vergote J, Duval S, Bodard S, Guilloteau D, Chalon S (2008) Evaluation of CLINDE as potent translocator protein (18 kDa) SPECT radiotracer reflecting the degree of neuroinflammation in a rat model of microglial activation. Eur J Nucl Med Mol I 35:2203–2211

Arruda AP, Milanski M, Coope A, Torsoni AS, Ropelle E, Carvalho DP, Carvalheira JB, Velloso LA (2011) Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. Endocrinology 152:1314–1326

Auernhammer CJ, Chesnokova V, Melmed S (1998) Leukemia inhibitory factor modulates interleukin-1 beta-induced activation of the hypothalamo-pituitary-adrenal axis. Endocrinology 139:2201–2208

Ballesteros-Zebadua P, Custodio V, Franco-Perez J, Rubio C, Gonzalez E, Trejo C, Celis MA, Paz C (2014) Whole-brain irradiation increases NREM sleep and hypothalamic expression of IL-1beta in rats. Int J Radiat Biol 90:142–148

Bartness TJ, Song CK (2007) Thematic review series: adipocyte biology. Sympathetic and sensory innervation of white adipose tissue. J Lipid Res 48:1655–1672

Benigni A, Cassis P, Remuzzi G (2010) Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med 2:247–257

Beretta E, Dhillon H, Kalra PS, Kalra SP (2002) Central LIF gene therapy suppresses food intake, body weight, serum leptin and insulin for extended periods. Peptides 23:975–984

Berkenbosch F, Vanoers J, Delrey A, Tilders F, Besedovsky H (1987) Corticotropin-releasing factor producing neurons in the rat activated by interleukin-1. Science 238:524–526

Blair M (2016) Diabetes mellitus review. Urologic nursing 36:27–36

Borges AH, O'Connor JL, Phillips AN, Ronsholt FF, Pett S, Vjecha MJ, French MA, Lundgren JD, SMART I, Grp ES, Comm SS (2015) Factors associated with plasma IL-6 levels during HIV infection. J Infect Dis 212:585–595

Braga VA (2010) Dietary salt enhances angiotensin-II-induced superoxide formation in the rostral ventrolateral medulla. Auton Neurosci Basic 155:14–18

Braun TP, Zhu XX, Szumowski M, Scott GD, Grossberg AJ, Levasseur PR, Graham K, Khan S, Damaraju S, Colmers WF, Baracos VE, Marks DL (2011) Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis. J Exp Med 208:2449–2463

Bremner P, Heinrich M (2002) Natural products as targeted modulators of the nuclear factor-kappaB pathway. J Pharm Pharmacol 54:453–472

Brown MA, Metcalf D, Gough NM (1994) Leukemia inhibitory factor and interleukin-6 are expressed at very-low levels in the normal adult-mouse and are induced by inflammation. Cytokine 6:300–309

Bubici C, Papa S, Dean K, Franzoso G (2006) Mutual cross-talk between reactive oxygen species and nuclear factor-kappa B: molecular basis and biological significance. Oncogene 25:6731–6748

Buckman LB, Thompson MM, Lippert RN, Blackwell TS, Yull FE, Ellacott KLJ (2015) Evidence for a novel functional role of astrocytes in the acute homeostatic response to high-fat diet intake in mice. Mol Metab 4:58–63

Burfeind KG, Michaelis KA, Marks DL (2016) The central role of hypothalamic inflammation in the acute illness response and cachexia. Semin Cell Dev Biol 54:42–52

Cai DS, Liu TW (2011) Hypothalamic inflammation: a double-edged sword to nutritional diseases. Ann N Y Acad Sci 1243:E1–E39

Cardinale JP, Sriramula S, Mariappan N, Agarwal D, Francis J (2012) Angiotensin II-induced hypertension is modulated by nuclear factor-kappa B in the paraventricular nucleus. Hypertension 59:113–282

Castanon N, Lasselin J, Capuron L (2014) Neuropsychiatric comorbidity in obesity: role of inflammatory processes. Front Endocrinol 5

Chauveau F, Boutin H, Van Camp N, Dolle F, Tavitian B (2008) Nuclear imaging of neuroinflammation: a comprehensive review of [C-11]PK11195 challengers. Eur J Nucl Med Mol I 35:2304–2319

Cheng LC, Yu YH, Szabo A, Wu YZ, Wang HQ, Camer D, Huang XF (2015) Palmitic acid induces central leptin resistance and impairs hepatic glucose and lipid metabolism in male mice. J Nutr Biochem 26:541–548

Chesnokova V, Melmed S (2000) Leukemia inhibitory factor mediates the hypothalamic pituitary adrenal axis response to inflammation. Endocrinology 141:4032–4040

Choi SJ, Kim F, Schwartz MW, Wisse BE (2010) Cultured hypothalamic neurons are resistant to inflammation and insulin resistance induced by saturated fatty acids. Am J Physiol Endocrinol Metab 298:E1122–E1130

Choi SS, Lee HJ, Lim I, Satoh J, Kim SU (2014) Human astrocytes: secretome profiles of cytokines and chemokines. PLoS ONE 9:e92325

Chovatiya R, Medzhitov R (2014) Stress, inflammation, and defense of homeostasis. Mol Cell 54:281–288

Cintra DE, Ropelle ER, Moraes JC, Pauli JR, Morari J, de Souza CT, Grimaldi R, Stahl M, Carvalheira JB, Saad MJ, Velloso LA (2012) Unsaturated fatty acids revert diet-induced hypothalamic inflammation in obesity. PLoS ONE 7:e30571

da Silva AA, do Carmo JM, Kanyicska B, Dubinion J, Brandon E, Hall JE (2008) Endogenous melanocortin system activity contributes to the elevated arterial pressure in spontaneously hypertensive rats. Hypertension 51:884–890

Daniel JA, Whitlock BK, Marks DL, Gard JA, Sartin JL (2016) Leukemia inhibitory factor as a mediator of lipopolysaccharide effects on appetite and selected hormones and metabolites. J Anim Sci 94:2789–2797

de Git KCG, Adan RAH (2015) Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. Obes Rev 16:207–224

Deleidi M, Jaggle M, Rubino G (2015) Immune aging, dysmetabolism, and inflammation in neurological diseases. Front Neurosci 9:172

Dolle F, Luus C, Reynolds A, Kassiou M (2009) Radiolabelled molecules for imaging the translocator protein (18 kDa) using positron emission tomography. Curr Med Chem 16:2899–2923

Dragano NRV, Solon C, Ramalho AF, de Moura RF, Razolli DS, Christiansen E, Azevedo C, Ulven T, Velloso LA (2017) Polyunsaturated fatty acid receptors, GPR40 and GPR120, are expressed in the hypothalamus and control energy homeostasis and inflammation. J Neuroinflamm 14:91

Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. Lancet 365:1415–1428

Erdos B, Broxson CS, King MA, Scarpace PJ, Tumer N (2006) Acute pressor effect of central angiotensin II is mediated by NAD(P)H-oxidase-dependent superoxide production in the hypothalamic cardiovascular regulatory nuclei. J Hypertens 24:109–116

Erridge C, Samani NJ (2009) Saturated fatty acids do not directly stimulate toll-like receptor signaling. Arterioscler Thromb Vasc Biol 29:1944–1949

Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD, Boyce A, Nuckolls G (2008) Cachexia: a new definition. Clin Nutr 27:793–799

Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging—an evolutionary perspective on immunosenescence. Mol Cell Gerontol 908:244–254

Fresno M, Alvarez R, Cuesta N (2011) Toll-like receptors, inflammation, metabolism and obesity. Arch Physiol Biochem 117:151–164

Fry CS, Nayeem SZ, Dillon EL, Sarkar PS, Tumurbaatar B, Urban RJ, Wright TJ, Sheffield-Moore M, Tilton RG, Choudhary S (2016) Glucocorticoids increase skeletal muscle NF-kappaB inducing kinase (NIK): links to muscle atrophy. Physiol Rep. https://doi.org/10.1481/phy2.13014

Gabuzda D, Yankner BA (2013) Physiology: inflammation links ageing to the brain. Nature 497:197–198

Gao Q, Horvath TL (2008) Neuronal control of energy homeostasis. FEBS Lett 582:132–141

Gao Y, Bielohuby M, Fleming T, Grabner GF, Foppen E, Bernhard W, Guzman-Ruiz M, Layritz C, Legutko B, Zinser E, Garcia-Caceres C, Buijs RM, Woods SC, Kalsbeek A, Seeley RJ, Nawroth PP, Bidlingmaier M, Tschop MH, Yi CX (2017) Dietary sugars, not lipids, drive hypothalamic inflammation. Mol Metab 6:897–908

Garcia-Caceres C, Yi CX, Tschop MH (2013) Hypothalamic astrocytes in obesity. Endocr Metab Clin 42:57–57+

Gayle D, Ilyin SE, PlataSalaman CR (1997) Central nervous system IL-1 beta system and neuropeptide Y mRNAs during IL-1 beta-induced anorexia in rats. Brain Res Bull 44:311–317

Gilmore TD (2006) Introduction to NF-kappaB: players, pathways, perspectives. Oncogene 25:6680–6684

Goldstein DS (2008) Computer models of stress, allostasis, and acute and chronic diseases. Ann N Y Acad Sci 1148:223–231

Goldstein DS (2010) Adrenal responses to stress. Cell Mol Neurobiol 30:1433–1440

Goldstein DS, Kopin IJ (2017) Homeostatic systems, biocybernetics, and autonomic neuroscience. Auton Neurosci 208:15–28

Gonzalez PV, Cragnolini AB, Schioth HB, Scimonelli TN (2006) Interleukin-1 beta-induced anorexia is reversed by ghrelin. Peptides 27:3220–3225

Gorina R, Font-Nieves M, Marquez-Kisinousky L, Santalucia T, Planas AM (2011) Astrocyte TLR4 activation induces a pro-inflammatory environment through the interplay between MyD88-dependent NF kappa B signaling, MAPK, and Jak1/Stat1 pathways. Glia 59:242–255

Graebner AK, Iyer M, Carter ME (2015) Understanding how discrete populations of hypothalamic neurons orchestrate complicated behavioral states. Front Syst Neurosci 9:111

Gregor MF, Hotamisligil GS (2011) Inflammatory mechanisms in obesity. Annu Rev Immunol 29:415–445

Grossberg AJ, Scarlett JM, Zhu XX, Bowe DD, Batra AK, Braun TP, Marks DL (2010) Arcuate nucleus proopiomelanocortin neurons mediate the acute anorectic actions of leukemia inhibitory factor via gp130. Endocrinology 151:606–616

Gupta S, Knight AG, Gupta S, Keller JN, Bruce-Keller AJ (2012) Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. J Neurochem 120:1060–1071

Hamilton JA, Brunaldi K (2007) A model for fatty acid transport into the brain. J Mol Neurosci 33:12–17

Han C, Rice MW, Cai D (2016) Neuroinflammatory and autonomic mechanisms in diabetes and hypertension. Am J Physiol Endocrinol Metab 311:E32–E41

Hill AG, Jacobson L, Gonzalez J, Rounds J, Majzoub JA, Wilmore DW (1996) Chronic central nervous system exposure to interleukin-1 beta causes catabolism in the rat. Am J Physiol 271:R1142–R1148

Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, Leonard B, Lorig K, Loureiro MI, van der Meer JW, Schnabel P, Smith R, van Weel C, Smid H (2011) How should we define health? BMJ 343:d4163

Jacobs AH, Tavitian B, Consortium I (2012) Noninvasive molecular imaging of neuroinflammation. J Cerebr Blood F Met 32:1393–1415

Jais A, Bruning JC (2017) Hypothalamic inflammation in obesity and metabolic disease. J Clin Invest 127:24–32

Jang PG, Namkoong C, Kang GM, Hur MW, Kim SW, Kim GH, Kang Y, Jeon MJ, Kim EH, Lee MS, Karin M, Baik JH, Park JY, Lee KU, Kim YB, Kim MS (2010) NF-kappa B activation in hypothalamic pro-opiomelanocortin neurons is essential in illness- and leptin-induced anorexia. J Biol Chem 285:9706–9715

Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, Yang ZM, Francis J (2009) Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. Cardiovasc Res 82:503–512

Kaur J (2014) A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014:943162

Kawai M, de Paula FJA, Rosen CJ (2012) New insights into osteoporosis: the bone-fat connection. J Intern Med 272:317–329

Khor S, Cai D (2017) Hypothalamic and inflammatory basis of hypertension. Clin Sci (Lond) 131:211–223

Kleinridders A, Schenten D, Konner AC, Belgardt BF, Mauer J, Okamura T, Wunderlich FT, Medzhitov R, Bruning JC (2009) MyD88 signaling in the CNS is required for development of fatty acid-induced leptin resistance and diet-induced obesity. Cell Metab 10:249–259

Koellhoffer EC, McCullough LD, Ritzel RM (2017) Old maids: aging and its impact on microglia function. Int J Mol Sci. https://doi.org/10.3390/ijms18040769

Kotchen TA (2010) Obesity-related hypertension: epidemiology, pathophysiology, and clinical management. Am J Hypertens 23:1170–1178

Lancaster GI, Langley KG, Berglund NA, Kammoun HL, Reibe S, Estevez E, Weir J, Mellett NA, Pernes G, Conway JRW, Lee MKS, Timpson P, Murphy AJ, Masters SL, Gerondakis S, Bartonicek N, Kaczorowski DC, Dinger ME, Meikle PJ, Bond PJ, Febbraio MA (2018) Evidence that TLR4 is not a receptor for saturated fatty acids but mediates lipid-induced inflammation by reprogramming macrophage metabolism. Cell Metab 27:1096–1110 e1095

Le Thuc O, Stobbe K, Cansell C, Nahon JL, Blondeau N, Rovere C (2017) Hypothalamic inflammation and energy balance disruptions: spotlight on chemokines. Front Endocrinol 8:197

Levine B, Kalman J, Mayer L, Fillit HM, Packer M (1990) Elevated circulating levels of tumor-necrosis-factor in severe chronic heart-failure. N Engl J Med 323:236–241

Li P, Cui BP, Zhang LL, Sun HJ, Liu TY, Zhu GQ (2013) Melanocortin 3/4 receptors in paraventricular nucleus modulate sympathetic outflow and blood pressure. Exp Physiol 98:435–443

Lian YL, Zhao FG, Wang WJ (2016) Central leptin resistance and hypothalamic inflammation are involved in letrozole-induced polycystic ovary syndrome rats. Biochem Biophys Res Commun 476:306–312

Lira FS, Yamashita AS, Rosa JC, Tavares FL, Caperuto E, Carnevali LC, Pimentel GD, Santos RVT, Batista ML, Laviano A, Rossi-Fanelli F, Seelaender M (2011) Hypothalamic inflammation is reversed by endurance training in anorectic-cachectic rats. Nutr Metab 8:60

Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194–1217

Lu W, Xu Y, Shao X, Gao F, Li Y, Hu J, Zuo Z, Shao X, Zhou L, Zhao Y, Cen X (2015) Uric acid produces an inflammatory response through activation of NF-kappaB in the hypothalamus: implications for the pathogenesis of metabolic disorders. Sci Rep 5:12144

McAteer MA, Sibson NR, von zur Muhlen C, Schneider JE, Lowe AS, Warrick N, Channon KM, Anthony DC, Choudhury RP (2007) In vivo magnetic resonance imaging of acute brain inflammation using microparticles of iron oxide. Nat Med 13:1253–1258

Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, Tsukumo DML, Anhe G, Amaral ME, Takahashi HK, Curi R, Oliveira HC, Carvalheira JBC, Bordin S, Saad MJ, Velloso LA (2009) Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci 29:359–370

Miller SC, Huang R, Sakamuru S, Shukla SJ, Attene-Ramos MS, Shinn P, Van Leer D, Leister W, Austin CP, Xia M (2010) Identification of known drugs that act as inhibitors of NF-kappaB signaling and their mechanism of action. Biochem Pharmacol 79:1272–1280

Moldawer LL, Georgieff M, Lundholm K (1987) Interleukin-1, tumor-necrosis-factor-alpha (cachectin) and the pathogenesis of cancer cachexia. Clin Physiol 7:263–274

Moreira APB, Texeira TFS, Ferreira AB, Peluzio MDG, Alfenas RDG (2012) Influence of a high-fat diet on gut microbiota, intestinal permeability and metabolic endotoxaemia. Br J Nutr 108:801–809

Munzberg H, Flier JS, Bjorbaek C (2004) Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. Endocrinology 145:4880–4889

Nedergaard M, Ransom B, Goldman SA (2003) New roles for astrocytes: redefining the functional architecture of the brain. Trends Neurosci 26:523–530

Njie EG, Boelen E, Stassen FR, Steinbusch HWM, Borchelt DR, Streit WJ (2012) Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. Neurobiol Aging. https://doi.org/10.1016/j.neurobiolaging.2010.05.008

Okoshi MP, Romeiro FG, Paiva SAR, Okoshi K (2013) Heart failure-induced cachexia. Arq Bras Cardiol 100:476–482

Ovadya Y, Krizhanovsky V (2014) Senescent cells: SASPected drivers of age-related pathologies. Biogerontology 15:627–642

Pahl HL (1999) Activators and target genes of Rel/NF-kappaB transcription factors. Oncogene 18:6853–6866

Pimentel GD, Ganeshan K, Carvalheira JB (2014) Hypothalamic inflammation and the central nervous system control of energy homeostasis. Mol Cell Endocrinol 397:15–22

Pinas V, Windhorst A, Lammertsma A, van Eck-Smit B (2009) Radiolabelled matrix metalloproteinase (Mmp) inhibitors for in vivo imaging of unstable plaques using pet and spect 1. J Label Compd Radiopharm 52:S42–S42

Posey KA, Clegg DJ, Printz RL, Byun J, Morton GJ, Vivekanandan-Giri A, Pennathur S, Baskin DG, Heinecke JW, Woods SC, Schwartz MW, Niswender KD (2009) Hypothalamic proinflammatory lipid accumulation, inflammation, and insulin resistance in rats fed a high-fat diet. Am J Physiol Endocrinol Metab 296:E1003–E1012

Prima V, Tennant M, Gorbatyuk OS, Muzyczka N, Scarpace PJ, Zolotukhin S (2004) Differential modulation of energy balance by leptin, ciliary neurotrophic factor, and leukemia inhibitory factor gene delivery: Microarray deoxyribonucleic acid-chip analysis of gene expression. Endocrinology 145:2035–2045

Purkayastha S, Zhang H, Zhang G, Ahmed Z, Wang Y, Cai DS (2011a) Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. P Natl Acad Sci USA 108:2939–2944

Purkayastha S, Zhang G, Cai D (2011b) Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK-beta and NF-kappaB. Nat Med 17:883–887

Quan N, Whiteside M, Herkenham M (1998) Time course and localization patterns of interleukin-1beta messenger RNA expression in brain and pituitary after peripheral administration of lipopolysaccharide. Neuroscience 83:281–293

Quarantelli M (2015) MRI/MRS in neuroinflammation: methodology and applications. Clin Transl Imaging 3:475–489

Rahman MH, Bhusal A, Lee WH, Lee IK, Suk K (2018) Hypothalamic inflammation and malfunctioning glia in the pathophysiology of obesity and diabetes: translational significance. Biochem Pharmacol 153:123–133

Rigas A, Farmakis D, Papingiotis G, Bakosis G, Parissis J (2018) Hypothalamic dysfunction in heart failure: pathogenetic mechanisms and therapeutic implications. Heart Fail Rev 23:55–61

Roatta S, Farina D (2010) Sympathetic actions on the skeletal muscle. Exerc Sport Sci Rev 38:31–35

Rocha DM, Caldas AP, Oliveira LL, Bressan J, Hermsdorff HH (2016) Saturated fatty acids trigger TLR4-mediated inflammatory response. Atherosclerosis 244:211–215

Romanatto T, Cesquini M, Amaral ME, Roman EA, Moraes JC, Torsoni MA, Cruz AP, Velloso LA (2007) TNF-alpha acts in the hypothalamus inhibiting food intake and increasing the respiratory quotient—effects on leptin and insulin signaling pathways. Peptides 28:1050–1058

Ropelle ER, Flores MB, Cintra DE, Rocha GZ, Pauli JR, Morari J, de Souza CT, Moraes JC, Prada PO, Guadagnini D, Marin RM, Oliveira AG, Augusto TM, Carvalho HF, Velloso LA, Saad MJA, Carvalheira JBC (2010) IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKK beta and ER stress inhibition. PLoS Biol 8:e1000465

Rossin R, Muro S, Welch MJ, Muzykantov VR, Schuster DP (2008) In vivo imaging of Cu-64-labeled polymer nanoparticles targeted to the lung endothelium. J Nucl Med 49:103–111

Rupprecht R, Papadopoulos V, Rammes G, Baghai TC, Fan JJ, Akula N, Groyer G, Adams D, Schumacher M (2010) Translocator protein (18 kDa) (TSPO) as a therapeutic target for neurological and psychiatric disorders. Nat Rev Drug Discov 9:971–988

Sadagurski M, Landeryou T, Cady G, Bartke A, Bernal-Mizrachi E, Miller RA (2015) Transient early food restriction leads to hypothalamic changes in the long-lived crowded litter female mice. Physiol Rep 3:e12379

Sanders KJ, Kneppers AE, van de Bool C, Langen RC, Schols AM (2016) Cachexia in chronic obstructive pulmonary disease: new insights and therapeutic perspective. J Cachexia Sarcopenia Muscle 7:5–22

Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W (1987) Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 238:522–524

Scarlett JM, Jobst EE, Enriori PJ, Bowe DD, Batra AK, Grant WF, Cowley MA, Marks DL (2007) Regulation of central melanocortin signaling by interleukin-1 beta. Endocrinology 148:4217–4225

Scarlett JM, Zhu XX, Enriori PJ, Bowe DD, Batra AK, Levasseur PR, Grant WF, Meguid MM, Cowley MA, Marks DL (2008) Regulation of agouti-related protein messenger ribonucleic acid transcription and peptide secretion by acute and chronic inflammation. Endocrinology 149:4837–4845

Schwartz MW, Seeley RJ, Tschop MH, Woods SC, Morton GJ, Myers MG, D'Alessio D (2013) Cooperation between brain and islet in glucose homeostasis and diabetes. Nature 503:59–66

Seoane-Collazo P, Ferno J, Gonzalez F, Dieguez C, Leis R, Nogueiras R, Lopez M (2015) Hypothalamic-autonomic control of energy homeostasis. Endocrine 50:276–291

Sergeyev V, Broberger C, Hokfelt T (2001) Effect of LPS administration on the expression of POMC, NPY, galanin, CART and MCH mRNAs in the rat hypothalamus. Mol Brain Res 90:93–100

Shao X, Zhang HA, Rajian JR, Chamberland DL, Sherman PS, Quesada CA, Koch AE, Kotov NA, Wang XD (2011) I-125-labeled gold nanorods for targeted imaging of inflammation. ACS Nano 5:8967–8973

Sheng JG, Mrak RE, Griffin WST (1998) Enlarged and phagocytic, but not primed, interleukin-1 alpha-immunoreactive microglia increase with age in normal human brain. Acta Neuropathol 95:229–234

Shi X, Wang X, Li Q, Su M, Chew E, Wong ET, Lacza Z, Radda GK, Tergaonkar V, Han W (2013) Nuclear factor kappa B (NF-kappa B) suppresses food intake and energy expenditure in mice by directly activating the Pomc promoter. Diabetologia 56:925–936

Shukuri M, Takashima-Hirano M, Tokuda K, Takashima T, Matsumura K, Inoue O, Doi H, Suzuki M, Watanabe Y, Onoe H (2011) In vivo expression of cyclooxygenase-1 in activated microglia and macrophages during neuroinflammation visualized by PET with C-11-ketoprofen methyl ester. J Nucl Med 52:1094–1101

Sierra A, Gottfried-Blackmore AC, McEwen BS, Bulloch K (2007) Microglia derived from aging mice exhibit an altered inflammatory profile. Glia 55:412–424

Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA (2014) Leptin mediates the increase in blood pressure associated with obesity. Cell 159:1404–1416

Smith JA, Das A, Ray SK, Banik NL (2012) Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. Brain Res Bull 87:10–20

Spector R (1988) Fatty acid transport through the blood-brain barrier. J Neurochem 50:639–643

Sriramula S, Haque M, Majid DS, Francis J (2008) Involvement of tumor necrosis factor-alpha in angiotensin II-mediated effects on salt appetite, hypertension, and cardiac hypertrophy. Hypertension 51:1345–1351

Streit WJ, Sammons NW, Kuhns AJ, Sparks DL (2004) Dystrophic microglia in the aging human brain. Glia 45:208–212

Swaab DF (2004) Chap. 20 Hypothalamic infections. Handb Clin Neurol 80:91–99

Tang Y, Purkayastha S, Cai D (2015) Hypothalamic microinflammation: a common basis of metabolic syndrome and aging. Trends Neurosci 38:36–44

Thaler JP, Choi SJ, Schwartz MW, Wisse BE (2010) Hypothalamic inflammation and energy homeostasis: resolving the paradox. Front Neuroendocrin 31:79–84

Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao XL, Sarruf DA, Izgur V, Maravilla KR, Nguyen HT, Fischer JD, Matsen ME, Wisse BE, Morton GJ, Horvath TL, Baskin DG, Tschop MH, Schwartz MW (2012) Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 122:153–162

Tiwari YV, Lu JF, Shen Q, Cerqueira B, Duong TQ (2017) Magnetic resonance imaging of blood-brain barrier permeability in ischemic stroke using diffusion-weighted arterial spin labeling in rats. J Cerebr Blood F Met 37:2706–2715

Trudler D, Farfara D, Frenkel D (2010) Toll-like receptors expression and signaling in glia cells in neuro-amyloidogenic diseases: towards future therapeutic application. Mediators Inflamm. https://doi.org/10.1155/2010/497987

Ulrich-Lai YM, Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10:397–409

Utsuyama M, Hirokawa K (2002) Differential expression of various cytokine receptors in the brain after stimulation with LPS in young and old mice. Exp Gerontol 37:411–420

Valdearcos M, Xu AW, Koliwad SK (2015) Hypothalamic inflammation in the control of metabolic function. Annu Rev Physiol 77:131–160

Valdearcos M, Douglass JD, Robblee MM, Dorfman MD, Stifler DR, Bennett ML, Gerritse I, Fasnacht R, Barres BA, Thaler JP, Koliwad SK (2017) Microglial inflammatory signaling orchestrates the hypothalamic immune response to dietary excess and mediates obesity susceptibility. Cell Metab 26:185–185+

Vaughan VC, Martin P, Lewandowski PA (2013) Cancer cachexia: impact, mechanisms and emerging treatments. J Cachexia Sarcopeni 4:95–109

Velickovic N, Drakulic D, Petrovic S, Grkovic I, Milosevic M, Stanojlovic M, Horvat A (2012) Time-course of hypothalamic-pituitary-adrenal axis activity and inflammation in juvenile rat brain after cranial irradiation. Cell Mol Neurobiol 32:1175–1185

Velloso LA, Schwartz MW (2011) Altered hypothalamic function in diet-induced obesity. Int J Obesity 35:1455–1465

Viatour P, Merville MP, Bours V, Chariot A (2005) Phosphorylation of NF-kappaB and IkappaB proteins: implications in cancer and inflammation. Trends Biochem Sci 30:43–52

von Bernhardi R, Tichauer JE, Eugenin J (2010) Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. J Neurochem 112:1099–1114

Vonroenn JH, Roth EL, Craig R (1992) HIV-related cachexia—potential mechanisms and treatment. Oncology 49:50–54

Wang XK, Ge AG, Cheng MJ, Guo FF, Zhao M, Zhou XQ, Liu LG, Yang NH (2012) Increased hypothalamic inflammation associated with the susceptibility to obesity in rats exposed to high-fat diet. Exp Diabetes Res. https://doi.org/10.1155/2012/847246

Watts AG (2015) 60 YEARS OF NEUROENDOCRINOLOGY: the structure of the neuroendocrine hypothalamus: the neuroanatomical legacy of Geoffrey Harris. J Endocrinol 226:T25–T39

Wierucka-Rybak M, Bojanowska E (2014) Bacteria, viruses, and hypothalamic inflammation: potential new players in obesity. Postepy Hig Med Dosw (Online) 68:271–279

Wilson JD, Foster DW, Kronenberg HK, Larsen PR (1998) Williams textbook of endocrinology. Saunders, Philadelphia

Wisse BE, Ogimoto K, Tang J, Harris MK, Raines EW, Schwartz MW (2007) Evidence that lipopolysaccharide-induced anorexia depends upon central, rather than peripheral, inflammatory signals. Endocrinology 148:5230–5237

Xanthos DN, Sandkuhler J (2014) Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci 15:43–53

Ye SM, Johnson RW (2001) An age-related decline in interleukin-10 may contribute to the increased expression of interleukin-6 in brain of aged mice. Neuroimmunomodulation 9:183–192

Zabolotny JM, Kim YB, Welsh LA, Kershaw EE, Neel BG, Kahn BB (2008) Protein-tyrosine phosphatase 1B expression is induced by inflammation in vivo. J Biol Chem 283:14230–14241

Zhang KZ, Kaufman RJ (2008) From endoplasmic-reticulum stress to the inflammatory response. Nature 454:455–462

Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D (2008) Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 135:61–73

Zhang M, Mao Y, Ramirez SH, Tuma RF, Chabrashvili T (2010) Angiotensin Ii Induced Cerebral Microvascular Inflammation and Increased Blood-Brain Barrier Permeability Via Oxidative Stress. Neuroscience 171:852–858

Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Li B, Liu G, Cai D (2013) Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. Nature 497:211–216