Peptides xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Review

Hypothalamic inflammation and food intake regulation during chronic illness

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ARTICLE INFO

Article history:
Received 14 January 2015
Received in revised form 14 May 2015
Accepted 22 June 2015
Available online xxx

Keywords:
Anorexia
Inflammation
Hypothalamus
Serotonin
NPY
Melanocortins

ABSTRACT

Anorexia is a common symptom in chronic illness. It contributes to malnutrition and strongly affects survival and quality of life. A common denominator of many chronic diseases is an elevated inflammatory status, which is considered to play a pivotal role in the failure of food-intake regulating systems in the hypothalamus. In this review, we summarize findings on the role of hypothalamic inflammation on food intake regulation involving hypothalamic neuropeptide Y (NPY) and pro-opiomelanocortin (POMC). Furthermore, we outline the role of serotonin in the inability of these peptide based food-intake regulating systems to respond and adapt to changes in energy metabolism during chronic disease.

Contents

1. Introduction

In many chronic illnesses including cancer, chronic obstructive pulmonary disease (COPD) and Acquired Immune Deficiency Syndrome (AIDS), an ongoing elevated systemic inflammatory status plays a pivotal role in both increased energy expenditure as well as a dysregulation of food intake. As a consequence, increased loss of lean body mass is often accompanied by decreased food intake, ultimately leading to severe malnutrition.

The hypothalamus is important for several metabolic processes including energy homeostasis. It acts as an integrator of metabolic and neuronal signals on energy balance, and regulates the balance between energy expenditure and energy intake. In conditions of increased energy requirements, hypothalamic adaptation generally results in increased food intake, which is for example seen in athletes or persons on incremental exercise training [1,2] or in individuals residing in a cold environment [1,3,4]. However, in conditions where increased energy expenditure is accompanied by the presence of chronic inflammation the hypothalamus is not able to respond adequately to changes in energy balance [5]. Here, this elevated inflammatory status causes loss of body weight, attributed to muscle wasting and increased white adipose tissue

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http://dx.doi.org/10.1016/j.peptides.2015.06.011
0196-9781/

lipolysis. On top of that, a loss of appetite beyond a level needed to compensate for increased energy demands is commonly seen, resulting in reduced food intake. This apparent failure of orexigenic (food intake-stimulating) systems of the hypothalamus to respond to peripheral triggers suggests the presence of some form of resistance [5]. This hypothalamic resistance to peripheral neuroendocrine starvation signals is believed to be directly caused by an increased inflammatory status [5]. Increased plasma levels of pro-inflammatory cytokines are associated with disease progression in a variety of cachectic conditions including cancer [6–8], HIV [9], heart failure [10,11] and COPD [12].

In experimental models, administration of IL-6, TNFα and IL-1β [13,14] directly reduces food intake by affecting pivotal food-intake regulating systems in the hypothalamus. At the same time, blocking the action of these cytokines in the presence of underlying disease such as cancer cachexia–anorexia [15–18] or HIV [19] only results in a partial, though significant, reversal of anorexia-cachexia. These studies underline that even though these cytokines are crucial in the pathogenesis of anorexia, their actions and also their interplay with other factors such as anti-inflammatory cytokines [20] are still dependent on the underlying illness via other mechanisms.

In this review we will focus on current insights on the role of hypothalamic inflammation in the reduced food intake during inflammatory conditions. In particular, changes which inflammatory mediators can have on two pivotal food intake regulating systems: (1) neuropeptide Y (NPY)/Agouti-related peptide (AgRP) and (2) pro-opiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART) will be discussed. It is still unknown how cytokines are able to induce alterations in these systems. The role of serotonin will also be studied in this respect, since serotonin is able to modulate food-intake regulatory systems in chronic inflammatory conditions and able to directly influence food intake. In this review, we explored recent literature to investigate the hypothesis that inflammation alters NPY/AgRP and POMC/CART regulated food intake via modulation of serotonergic signalling pathways.

2. Hypothalamic inflammation

Food intake is an outcome of various physiological and behavioural processes controlling hunger, satiety and reward systems of which many originate in the hypothalamus. The hypothalamus consists of a tightly interconnected network of diverse neuronal populations, among them the arcuate nucleus (ARC) and the paraventricular nucleus (PVN). Even though the exact role of the distinct neuronal populations in the complex network of processes is not entirely clear, the observation of dense neuronal projections from the ARC into the PVN [21,22], provides anatomical substrate for the ARC-PVN axis. This ARC-PVN axis is widely studied in the regulation of food intake behaviour in response to a negative energy balance [23–25]. In relation to this, the ARC-PVN axis is involved in different physiological processes, while interacting with several other neuronal populations. In the present review, we will primarily focus on this ARC-PVN axis in relation to the effect of neural inflammation and food intake. The hypothesis that the hypothalamus plays a crucial role in both reduced food intake and cachectic body wasting is supported by a combination of findings. Firstly, neuroinflammation and disturbed hypothalamic signalling is present in cachectic chronic diseases such as cancer [5], HIV [26,27], COPD [28] and heart failure [29,30]. Secondly, the hypothalamus has the highest density of receptors for these pro-inflammatory cytokines in the brain [31]. This inflammatory response in the hypothalamic area can be a consequence of elevated plasma cytokines entering the brain, as several cytokines are able to cross the BBB including TNFα [32], IL-6 [33] and IL-1α [34,35] and IL-1β [36].

In addition, hypothalamic neurons from the ARC are able to sense systemic circulating factors, including cytokines, and peripheral hormones like leptin and insulin from the adjacent median eminence (ME), which is not protected by the blood-brain barrier. In conditions of food deprivation, permeability and fenestration of microvessels from the ME are increased. This results in an enhanced access of circulating factors entering this region reaching ARC neurons [37]. In this way ARC neurons might be able to sense peripheral triggers and to project these signals to other neuronal populations including the PVN [38–40]. Subsequently, this response might lead to *de novo* production of cytokines within the hypothalamus itself. For IL-1β [41], TNFα and Il-6 [42], such *de novo* synthesis in the hypothalamus has been shown after lipopolysaccharide (LPS) injection in rodents, suggesting that the hypothalamus is both a receiver and an amplifier of the peripheral cytokine signals. Indeed, activation of hypothalamic microglial and astrocyte cells, macrophage-like cells of the central nervous system, appears to be a common phenomenon in chronic inflammatory diseases including myocardial infarction [43], obesity [44] and HIV [45]. Finally, also the vagus nerve is likely to play a role in cytokine signalling to the brain. Vagotomy partially attenuates LPS-induced increases in IL-1β expression in murine hypothalamus, while not affecting elevated IL-1β plasma levels [46]. In summary, inflammatory signals reach the hypothalamus by different routes apparently dependent on the type of inflammatory mediator, the hosts'specifics and the underlying disease.

3. Hypothalamic inflammation: Orexigenic signalling

The arcuate nucleus (ARC) includes two important populations of neurons: orexigenic NPY/AgRP and anorexigenic POMC/CART neurons. NPY and POMC neuronal populations have opposing effects on food intake. Furthermore, they are oppositely regulated by peripheral triggers including insulin [47], gut hormones including glucagon like peptide-1 (GLP-1) [48] and peptide YY (PYY) [49], and leptin [50]. This is for example indicated by the fall in leptin levels during energy deficit, a condition that generally drives an increase of food intake [51–53]. Subsequently, this drop in leptin levels attenuates the activation of POMC neurons and allows the activation of NPY signalling [47], actions both in favour of stimulation of food intake. This stimulation of food intake during energy deficit is also supported by an increase in gut-derived ghrelin [54,55]. Ghrelin is a potent stimulator of food intake [56] and acts via activation of ARC NPY [57]. Elevated levels of orexigenic ghrelin have been measured in various chronic cachectic conditions including cancer, COPD and chronic heart failure [58–62]. The ability of ghrelin to initiate and stimulate food intake is contradictive to the high occurrence of anorexia in these diseases, suggesting the occurrence of hypothalamic resistance to ghrelin [63,64]. This elevation of orexigenic ghrelin might be a compensatory response to negative energy balance in these patients. Furthermore it is likely that this elevation of ghrelin is an attempt to suppress inflammation, as ghrelin has strong anti-inflammatory actions by inhibiting pro-inflammatory cytokines, augmenting anti-inflammatory cytokines [65,66] and reducing hypothalamic glial activation [67]. Furthermore, administration of ghrelin showed to be beneficial in fasting or high-fat diet induced inflammation [68,69].

Orexigenic neuropeptide AgRP is exclusively located in the ARC [70,71], while NPY is abundant throughout the entire mammalian brain, with the highest expression of NPY synthesizing neurons located in the ARC [72]. In contrast, NPY release is found to be highest in the PVN [73], supporting the importance of the ARC-PVN axis in NPY and food intake signalling [74].

Please cite this article in press as: J.T Dwarkasing, et al., Hypothalamic inflammation and food intake regulation during chronic illness, Peptides (2015), http://dx.doi.org/10.1016/j.peptides.2015.06.011