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The hypoxia response and nutritional peptides

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ABSTRACT

Hypoxia controls metabolism at several levels, *e.g.*, via mitochondrial ATP production, glucose uptake and glycolysis. Hence it is likely that hypoxia also affects the action and/or production of many peptide hormones linked to food intake and appetite control. Many of those are produced in the gastrointestinal tract, endocrine pancreas, adipose tissue, and selective areas in the brain which modulate and concert their actions. However, the complexity of the hypoxia response and the links to peptides/hormones involved in food intake and appetite control in the different organs are not well known. This review summarizes the role of the hypoxia response and its effects on major peptides linked to appetite regulation, nutrition and metabolism.

1. Introduction

Weight loss at high altitudes, *i.e.,* exposures to hypoxia, was recently suggested to be a novel weight-loss strategy [56,85,90]. The reduced body weight at high altitudes seems to be the result of reduced appetite and a decreased food/energy intake [12,55,123]. Thereby, peptides that increase appetite and which are called orexigenic peptides such as ghrelin as well as appetite reducing, *i.e.*, anorexigenic factors, such as leptin, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), cholecystokinin (CCK) appear to control the physiologic mechanisms underlying this phenomenon of weight loss which is not yet fully understood.

At the cellular level the long-term hypoxia response is primarily regulated by hypoxia-inducible factors (HIFs), which are αβ-heterodimeric transcription factors binding to hypoxia response elements (HREs) in target genes. While the β-subunit (HIF1β/ARNT) is stable, there are three α-subunits, HIF-1α, -2α, and -3α, that are susceptible to post-translational hydroxylations by oxygen-, Fe(II)-, and 2-oxoglutarate (2-OG)-dependent prolyl hydroxylases (PHDs or EglNs); with ascorbate sustaining the reaction. Hydroxylation at proline residues marks HIFα subunits for ubiquitinylation by the von Hippel-Lindau (pVHL) protein and subsequent degradation by proteasomes [52,80]. Under hypoxic conditions PHDs are less active, VHL cannot bind, and consequently HIFα remains stable and can undergo nuclear translocation and dimerization with ARNT [110]. The asparagine hydroxylase FIH, which shares the same reaction mechanism and cofactors with PHDs but is less dependent on oxygen, hydroxylates an asparagine residue in HIF-1α or HIF-2α that prevents binding of CBP/p300 and transcriptional activation of HIF target genes [86]. The HIF system regulates more than 300 genes, which regulate metabolism, mitochondrial function, angiogenesis, inflammation, circadian rhythm, tumorigenesis and many other important functions of the organism [54,87].

Apart from the activation by hypoxia, HIFs were also found to be activated under normoxic conditions by stimuli such as cytokines, growth factors, and peptide hormones such as insulin, incretins, or leptin indicating existence of a feed-forward mechanism at the cellular level [80]. As hypoxia, via HIFs, affects severely mitochondrial ATP production, and metabolism such as glucose uptake and glycolysis, it is likely that hypoxia also affects either the action and/or production of many peptide hormones ultimately linked to appetite and regulation of metabolism and nutrition [65]. Food ingestion starts in the gastrointestinal tract and major peptides affecting nutrition and metabolism are produced in the stomach and enteroendocrine cells of the intestine. Additional peptides are synthesized in the endocrine pancreas, adipose tissue and finally their action is modulated and concerted by peptides from the brain. However, the complexity of the hypoxia response and the links to peptides/hormones involved and produced by different organs are less known.

Therefore, this review aims to give an overview on the hypoxia response and its effects on major peptides linked to appetite regulation, nutrition, and metabolism.

2. Gastro-intestinal peptides

2.1. Gastrin and hypoxia

Gastrin is a peptide hormone found to be synthesized and released

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from the G cells of the gastric antrum and duodenum in response to food intake (Fig. 1). By stimulating enterochromaffin-like cells to release histamine that acts on H_2 histamine receptor of gastric parietal cells it promotes gastric motility and production of hydrochloric acid [88]. Gastrin expression was shown to be inducible by hypoxia in a human gastric adenocarcinoma cell-line. However, deletion experiments with gastrin promoter reporter gene constructs harboring potential HIF binding sites as wells as HIF-1α or HIF-1β knockdown experiments did not affect gastrin promoter inducibility suggesting that the enhanced gastrin expression under hypoxia is likely HIF independent [125]. On the opposite, gastrin was able to induce HIF-1α levels and thereby to promote VEGF expression and angiogenesis in gastric adenocarcinoma cells [109] (Table 1) supporting the view that gastrin has a much broader spectrum of actions than on appetite and nutrition.

2.2. Hypoxia and ghrelin

One major peptide affecting the appetite is ghrelin, also called the "hunger" hormone. Ghrelin is produced by enteroendocrine cells of the gastrointestinal tract, especially the stomach, and by increasing gastric motility and reduction of fat utilization it causes the feeling of hunger. To exert its effects, ghrelin needs to be acylated; a modification that is found in only ~15–20% of total circulating ghrelin. A primary site of ghrelin's action are neurons in the brain, mainly neuropeptide Y (NPY) and agouti-related protein (AGRP) neurons in the nucleus arcuatus, and vagal afferent nerve terminals within the intestinal layers [124].

Hypoxia appears to modulate appetite through the levels of ghrelin as appetite and weight loss are frequently observed at higher altitudes. Indeed, when examining the effect of hypobaric hypoxia on body weight at high altitude (2650 m) in 20 male obese subjects (age 55.7 +/- 4.1 years, BMI 33.7) it was found that obese subjects lost weight [72] likely due to reduced food intake. Furthermore, when human volunteers were examined for appetite, gut hormone levels, energy intake and substrate oxidation after breakfast or exercise at sea level, 2150 m (~15.8% O_2) and 4300 m (~11.7% O_2) in a normobaric chamber; it was found that especially levels for acylated ghrelin, pancreatic polypeptide and composite appetite score were lower at 4300 m compared with sea-level [76] in line with the reduced appetite. Further, when ten healthy males completed four, 7 h trials in a hypobaric chamber at 12.7% O_2 (~4000 m) acylated ghrelin concentrations were lower in hypoxia [121]. In addition, a recent meta analyses confirmed the decrease in postprandial acylated ghrelin levels along with an increase in fasted insulin under hypoxia [77]. However, when nine male elite climbers were examined after seven weeks at sea level and at 5200 m, ghrelin levels did not change [12] suggesting that physical constitution and exercise may affect the ghrelin response. Further, intermediate hypoxia, as achieved during a 4-week period upon exposure to 15% O_2 for 3 days per week did not affect postprandial plasma ghrelin levels [79,84] (Table 1).

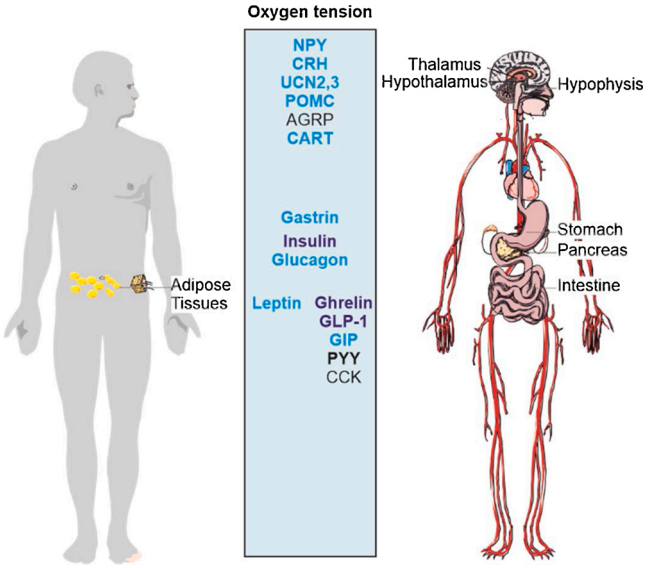

Fig. 1. Oxygen regulated peptide hormones involved in nutrition control. Different oxygen tensions that can be caused physiologically, *e.g.,* at high altitude, or pathophysiological by *e.g.,* anemia, hypoxemia, ischemia, can affect the levels of major peptides involved in nutritional control. This may affect, depending on the situation and cause, either only one peptide, several, or all. In each case this contributes to a shift in whole body homeostasis. Cyan, peptides induced by hypoxia; Dark blue, peptides reduced by hypoxia; Black, unknown or conflicting result.
AGRP, agouti-regulated protein, CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CRH, corticotropin releasing hormone; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide; NPY, neuropeptide Y; POMC, proopiomelanocortin; PYY, peptide YY; UCN, urocortin.

Table 1
Nutrition involved peptides modulated by oxygen tension.

Peptides	Function	Relation to hypoxia	Refs.
Ghrelin	Orexigenic	↓levels in acute hypoxia only	[76,121]
AGRRP	Orexigenic	unknown	
NPY	Orexigenic, Growth-inhibitory	↑ Shifts function to growth-promoting	[27]
CCK	Anorexigenic	Conflicting results	[1,5,6] [64,82] [94]
Leptin	Anorexigenic	↑ levels during hypoxia	[72,79, 102,103]
CRH	Anorexigenic	↑ levels under hypoxia	[99]
Urocortins	Anorexigenic	↑ levels during hypoxia	[18]
CART	Anorexigenic	↑ levels under intermittent hypoxia	
PYY	Anorexigenic	- unchanged during hypoxia	[1,7,29, 79,121]
POMC	Anorexigenic; α-MSH precursor	↑ levels under hypoxia	[116,130]
Glucagon	Slightly anorexigenic; Increases blood glucose concentration	↑ levels in acute hypoxia only	[25]
GLP-1	Anorexigenic; Regulates glucagon and insulin	↓ levels during hypoxia	[62,63]
Insulin	Decreases blood glucose concentration	↓ activity of receptor	[47,89]
GIPR	Promotes insulin secretion	↑ levels during hypoxia	[24]
Gastrin	Gastric motility	↑ levels during hypoxia	[125]

While the effects of hypoxia on appetite and ghrelin in healthy volunteers may result in a decrease in ghrelin levels, hypoxia caused or associated with other pathologies may have a different impact. Indeed, a study in acyanotic and cyanotic patients with congenital heart disease showed that serum ghrelin levels were found to be elevated in cyanotic patients [127] whereas placentas of gestations with birth asphyxia or chronic hypoxia did not display a change in ghrelin mRNA levels [113]. While the latter study is one of the few that has looked at the mRNA, *i.e.*, at the transcriptional response, there is no study yet available that has attempted to see whether the HIF system is involved in ghrelin transcription.

Overall, hypoxia appears to reduce hunger and energy intake under physiological conditions, which may be partially mediated by decreased ghrelin levels.

2.3. Hypoxia and glucagon-like peptide-1 (GLP-1)

The peptide hormone glucagon-like peptide 1 (GLP-1) is one of the

two hormones known as incretins; the other being the glucose-dependent insulinotropic polypeptide (GIP; also known as gastric inhibitory peptide). Both are responsible for the so-called incretin effect, *i.e.,* the increased release of insulin and subsequent decrease in blood glucose levels upon enteral glucose supply compared to parenteral glucose supply.

In humans, active GLP-1 is produced by post-translational processing of the pre-glucagon protein and consists of amino acids 7–36 (> 80%) or 7–37. GLP-1 is mainly synthesized in L cells of the intestinal epithelium and some neurons of the brainstem's solitary tract. Upon carbohydrate containing food ingestion, GLP-1 is released from the gut and augments insulin production as well as inhibits glucagon release from the pancreas. At the same time, it inhibits gastric acid production in the stomach [74]. The intestinal mucosa is known to have a particularly unique oxygenation profile that exhibits fluctuations in blood perfusion on regular intervals throughout the day [131]. Hypoxia has been shown to reduce GLP-1 secretion in GLUTag cells, a model of intestinal L cells, in response to 1% O_2, likely through the cAMP-PKA pathway [62]. The reduction of GLP-1 secretion under hypoxia is also supported by experiments demonstrating that deletion of HIF-1α in adipocytes enhanced GLP-1 secretion [63]. Although further mechanistic details are pending, this is suggesting that, *e.g.,* the postprandial decrease in oxygen tension in the intestine attenuates GLP-1 secretion (Fig. 1). Interestingly, several studies on human volunteers did not reveal any difference in GLP-1 levels upon exposure to hypoxia [7,29,79,83,103]. *Vice versa*, GLP-1 receptor signaling was shown to activate HIF-1α via mTOR signaling, thereby promoting glucose uptake and consumption in pancreatic beta-cells [22,115] (Table 1).

Together, it remains open whether and to what extend hypoxia and related fluctuations in the intestinal oxygen tension have an impact on GLP-1 secretion and appetite regulation.

2.4. Hypoxia and glucose-dependent insulinotropic polypeptide (GIP)

Active GIP circulates as a 42-amino acid peptide that is derived from a 153-amino acid precursor. It is synthesized in duodenal and jejunal K cells. Like GLP-1, the prime function of GIP is to induce insulin secretion in response to glucose arriving in the duodenum. Apart from that, GIP is able to promote pancreatic beta cell proliferation and to protect them from cell death [4,32]. Along that line, it was found that GIP levels are elevated in obesity and diabetes where it stimulates glucagon secretion and fat accumulation. In addition, in humans and mice GIP administration increased monocyte chemoattractant protein-1 (MCP-1) expression and macrophage infiltration into adipose tissue [24,42], respectively; hence, linking it to obesity associated inflammation. Moreover, expression of the GIP receptor (GIPR) and HIF-1α displayed a positive correlation in mouse adipose tissue. HIF-1α gene silencing in mice diminished both macrophage- and hypoxia-induced GIPR expression and GIP-induced IL-6 expression in adipocytes [24]. Thus, increased GIP signaling plays a significant role in adipose tissue inflammation and thereby insulin resistance in obese mice, and HIF-1α may contribute to this process (Table 1).

2.5. Hypoxia and peptide YY (PYY)

Another satiety peptide, PYY is concurrently released with GLP-1 from intestinal L-cells. PYY which exists in two forms, $PYY_{1–36}$ and $PYY_{3–36}$, increases rapidly in response to food ingestion [23]. Once in the circulation, with $PYY_{3–36}$ as the major variant, it acts mainly on neuropeptide Y receptors, in particular the Y2 receptor, to reduce appetite. However, it is found also to be involved in augmenting electrolyte absorption in the gut and in reducing gastric motility [11]. Several investigations have tested whether hypoxia in response to high altitude affects PYY levels and there seems to be consistence that PYY levels are not altered upon exposure to hypoxia/high altitude [1,7,29,79,121] (Table 1).

2.6. Hypoxia and cholecystokinin (CCK)

Cholecystokinin (CCK) (Fig. 1) is an anorexigenic peptide hormone released by the I-cells of the small intestine as a response to fatty acid ingestion. It has its receptor within the hypothalamus, wherein it causes reduction in appetite and increase in fat digestion by stimulating gallbladder contraction and pancreatic enzyme secretion [64,82]. Hypoxia appears to have differential responses with respect to serum CCK levels. While one study found that CCK levels increased after 2 days at ~5100 m [6], another study found that exposure to ~4500 m did not result in any change of CCK levels [1]. By contrast, another study found that a rapid passive ascent to ~3454 m over the course of three days decreased CCK but increased gastrin levels [94]. In addition, when high altitude was combined with exercise at normobaric hypoxia it was found that exercise increase CCK levels only under normoxia but not under hypoxia [5] (Table 1). Thus, whether CCK plays an important role in hypoxia-related appetite modulation remains open and requires more investigations.

3. Pancreatic peptides

3.1. Hypoxia and insulin

Insulin is a well-known peptide hormone produced within the pancreatic beta cells (Fig. 1). Insulin levels increase with or directly after a meal and generally promote the uptake and utilization of glucose from blood into tissue. The high energy demand of pancreatic beta cells during insulin secretion requires a high level of mitochondrial respiration that consumes large amounts of oxygen in a short time period. This makes pancreatic beta-cells sensible to hypoxia and several lines of evidence indicated that acute, chronic and intermittent hypoxia via the HIF pathway are important for beta cell function and pancreas development [20,26,71,118,129]. In line, rapid ascent to high altitude (~4000−5000 m) acutely elevated plasma glucose [10] whereas plasma insulin and pancreatic ATP/ADP ratio was found to be reduced [47]. Whether these effects are entirely mediated by participation of the HIF response is open; however, activation of the HIF response due to deficiency of VHL led to a severe glucose-intolerant phenotype in mice [20] and that appeared to be mainly based on a defect of insulin secretion in the presence of high glucose [89]. Similarly, cell culture experiments with the human β-cell line EndoC-βH3 showed that exposure to hypoxia (3% O_2) or presence or absence of the pan-hydroxylase inhibitor dimethyl oxalylglycine (DMOG) compromised insulin secretion. Surprisingly, insulin secretion was increased under hypoxia in the presence of low glucose (2.8 mM) whereas that effect was diminished and even reduced under high glucose (15 mM) or in the presence of DMOG, respectively. Moreover, usage of DMOG reduced cell number and insulin content by ~30% [69] suggesting that permanent stabilization of HIFs may be a double-edged sword when considering β-cell function (Table 1).

In line with that are data, indicating that exposure of mouse or human islets to hypoxia (1% O_2) before islet transplantation impaired islet graft function and glucose homeostasis [21]. By contrast, HIF-1α pathway activation appears to be beneficial for beta cell survival and proliferation after islet transplantation, as indicated from mouse experiments with HIF-1β-deficient islets and human studies where islets were treated with the iron chelator and HIF stabilizer desferrioxamine [107].

While those data indicate sensitivity of the secreting and survival capacity of pancreatic beta cells to hypoxia, other studies indicate that insulin itself can activate the HIF pathway. Mechanistically, this involves stabilization of HIF-1α mRNA by the RNA binding factors CPEB1 or CPEB2 [45], translational induction via phosphatidylinositol 3-kinase mTOR [112], and stabilization by involving the AKT-GSK3 axis [39,40].

Moreover, another direct link between oxygen sensing and insulin signaling was shown in mice where systemic activation of the HIF

pathway [67] and that of HIF-2α in liver and adipocytes were protective against obesity-induced glucose intolerance and insulin resistance [70,91,122]. Furthermore, administration of HIF prolyl hydroxylase inhibitors after the onset of obesity and insulin resistance improved glycemic control by increasing insulin and decreasing glucagon sensitivity by employing HIF-2α induced increases in insulin receptor substrate-2 and cyclic AMP-specific phosphodiesterase expression [95].

3.2. Hypoxia and glucagon

Low blood glucose levels are sensed within the ventromedial hypothalamus and are relayed by the parasympathetic nervous system to the pancreatic α-cells which then release glucagon. This response can be modulated by sympathoadrenal signaling and intra-islet glucose levels [9,97,108]. The 29 amino acid long glucagon is produced by proconvertase 2-dependent posttranslational processing of pre-pro-glucagon [108]. The main function of glucagon is to increase blood glucose, lipolysis, ketogenesis, ureagenesis and amino acid uptake into hepatocytes [14,35,96].

When human volunteers where examined for changes in glucagon levels after a three-day ascent to ~4559 m, no changes in plasma glucagon were detected [1]. By contrast a study on rats exposed for up to 15 days to simulated high-altitude oxygen levels (~5000 m) found that glucagon levels in plasma rise during the first 48 h of hypoxia, thereafter they returned to normal. This was accompanied by a transient decline in hepatic glycogen. In addition, body weight, food intake and blood glucose levels dropped during the study and it was assumed that adaptation to lower food intake during hypoxia requires conversion of hepatic glycogen to glucose to maintain glucose homeostasis, which is done by glucagon [25] (Table 1).

While hypobaric hypoxia seems to enhance serum glucagon levels in rats, it appears that glucagon secretion from the pancreas can also be inhibited by hypoxia. For example, when activating the HIF system by deleting VHL from pancreatic islets, no increase in serum glucagon levels could be detected, neither under fed nor fasted conditions despite decreased blood glucose levels. Similarly, when glucagon-producing α-TC6.1 cells were cultured under normoxia (20% O_2) and hypoxia (1% O_2) glucagon secretion in response to low glucose was reduced whereas total cellular glucagon content was not affected [89]. In addition, another study demonstrated that pancreatic islets cultured under normoxia showed a higher glucagon release at low glucose supplemented with L-arginine whereas that response was lost in islets exposed to hypoxia [13]. In line with those data are observations showing that glucagon action in liver is reduced under hypoxia and that this would contribute to metabolic zonation of the liver [57,58] and expression of HIFs [59]. In particular, this is exemplified by the reduced glucagon-dependent expression of the phosphoenolpyruvate carboxykinase-1 gene under perivenous oxygen tensions [60,61].

4. Adipose tissue peptides

4.1. Hypoxia and leptin

The action of ghrelin is principally opposed by leptin. Synthesis and secretion of leptin takes place mainly in adipocytes (Fig. 1) and the concentration of circulating leptin in blood is directly proportional to the amount of fat in the body; thus, reflecting its energy status. Leptin can cross the blood-brain barrier and is particularly effective in the area of the hypothalamus and mediates effects on hunger, food use and energy balance as well as physical exercise [73,100]. Thereby, leptin binds to leptin receptors on target cells causing an increased synthesis of anorexigenic and a reduced synthesis of orexigenic hormones in the hypothalamus. This leads to a decreased feeling of hunger and increased satiety and places it in antagonistic redundancy to ghrelin. Although the hormone is found in high concentrations in the blood of most overweight people, it does not inhibit appetite as it does in people of normal weight. This effect is also known as leptin resistance [28,46]. In addition, leptin stimulates the synthesis of thyrotropin-releasing hormone and gonadotropin-releasing hormone in the hypothalamus and appears to play a role in inflammation processes and embryonic implantation; it is also considered to stimulate pancreatic beta-cell functions, and action of growth hormones [38,48].

Following the initial finding that high altitude-increased leptin levels were associated with loss of appetite [114], several other studies with human volunteers also demonstrated that especially hypobaric hypoxia, *i.e.,* high altitude, increases leptin levels [72,79,102,103]. These findings can be mechanistically explained by the fact that the leptin gene is transcriptionally regulated by HIF-1 in a placental cell line. Thereby, HIF-1 binds a consensus hypoxia-responsive site located at -116 in the proximal leptin gene promoter [44] (Table 1).

Interestingly, these findings are contrasted by numerous studies showing that hypoxia has either no effect on leptin levels [12,29,83], leptin mRNA expression [92], or even decreases leptin levels [15,30,128]. While most studies confirmed the beneficial aspects of high-altitude exposure on weight, the differences with respect to leptin levels cannot be easily explained. Several confounding aspects such as physical activity, temperature, humidity, gender, time of sampling and differentiation status as well as tissue specific effects may compromise the results with respect to leptin. In line with the latter are studies showing that leptin expression is increased in response to hypoxia in human preadipocytes [117] and differentiated human Simpson-Golabi-Behmel syndrome (SGBS) adipocytes [41] whereas tissue specific effects were noted when rats were exposed to hypoxia; with unchanged or even reduced levels in adipose tissue and increased levels in liver, kidney, and lungs but no change in plasma leptin levels [78]. Overall, more, and better standardized investigations are needed to proof to which extend leptin is involved in hypoxia-promoted weight loss.

Apart from the potential role of hypoxia on leptin expression, several lines of evidence indicate existence of a feedback regulation where leptin affects the hypoxia response. For example, leptin appears to contribute to to long-term stabilization of HIF-1α in cancer cells via SIRT1 [19] and was found to induce VEGF expression in breast cancer cells via HIF-1α and NFkB activation [43]. Along that line, leptin promoted angiogenesis and reactive oxygen species formation in hepatic stellate cells via mTOR [2]. Furthermore, the leptin receptor gene was shown to be a direct target of HIF-1α [93].

Altogether, hypoxia and leptin seem to undergo a reciprocal relationship with hypoxia having varying effects on leptin expression and with leptin promoting hypoxic adaptation.

5. Central brain peptides

5.1. Hypoxia and NPY

Neuropeptide Y (NPY) is like PYY and PP a 36 amino acid peptide that is one of the most common neuropeptides found both in the central and peripheral nervous system (Fig. 1). NPY is synthetized mainly by neurons of the sympathetic nervous system and by neurons in the hypothalamus. It acts via Y-receptors, from which several subtypes (Y1R-Y5R) are known, and apart from increasing food intake and fat storage, NPY is involved in reducing anxiety, pain perception, and blood pressure [66]. Hypoxia may have a role in the NPY driven processes including regulation of appetite via HIF-1 and nuclear factor-kappa B (NF-κB). In rats intracerebroventricular injection of an HIF-1α inhibitor caused a decrease in NPY levels and feeding behavior [27] (Table 1).

Moreover, in Ewing sarcoma cells it was found that hypoxia influenced the Y-receptors. There, hypoxia increased a special NPY receptor, Y2R. At the same time, hypoxia was shown to increase dipeptidyl peptidase IV which cleaves NPY to a smaller form (NPY_{3-36}). That smaller variant shifts its binding preference away from Y1R and binds more to Y2R and Y5R. As a consequence of Y2R binding, cells gained a

growth advantage and promoted angiogenesis [111]. Thus, hypoxia seems to influence NPY and the Y receptors making it important in appetite but also cell growth regulation.

5.2. Hypoxia and corticotropin-releasing hormone (CRH)

CRH is primarily produced as a 41 amino acid long peptide by neuroendocrine cells in the hypothalamic paraventricular area in response to stress (Fig. 1). Apart from its major role to promote production of pre-pro-opiomelanocortin (pre-POMC) in the pituitary gland, it inhibits food intake, increases attention and anxiety, and modulates the immune response as well as reproduction [8,33,106].

Hypoxia was shown to affect CRH expression and that of the CRH receptors (CRHR). Thereby, it was found that CRH mRNA expression increased after 2, 8, and 24 h of hypoxia equivalent to ~7000 m. By contrast, CRHR1 mRNA was decreased when rats were exposed for periods of 1 h and 8 h to hypoxia whereas intervals (4 h hypoxia/day for a period of 2- or 5 d at ~5000 m) increased CRHR1 mRNA in adult male rat pituitaries. Further analyses revealed, that HIF-1α and NFκB were involved in the upregulation of CRHR1 expression whereas AP-1 contributed to the negative CRHR1 promoter response [99]. Further, gestational intermittent hypoxia elicited a sex-dependent anxiety-like behavior [34] and demethylation of the CRHR1 promoter at several specific CpG islands [119] (Table 1). Together, changing oxygen tensions, either acute, chronic, or intermittent seem to be of importance for CRH and CRHR1 gene regulation and hence for the regulation of the hypothalamic pituitary axis and whole-body homeostasis.

5.3. Hypoxia and urocortins (UCNs)

In addition to CRH, there exist several other peptides that share a high level of identity with CRH. These peptides are known as urocortins, and until today three members were identified. These are UCN1, UCN2 and UCN3 [105]. UCNs appear to be expressed in the brain including the hypothalamus, hippocampus and several other areas (Fig. 1) [105] as well as in heart and in placenta [51,68]. Like CRH, UCNs can act via the CRH receptor 1 and -2 (CRHR1, -2) and affect metabolism by reducing appetite via suppression of gastric emptying [37]. Thereby, systemic UCN2 seemed to be primarily effective, since UCN2 but not UCN1 suppressed feeding via CRHR2 receptors [36].

The effects of hypoxia or high altitude on UCN levels with respect to appetite regulation have not been studied yet. However, UCN expression in the placenta which is highly vascularized and crucial for nourishing the developing embryo, has been investigated. When primary trophoblast cell cultures from early first-trimester placental donors were incubated under normoxia, different levels of hypoxia (8%, and 3% O_2) as well as exposed to hypoxia-reoxygenation, it was found that UCN2 and UCN3 mRNA levels increased upon exposure to hypoxia. Hypoxia-reoxygenation increased only UCN2 mRNA. A link to the HIF system was further established by using the pan-prolylhydroxylase inhibitor DMOG that already induced UCN2 and UCN3 mRNA levels under normoxia [50]. Similiarly, UCN2 expression in rat neonatal cardiomyocytes and in cardiac-derived H9c2 cells was found to be increased by hypoxia, and a HIF-1 binding site was identified in the 3′-flanking region of the UCN2 gene [18] (Table 1). Along that line are findings, showing that UCN2 and UCN3 inhibit apoptosis in cardiomyocytes during hypoxia-reoxygenation. Mechanistically, these effects were mediated by the p42/44 mitogen-activated protein kinase and protein kinase B/Akt pathway [16,17]. Together, UCNs appear to be important regulators of metabolism and to respond to hypoxia. Their mechanistic action, apart from that via CRHRs, requires further investigations.

5.4. Hypoxia and proopiomelanocortin (POMC)

The anterior lobe of the pituitary gland and the arcuate nucleus of the hypothalamus are the prime sites that produce pre-POMC, which is post-translationally processed to yield POMC (Fig. 1). Further post-translational cleavage out of POMC produces several peptides among them ACTH (also known as adrenocorticotropin, or corticotropin), β-lipotropin, γ-lipotropin, α-melanocyte-stimulating hormone (α-MSH), β-MSH, γ-MSH, β-endorphin, met-enkephalin and corticotropin-like intermediate peptide. From them, α-MSH inhibits, opposite to NPY, food intake. Hence, both POMC gene regulation and POMC cleavage are of importance for appetite regulation. The posttranslational processing depends on several enzymes, especially endoproteases, that are tissue specifically expressed. For example, prohormone convertase 1 in the anterior pituitary gland converts POMC to ACTH while prohormone convertase 2 in the intermediate pituitary gland and arcuate nucleus are thought to generate α-MSH from ACTH. In rodents, intracerebroventricular administration of α-MSH reduced appetite and body weight [49] indicating a major role in metabolic homeostasis. The generation of α-MSH is then connected with its action at the melanocortin receptors (MCR), in particular MC4R as MC4R knockout mice are hyperphagic and obese [49]. The action of α-MSH at MC4R can be antagonized by another peptide that is known as the agouti-related protein (AGRP) [49].

Glucose appears to be a major inducer of POMC transcription. As glucose metabolism is linked to hypoxia and HIFs, recent studies found that glucose-induced POMC transcription can be regulated by HIF-1α [116] and HIF-2α [130]. In addition, the mTOR and AMPK pathways acting upstream from HIFs were found to contribute to this process. Moreover, ablation of HIF-2α in POMC producing neurons resulted in a hyperphagic-hypometabolic phenotype [130] (Table 1). Thus, HIFs appear to be important regulators for POMC gene expression in the hypothalamus and hence for the regulation of whole-body energy balance.

While the above mentioned studies clearly indicate a role of HIFs for POMC gene transcription, another study investing intermittent hypoxia in neuronal cell lines found that the -705 to -686 promoter region of the POMC gene containes GATA2 and GATA3 binding sites which mediate POMC gene up-regulation by intermittent hypoxia independent from HIFs [101].

Overall, by employing different mechanisms and similar to CRH, changing oxygen tensions, either acute, chronic, or intermittent seem to be of importance for POMC gene regulation and hence for the regulation of whole-body homeostasis.

5.5. Hypoxia and agouti-related protein (AGRP)

As mentioned, AGRP has been demonstrated to be an antagonist of melanocortin receptors and therefore to be appetite-stimulating [53]. AGRP is co-expressed with NPY in the ventromedial part of the arcuate nucleus in the hypothalamus, subthalamic areas, and in the adrenal glands; low levels are found in kidneys, lungs, and testis (Fig. 1). While a direct regulation of AGRP levels by hypoxia has not been well documented, there may be indirect effects present that are transmitted by hypoxia affected leptin or ghrelin regulation as AGRP effects are also augmented by ghrelin, and antagonized by leptin [3].

5.6. Hypoxia and cocaine- and amphetamine-regulated transcript (CART)

Another important satiety regulator in the hypothalamus is cocaine- and amphetamine-regulated transcript (CART), which in humans is co-expressed with POMC, AGRP and NPY [81] (Fig. 1) and stimulated by leptin [104] whereas food restriction decreased CART mRNA levels [104]. Hypoxia or HIFs were not reported to regulate CART expression, although intermittent hypoxia increased CART expression in a GATA2- and GATA3-dependent manner in neuronal NB-1 cells [101]. *Vice versa*, CART was shown to be protective against focal cerebral ischemia *in vivo* and against oxygen/glucose-deprivation dependent cell death in culture [75]. Thereby, mitochondrial complex II activity [75,98,98,120] as well

as increased expression of growth-associated protein 43 and pleiotrophin appeared to be crucial [120] (Table 1). Thus, CART seems to be an important molecule in appetite regulation that is rather responsive to acutely changing oxygen levels and also a protective factor in neurons suffering from oxygen and glucose deprivation.

6. Conclusion

Overall, hypoxia appears to affect the levels of almost all crucial peptides responsible for regulation of nutrition and appetite (Fig. 1). However, when comparing hypoxia effects caused by an ascent to high altitude with the effects of hypoxia exerted in hypobaric chambers one needs to be aware of many confounding factors. For example, ascent to high altitude is accompanied with increased physical activity, change of diet, quality and amount of drinking water, physical status, as well as psychological factors that depend on environmental influences. Hence, it might be difficult to detangle the effects of high-altitude hypoxia from those caused by the confounders. In addition, the degree of acclimation to high altitude is an important key factor that should be considered when evaluating the data and which could explain possible discrepancies between studies. By contrast, placing individuals in hypobaric chambers, allows a much better control of the confounding factors influencing body metabolism mentioned above, but those are currently limited.

Although the hypoxia/HIF system appears to play a role in the regulation of most of the anorexigenic peptides, it is currently unknown whether HIF prolyl hydroxylase inhibitors or HIF inhibitors directly influence appetite. However, they can influence metabolic parameters. For example, the HIF-prolyl hydroxylase inhibitor Roxadustat that has recently been approved for the treatment of anemia in patients with chronic kidney disease [31], not only corrected anemia but also reduced serum cholesterol and improved the HDL/LDL ratio. Similar effects were reported for Daprodustat whereas Vadadustat did not alter serum cholesterol levels. Furthermore, Molidustat and Vadadustat have been associated with lowered blood pressure in preclinical and clinical studies (for review see [65]). Not much is known for metabolic parameters with HIF inhibitors, especially for the HIF-2α inhibitor PT2385 that is in phase-II clinical trials against renal clear cell carcinomas. One study with mice reported that PT2385 had beneficial effects on high fat diet-induced hepatic steatosis [126]; metabolic parameters from the clinical trials are not yet available.

Together, it appears that several, partially conflicting, aspects about how hypoxia affects nutrition and appetite with respect to single peptides and single organs/cells have been unraveled. However, a concise view has not been reached. In particular, the mechanisms governing the function of the entire hormonal network controlling nutrition and appetite and the role of the hypoxia and HIF response therein are still lacking. Thus, new research initiatives investigating those molecular networks under consideration of the nervous system connecting peripheral organs with the centers in the brain are necessary.

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