AHR in Energy Balance Regulation

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Abstract

Recent studies on mice genetically modified at the Ahr locus and fed on high-fat diet have revealed a novel physiological role for the AHR in energy balance. Globally impaired function of the receptor counteracts the development of obesity by increasing energy expenditure, which appears to occur mostly in the skeletal muscle and brown adipose tissue. On the other hand, global and tissue-specific loss of AHR signaling can have opposite effects on liver fat content and their impact on insulin sensitivity is also context-dependent. As tryptophan metabolites are key AHR activators, these findings suggest that the AHR may act as a protein sensor enabling adequate protein intake from low-protein diets by allowing calorie overfeeding without resultant obesity.

Introduction

One of the most characteristic and conspicuous signs of the acute toxicity of TCDD, an extremely potent agonist of the AHR, is the wasting syndrome, which is especially pronounced in the rat and denotes a profound body weight loss (up to over 50% of initial body weight) before death ensues. It primarily results from reduced feed intake [1,2]. The fact that this dramatic response did not appear to be due to nausea or malaise [3] suggested a specific impact on the regulation of energy balance or body weight. This view was reinforced by the findings that rats treated with sublethal doses of TCDD defended their lowered body weight level against external manipulation attempts by even exhibiting hyperphagia if necessary [4], and that TCDD exposure appeared to permanently imprint peculiar deviations on rats' feeding behavior and responses to feeding regulatory challenges [5-7]. Moreover, female C3H/HeN mice treated with a high dose of TCDD (100 µg/kg, once every 2 weeks for 8 weeks) and fed on a high-fat diet surprisingly exhibited augmented body gain compared with their vehicle-treated controls on the same diet [8]. Thus, it was somewhat disappointing to find out that genetic deletion of the AHR in mice or rats did not markedly influence the growth of the animals, although a transient retardation during the first few weeks of postnatal life was reported in mice [9].

However, more recent studies with congenic and genetically bioengineered mouse models have convincingly demonstrated that the AHR does indeed play an important modulating role in energy homeostasis. Initially, Kerley-Hamilton et al. [10] reported that when fed on high-fat chow

("Western diet") for 28 weeks, male C57BL/6J (B6) mice with a high-affinity AHR (Ahr^{b1} allele) became more obese than their congenic counterparts, B6.D2N-Ahr^{d}/J (B6.D2) mice with a low-affinity AHR (Ahr^{d} allele). The difference in body weight emerged by 17 weeks and broadened thereafter until the end of the study. At termination, the B6 mice had larger gonadal fat pads, greater total volume of lipid vacuoles in the liver and higher plasma cholesterol levels than did B6.D2 mice on the same high-fat diet. Interestingly, however, these differences were not recorded when the mice were fed regular chow, and they did not appear to result from dissimilar feed intake levels. Moreover, in B6 mice high-fat diet repressed hepatic Cyp1a2 gene expression by approximately 3-fold (data on Cyp1a1 were lacking) compared with the standard diet, suggesting that the canonical AHR signaling pathway was not activated by the special diet. On the other hand, the expression levels of a wide variety of nuclear receptors were affected by diet and/or genotype in the liver. In most cases, high-fat diet exhibited a depressing influence in B6 mice, but Pparg (encoding PPARγ) was induced by 61% in them. On high-fat diet, a genotype difference was recorded for Ppara expression [encoding PPARα], which was diminished by 34% in B6 vs. B6.D2 mice [10]. These might have contributed to the outcome because PPARα promotes fatty acid oxidation in the liver [11] while increased expression of PPARγ is involved in liver steatosis [12,13].

Impact of global AHR deficiency on diet-induced obesity

Two subsequent studies in which AHR function was affected at the whole animal level corroborated the role of AHR in dietary obesity. Xu et al. [14] showed that on a high-fat diet, both AHR-deficient $Ahr^{-/-}$ and hemizygous $Ahr^{+/-}$ mice gained significantly less weight than wildtype mice from 8 weeks on. Compared with the mutant strains, the wildtype mice had more epididymal and hepatic fat. The hepatic expression of genes involved in fatty acid translocation (Cd36), lipogenesis (Fas, Acc), β-oxidation (Cpt1a, Acox1, Ppara), gluconeogenesis (Pck1, G6pc) and glucose oxidation (Pdk4) was higher in wildtype animals. These also had higher concentrations of insulin and leptin but lower levels of adiponectin in the serum. The obese wildtype mice displayed glucose intolerance and insulin insensitivity, whereas both were improved in the mutant strains in line with their higher serum adiponectin levels. In mice fed the high-fat diet, there was further evidence of aggravated inflammatory reaction in both the liver and white adipose tissue in the wildtype animals vs. $Ahr^{-/-}$ and $Ahr^{+/-}$ mice. Again, feed intake was not affected, and neither was locomotor activity. However, energy expenditure was higher in high-fat-fed $Ahr^{+/-}$ mice than in wildtype mice on either control or high-fat diet ($Ahr^{-/-}$ mice were not analyzed). This was associated with enhanced expression of the genes for the primary uncoupling protein (Ucp1) and for the regulator of mitochondrial biogenesis (Pgc1a) in the brown adipose tissue as well as those for Ppard (a major regulator of muscle fuel utilization favoring lipid oxidation [15]), Pgc1a, Acox1, Cpt1b, Ucp2 and Ucp3 in skeletal muscle, which may account for the increased energy expenditure. It is noteworthy that compared with wildtype mice, the $Ahr^{+/-}$ mice expressed approximately 30% of the AHR mRNA in the liver, and that Cyp1a1 or other AHR battery genes were not influenced by high-fat diet in wildtype mice [14]. This indicates that even partial elimination of AHR expression can have a substantial influence on energy homeostasis and that high-fat diet does not seem to elicit a general AHR activation as measured by expression of genes regulated by it.

Modulation of diet-induced obesity by AHR antagonists

Moyer et al. [16] proved that also pharmacological inhibition of AHR function is capable of preventing obesity in mice fed on a high-fat diet. Initially, they tested two AHR antagonists, α-naphtoflavone (aNF) and CH-223191 (approximate doses 3 and 10 mg/kg/day, respectively; added into diet), and found that during a 5-week exposure, both effectively counteracted the increasing impacts of high-fat diet on body, fat and liver masses. For CH-223191, the outcome was somewhat surprising, because this compound has been reported to be a selective antagonist of dioxin-type AHR agonists [17]. The team next extended the duration of aNF exposure to 26 weeks. In this case, aNF prevented B6 mice from gaining extra weight on high-fat diet, ameliorated hepatic steatosis and reduced serum LDL-cholesterol levels. However, it also decelerated the growth of control mice on regular chow, increased their liver-to-body mass ratio, and caused degenerative changes in their hepatocytes, indicating liver toxicity of the compound. The researchers then showed that the gene for indoleamine 2,3-dioxygenase (Ido1), an important tryptophan-metabolizing enzyme, is required for the full development of high-fat diet-induced obesity in mice. Their additional in vitro studies revealed that kynurenine rather than kynurenic acid is the probable tryptophan metabolite to activate the AHR. Furthermore, TGFβ1 (an indirect Ido1 inducer [18] whose hepatic gene expression is enhanced by high-fat diet [19]) and oxidized LDL (a ligand for toll-like receptors 2 & 4 [20]) stimulated AHR activity, but more slowly than kynurenine or TCDD. Finally, antagonism of toll-like receptors 2/4 was shown to prevent oxidized LDL-induced AHR activation, while IDO1 inhibition could only diminish it [16]. The effects of a global reduction in AHR activity caused by genetic or pharmacological means are compiled in Fig. 1.

Liver-specific AHR deficiency and energy balance

In contrast to the amelioration of hepatic steatosis by global AHR deficiency, targeted knockout of Ahr in hepatocytes exacerbated it in B6 mice fed on a high-fat diet, without interfering with body weight gain [21]. This appeared to result from augmented expression of genes involved in de novo lipogenesis such as Srebp1c, Scd1, Acc1 and Gpat1, whereas those related to fatty acid uptake, β-oxidation or gluconeogenesis were not differentially affected from control mice on the same diet. High-fat diet-induced hepatic inflammation was also aggravated in knockout mice, coinciding with reduced induction of Socs3, the gene for a negative regulator of STAT3 (a mediator of cytokine signaling [22]). Rescue of hepatic Socs3 expression largely reversed the deleterious effects of hepatic AHR deficiency; the authors further demonstrated Socs3 to be transcriptionally regulated by the AHR [21]. In two other studies using B6 mice on regular chow, both cholesterol and fatty acid biosynthesis in the liver were enhanced by hepatocyte-specific ablation of AHR and repressed by AHR activation (instigated by β-naphtoflavone) through coordinated transcriptional regulation; the AHR proved to exert these effects by a non-canonical pathway [23,24]. These findings are illustrated in Fig. 2.

Constitutively active hepatic AHR and energy balance

In FVB mice fed regular chow, the reverse setting, expression of a constitutively active AHR in the liver (and intestine), also resulted in accumulation of lipids in the liver [25]. While hepatic trigycerides were increased compared with the wildtype control, hepatic cholesterol and plasma triglyceride levels were not. Both body and fat mass decreased in the transgenics, whereas lean body mass was elevated. In the liver, the expression of Ppara and Acox1 was reduced but that of Cd36 and two fatty acid transporters, Fatp1 and Fatp2, augmented, suggesting enhanced uptake of fatty acids in the face of their impaired utilization. Moreover, oxidative stress was aggravated [25].

Adipose tissue-specific AHR deficiency and energy balance

The impact of organ-specific AHR deficiency has also been tested for the adipose tissue. Compared with wildtype controls, transgenic mice on B6-FVB background, devoid of AHR in mature white adipocytes and with reduced (by 35%) Ahr expression in the brown adipose tissue, exhibited increased relative fat mass and decreased relative lean mass, without any difference in body weight, on standard mouse diet [26]. No effect was found on glucose tolerance but insulin sensitivity was slightly enhanced. When fed on a high-fat diet, the AHR-deficient mice gained weight more rapidly than their controls from week 5 on due to enhanced subcutaneous fat accumulation, but both glucose tolerance and insulin sensitivity remained unchanged (as measured 4 weeks after an induced weight loss period following 12-week feeding of the high-fat diet). Relevant to these findings, aNF dose-dependently promoted triglyceride accumulation and IL-6 secretion in mature murine 3T3-L1 adipocytes in vitro [27]. The reported consequences of adipose tissue-specific reduction in AHR activity on factors related to energy homeostasis are summarized in Fig. 3.

Is AHR a protein sensor?

Based on the evidence available at present, AHR signaling is not indispensable for the regulation of energy homeostasis in the body but rather a modulator whose involvement mainly requires high energy intake to become manifest. At the whole organism level, the predominant effect appears to be curtailment of resting energy expenditure in extrahepatic tissues, particularly in brown adipose tissue and skeletal muscle, although this has yet to be verified by functional measurements. These two are crucial tissues for adaptive thermogenesis instigated by exposure to cold or excess dietary energy [28]. In brown adipose tissue, the protein product of Ucp-1 enables protons to bypass ATP synthase in mitochondria, thus generating heat. It is mainly regulated by the sympathetic nervous system, the three PPARs and PGC-1α [29]. In skeletal muscle, the molecular mechanisms of non-shivering thermogenesis are still poorly defined, but major mediators of fatty acid oxidation and upregulation of energy expenditure in that tissue are PPARδ and PGC-1α [11,30]. Because in mice harboring adipose tissue-specific AHR deficiency body weight gain was accelerated on high-fat diet vs. wildtype animals on the same diet, global AHR ablation might act at a higher regulatory level than the brown adipose tissue itself, i.e. the brain or the

sympathetic nervous system (see Fig. 4). However, it is also possible that the reduction in AHR activity in the brown adipose tissue was too small to effectively trigger heat generation.

As regards feeding, the ability to dissipate surplus energy in the form of heat is beneficial for animals if the protein concentration in the food is low, since it allows them then to meet the adequate protein intake requirement without getting fat. Some of the major dietary activators of the AHR are related to tryptophan, an essential amino acid, and already a partial impairment of global AHR function enhances energy expenditure preventing or mitigating obesity. It is thus conceivable that the AHR's primary function in energy balance might be to secure sufficient protein intake by monitoring the levels of an indicator amino acid (tryptophan) and, in case of a severe shortage of it threatening protein homeostasis, enable overfeeding of calories without the harmful consequences of substantial overweight such as an impaired ability to escape predators. This scheme is illustrated in Fig. 4. (Note that reduced AHR activity as such does not increase food intake.)

Conclusions and future prospects

Considered collectively, the data gleaned hitherto show that AHR functionality is essential for obesity to develop in full in mice on a high-fat diet. AHR activity appears to critically modulate energy expenditure at the whole animal level. If AHR function is globally impaired, the adaptive non-shivering thermogenesis is enhanced in the brown adipose tissue and skeletal muscle to the extent that obesity can be prevented. Importantly, the AHR need not be totally eliminated for prevention of obesity, but even partial (70%) reduction will suffice. On the other hand, global and tissue-specific loss of AHR signaling can have opposite effects on liver fat content and their impact on insulin sensitivity is also context-dependent.

Regarding whole body energy expenditure, the studies expounded here were all conducted in mice. It would therefore be of importance to examine (e.g., with the newly generated AHR knockout rats [31,32]) whether the findings are specific to them or generalizable to other species. Another issue to address in the future concerns further clarification of the tissues that are essential to the augmentation of energy expenditure by global AHR functional impairment. In addition to brown adipose tissue and muscle, the upstream neural regulators of their function (Fig. 4) should be subjected to scrutiny. Nervous system-, brown adipose tissue- and striated muscle-specific knockouts should help discern whether the effector or the regulatory tissue is critical in this regard. Finally, a mechanistic key question to address in more detail in the future is the contribution of canonical and non-canonical AHR signaling pathways to obesity.

It is clear that these findings have implications also for human health, since obesity or being overweight are currently very common ailments world-wide. In humans, serum AHR ligand concentrations (total TEQs as measured by a cell-based AHR ligand activity assay or HRGC/HRMS)

have been reported to be associated with the metabolic syndrome, mitochondrial dysfunction and insulin resistance in Korea [33,34]. Hence, these obesity-related disorders seem to correlate with AHR activity also in humans, and blocking AHR activity by dietary or pharmacological means might offer a novel way to treat them. To that end, it is interesting that resveratrol, a natural AHR antagonist [35] present in red wine, has been shown to cause brown adipose tissue activation and white fat browning in rodents, albeit at high doses [36]. As global AHR antagonism may result in untoward side effects such as reduced disease tolerance [37], selective inhibition of AHR function in the tissue(s) responsible for the protection against obesity should be an important aspect of future AHR research.

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Legends for the figures

Fig. 1. A synopsis of the interference by a global decrease in AHR activity with diet-induced obesity and factors related to energy balance in mice. The small arrows depict the direction of change compared with wildtype mice on the same diet (↔: no change).

Fig. 2. Effect of hepatocyte-specific AHR knockout on some key aspects of energy balance and metabolism in mice fed on either a high-fat or standard diet. The small arrows depict the direction of change compared with wildtype mice on the same diet (↔: no change).

Fig. 3. Effect of adipose tissue-specific diminution of AHR activity on some variables related to energy balance and metabolism in mice fed on either a high-fat or standard diet. The small arrows depict the direction of change compared with wildtype mice on the same diet (↔: no change).

Fig. 4. Proposed scheme of AHR's function as a protein sensor. A low protein concentration in food results in reduced generation of tryptophan metabolites and thereby in lowered AHR activity. This, in turn, kindles non-shivering thermogenesis in the brown adipose tissue and skeletal muscle. The augmented energy expenditure enables the animal to overeat energy without getting obese while satisfying its protein needs. The molecular activation pathway of non-shivering thermogenesis shown is valid for the brown adipose tissue, for skeletal muscle it is less well defined (molecules in red: enhanced gene expression recorded in globally AHR-deficient mice on a high-fat feed). The site at which the reduced activity of the AHR ultimately exerts its action is unknown at present, but findings in adipose-specific AHR knockout mice suggest that the regulatory systems might be affected (red arrows with question marks). BAT, brown adipose tissue; NE, norepinephrine (= noradrenaline); cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MAPK, mitogen-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; UCP-1, uncoupling protein 1; PPAR, peroxisome proliferator-activated receptor.

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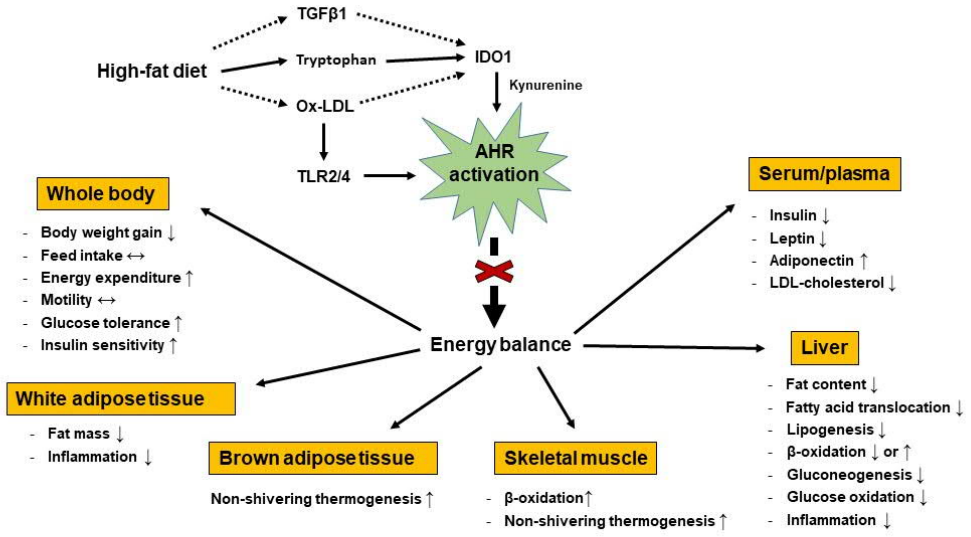
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High-fat diet
Tryptophan
IDO1
Kynurenine
Ox-LDL
TLR2/4
AHR activation
Whole body
- Body weight gain ↓
- Feed intake ↔
- Energy expenditure ↑
- Motility ↔
- Glucose tolerance ↑
- Insulin sensitivity ↑
Serum/plasma
- Insulin ↓
- Leptin ↓
- Adiponectin ↑
- LDL-cholesterol ↓
Energy balance
Liver
- Fat content ↓
- Fatty acid translocation ↓
- Lipogenesis ↓
- β-oxidation ↓ or ↑
- Gluconeogenesis ↓
- Glucose oxidation ↓
- Inflammation ↓
White adipose tissue
- Fat mass ↓
- Inflammation ↓
Brown adipose tissue
Non-shivering thermogenesis ↑
Skeletal muscle
- β-oxidation ↑
- Non-shivering thermogenesis ↑

Fig. 1

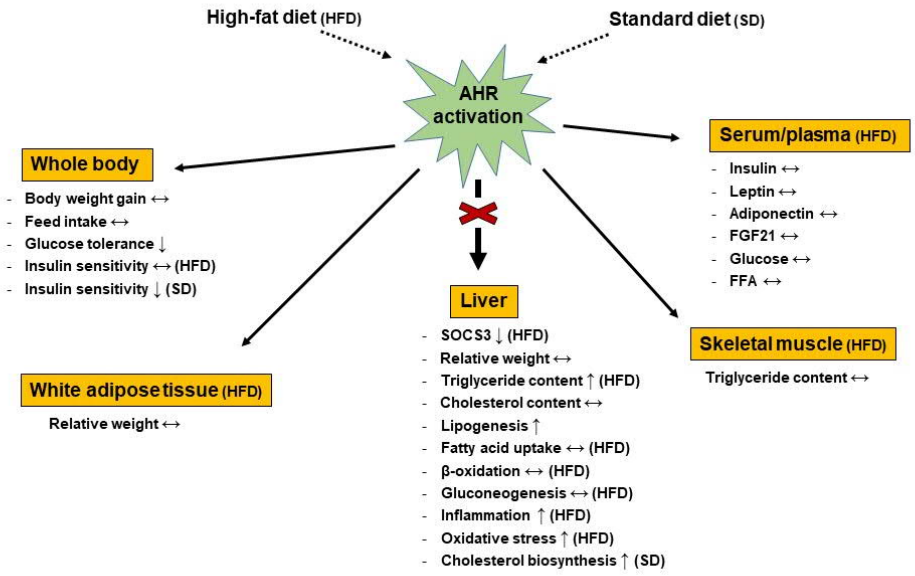
High-fat diet (HFD)
Standard diet (SD)
AHR activation
Whole body
- Body weight gain ↔
- Feed intake ↔
- Glucose tolerance ↓
- Insulin sensitivity ↔ (HFD)
- Insulin sensitivity ↓ (SD)
Serum/plasma (HFD)
- Insulin ↔
- Leptin ↔
- Adiponectin ↔
- FGF21 ↔
- Glucose ↔
- FFA ↔
Liver
- SOCS3 ↓ (HFD)
- Relative weight ↔
- Triglyceride content ↑ (HFD)
- Cholesterol content ↔
- Lipogenesis ↑
- Fatty acid uptake ↔ (HFD)
- β-oxidation ↔ (HFD)
- Gluconeogenesis ↔ (HFD)
- Inflammation ↑ (HFD)
- Oxidative stress ↑ (HFD)
- Cholesterol biosynthesis ↑ (SD)
Skeletal muscle (HFD)
Triglyceride content ↔
White adipose tissue (HFD)
Relative weight ↔

Fig. 2

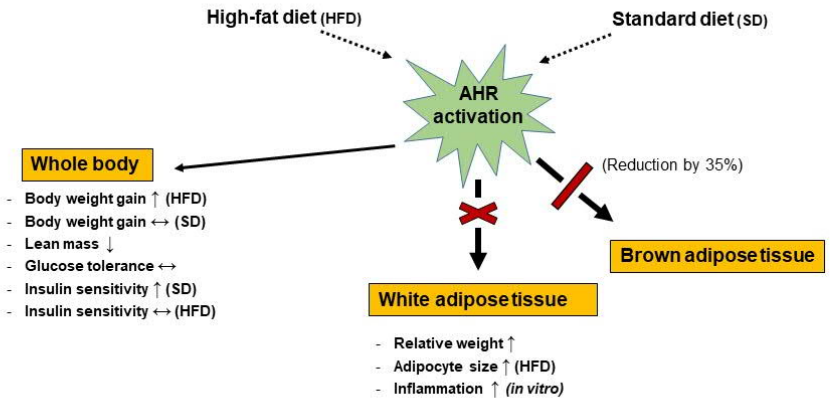
High-fat diet (HFD)
Standard diet (SD)
AHR activation
Whole body
- Body weight gain ↑ (HFD)
- Body weight gain ↔ (SD)
- Lean mass ↓
- Glucose tolerance ↔
- Insulin sensitivity ↑ (SD)
- Insulin sensitivity ↔ (HFD)
(Reduction by 35%)
Brown adipose tissue
White adipose tissue
- Relative weight ↑
- Adipocyte size ↑ (HFD)
- Inflammation ↑ (in vitro)

Fig. 3

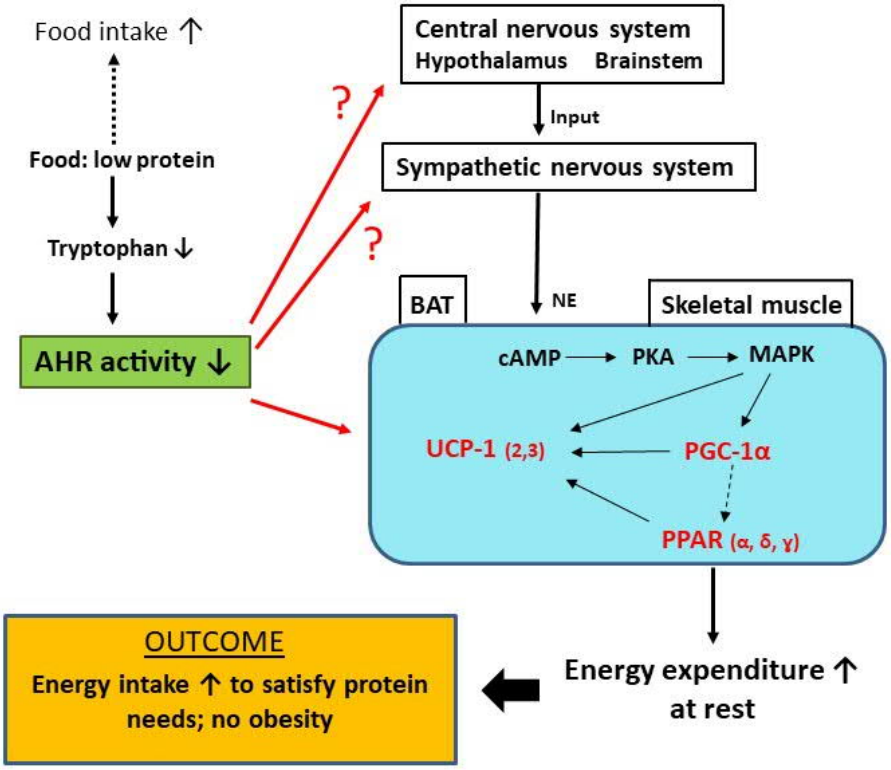
Food intake ↑
Food: low protein
Tryptophan ↓
AHR activity ↓
?
?
Central nervous system
Hypothalamus Brainstem
Input
Sympathetic nervous system
NE
BAT
Skeletal muscle
cAMP → PKA → MAPK
UCP-1 (2,3)
PGC-1α
PPAR (α, δ, γ)
Energy expenditure ↑
at rest
OUTCOME
Energy intake ↑ to satisfy protein needs; no obesity

Fig. 4