Adipose tissue as endocrine organ during prehibernation

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Summary

Hibernating animals deposit their adipose tissue in order to prepare for winter. Adipose tissue secretes several hormones and other peptides, e.g. leptin, adiponectin and IL-6, what makes adipose tissue and endocrine organ. The role of these different peptides in prehibernation are elucidated in this review. Thought, the function of these proteins is know, the mechanisms in prehibernation are still cloudy. This review focuses on different findings that are described. It appears that some mammals have different mechanism to increase their adiposity.

A research conducted in racoon dogs showed increase in ghrelin, an antagonist of leptin. While arctic ground squirrels shows a partially leptin resistance. Leptin resistance may caused by several mechanisms. IL-6 (also secreted by adipose tissue) can induce SOCS3, a negative regulator of leptin and insulin signalling. The other mechanism is yet not proven in prehibernating animals but leptin-binding proteins were seen in hyperleptinemic mice during pregnancy.

The role of adiponectin in prehibernation is also still unknown. Adiponectin affects the mitochondrial activity but no experiments were described with regard to hibernation. Although a low concentration adiponectin correlates with obesity and insulin resistance, no similarities were found between hibernation and obesity along with insulin resistance. When hibernators entering torpor their body temperature and metabolic rate decreases en oxygen consumption becomes very low. Hypoxia has also effect on adipose tissue and the secretion of several hormones but no research is conducted where the existence of hypoxia in adipocytes was proven though it was in skeletal muscle in the thirteen-lined ground squirrel and the little brown bat.

It is highly possible adipose tissue is neurologically affected. Adipose tissue is influenced by the adrenergic system. And therefore it is interesting to investigate the brain-activity, by using brain mapping, prior to and during hibernation.

Abbreviations

AdidpoR1/2	Adiponectin Receptor 1 or 2
AMPK	Adenosine Monophosphate Kinase
ARC	Arcuate nucleus
ATP	Adenosinetriphosphate
BAT	Brown Adipose Tissue
CaMKKβ	Ca(2+)/calmodulin-dependent protein kinase kinase-β
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
FA	Fatty Acid
GH	Growth Hormone
HIF-1α	Hypoxia-inducible factor
IL-6	Interleukine-6
MR	Metabolic Rate
mRNA	mitochondrial Ribonucleic Acid
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha
POMC	Pro-opiomelanocortin
PVN	Paraventricular Nucleus
SNS	Sympathetic Nevous System
SIRT1	Sirtuin 1
SOCS3	Suppressor of cytokine signalling 3
Tb	Body temperature
TNFα	Tumor Necrosis Factor alpha
UCP1	Uncoupling Protein 1
VEGF	Vascular Endothelial Growth Factor
WAT	White Adipose Tissue

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1 Introduction

1.1 Hibernation

During winter, animals have to adapt to the cold circumstances. To survive this cold period of time the animals go into hibernation. Hibernation is characterized by a low body temperature (T_b), hypoxia, bradycardia and a decrease in metabolic rate (MR). Therefore, it is possible for mammals to conserve energy when there is insufficient food. The process of hibernation can be divided in several phases.
Hibernating animals deposit adipose tissue before hibernation to withstand long periods of reduced food-intake. After that they withhold themselves a short period of consuming food before entering torpor. After the fasting the MR drops by over 90%[a] and T_b falls subsequently towards ambient temperature.[1] In torpor, the low T_b and MR remain low for several days. After this period of torpor, the animals arouse where the MR spontaneously increases and T_b reach 37°C. After the arousal there is a period of interbout euthermia where the mammal stays at a temperature of 37°C and a normal MR for several hours. After this the mammal starts again in torpor (see figure 1).
During the winter, mammals enter hibernation in which major changes occur like physiological, pathological and behavioural changes. To understand the underlying mechanisms of the metabolic processes in hibernation is very important for applied sciences. Knowing that mammals prior to hibernation develop obesity and insulin resistance. Additional, hibernators suffer from brain damage due hypoxia and also hibernators do not develop DNA or organ damage during the repeated torpor and arousal phase. Therefore it is interesting to understand those potential protection mechanisms.

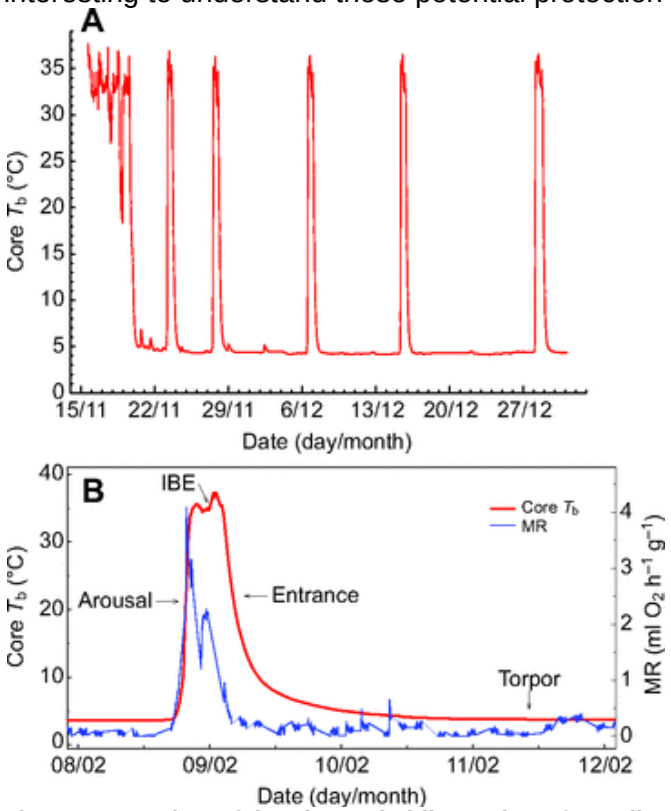

Figure 1 Overview of the phases in hibernation of a 13-lined ground squirrel at the beginning of the hibernation season, shown in A: at first the entrance in hibernation followed by several cycles of torpor and arousal. Shown in B: the MR (Metabolic Rate, measured by O_2-consumption) followed by a decrease in T_b (body temperature).

[a]These value's differ between species

1.2 Metabolic suppression

As indicated in figure 1, metabolic suppression occurs before the T_b drops instead of a decrease in MR due the drop in T_b. Suggesting that lowering of Tb is not the main reason for metabolic suppression. Mitochondria have been examined for years in hibernators but not always where the conditions comparable. A review of J. Staples, suggests that mitochondrial metabolism is suppressed by active mechanisms early in entrance.[2] But the mechanisms of metabolic suppression in hibernators are still unknown.

This literature review focuses on period before going in to torpor, where the first metabolic changes occur. The hibernators fattens up for hibernation often leading to a doubling of body mass[3]. And therefore growth of adipose tissue. Adipose tissue is responsive to both central and peripheral metabolic signals and is itself capable of secreting a number of proteins. These adipocyte-specific or enriched proteins, termed adipokines, have been shown to have a variety of local, peripheral, and central effects. These secreted proteins seem to play important regulatory roles in a variety of complex processes, including fat metabolism, feeding behaviour, haemostasis, vascular tone, energy balance, and insulin sensitivity.[4]
So the main question is how adipose tissue plays a role in the prehibernation? And what are the effects of the several secrete adipokines? To answer this question, the effects of the multiple adipokines will be discussed and their possible role in prehibernation.

2 Adipose tissue as an endocrine organ

Adipose tissue is a complex and highly active metabolic and endocrine organ.[5] Although adipocytes express and secrete several endocrine hormones such as leptin and adiponectin, many secreted proteins are derived from the non-adipocyte fraction of adipose tissue.[6] Regardless, these components function as an integrated unit, making adipose tissue a true endocrine organ.

2.1 Leptin

Adipose tissue secretes several peptides, most well known is leptin. Leptin is discovered in 1994 by a group of scientists led by Jeffrey Friedman at Rockefeller University. Leptin regulates body mass by acting directly on neurons of the hypothalamus that decrease appetite and increase the MR.[7] And therefore is leptin a critical regulator of energy balance in mammals. And its concentration is normally correlated with the body adiposity. (Fig 2)
The expression of and secretion of leptin is also regulated by a variety of other factors. Leptin is namely increased by insulin, glucocorticoids, TNFα and estrogens and leptin is decreased by β3-adrenergic activity, androgens, free fatty acids and GH.[8]

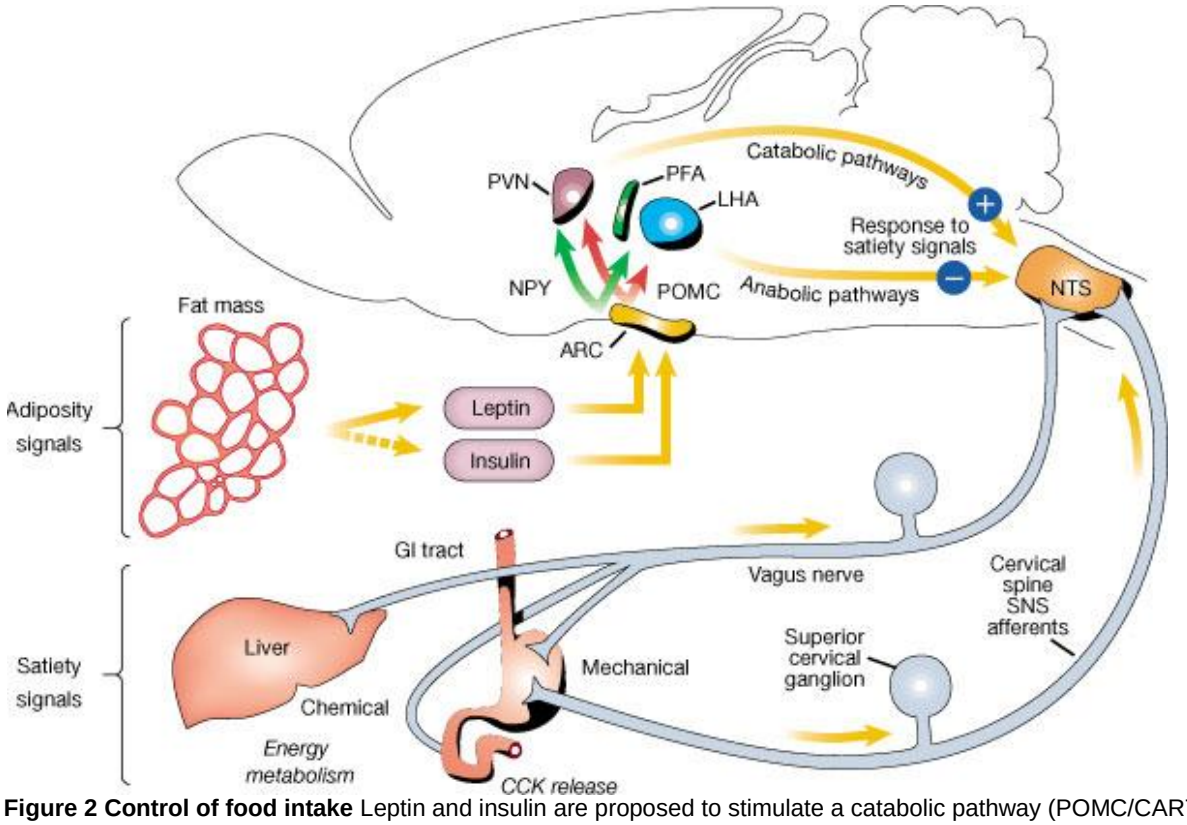

Figure 2 Control of food intake Leptin and insulin are proposed to stimulate a catabolic pathway (POMC/CART neurons) and inhibit an anabolic pathway (NPY/AGRP neurons) that originates in the arcuate nucleus (ARC) beneath the hypothalamus. These pathways project to the PVN and LHA/PFA, where they make connections with central autonomic pathways that project to hindbrain autonomic centres that process satiety signals. Afferent input related to satiety from the liver, gastrointestinal tract and from peptides such as CCK are transmitted through the vagus nerve and sympathetic fibres to the nucleus of the solitary tract (NTS), where they are integrated with descending hypothalamic input. Net neuronal output from the NTS and other hindbrain regions leads to the termination of individual meals, and is potentiated by catabolic projections from the PVN and inhibited by input from the LHA/PFA. Reduced input from adiposity signals (for example, during diet-induced weight loss), therefore, increases meal size by reducing brainstem responses to satiety signals. Not shown are ascending projections from hindbrain to forebrain that may also contribute to adaptive changes in food intake.[9]

2.2 Adiponectin

Adiponectin has been postulated to play an important role in the metabolism of glucose and lipid in insulin-sensitive tissues. Decreased circulating adiponectin levels have been demonstrated in genetic and diet-induced murine models of obesity. Low adiponectin levels have also been strongly implicated in the development of insulin resistance in mouse models of both obesity and lipoatrophy.[10] There are two different receptors for adiponectin; AdipoR1 and AdipoR2. AdipoR1 is expressed primarily in muscle and adipoR2 is expressed primarily in the liver.

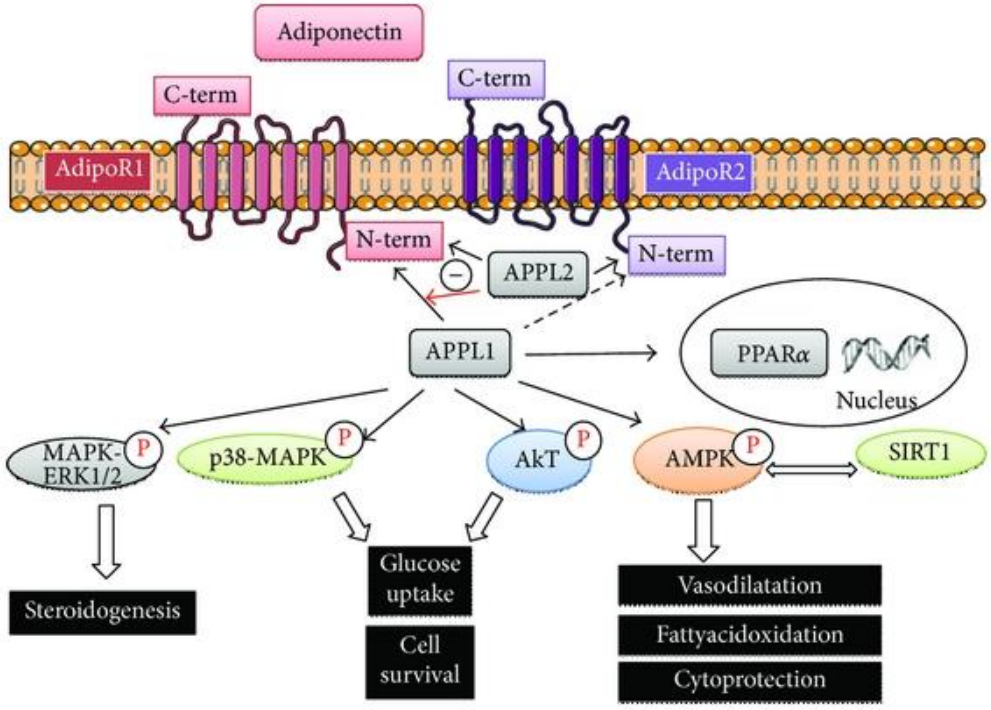

Figure 3 Signalling transduction via adiponectin receptors (AdipoR1 and AdipoR2) activation. The binding of the different forms of adiponectin to the two known adiponectin receptors, AdipoR1 and AdipoR2, can lead to stimulation of various signalling pathways. According to the tissue, activation of both receptors results in modulation of different biological effects such as steroidogenesis, glucose uptake, cell survival, fatty acid oxidation, vasodilatation, and cytoprotection.[11]

2.3 Effects of adipose tissue in prehibernation

Because adiposity increases in prehibernation, it follows that plasma concentrations of leptin would also increase as a consequence. But high levels of leptin, however, should decrease food intake and increase energy expenditure, preventing the increase in body mass and adiposity. Thus it appears that prehibernating animals somehow overcome the satiety and metabolic signals associated with leptin to deposit large fat stores,[12] or you could expect a lack of leptin in hibernators. A lack of leptin leads to obesity due to hyperphagia and lipogenesis.[13]

Noga Kronfeld-Schor et al, conducted a research[12] in bats (*Myotis lucifugus*) at prehibernation. They measured an increase in body mass and percent body fat, the results of that research is shown below. Interestingly, plasma leptin and secretion of leptin from adipose tissue was increased before they measured an increase in body fat. Normally an increase of leptin is correlated with an increase in body fat but this phenomenon suggests that leptin and adiposity are dissociated in prehibernation period. This is also supported by the fact that later in the prehibernation a decrease in leptin was measured despite a high body fat percentage.

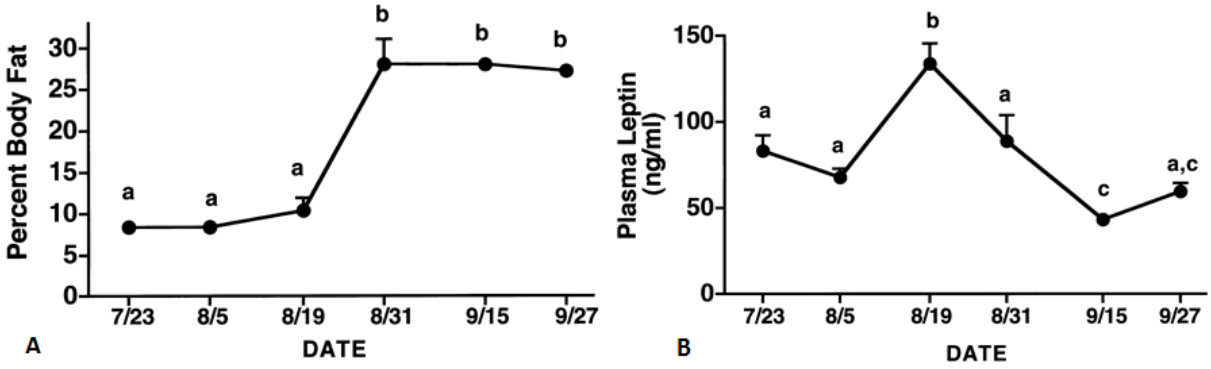

Figure 4 the measured percent body fat and plasma leptin in prehibernation bats, the plasma leptin increases before an increase in percent body fat was measured. And when adiposity increases, the bats had a decrease in plasma leptin.

2.4 The balance of feeding behaviour

For the fact that leptin and adiposity are dissociated in prehibernation, it is clear that this period has a more complicated mechanism for causing adiposity at prehibernating animals.

Leptin would increase later in hibernation according to Florant et al[14]. They also suggest that during fattening animals develop a leptin resistance. Although the mechanism of this putative resistance, if it exists, is unknown, it is possible that plasma leptin may be sequestered by circulating leptin binding-proteins, as appears to be the case in mice during the hyperleptinemic period of pregnancy.[15] The high peak of leptin measured in prehibernating bats, could be supported by those leptin-binding proteins. By an increase in plasma leptin, is it possible that an increase in production of leptin-binding proteins is formed and that the prehibernating mammal finds a way to increase their adiposity.

A research conducted Xing et al[16] showed no evidence of suppressed leptin signal in fattening squirrels. What is adversative of the results in figure 4, where there is a decrease of leptin. But the same research though, showed an increase in orexigenic neuropeptide Y(NPY) mRNA by 67%; however agouti-related peptide(AgRP) remained unchanged.

NPY is an appetite stimulant in the brain and is regulated by a hormone secreted from gherlinergic cells in the GI-tract. Ghrelin stimulates indirectly (via NPY) the hunger feeling and can decrease MR. NPY is co-expressed with AgRP. But an increase in NPY would suggest an altering in ghrelin secretion. There would not be a leptin resistance needed when the antagonist of leptin is sky-high. Little research is done on ghrelin and its concentrations in prehibernation.
A research though from Nieminen et al, about seasonal weigh regulation[17], showed a relatively high ghrelin levels what was correlated with the food intake by racoon dogs, but there was a low level of leptin measured. So for further investigation, the question is if ghrelin and leptin compete for their effect on feeding behaviour in prehibernation.

2.5 Obesity and insulin resistance

As expected, adiponectin could play a large role in prehibernation because a decreased adiponectin level play part in obesity and lipoatrophy. Little research is done at adiponectin levels during prehibernation but a research of Weitten M et al, showed an unexpected result in Syrian hamsters. They showed that fat store mobilization in hamsters during torpor bouts is associated with decreased circulating levels of glucagon, insulin, leptin, and an increase in adiponectin.[18] And still research showed that adiponectin administration represents a promising target for managing obesity, hyperlipidemia, insulin resistance, type 2 diabetes, and vascular inflammation and so is this in conflict of the findings of an increase in adiponectin in the research of Weitten et al. Further, a study of Wever et al, showed that adiponectin serum concentrations were decreased under conditions of obesity, insulin resistance, and type 2 diabetes in humans and rodents.[19] These different findings raises the question how adipose tissue develops itself for fat mobilization in prehibernation. The secretion of adiponectin depends on multiple factors. A research of Gang Li et al showed a neurologically involvement in the secretion of adiponectin. They concluded that adiponectin secretion and expression are regulated in vivo by nutritional status and that insulin and β-agonists act directly at the adipocyte to regulate adiponectin secretion and expression.[20] But if adiponectin plays a role in obesity and insulin for fattening prior to hibernation is yet unknown.

2.6 IL-6 and SOCS3 pathway

Next to adiponectin and leptin, there are several others proteins secreted from adipose tissue, one of those is interleukine-6 (IL-6). IL-6 is another cytokine associated with obesity and insulin resistance. The receptor of IL-6 (IL-6R) is almost identical as the leptin receptor. IL-6 circulates at high levels in the bloodstream and more than one third originates from adipose tissue. IL-6 expression from adipose tissue and circulating IL-6 concentrations are positively correlated with obesity, impaired glucose tolerance, and insulin resistance.
Both expression and circulating levels decrease with weight loss.[22] IL-6 also decreases insulin signalling in peripheral tissues by reducing expression of insulin receptor signalling components and inducing suppressor of cytokine signalling 3 (SOCS3), a negative regulator of both leptin and insulin signalling.[21] IL-6 also inhibits adipogenesis and decreases adiponectin secretion.[22] When adiposity increases, IL-6 and leptin also increase. But as mentioned before, in prehibernation, leptin is increased before an increase in adiposity and decreased when adiposity increases. In this mechanism IL-6 could play a role because IL-6 down regulates indirect leptin signalling by inducing SOCS3. So in prehibernating mammals you would expect an increase of IL-6.

The leptin resistance in prehibernating mammals could be explained by a research of Mori et al. They demonstrated that peripherally administrated leptin rapidly increased the induction of hypothalamic SOCS3 in areas that are relevant for control of food intake and energy expenditure. They showed that SOCS3 was involved as negative regulator of leptin-induced intracellular signal transduction. In rodent models, it was shown that SOCS3 could also be involved in leptin resistance that occurs during the aging process, and that lack of SOCS3 within the brain was effective to increase leptin sensitivity and to prevent diet-induced obesity.[23] This would mean that obese prehibernating mammals protect their adiposity by leptin sensitivity by increasing IL-6 secretion that involves SOCS3.

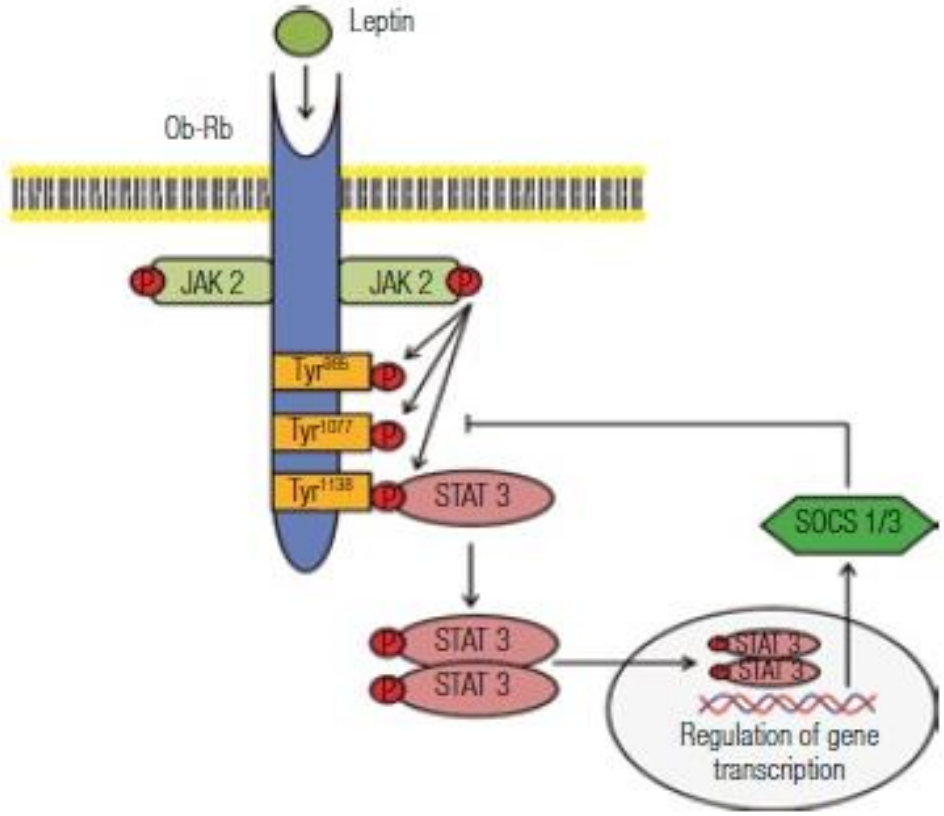

Figure 5 Leptin and the JAK-STAT pathway, Leptin binds to the leptin receptor (Ob-Rb) and activates JAK-STAT pathway as promoter of gene transcription of the SOCS family that can suppress the action of binding JAK2 at the tyrosine residues.[24]

IL-6 is a multifunctional cytokine produced by many different cell types, including immune cells, endothelial cells, fibroblasts, myocytes, and adipose tissue, mediating inflammatory as well as stress-induced responses. IL-6 also stimulates the CNS and the SNS, which may result in hypertension.[25] Finally, IL-6 might also result in hypertension via effects on angiotensinogen expression[26], leading to higher concentration of angiotensin II, which is a potent vasoconstrictor. Interestingly, a cytokine-like molecule increasingly recognized to regulate several inflammatory pathways acting on a receptor of the IL-6 family seems also to be associated with hypertension. The leptin signal, via central leptin receptors, is believed to interact with the central sympathetic nervous system.[27] Infusion of leptin leads to increases in blood pressure. But the plasma level of leptin is decreases during hibernation and yet a reasonably high blood pressure is maintained during the prehibernation and hibernation by an increased peripheral resistance produced in part by vasoconstriction.[28] This would probably be the effect of angiotensin II.

But if IL-6 plays a role in prehibernation is not most likely, despite its control on the SOCS3 mechanism. No change of SOCS3 was detected during the fattening process in the Daurian ground squirrel (Spermophilus dauricus).[16] And so is this conflicting with other findings where IL-6 is induced and therefore most likely SOCS3 also induced. If this is a difference between the species or this is a more complicate mechanism is still unknown.

So the effects of adipose tissue in prehibernation are still unclear. The function of several peptides secreted from adipocytes is known, but to understand the mechanisms together in prehibernation is yet cloudy. Mainly by little number of publications on this matter and also by the complicated mechanisms in and between several hibernating animals. Further research is required for this.

2.7 Mitochondrial regulation of adiponectin

Adiponectin signalling through AdipoR1 appeared to increase the abundance of the mRNA encoding PGC-1α[b] through a CaMKKβ-dependent pathway that did not require AMPK and to stimulate PGC-1α deacetylation by SIRT1, and thereby its activation, through an AMPK-dependent pathway. Adiponectin also elicited an AdipoR1-dependent increase in Ca2+ influx, which played a critical role in the pathway leading to increased PGC-1α expression and also contributed to adiponectin-mediated AMPK phosphorylation. Thus, the authors conclude that adiponectin signalling through AdipoR1 plays a crucial role in the regulation of mitochondrial function and glucose metabolism.[29]
This would mean, because the expectations of adiponectin concentrations would be decreased in prehibernation, that a decrease of AdipoR1 signalling would occur. As a result decrease signalling, would a decrease in gene expression of the energy metabolism arise due reduced PGC-1α. In prehibernation would this be very useful because their adiposity would increase faster when MR is down regulated via this mechanism.

[b] PGC-1α is a transcriptional coactivator that regulates the genes involved in energy metabolism.

2.8 Role of hypoxia on adipose tissue

When mammals go into hibernation their MR decreases and so also their oxygen consumption. Whether the decrease in oxygen is the cause or effect for the drop in MR is still unproven.

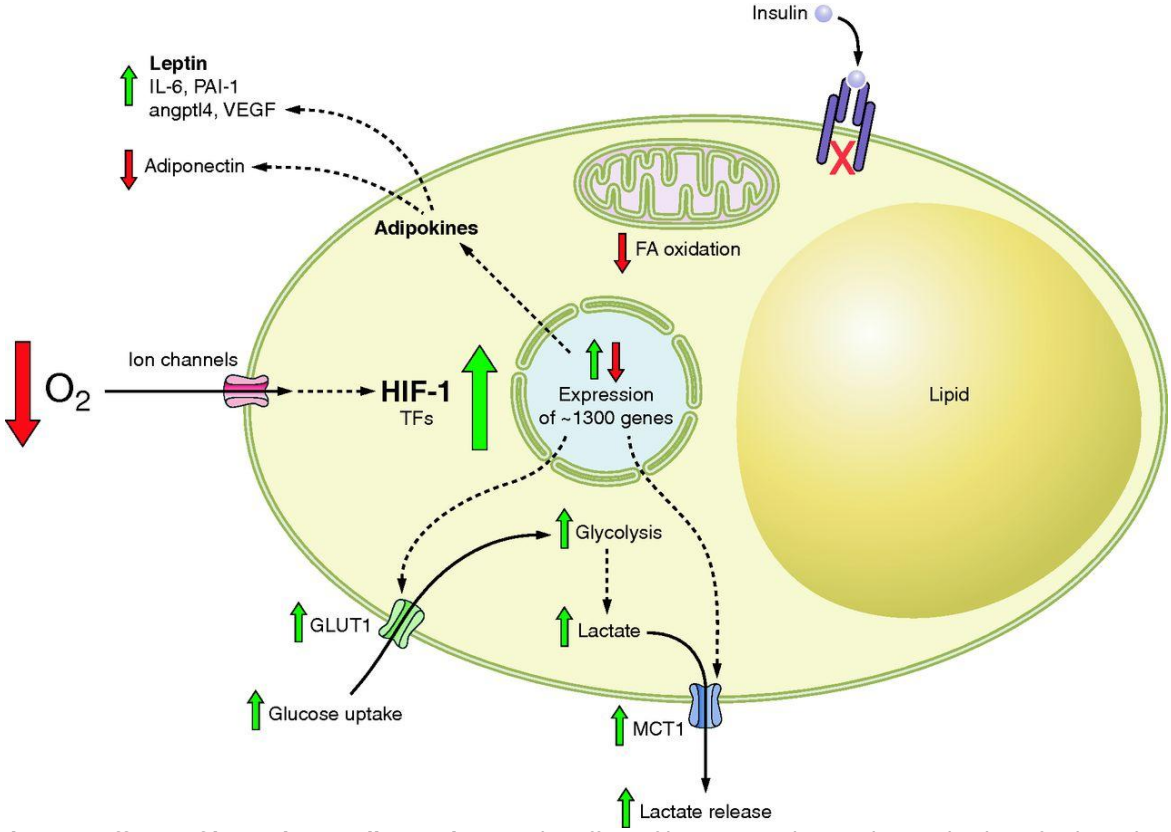

Figure 6 Effects of hypoxia on adipose tissue. The effect of low O2 tension on the production of selected adipokines and on glucose uptake and utilization is shown, together with effects on other processes. [30]

But in both cases hypoxia can have an effect on adipose tissue as shown in figure 6. Importantly, hypoxia induces insulin resistance in fat cells and leads to the development of adipose tissue fibrosis. Many of the responses of adipocytes to hypoxia are initiated at pO2 levels above the normal physiological range for adipose tissue. The other cell types within the tissue also respond to hypoxia, with the differentiation of preadipocytes to adipocytes being inhibited and preadipocytes being transformed into leptin-secreting cells.
The effects of hypoxia on adipose tissue fit the expectations of the plasma levels for adiponectin and IL-6. As mentioned before, adiponectin is decreased in obesity and insulin resistance. However, an increase was measured in hibernating Syrian hamsters.

On the other hand, when MR drops, oxygen consumption is also decreased, but this does not mean whether the body suffers from hypoxia. No research has found where HIF-1α was increased in adipose tissue. But an increase was shown in skeletal muscle in two species; the thirteen-lined ground squirrel (Ictidomys tridecemlineatus) and the little brown bat (Myotis lucifugus)[31], yet on the other hand was this increase measured during hibernation and not during the fattening process were the effects of hypoxia could play a role in the prehibernation. And so further research is required.

3 Conclusions and discussions

The main goal of this literature review was to elucidate the role of adipose tissue during the prehibernation. The function of the secreted adipokines are known but the effects in the fattening process of the several peptides are yet unknown, mainly because unexpected concentrations of the described adipose tissue-derived hormones. Leptin concentrations were decreased in bats (after an increase) and percentage body fat increased. While another research showed no leptin resistance but an increase in NPY. This would mean that ghrelin should be increased what was only supported by one other conducted research in racoon dogs. Further, research of Orsmeth et al[32] showed that arctic ground squirrels had a partially resistance for leptin. And yet therefore it is impossible to compare mechanisms between species because they may have different mechanisms to increase their adiposity.

The effect of adiponectin is still unclear, in prehibernation an increased level was measured while a low level is associated with obesity and insulin resistance. But ordinary obesity in mammals is not comparable with the obesity due the fattening process. It could be possible that the composition of adipose tissue is slightly different which may have a different effect. But yet no evidence is given for this.
Adiponectin can have high influences on mitochondrial regulation by AdidpoR1 and it would make sense that mitochondrial suppression occurs due a decrease of oxygen what results in a lowering of adiponectin level. But no proof is given that adipose tissue suffers from hypoxia and if it was so, no influences are involved with prehibernation but only in hibernation.

But to remember is that adipose tissue is impressionable by the adrenergic system. Little research is done on this matter. It is convincing that adipose tissue is neurologically affected. The feeding behaviour is controlled by ARC (Arcuate Nucleus) but this region lies next to the suprachiasmatic nucleus (SCN) in the hypothalamus. It is responsible for controlling circadian rhythms. But this region is more then only the 24-hour cycle, it can also affect seasonal changes.[33] And so it is much more convincingly that changes in adipose tissue could be explained by control of the SCN.

4 Recommendations

I would recommend to investigate the role of adipose tissue prior to and during hibernation. Therefore I am suggesting to investigate the effect when adipokines or the antagonist (e.g. ghrelin) is administered to the animal. In this case could the effect of ghrelin and leptin in prehibernating animals be elucidated.

Further investigation on the effect of the symphaticus on adipose tissue would also give insight in the mechanism of hibernation. Mainly because the adrenergic receptors located on adipocytes. Therefore it could be useful to use agonist of the adrenergic system and to analyze the phenotypically changes, or the other way around by using an antagonist. It is also possible to carry out a sympathectomy. When performing this on one side of the animal is it also still possible to compare the composition of adipose tissue. There for you can use the part of adipose tissue under influence of the SNS and the part what was cut off.

Little is known about the composition of adipose tissue. No literature has found about the consequences of prehibernation on WAT (White Adipose Tissue) and BAT (Brown Adipose Tissue). BAT plays a large role in hibernating animals from which their body temperature drops below 15°C. This because BAT shows a high density of mitochondria with UCP1 (Uncoupling Proteins 1). UCP's are leaks in the inner mitochondrial membrane and use protons, not to produce ATP, but to create heat. Creating heat is very important when hibernating animals arouse from torpor. And WAT is mainly for energy storage. But to investigate the effect of adipokines on WAT and BAT and to examine the origin of the adipokines could elucidate the mechanism of prehibernation. Next to that, there are animals who deposit their adipose tissue for one long period while some other species needs to eat between de periods of torpor. And therefore also very interesting to investigate the composition of the adipose tissue.

And as aforementioned, it is unproven whether adipose tissue suffers from hypoxia. It is confirmed that skeletal muscle endures hypoxia but no similar experiment was described for adipose tissue. This could be done by measuring HIF-1α in adipose tissue from hibernating animals.

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