Brain-White Adipose Tissue Relationship: Early Features

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Central and autonomic nervous systems are involved in the regulation of whole body energy by regulating its different components: intake, expenditure and storage. The different functions (metabolic, secretory, plasticity) of adipose tissues are indeed deeply controlled by the autonomic nervous system.

In most mammals, two types of adipose tissue, white and brown, are present. Both are able to store energy in the form of triacylglycerols and to hydrolyze them into free fatty acids and glycerol. Whereas white adipose tissue (WAT) provide lipids as substrates for other tissues, brown adipose tissue (BAT) uses fatty acids for heat production. Over a period of time, white fat mass reflects the balance between energy expenditure and energy intake. Remarkably body fat mass remains relatively constant in adult suggesting that food intake and energy expenditure are linked. This has been supported by numerous studies that demonstrated the inter-dependency of these parameters and thus a feedback loop between the brain and adipose tissues with the involvement of the autonomic nervous system on one side and that of sensory fibers and metabolites or hormonal signals on the other.

From the brain to white adipose tissue

Efferent innervation

It is well known that adipose tissues are innervated by sympathetic endings of the autonomic nervous system. It is currently recognized that brown adipose tissue is much more innervated than the white one. In WAT, catecholaminergic fibers have initially been reported as closely associated with the blood vessels (1, 2). However there are more and more data demonstrating direct neuro-anatomical innervation of white adipocytes. Although sparse, these sympathetic endings were of the "en passant" type thus allowing multiple sites of norepinephrine release. Using single neuron retrograde tracer and viral transynaptic tracing methodologies, the sympathetic outflow from brain to WAT has been identified. Altogether WAT receives input from central nervous system (CNS) cell groups that are part of the general SNS outflow from brain (hypothalamic nuclei, brainstem regions, intermedio-lateral cell groups of the spinal cord) (3, 4). More recently, Stanley and coworkers have elegantly demonstrated that most of neurons involved in the sympathetic input to WAT pads also projected to the liver, another key metabolically organ thus allowing a coordinated control of peripheral metabolism (5).

There are striking differences between white and brown neuronal circuitry. First pseudorabies virus infections are much more marked after injections into BAT than into WAT, this could reflect the higher innervation of the former. Second, some areas were marked when the injection was performed in BAT but not when performed in WAT such as the lateral hypothalamus. The significance, if any, of these differences remains to be determined. Moreover, Bartness and al. demonstrated both shared and separate populations of brain, spinal cord, and sympathetic neurons innervating subcutaneous and visceral fat pad (6) (Figure 1).

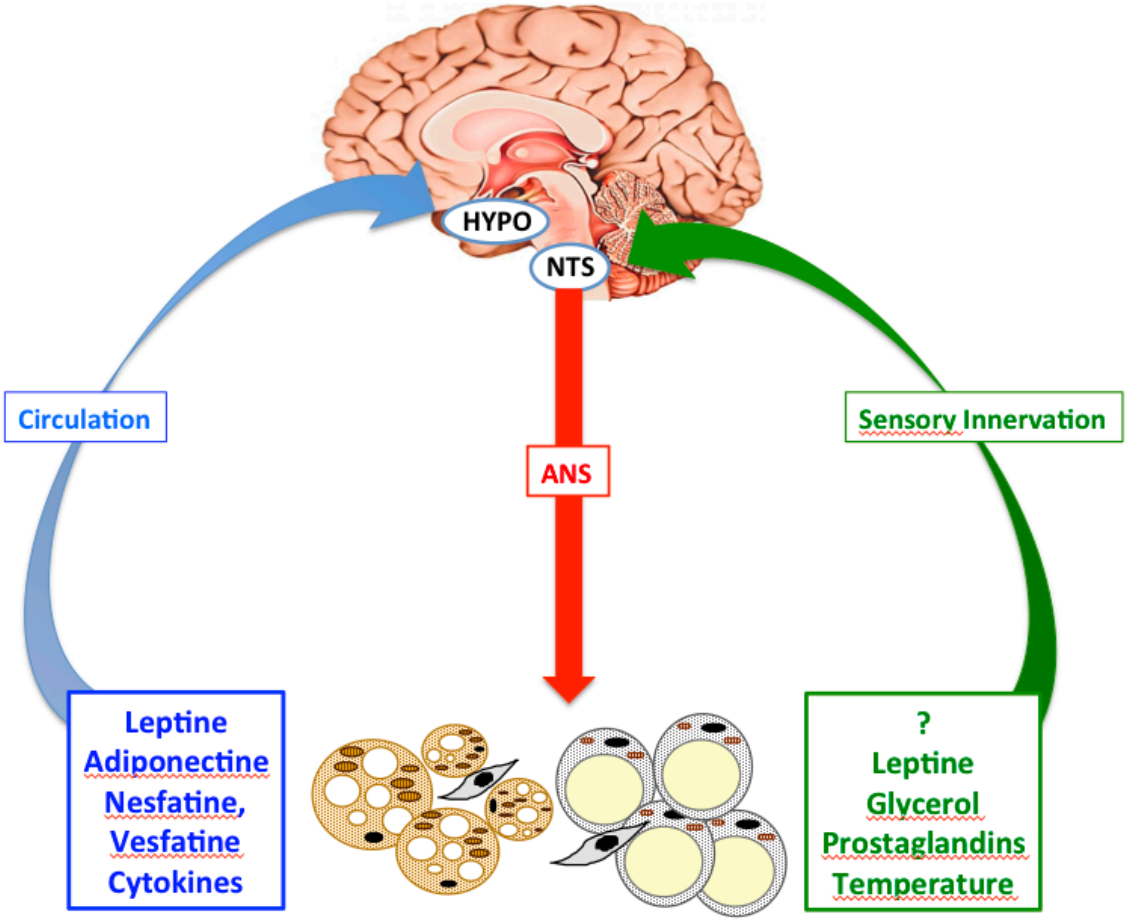

Figure 1: ***Feedback loop between the brain and adipose tissues.*** *The brain is informed of white and brown fat mass and their metabolic activity via sensory innervation and metabolic and hormonal signals traveling through the general circulation. Two main brain areas are involved in this detection the hypothalamus (Hypo) and the brain stem (NTS for Nucleus of the Tractus Solitarius). In turn the brain modulates adipose tissues activity via the autonomic nervous system mainly the sympathetic one.*

The main neurotransmitter of SNS is norepinephrine although these nerves contain and release various neurotransmitters among which neuropeptide Y (7). Both NE and NPY control lipolysis by activating different receptors subtypes present on adipocytes (8, 9). In WAT it has been demonstrated that the lipolytic activity of adipocytes depends on a balance between lipolysis-promoting ß-adrenergic receptor and lipolysis-inhibiting a2-adrenergic receptor (10, 11). Depending on this balance an increased sympathetic tone can lead to an increase or a decrease in lipolysis.

For a long time it was thought that white adipose tissues did not received parasympathetic nerves. Recent neuro-anatomical studies in rats have reported parasympathetic innervation of WAT. A physiological role of such input was proposed since vagotomy was shown to reduce the insulin-dependent glucose and free fatty acid uptakes (12). Such role of PNS can be also sustained by the demonstration of the presence of functional nicotinic receptor on white adipocytes as well as an increased insulin sensitivity of these cells

under nicotine stimulation (13). However the PNS innervation of WAT remains a subject of debates (14, 15).

Although adipose tissue is used as a general term, event the white-fat pads are quite different in regards of their origin, anatomical characteristics and functions so that one should rather speak about white adipose tissue**s**. Indeed both autonomic innervation (fibers density or sub-location) and the number and affinity of neurotransmitter receptors of fat depots are heterogeneous. First a relatively separated sympathetic innervation of inguinal and epididymal pads exist, since there are no overlapping patterns of labeled postganglionic cells within the sympathetic chain innervating these two deposits using fluorescent tracers (3). In addition to this peripheral viscerotopic separation of sympathetic nerves, viscerotopy could also occur centrally, within spinal cord or brain (3, 12, 16, 17). Moreover, this heterogeneity of innervation may change according to nutritional, and probably other, status (18). Second, taking NE turn-over as an index of SNS activity, specific pattern has been delineated which might also depend of the stimulus considered (19). Altogether these last data indicate a higher lipolysis in intra-abdominal fat pads as compared to subcutaneous one. Third, this is reinforced by the distribution of the different subclasses of receptors that depends on species, sex, and fat depot (10, 20).

Effects of the autonomic nervous system on white adipose tissue functions

The two main metabolic pathways of adipocytes are on one hand the synthesis and accumulation of triglycerides and on the other their degradation into free fatty acid and glycerol (34). The increase in lipids store in adipocytes is performed by two ways. First by the direct uptake of triglycerides associated with lipoproteins coming from the circulation and which are hydrolized by lipoprotein lipase in non-esterified free fatty acids. These fatty acids are then transported into and in the cells by a family of fatty acid binding protein (FABP, FAT, FATP, aP2,….). Second by the lipogenic pathways i.e. the de novo synthesis from glucose. This last one is transported into the cell mainly via the insulin-sensitive glucose transporter isoform Glut 4. The glucose allows the synthesis of pyruvate and glycerol-3-phosphate, substrates, which will lead to the synthesis of triglycerides. Indeed, pyruvate will be utilized for the formation of acetyl-CoA and then its transformation into malonyl CoA under the control of acetyl-CoA carboxylase. The last step catalyzed by fatty acid synthase, a multienzyme complex, leads to the formation of long chain fatty acids. These anabolic pathways are mainly under the control of insulin.

It is now recognized that lipolytic pathways is mainly under the dependency of three main players: adipose triglyceride lipase, hormone sensitive lipase, and perilipin A (21). In white adipocyte, both free fatty acids and glycerol are released into the adjacent blood vessels to provide fuel for other tissues. As already mentioned, catecholamines are the main factor involved in the control of lipolysis. However one has to underline that, the antilipolytic effect of insulin is predominant and thus catecholamines exert their effect when insulin level is low. From what is said above it is easy to conclude that the sympathetic nervous system is the main driver for adipose tissues lipolysis.

Apart its well-known effect on lipolysis, sympathetic nervous system plays a role in regulating the anabolic pathways (10). Thus it has been shown that stimulation of sympathetic nerves has no main effect on glucose uptake, utilization and lipogenesis in WAT (22, 23). Whereas, as already mentioned, there are evidences that PNS innervation increases insulin sensitivity in WAT (12).

Brown adipose tissue activity is mainly under the control of the sympathetic system via the binding of norepinephrine on beta adrenoceptor that induces lipolysis and thus the activity of UCP. This leads to an enhanced thermogenesis. Norepinephrine induces also an increase in the amount of UCP by stimulating its gene transcription (1).

Over the last 20 years the notion has emerged that WAT is not only involved in the storage and release of energy but could also be part of other physiological functions due to its capabilities in synthesis and secretion of numerous factors such as leptin, adiponectin and many proteins involved in inflammation and immunity (24, 25). So that adipose tissue is now considered as a true endocrine organ.

The synthesis and secretion of some of these compounds are under the control of numerous factors among which the sympathetic nervous system *via* catecholamines plays a role. Leptin control has probably been the most studied. They are evidence that stimulation of ß-adrenoceptor decreases the release of leptin. In human adipose tissue this occurs through a posttranslational mechanism, most likely secretion *per se*. In contrast, in rat adipose tissue, isoproterenol does not affect basal leptin secretion but has a short-term action to antagonize the insulin-stimulated leptin biosynthesis (26). Also an elegant study demonstrates a decrease leptin secretion when 3T3L1 adipocytes (a well-characterized white adipose cell line) are cultured in the presence of primary sympathetic neurons. It has then been proposed that catecholamines may mediate short-term decrease in plasma leptin that occur within hours of fasting and cold exposure (27).

Adiponectin is also negatively regulated by ß-adrenoceptor (28). By contrast the secretion of cytokines such as TNFa and IL6 are increased under ß-adrenergic stimulation (29). Overall these data suggest that up-regulation of pro-inflammatory cytokines and down-regulation of adiponectin by ß-adrenoceptor activation may contribute to the pathogenesis of catecholamine-induced insulin resistance.

Effects of the autonomic nervous system on WAT growth

Fat mass is the result of two processes i.e. the regulation of the size and the number of adipocytes. There are also numerous evidence showing that the SNS is involved in the control of proliferation and differentiation and to a lesser extend of apoptosis of white adipocytes.

Norepinephrine inhibits proliferation of adipocyte precursor cells in vitro and this can be blocked by propranolol, a general ß-adrenoceptor antagonist (30). *In vivo* surgical or pharmacological denervation of WAT triggers significant increase in the number of white preadipocytes and adipocytes (4, 23). One week after denervation of one retroperitoneal fat pad, DNA content is increased without change in the number of mature white adipocytes. Furthermore, the amount of A_2COL_6, an early marker of white adipocyte differentiation is enhanced in the denervated pad. One month later, the number of mature adipocytes is significantly increased in the denervated pad (23). This was confirmed using transgenic mice having a massive reduction of innervation due to the lack of Nscl-2, a neuronal specific transcription factor (31). These mice present an increase preadipocytes number and a bimodal distribution of the size of adipocytes indicating an increase in the number of small adipocytes. Moreover, recent data demonstrates that increase in sympathetic drive to WAT pads may induce emergence of brown (or brown-like) adipocytes

within WAT depots, an effect likely due to beta3 receptors activation (32, 33). Altogether, these data agree with a major role of SNS. Nevertheless, one must keep in mind that sympathetic efferent fibers synthetize and release other neurotransmitters such as NPY. Indeed, it has been demonstrated that sympathetic NPY release stimulates fat angiogenesis, proliferation and differentiation of new adipocytes, resulting in adipose tissue growth (55, 56). These effects which are mediated through Y1 and/or Y2 receptor subtypes can thus antagonize or minimize NE effects (34) (Figure 2).

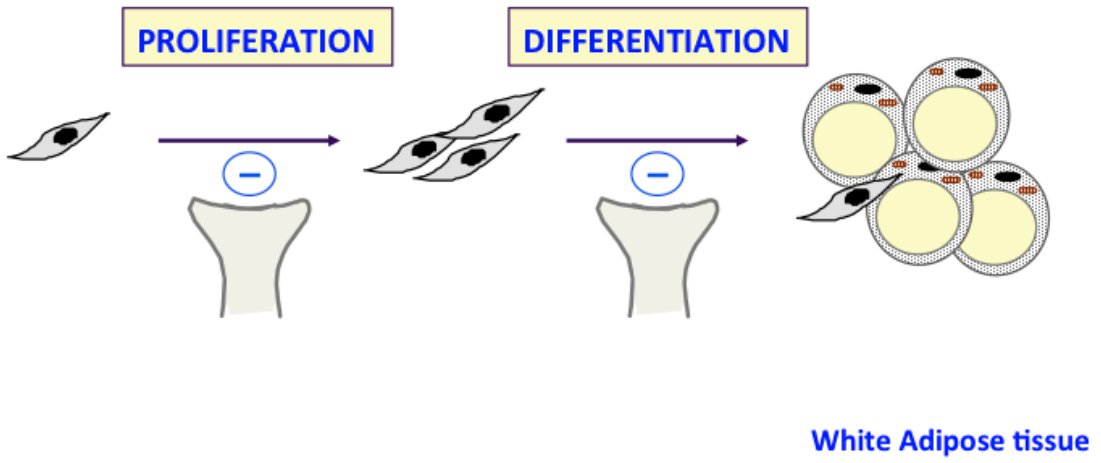

Figure 2: ***Control by the sympathetic nervous system of white adipocyte proliferation and differentiation.***

Although the importance of apoptosis in the biology of adipose tissues is still a controversial issue, there are different reports describing such process in white adipocytes. To our knowledge there is no direct demonstration of a role of the SNS in regulating the rate of apoptosis in adipose tissues, however several observations are in support of such role. In brown adipocytes, the pro-apoptotic effect of TNFa is abrogated by NE and this neurotransmitter protects the cells from apoptosis (35). Nothing is known concerning such effects on white adipose cells. Nevertheless, leptin is indeed known to induce a reduction in fat pads weight, this effect being observed after peripheral or central injection. Furthermore adipocyte apoptosis occurs after intracerebroventricular administration of leptin in rats (35). On the other hand it is well demonstrated that leptin induces an increased SNS activity (37, 38). From these data, it can be proposed that the signal that promotes apoptosis under leptin CNS activation is probably NE or another co-secreted neurotransmitter.

From adipose tissues to the brain

Circulating signals

Energy balance is the result of ingestive behavior, energy expenditure and energy storage in adipose tissue. To explain the precise overall regulation of these parameters it has been hypothesized, at first by Kennedy in the 50th, that signals generated in proportion to body fat stores will act in the brain to

modulate food intake and/or energy expenditure (39). Among these signals the first to be proposed was insulin; since it was demonstrated that the pancreatic hormone increases proportionally to body fat mass and acts in the CNS to reduce food intake (40). In the nineties, Friedman and his colleagues identified leptin and its receptors (41). Leptin is predominantly expressed in adipose tissue and the long form of its receptor (ob-Rb) is highly expressed in specific sites within the CNS. As expected, administration of leptin reduced food intake and body in different animal-models of obesity as well as in humans. Leptin is secreted in direct proportion to the amount of stored body fat (42). As a consequence plasma leptin concentration increases while body fat rises whereas fasting and leanness lead to decreased leptin secretion.

Since the discovery of leptin other factors synthesized and released by adipocytes have been characterized and are grouped under the term adipokines (Figure 1). Among them, adiponectin, nesfatin, visfatin as well as cytokines such as IL6, TNFalpha have been shown to be involved in energy homeostasis partly via their action in the brain (43). Adiponectin is the most abundant protein secreted by white adipose tissue (44). The protein is found in the cerebro spinal fluid (45). Its receptors are present in neurons of the hypothalamus known to control food intake and energy expenditure (45, 46). Adiponectin injected icv increases energy expenditure and reduces food intake (45, 47). Nesfatin (NEFA/nucleobinding2-encoded satiety-and fat-influencing protein) is an adipokine having strong anorectic effect by acting centrally (48, 49). It mainly interacts with the melanocortin system. It is synthetized by different tissues among which WAT but is also present in the CNS (48). Visfatin is mainly synthesized by visceral fat although its expression is not restricted to WAT (50). It has an orexigenic effect and a positive correlation exists between plasma visfatin level and body fat mas and body weight in human (51). TNFa and IL6 are secreted by adipose tissues but the main source is not the adipocyte itself but rather macrophages (52). Their release is proportional to the amount of fat and their anorectic effect has been demonstrated since many years (53).

Last, one has also to stress the role of nutrients of which the concentration might depend on the metabolic activity of adipose tissues such as glucose and particularly free fatty acids. Indeed both of these metabolites have been shown to play an important role as signals, reflecting energy homeostasis, to some part of the brain (54, 55). Glucose and lipids are detected by specialized fuel-sensing neurons that are incorporated in specific hypothalamic neuronal circuits. Hence, circulating nutrients cooperate with hormones (insulin) and adipokines (mainly leptin) to regulate the activity of distinct neuronal populations that control food intake, energy expenditure, and glucose homeostasis.

Sensory innervation

Apart these circulating signals acting directly in the hypothalamus and other areas, adipose tissues sensory nerves may be part of this system. The identification of substance P and calcitonin gene-related peptide, markers of sensory neurons was a first demonstration of sensory innervation of WAT (7). Then a direct neuroanatomical demonstration was given by use of anterograde tracer (56). Labelled cells were found at all levels of the neuroaxis: nodose ganglia (visceral afferents), dorsal horn of the spinal cord (nociceptive and/or proprioceptive afferents) and in almost all the autonomic outputs areas in the brainstem and midbrain" (13, 57) (Figure 1).

Although one does not know which molecules (leptin, lipid molecules such as glycerol, free fatty acids, prostaglandins) these nerves "sense", data are in support of their role in informing the brain on lipid stores. When selective an bilateral destruction of sensory fibers innervating epididymal fat pad was performed in hamster by injecting capsaicin, the weight of the others WAT pads (retroperitoneal and inguinal) was increased in a degree that approximated the lipid deficit if the pads have been removed by lipectomy (58). Second, leptin microinjection in WAT pad significantly increased electrical activity of sensory afferent neurons emanating from the pad and elicited increase in sympathetic efferent neurons in the contra-lateral pad suggestive of a reflex arc (59).

Autonomic nervous system and obesity

As described above, in white adipose tissue, an increased sympathetic tone will slow down proliferation and differentiation and might also enhance apoptosis. By contrast in brown adipose tissue, there is an increased proliferation and differentiation and possibly a reduction of brown adipocytes apoptosis all phenomenon leading to higher thermogenic capacity (Figure 3).

Figure 3: ***Involvement of the autonomic nervous system in obesity.*** *Decreased sympathetic activity can explain development of abnormal fat mass. This decrease results in a lower thermogenic activity and growth of brown adipose tissue which lead to a decreased energy expenditure. It also drives a higher proliferation and differentiation of white adipocytes which together with a decreased lipolysis will result in a higher fat mass.*

As a consequence, dysregulation of the sympathetic nervous tone can play a role in some pathological situations. Such can be the case in obesity at least in rodents and possibly in adult human in which a decreased sympathetic activity has been described (61-64). Although there are some opposite results in man which might be due to the characteristic of the subjects as well as the methods used (65). Although scarce, there are a recent study showing a decreased sympathetic activity in childhood obesity (66). Such a decrease will lead, in white adipose tissue, to the disappearance of the inhibition of adipocytes proliferation and differentiation normally found in lean rats. This would result in the recruitment of new precursors and the appearance of new adipocytes. Together with decreased lipolysis and the influence of hyperinsulinemia that will favor hypertrophia of both pre-existing and new cells (61), will lead to over-development of this tissue. On the other hand, a decrease sympathetic tone will result in an overall decreased thermogenesis by first decreasing the amount and the activity of UCP1, second lowering the number of brown adipocytes. This last point can be due to both decreased proliferation and differentiation, increased apoptosis and although possible changes from one phenotype to the other (61, 67, 68).

Conclusions

In summary there are compelling evidences of the importance of the nervous regulation of the adipose mass, either brown or white, by acting on the metabolic and secretory activities but also on the plasticity (proliferation, differentiation, trans-differentiation, apoptosis) of these tissues. The neural feedback-loop between adipose tissues and the brain plays a crucial role in numerous physiological phenomena in particular the regulation of energy homeostasis and body fat mass but also reproduction and immune function. This loop could be altered in various metabolic pathologies such as obesity, type II diabetes and their complications.

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Dr. Pénicaud is Research Director at the Centre National de la Recherche Scientifique (CNRS) since 1989. From 1995 to 2007, Dr. Pénicaud was director of a CNRS unit affiliated to the University of Toulouse. Earlier, Dr. Pénicaud held a CNRS position in the Laboratory of Nutrition at the University of Paris VI as a team leader. He earned his PhD. from the University of Paris VI and VII, and completed postdoctoral studies at the University of Rochester NY, USA; the University Medical Center, Geneva, Switzerland, and the Nutrition Center, Paris. He is now since 2010 the Director of the Center for the Study of Taste and Feeding Behavior in Dijon, a Centre of over 220 members affiliated to CNRS, INRA and University of Burgundy. He is the recipient of several awards for his research in neurobiology, energy homeostasis and associated pathologies such as diabetes and obesity. Dr. Pénicaud is a member of several international societies such as the European Association for the Study of Diabetes (EASD), the American Diabetes Association ADA), the European Association for the Study of Obesity (EASO), the European and International Society of Neuroscience. Dr Pénicaud is member of different boards: among which President of the scientific commission on Physiology at the CNRS, Scientific council at the Institut National de la Recherche Agronomique (INRA), Scientific council of the Nutrition department at the same Institute, commission of the National Program on Diabetes. Dr. Pénicaud is the author of over 200 scientific articles and publications and is regularly invited as a speaker in national and international meetings.

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