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Brain Circuits Regulating Energy Homeostasis

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Introduction

The past twenty years have witnessed tremendous advances in the understanding of the central mechanisms regulating food intake and energy balance, perhaps in response to the accelerated increase in the incidence of obesity in industrialized nations. Some of the most striking discoveries have included descriptions of hypothalamic neuropeptidergic circuits that respond to changes in peripheral metabolic signals, and that regulate metabolism through their multiple output pathways. In addition, the sophistication of research tools afforded by genetically engineered animals has provided a degree of certainty to the data that is unparalleled. Finally, much insight has been gained of the potential mechanisms that underlie the dynamic functioning of hypothalamic circuits. This chapter will attempt to provide a synopsis of these advances, leading to the idea that synaptic plasticity as an important factor in the regulation of food intake and energy homeostasis.

Hypothalamic Homeostatic Circuits

It is now well established that the hypothalamus plays a critical role in the regulation of energy balance. This was first suspected after descriptions of obesity in patients with hypothalamic tumors over a hundred years ago [1], but at the time, it was thought that the pituitary gland regulated most endocrine functions and that alterations of the pituitary lead to metabolic disorders [1]. Confirmation of the hypothalamus as important for regulation of food intake and energy balance was obtained from animal studies using brain lesions of hypothalamic structures [2–4]. In essence, evidence obtained from both the clinical descriptions in tumor patients, and from the lesion work, showed that gross damage to mediobasal hypothalamic areas, in particular the ventromedial hypothalamic nucleus (VMH), was clearly associated with increased food intake, morbid obesity and insulin resistance, while damage to more lateral hypothalamic structures was associated with anorexia and adipsia [5]. In turn, electrical stimulation of the VMH resulted in decreased feeding, whereas stimulation of the lateral hypothalamic region increased appetite [6–8]. As a whole, these data suggested that the mediobasal hypothalamus was a satiety center, and that the lateral hypothalamus was an orexigenic center [9,10].

This dual center hypothesis dominated the field for several decades until a number of studies began to trickle data showing that neither the VMH and adjacent structures were solely satiety centers, nor was the lateral hypothalamus uniquely involved in appetite [11,8]. For example,

it was found that knife cuts that separated the ventral from the lateral hypothalamus without damage to the VMH were sufficient to cause hypothalamic obesity [12]. Similarly, vagotomy appeared to ameliorate obesity caused by VMH destruction [13,14]. Finally, destruction of dopaminergic fibers of the medial forebrain bundle (mfb), which course through the lateral hypothalamus, resulted in animals that showed similar anorexic and adipsic symptoms as animals with lesions to the lateral hypothalamus [15]. Indeed, it seemed that disconnections of pathways coursing through these regions were as effective in inducing obesity or anorexia as the lesions themselves. For many years, the study of ingestive behavior and obesity focused on exploring the relative contribution of different neurotransmitter systems on the regulation of energy balance.

While a tremendous amount of data was obtained during this time, the discovery of neuropeptide Y (NPY) and leptin can be regarded as the most important discoveries in the past 25 years. First, NPY, a 36-amino acid peptide homologue of the pancreatic polypeptide family [16], was found to be produced within the brain primarily (although not uniquely) in the arcuate nucleus (ARC), a hypothalamic nucleus ventral to the VMH previously implicated in the regulation of body weight and energy balance [17]. When injected into the ventricles of rats or within other hypothalamic nuclei, NPY potently elicited food intake [17–21]. Moreover, NPY synthesis and content within the ARC was elevated in fasted and in genetically obese animals [22,23]. NPY infusions also increased fat deposition and decreased brown fat thermogenesis and oxygen consumption, suggesting that NPY was not only an orexigenic peptide but also one important in the regulation of metabolism [24,25].

A few years later, Dr. Jeff Friedman and his associates cloned the gene that produced leptin, a peptide hormone produced in adipocytes, and that was mutated in the ob/ob line of genetically obese mice [26]. Treatment with leptin reversed the phenotypic abnormalities seen in ob/ob mice and was also effective in reducing body weight and food intake while increasing energy expenditure in normal animals [27–29]. A second line of genetically obese and diabetic mice known as the db/db, was soon after found to be the result of a deletion of the gene encoding the long form of the leptin receptor (ObRb) [30–32]. Finally, it was established that leptin targeted NPY neurons within the ARC to produce these dramatic changes in metabolism [33]. These groundbreaking discoveries laid the foundation of what could be termed as a renaissance in the study of neural control of obesity and energy balance. Reports of other peptides with either anorexic or orexigenic properties began to routinely appear in high impact journals, and continue to make headlines.

Because the ARC contains the largest concentration of cells that produce NPY and have the densest concentration of leptin sensitive neurons in the brain, it is generally accepted that this region is key to the regulation of energy balance (Fig. 1). This is supported by the fact that, in addition to NPY, the ARC also contains a second set of neurons that produce α?melanocyte stimulating hormone (α-MSH), an anorectic peptide formed from the cleavage of the proopiomelanocortin (POMC) protein [34]. This protein acts on melanocortin receptors types 3 and 4 (MC3/4, respectively) present in various hypothalamic nuclei to reduce food intake and energy expenditure in a manner similar to leptin [35]. Moreover the pharmacological blockade of MC3/4 receptors or the deletion of the gene encoding the MC4 receptor, result in obesity and leptin resistance in rodents and primates [36–38]. In addition, NPY neurons produce a second orexigenic peptide, the agouti related peptide (Agrp), an endogenous antagonist to the MC3/4 receptor [38]. This peptide, like NPY, increases food intake dramatically, but the increase in food intake produced by this peptide is long lasting, and effect that is still not well understood [39]. Similarly, POMC cells also synthesize a second anorexic peptide, the cocaine and amphetamine related transcript (CART) [40]. The relative contribution of CART versus α?MSH in the regulation of food intake and energy expenditure remains unexplained. What is known is that both NPY/Agrp and POMC/CART neurons within the

ARC appear to primarily modulate food intake via their output targets (Fig. 1). Both POMC and NPY cells have a widespread projection field that has been implicated in a variety of physiological and behavioral events that include reproduction, water balance, body temperature and energy balance. The main output of both NPY/Agrp and POMC/CART cells appears to be the PVN where NPY, α-MSH and Agrp have strong effects on food intake and body temperature. These cells, however, target other hypothalamic nuclei like the VMH, dorsomedial hypothalamus (DMH), and LH among others to potentially modulate food intake end energy expenditure, and the relative contribution of these nuclei to produce the orexigenic or anorexic effects of these peptides continues to be investigated [41–43]. Finally, NPY/Agrp neurons the ARC appear to synapse onto neighboring POMC/CART cells to inhibit them using GABA as a neurotransmitter [44,45].

While the lateral hypothalamus had been previously described as a “hunger” center, it was not until recently that two orexigenic peptides, hypocretin/orexin and melanin concentrating hormone (MCH), were identified and localized within this area [46,47]. Interestingly, both hypocretin/orexin and MCH increase food intake via different mechanisms. In the case of hypocretin/orexin neurons, their role in the regulation of food intake has been questioned given that their effects on food intake are short lived [48], and that ob/ob and db/db mice show lower levels of hypocretin/orexin mRNA and peptide content than their wild type littermates [49]. Nevertheless, mice with genetic deletion to the gene encoding the prepro-orexin peptide are hypophagic [50]. Hypocretin/orexin cells send projections to the ARC where they synapse onto NPY/Agrp cells, which in turn project back to hypocretin/orexin cells [51]. This particular circuit is thought to play an important role in hypocretin/orexininduced food intake [51–54]. Moreover, the presence of receptors for signals like leptin and ghrelin, as well as changes in electrophysiological activity of hypocretin/orexin neurons in response to these signals demonstrates that hypocretin/orexin cells can be directly modified by peripheral signals [55, 51]. Sakurai and his associates have determined that hypocretins/orexins play a crucial role in activating arousal circuits in response to energetic challenges resulting in food seeking behaviors and in food anticipatory behaviors [56,57].

In contrast, the role of MCH hypothalamic neurons in the regulation of energy balance appears to be more straight forward. For example, ob/ob, db/db mice have high levels of MCH expression in the hypothalamus, and MCH transgenic mice are overweight and gain more weight under a high fat diet [58,46]. In contrast, MCH or MCH receptor knockout mice are leaner, eat less and have increased metabolism than their wild type littermates [59,60]. Interestingly, α-MSH/POMC cells inhibit the activity of MCH neurons, and thus prevent increases in food intake [61,62]. Given the widespread distribution of both hypocretin/orexin and MCH projections [52], it has been suggested most aspects of food intake and energy regulation could be modulated by the interaction between these two cells groups at these target sites [63,64], and given their close proximity and synaptic interconnections, perhaps by reciprocally modulating each other’s cellular activity [65–67].

The list of peripheral factors that, like leptin, target the ARC to modulate energy balance has also grown [68]. Metabolic signals such as glucose availability, insulin, cholecystokinin (CCK), pancreatic polypeptides (PP and PYY) and ghrelin have, among others, all been found to modulate NPY and POMC in the ARC to alter food intake and metabolism. Of these, ghrelin has received special attention given that, in contrast to the other peptides, ghrelin acts in NPY cells within the ARC to increase food intake, adiposity and the secretion of growth hormone [69–72]. Although ghrelin is produced primarily in the stomach [71,73], a sub-set of ghrelin secreting neurons has been identified in the dorsal portion of the ARC and in the spaces that surround different hypothalamic nuclei implicated in the regulation of energy balance [55, 71]. The role of these neurons remains to be determined fully, but anatomically, it appears that these cells integrate metabolic and circadian outputs to regulate energy balance [55].

We are then left with a model where metabolic signals that monitor energetic state, signals like leptin, ghrelin, insulin and PYY, target the hypothalamus, and particularly the ARC to modulate the activity of NPY/Agrp and POMC neurons. The activation of these neurons by "satiety" signals leads to a reduction in NPY/Agrp and an increase in the release of α-MSH from POMC neurons. Consequently, α-MSH binds to MC3/4 receptors in MCH cells in the lateral hypothalamus to reduce food intake and with thyroid hormone and corticotropin releasing hormones (THS and CRH) in the PVN to increase energy expenditure. In contrast, hunger signals like a reduction in the glucose availability, or increased circulating ghrelin will lead to increases in ARC nucleus NPY release that inhibit POMC, THS and CRH and stimulate the secretion of hypocretin/orexin and MCH from the LH to ultimately increase food intake and reduce metabolic rate. The ARC appears to be, therefore, a brain nucleus orchestrating brain responses to changes in energy demands [34].

Tools for the Study of Feeding Circuits

In addition to improved lesion techniques and increased availability of agonists or antagonists that specifically target different neuropeptide receptors, the molecular biology and molecular genetics revolution have proven pivotal for the unveiling of feeding circuits. Molecular biological techniques have revealed that the ObRb leptin receptor belongs to the same family (gp130) of receptors associated with cytokines such as the interleukins [32]. Activation of this receptor by leptin can achieve gene transcription by at least three signaling cascades that include the activation of the JAK2/STAT3, the ERK/MAP kinase and the phosphoinositol 3 kinase (PI3K) pathways [74–76]. Much attention has been focused on the ability of leptin to activate STAT3 that, in turn, will act as a transcription factor for several genes that include the suppressor of cytokine signaling 3 (SOCS 3) gene, an intracellular protein that prevents further activation of the ObRb [77,78]. The pivotal role of STAT3 as a transcription factor that mediates the effects of leptin on energy balance has been highlighted recently by the generation of mice with targeted deletions to different sites for STAT3 phosphorylation, rendering animals with deficient STAT 3 signaling. These mice are severely obese and insulin resistant, and show high expression of NPY and Agrp, and diminished expression of POMC in the ARC [79–81]. Several knock out mice lines have underlined the importance of the melanocortin system in the regulation of leptin's effects and in energy balance in general. Thus, targeted deletions to the genes that encode α-MSH, MC4 receptor, and the specific deletion of the ObRb in POMC neurons also result in obese, hyperinsulinimic and leptin resistant mice [82,83,37]. Moreover, naturally occurring mutations of the Ob and α-MSH genes also produce the same symptoms in humans [84].

In contrast, deletions to the genes that encode NPY, ghrelin, or the active form of the ghrelin receptor (growth hormone secretagogue receptor 1a or GHS-R 1a) result in few phenotypic abnormalities [85–88]. Nevertheless, NPY /leptin double knockout animals show decreased food intake, body weight, and adiposity in comparison to the regular leptin (ob/ob) deficient mice [86], and ghrelin deficient animals appear to be slightly resistant to diet induced obesity [88]. Physiological responses of NPY, ghrelin and GHS-R deficient animals remain to be fully determined. In any event, there are a variety of mutations that lead to a lean phenotype (i.e. MCH KO mice), and some like in the dopamine deficient mice, become completely aphagic, needing dopamine replacement to continue eating [89,90]. The relative contribution of these genes in the regulation of hypothalamic homeostatic circuits is a matter of continuous research efforts.

Finally, the development of reporter genes that can be used as tags has become a welcome addition to the study of hypothalamic circuits. For example, the gene that encodes the green fluorescent protein (GFP), a protein that is produced in a specific species of jellyfish, has been tagged onto the promoters of several of the peptides implicated in energy regulation. These

gene “knock ins” have enabled the visualization of cells that synthesize neuropeptides such as NPY and POMC, or neurotransmitters like GABA that are difficult to visualize using immunocytochemical techniques. The use of mice with specific insertions of the GFP gene has proven invaluable to the study of anatomical and physiological properties of specific hypothalamic neuropeptides. For instance, Cowley and colleagues used mice with the GFP gene inserted in the POMC promoter to unveil the electrophysiological properties of POMC neurons in response to signals like leptin, NPY, ghrelin, and PYY [91,92]. Friedman and colleagues have used mice with the GFP gene inserted in the NPY and POMC promoters to determine the mechanisms by which different metabolic signals and neurotransmitters act on NPY and POMC cells [93]. In collaboration with Friedman’s laboratory, we have used these mice lines crossbred with ob/ob mice to describe the dynamic synaptic remodeling that occurs in both POMC and NPY cells in response to leptin and ghrelin and that may be critical for the regulation of energy balance, a mechanisms that will be described in ensuing pages.

Synaptic Plasticity and Energy Balance

The concept of homeostasis implies that physiological events in all organisms necessitate a degree of plasticity or flexibility to allow for constant dynamic changes to achieve balance. Within the brain, this plasticity is afforded by systems that can change in response to given stimuli, and that rearrange in ways that allow for more efficient responses to future stimuli. In contrast to old dogma, it is now well accepted that connections between cells within the adult brain are capable to change in response to a variety of stimuli, and that these changes play an important role in critical brain functions as learning, memory, and motivated behavior. Such changes are referred to as synaptic plasticity.

Within the hypothalamus, synaptic changes have been implicated in a variety of processes that include osmoregulation, lactation, circadian rhythmicity, and reproductive function [94–100]. Interestingly, proteins that are commonly found in the developing brain and that are associated with the formation of new synapses are expressed selectively in the hypothalamus of adult organisms, and particularly in the ARC [101]. Interestingly, ultrastructural studies of the ARC revealed that synaptic remodeling occurs on cells within this region across the estrus cycle in female rats [99]. Garcia ?Segura and his associates then revealed that this effect was produced by estrogen, and that, in addition to rats, it was also observable across the reproductive cycle of non-human primates [101]. The ARC contains both estrogen receptor alpha and beta subtypes, yet the effects of estrogen on ARC nucleus cells can occur within minutes of the presence of estrogen in the media, and mimic those elicited in cells by growth factors [102]. While these studies were correlated with the onset and termination of the preovulatory luteinizing hormone surge, it has become clear that these changes may mediate the metabolic effects of estrogen.

Coinciding with these data, researchers soon discovered that leptin, like estrogen, targeted hypothalamic and extrahypothalamic structures that demonstrated a high degree of synaptic remodeling, including the ARC, VMH, and hippocampus [103–105]. Within the hippocampus, it has been demonstrated that leptin can lower the threshold for the induction of long term potentiation (LTP) after activation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors [106–108]. Because LTP is thought to result from synaptic changes, these data suggest that leptin can induce synaptic remodeling to increase sensitivity to excitatory stimulation.

Taken together, this information made it plausible that leptin, like estrogen, could target the ARC and other structures to modulate energy balance by actually remodeling inputs to the different cell groups in the ARC. In collaboration with Jeff Friedman, our laboratory engaged in a project examining the effects of leptin on the number and type of synapses contacting both

POMC and NPY neurons [109]. To do this, mice in which the gene encoding the GFP protein was inserted in the promoter for either NPY or POMC were cross-bred with heterozygous leptin deficient (ob/ob) mice, to produce ob/ob GFP transgenic mice. Electron microscopic examination, determined that NPY cells in the ARC of ob/ob mice had more synapses than NPY cells of wild type mice. Surprisingly, POMC neurons of ob/ob mice had a lower number of synapses than those of wild type mice. Nevertheless, synapses onto POMC cells of ob/ob mice were predominantly putative inhibitory (symmetric), whereas NPY cells of ob/ob mice primarily exhibited putative excitatory (asymmetric). These data were consistent with electrophysiological recordings showing that the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) onto POMC cells of ob/ob mice was higher than that on POMC cells of wild type mice, with no significant differences in the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) on these cells. In contrast, the frequency of sEPSCs was increased and that of sIPSCs was decreased in NPY neurons of ob/ob mice compared to NPY neurons of wild type mice. Finally, leptin administration to ob/ob mice rapidly restored the balance of excitatory and inhibitory synapses to the levels observed in untreated wild type mice, whereas ghrelin treatment to wild type mice had just the opposite effect. The outcome of these experiments provided anatomical and electrophysiological evidence of a dynamic model of energy regulation in which hypothalamic neurons are in a constant “tug of war” between inhibitory and excitatory synapses, and where peripheral signals like leptin, ghrelin and estrogen shift the balance to ultimately increase or decrease food intake providing for a dynamic framework we have termed the ‘floating blueprint” [110].

Plasticity and mitochondrial UCP2

The plastic nature of ARC nucleus cells, and indeed that of any system that is capable of actual architectural remodeling, may involve high energy expenditure, which may be reflected in the activity as well as in the proliferation of the mitochondria. The mitochondria are involved in the generation of cellular metabolism, and optimal mitochondrial functioning determines the fate of individual cells [111]. Increased mitochondrial activity may, however, also result in the generation of free radicals that can lead to cellular stress and degeneration [111]. It has been suggested that uncoupling proteins (UCPs) are capable of preventing cell damage by dissociating the production of energy in the form of ATP and the resultant high levels of free radicals by regulating the proton leak from the inner membrane of the mitochondria [112, 113].

Of the different UCPs identified, UCP2 has been shown to play an important role in neuroprotection and may, as has been previously suggested, play a role in neurotransmission [114,115]. This may indeed be the case in the mammalian hypothalamus, where UCP2 is constitutively expressed [115–117]. Within the ARC, UCP2 appears to be present in NPY/Agrp producing cells, as well as in estrogen and leptin sensitive cells, which could also be POMC secreting neurons [115]. The role of UCP2 in these systems remains to be determined although it has been suggested that locally produced active thyroid hormone (T3) activates UCP2 in NPY/Agrp cells, a response that may be critical to activate these cells during negative energy balance [110]. A role for UCP2 in obesity continues to be considered, although UCP2 knock out mice do not seem to be obese [113]. Nevertheless, spontaneously obese yellow agouti mice have a leaner phenotype when crossbred with mice that overexpress the human form of UCP2 (hUCP2) [118]. Interestingly, although these mice are heavier than their wild type littermates at the age of three months, they appear to have less body fat. As they age, hUCP2 transgenics do not continue to gain weight, and by the age of 10 months they are leaner than their wild type counterparts [118]. It is therefore tempting to suggest that UCP2 protects ARC cells from free radical damage that results from the high metabolic rate of these cells. As animals age, uncoupling mechanisms that include the induction of UCP2 and the production of new mitochondria may become deficient leading to alterations in cell function and ultimately

obesity. Finally, it could be argued that UCP2 is a potential factor sustaining synaptic plasticity in the ARC. Recently, dendritic mitochondria have been directly implicated in the generation and maintenance of new synapses following hippocampal stimulation. In general it appears that increases the number of mitochondria present in dendrites is directly related to the number of synapses that are formed [119–121]. Because the induction of UCP2 also increases the number of mitochondria in hippocampal cells [122], one can speculate that UCP2 modulates synaptic remodeling through increases in the number of mitochondria.

Parallel Systems Regulating Food Intake and Body Weight

While it appears that the hypothalamus and in particular, the ARC, are key regions regulating energy balance, previous and emerging data demonstrate the existence of other circuits that, when activated, modulate food intake and body weight [63,64,123–125]. The importance of these circuits has often been overshadowed by the attention paid to hypothalamic homeostatic circuits, yet their study may prove to be more relevant to human obesity [63,64]. In addition, these systems are often viewed as either secondary or connected in series with the hypothalamus, that is, they only function once the hypothalamus has been activated. Although these systems cannot be fully considered homeostatic, they may be activated in parallel with, and/or perhaps recruit homeostatic centers to modulate the ingestion of food. In addition, activation of these pathways may override regulatory signals from hypothalamic homeostatic centers to either increase or decrease appetite. For example, it is well established that rats whose brain stem is isolated continue to regulate the food they consume and even show affective responses to palatable foods [126]. Corticolimbic pathways are capable of integrating sensory inputs and produce cognitive as well as affective representations that are stored and used for making decisions, and lesions to various corticolimbic regions result in obesity [127–129]. Feeding is also associated with motivational mechanisms, the “liking” and “wanting”, which are required for the behavioral responses that are necessary to seek and obtain food [130, 131]. These mechanisms are commonly associated with mid brain and forebrain centers that regulate arousal, locomotor activity, mood, and reward. Reward pathways in particular have received special attention given the universality of food as a natural reinforcer. Dopamine produced in cells within the mid brain ventral tegmental area (VTA) is released into several forebrain structures like the hippocampus, ventral striatum, and prefrontal cortex, and this release is commonly associated with the experience or the expectation of reward [132–134]. Within the ventral striatum, dopamine release into the nucleus accumbens has been implicated in the rewarding aspects of food, sex, and drugs of abuse [135,136]. Interestingly, genetic deletion of dopamine markedly suppresses food intake in a manner that is similar to that of lesions of the lateral hypothalamus [89,90]. Numerous papers have appeared suggesting that hypothalamic peptides like NPY, α-MSH, Agrp, Orexin and MCH play an important role in modulating the activity of dopaminergic cells targeting the nucleus accumbens [137]. The idea in these papers is that the ARC funnels metabolic information from signals like leptin or ghrelin, to modulate the activity of the mesolimbic dopaminergic system via direct projections to the nucleus accumbens, or indirectly through the activation of hypocretin/orexin or MCH cells that also project to both the VTA and nucleus accumbens [63,137]. Emerging evidence, however, supports the notion that at least the VTA is sensitive to leptin, insulin and ghrelin, and that the activity of dopaminergic cells within the VTA can be modulated by these signals [138,139]. Further research may reveal that, in contrast to the funnel hypothesis, metabolic signals may act directly on reward systems to modulate motivational aspects of feeding in tandem with homeostatic systems to increase or reduce food intake.

Future Considerations

We believe that the ability of the ARC to dynamically rewire in response to ever changing signals is necessary for cells within this nucleus to efficiently modulate energy balance.

Interestingly, synaptic plasticity also appears to be an important feature in extrahypothalamic circuits affecting food intake. For instance, synaptic rearrangement within the VTA and nucleus accumbens has been implicated in the mechanisms that lead to addiction to substances like opioids, cocaine and amphetamine [140,141]. Within the VTA, the crosstalk between astrocytes and dopaminergic neurons appears to be important in the sensitization to amphetamine [142,143]. Chronic cocaine stimulation leads to long lasting changes in gene expression within the nucleus accumbens that perhaps reflect permanent changes in the inputs to cells within this region [144]. We know that, in addition to targeting the ARC to modulate homeostatic pathways, leptin and ghrelin potentially reach cells in the VTA, where they may also alter their synaptic inputs to enhance or decrease their activity. Whether the modulation of synapses in the VTA and ucleus accumbens occurs in response to exposure to natural rewards, or in response to changes in metabolic signals like leptin or ghrelin, remain to be determined. In any event, the examination of this issue will lead to a better understanding of the mechanisms that cause food cravings, and those that increase or decrease the incentive value of palatable foods. They may also lead to insight in the study of eating disorders like obesity and anorexia nervosa, and ultimately lead to more efficient treatments for these disorders.

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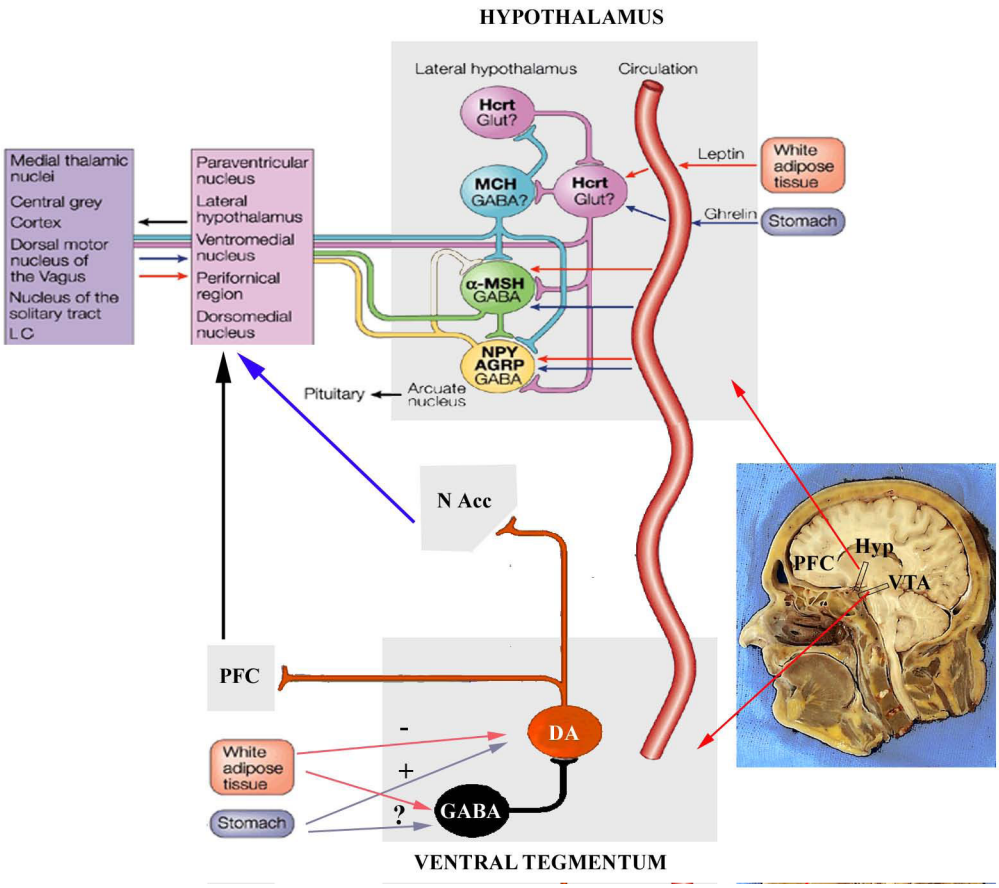

Figure 1.