Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 55 (Suppl 2) (2006) S24–S29
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Metabolic mechanism of wakefulness (and hunger) and sleep (and satiety): role of adenosine triphosphate and hypocretin and other peptides

Stylianos Nicolaidis*

Centre National de Recherche Scientifique (CNRS) of the Collège de France, Paris 5, France
University of Maryland, MD, USA

Abstract

The concurrent background level of metabolic activity may control state of vigilance, promoting wakefulness (and hunger) when it is low, or sleep (and satiety) when it is high. In a series of experiments, we have shown that sleep is dependent on feeding, but only because of the metabolic consequences of food ingestion. These consequences are sensed by glioneuronal populations (at least in the rostromedial hypothalamus), which probably respond to channel-bound adenosine triphosphate/diphosphate turnover (ischymetric monitoring) rather than to the binding of such downstream molecules as adenosine and cytochrome *c* oxidase. This basic signal is communicated to the vigilance-controlling centers by a cascade of peptidic and nonpeptidic messengers—messengers that promote wakefulness and hunger, possibly via a hypometabolic action (as in the case of neuropeptide Y or hypocretins), or somnolence and satiety, possibly via a hypermetabolic action (as in the case of leptin or certain serotonergic agents).

1. Introduction

This review does not deal with the perennial question, "What is the function or the purpose of sleep?" The intuitive answer to that question is that sleep is a restorative state whereby anabolic processes take place for recuperation. Such a function seems obvious and is well documented experimentally [1]. Herein, we ask, "What causes or promotes sleep? Might the concurrent metabolic state control or, rather, promote the states of vigilance, just as it controls hunger and satiety? Might the concurrent metabolic state be, not the effect (certainly restorative) of sleep, but, in fact, the promoter, if not the determinant, of the proximate level of vigilance?"

Both sleep and feeding behavior are involved in energy homeostasis. Under natural conditions, both are time-consuming and occur in cyclic patterns, competing with each other in the sense that they cannot take place at the same time. It makes sense that central monitoring of the current metabolic needs of the organism could orient an animal's behavior, either toward seeking food and ingesting it when depleted and hypometabolic, or toward resting and sleeping once the meal is finished and the organism is now replete and eumetabolic or hypermetabolic.

Herein, we examine evidence showing the dependence of sleep on feeding and suggesting that energy depletion or repletion could be sensed by some brain glioneuronal populations. We begin with a review of experiments (*a*) supporting the concept that the ongoing basal (background) metabolic rate is monitored by glioneuronal cells that sense the turnover of adenosine triphosphate/diphosphate (ATP/ADP) at the level of their excitable membrane. When this turnover is high, it promotes sleep and satiety; when it is low, it promotes wakefulness and hunger [2,3]; (*b*) describing candidate brain structures capable of sensing the concurrent "background metabolic rate" (see below) and of transducing this metabolic rate into a biologically relevant message (ie, spiking and/or synaptic trafficking); (*c*) identifying neurosubstances (peptides, monoamines) acting, in a cascade, on the centers that control the states of vigilance, either as messengers proper or, indirectly, via their upstream effect on the background metabolism.

In effect, we shall see that most of these neurosubstances, by acting on metabolism, also affect feeding. By extension, we can predict that whenever a neurosubstance affects feeding, it could also affect the states of vigilance and vice versa [4]. The prototype of such dual-acting neurosubstances

* 92340 Bourg La Reine, France. Tel.: +33 1 46604760.
E-mail address: snicolaidis@laposte.net.

0026-0495/$ – see front matter © 2006 Published by Elsevier Inc.
doi:10.1016/j.metabol.2006.07.009

is hypocretin 1, first discovered as an enhancer of hunger [5] and, only later, as an enhancer of wakefulness [6]. The initial idea that metabolic changes may underlie the alternation of sleeping and feeding (the ischymetric control of feeding and sleep) [2,3] and that certain neurosubstances may act on these 3 parameters [4] is, today, increasingly given credence in the sleep literature [7].

Before describing the data, it is necessary to clarify how the term "metabolism" should be understood in this context. There is often confusion when we speak about metabolism and its monitoring by brain centers. Almost all of the current laboratory instruments measure total energy metabolism, which is the sum of mainly 2 components: resting metabolism and locomotion-related metabolism. Although the first is relatively stable, the second is extremely variable. The metabolic changes described in this review refer to the fraction of resting metabolism referred to as "background metabolism." Background metabolism is, therefore, the fraction of total metabolism that remains after the metabolic cost of locomotor activity has been factored out. Background metabolism would be equal to "basal metabolism" if the appropriate conditions (eg, temperature, fasting, prolonged rest) were met.

Only background metabolism can decrease or increase in response to depletion or repletion because the fraction of energy expended in locomotion is inevitably imposed by environmental factors such as seeking food or escaping predators. Thus, a hypometabolic but physically active animal has a much higher (total) metabolism than a hypermetabolic animal that remains quiet. More specifically, the food-seeking hungry rat has a much higher total metabolism but yet a lower background metabolism (it is hypometabolic) than the sleepy, replete animal, which is hypermetabolic despite its low total metabolism. Unfortunately, only a few laboratories are equipped with computerized measuring devices capable of extracting background metabolism from "total metabolism" [8]. For this reason, we must be cautious when we attempt to interpret the meaning of " metabolic effects" described in the literature.

2. Dependence of sleep/wake on metabolic rate

2.1. Relationship between feeding and sleep

Everyone has experienced a strong feeling of somnolence after a large meal. Despite the prevalence of this phenomenon, the physiologic basis for the association of food ingestion and sleep only began to be investigated in the late 1970s [9].

In these early experiments, rats were equipped with somnographic electrodes for continuous recording over a 5-day period of their somnograms under ad libitum conditions. Their feeding patterns (rats consume 7 to 12 meals per 24 hours, mainly at night) were also monitored. Statistical analysis of these meal and vigilance patterns showed that the energy size of a meal (MS 1) was highly correlated with the duration of both slow wave sleep (SWS) and rapid eye movement sleep (REMS) during the interval after the meal (ie, between MS 1 and the subsequent meal, M 2). The correlation of the MS 1 was even higher with the interval that followed the next meal (between MS 2 and M 3), when the nutrients ingested during M1 are actually absorbed from the intestine and metabolized. The larger the amount ingested during a meal, the longer the rat will sleep after the meal—to the point at which the postprandial background metabolism can be shown to have reached its highest levels [9].

We applied the same protocol in rats bearing lesions of the ventromedial nucleus of the hypothalamus (VMH). The large meals consumed by these hyperphagic rats were followed by long-lasting episodes of SWS and REMS [10].

We also applied the same protocol in rats made aphagic, and then hypophagic, by means of lesions in the lateral hypothalamus. During the period of their slow recovery, the small meals of these animals were also followed by shorter sleep episodes. Analysis of their meal and sleep patterns showed that the usual postprandial positive correlation was preserved. Interestingly, the effect of these meals on sleep was delayed in tandem with the well-known slowing of gastrointestinal transit of ingestants in these rats. Thus, the effects on sleep tracked the curve of metabolization of the nutrients, rather than the act of feeding [11].

The most common way to reduce metabolism is by imposing food starvation. In our studies on starved rats, sleep parameters were diminished in proportion to their depletion. Decrease in sleep occurred rapidly (from the first day on) in young, lean rats. In contrast, when starvation was induced in more mature adipose rats (animals that maintain their metabolic rate by mobilizing their abundant fat stores) diminution of sleep duration was delayed for several days [2].

These feeding/sleep correlations could have been due to the gastric distension and other gastrointestinal consequences of food ingestion. To obviate this problem, we conducted a series of experiments in which rats were equipped with indwelling intravenous catheters that allowed administration of continuous, weeklong infusions of carbohydrate and/or amino acid and/or lipid solutions. Somnograms and feeding patterns were recorded concurrently.

To summarize the findings, the influence of these intravenous infusions on sleep was proportional to their nutritional effect. For example, when a glucose infusion was given in conjunction with an infusion of insulin, the resulting improvement in glucose utilization gave rise to an increase in SWS and REMS [12].

Finally, the normal circadian meal pattern was modified experimentally. (In the rat, light phase–reduced feeding is attributed to diurnal lipolysis [with nutrients provided from fat reserves], and the larger proportion of feeding that occurs during the following dark phase is attributed to the compensatory lipogenesis that restores the previously borrowed fat reserves.) In this study we used the same

preparations as in the previous one; the light/dark lighting was unchanged, but an insulin infusion during the light phase induced lipogenesis instead lipolysis, and an adrenalin infusion during the dark phase induced lipolysis instead of lipogenesis. This reversal of the normal circadian metabolic sequence resulted in a corresponding reversal of both meal and sleep patterns. As for the correlation between the size of a meal and the duration of SWS and REMS during the following intermeal interval—it was preserved [13].

A first conclusion drawn from the above observations is that it is the concurrent (feeding-related) background metabolic rate and not feeding per se that modulates the amount of sleep. Whenever the metabolic rate increases, it promotes sleep (and satiety); whenever it decreases, it promotes wakefulness (and hunger).

2.2. An "*ischymetric mechanism*" controls wakefulness (and hunger) and sleep (and satiety)

To affect states of vigilance, the phases of nutritional depletion and repletion that occur alternately in the animal and the respective effects of such depletion and repletion on metabolic rate must be sensed quantitatively. In line with epistemological tradition, we tend to think that monitoring quantitative changes in energy metabolism necessarily involves sensing of changes in concentration of some molecule acting as a ligand and binding with an extra- or intracellular receptor. Accordingly, since Mayer's [14] glucostatic theory and lipostatic hypothesis were advanced in 1955, glucose and other circulating metabolites have been, and continue to be, proposed as signals of depletion and repletion (see below).

Alternatively, because the final common pathway of metabolism is the turnover of ATP/ADP, we have proposed that it is this turnover that is transduced into a signal of the ongoing metabolic rate [3,15].

The term "ischymetric" was derived from the Greek ischis, meaning "power," ie, rate of energy production. In the present context, "ischymetric mechanism" is taken to mean that the decisive event is the rate of ATP/ADP turnover reflecting the background metabolism at the level of the neuron's excitable membrane.

2.3. How and where in the brain can nutrient availability, via ATP/ADP turnover, be transduced into a signal that promotes either wake or sleep (and hunger or satiety)?

For ATP/ADP turnover to be translated into a biologically exploitable message, it has to be transduced, either (*a*) by one of its downstream or collateral products acting as signaling receptor-binding ligands such as adenosine or cytochrome *c* oxidase or (*b*) by the energy that the more or less elevated ATP/ADP turnover liberates at the level of the neuronal membrane and thereby increasing or decreasing its excitability and the activity of spike-generating and/or synaptic-transmission machinery.

(*a*) In the case of the first alternative—that of central monitoring of a molecular concentration—several molecules have been proposed as serving as proxies for the ongoing metabolic state of the brain tissue. One is adenosine, a product of cerebral energy metabolism reported to rise in the brain and to accumulate during waking [16]. Adenosine contributes to replenishment of cerebral glycogen stores. It also possesses sedating and neurotransmission-inhibitory effects. Caffeine antagonizes the effect of adenosine. Activation of adenosine's A1 receptor in the rostrobasal forebrain can promote SWS and REMS. Its action depends on cyclic adenosine monophosphate, where adenosine may interact with other neuroactive agents in brain areas that control vigilance.

Another molecule that expresses the level of energy metabolism is cytochrome *c* oxidase. In multiple brain areas, state of wakefulness is associated with an increase in cytochrome *c* oxidase activity, compared with its activity during sleep. Niconova et al [17] have concluded that "... this increase will likely contribute to an increase in ATP production that is increased during wakefulness as a result of increased neuronal activity." This observation is consistent with earlier findings that messenger RNA and complementary DNA for cytochrome *c* oxidase, subunit 1, are up-regulated in the rat cortex during wakefulness [18]. However, when measurements are made in rats deprived of sleep for 8 instead of 3 hours, up-regulation of messenger RNA for cytochrome *c* oxidase is lost. The same authors suggest that this change might help reduce ATP production during forced wakefulness with a subsequent increase in adenosine—a signal for sleep promotion.

But, is the enhancement of brain metabolism during vigilance a cause or an effect? The significance of increases or decreases of neuronal metabolism concomitant to changes in vigilance may lead to erroneous assumptions. Of course, neuronal metabolism increases during wakefulness, but this increase occurs in response to numerous inputs from the periphery. Such findings merely indicate that the brain is more reactive during wakefulness. Thus, it is important to point out that an increased amount of cytochrome *c* oxidase or of adenosine is the result of the brain's being alert; it does not indicate that such indicators of glioneuronal activity are the cause of wakefulness.

(*b*) In the case of the second alternative (returning to the concept of an ischymetric mechanism), we have hypothesized that the level of the background metabolism, and the resulting ATP/ADP turnover rate, is being constantly monitored by a glioneuronal population that shares the metabolic properties of the organism and thus acts as a central surrogate of the periphery. As shown below, such glioneuronal populations exist in the VMH, the dorsomedial hypothalamus (DMH), and the paraventricular nucleus (PVN) of the hypothalamus.

Neurons generate a signal by changing the frequency of their spiking and/or the potency of their synaptic transmission. Both of these neuronal activities require energy expenditure for opening or closing ionic channels and further processing. As a result, an increase in neuronal ATP/

ADP turnover can be directly transduced by an increase in spiking and transmission. It becomes a biologically understandable signal.

However, can neuronal ATP/ADP rate and turnover reflect the overall background metabolic rate? In principle, no, because we understand brain metabolism to be "selfish" and rather independent of peripheral metabolism. Peripheral tissues are more dependent on nutrient availability.

This state of affairs, however, does not apply in all brain structures. It has been shown repeatedly that neurons within and around the VMH are endowed with specific metabolic properties (see review by Nicolaidis and Even [19]). For example, Oomura [20] has shown that glucoreceptive neurons are present in the VMH. Using multibarrel electrodes, we found a cell population in the ventral DMH where the iontophoretic application of glucose results in a peculiar enhancement of neuronal activity [19]. This effect is not immediate, but delayed and progressive, as if the extracellular glucose had first to be taken up and then catabolized for spiking. Furthermore, the same glioneuronal population in the DMH, unlike the glucoreceptive neurons in the VMH, also responded—and with a more prolonged activation—to the neuronal application of ketone bodies.

More recently, the metabolic specificity of the glioneuronal populations in the VMH and the PVN was investigated by use of the technique of microdialysis in freely moving and feeding rats. These rats, in addition to the catheters needed for microdialysis, were also equipped with an indwelling jugulo-atrial catheter allowing, whenever necessary, nutritional infusions and blood sampling. Serial assays before, during, and after spontaneous or imposed meals allowed measurements of extracellular lactate, a way of monitoring astroneuronal metabolic delivery, and of extracellular glutamate, a way of monitoring neuronal activity [21].

Unlike the changes in control locations such as hemispheric or cerebellar, the VMH/PVN populations showed increases in lactate delivery and glutamate responses that matched the onset of prandial and postprandial hypermetabolism. The curve of elevation of lactate delivery was dissociated from that of the plasma lactate. Astroneuronal elevation of lactate was also observed in response to local glucose superinfusion via reverse dialysis, indicating that lactate is locally generated. Moreover, elevation of periprandial lactate delivery was blocked by a local superinfusion, via reverse dialysis, of the glucose analog, 2-deoxyglucose [21].

These observations indicate that the above-described metabolically strategic areas within the hypothalamus display a profile of activation consistent with the concept that they reflect and transduce metabolic changes occurring in peripheral tissues. In other words, specific areas within the brain are capable of reflecting metabolic changes resulting from bodily depletion and repletion.

Recently, it was shown that another brain region affects sleep in response to local depletion. Kalinchuk et al [22] found that microinfusion into the basal forebrain of the ATP synthesis blocker, 2,3-dinitrophenol, created a degree of local hypometabolism similar to that associated with a 3-hour sleep deprivation. This response was followed by an elevation in extracellular lactate, pyruvate, and adenosine, with prolongation of SWS duration, probably because of this elevation in local metabolites.

2.4. Messengers for sleep or wakefulness and their joint action on metabolism and feeding

A large number of substances tested for their effects on wakefulness, SWS, and REMS have also been found to have an effect on hunger or satiety. We will review some of the agents known to influence vigilance as well as feeding and will examine the available information about the effects of such substances on background metabolism.

The notion of a double or triple action of certain messengers first arose from studies of serotonergic substances (including serotonin reuptake inhibitors). These messengers were often found to be potent anorexigens that also had soporific side effects. One such anorexigen was shown to induce a dramatic increase in background energy metabolism, as well as to increasing the energy cost of muscular contraction during locomotion [23]. A possible interpretation of these responses was that the primary effect of this serotonergic substance is to enhance metabolic rate in general and in a key brain area in particular, an effect that promotes both satiety and sleep.

Other neurosubstances were found to possess similar joint properties:

Bombesin is a gastric peptide shown to have anorexigenic properties. It also enhances SWS and REMS [24]. As anticipated, bombesin increases the background metabolic rate [25].

Insulin is now known to be a potent centrally acting anorexigen, as initially shown in the rat in 1976 [26] and subsequently confirmed in the baboon [27]. When infused into the cerebral ventricular system, insulin also promotes SWS, but not REMS [28]. Furthermore, intracerebroventricular infusion of polyclonal anti-insulin antibody results in a decrease of SWS without a rebound effect upon discontinuation of the infusion. As might be predicted, insulin, in nonhypoglycemic doses, enhances the metabolic rate. Insulin is naturally present in the cerebrospinal fluid and in the brain, where it can be transported via the circumventricular organs or produced by neural tissue itself [29].

Leptin is the principal anorexigenic peptide involved in the regulation of body fat content. As anticipated, leptin also promotes somnolence and has been shown to increase the background metabolic rate [30].

Neuropeptide Y is well known for its orexigenic property. It also enhances alertness and wakefulness. As anticipated, neuropeptide Y has been found to decrease the background metabolic rate [31].

Interleukin-6, like the above-described peptides, produces a profile of effects (anorexia and increased metabolic rate) consistent with its role as a sleep factor (see VanItallie, this issue).

Ghrelin is an especially interesting orexigenic peptide. However, its effects on sleep and metabolism (including background metabolism) remain to be worked out. Although the currently available data are somewhat controversial, there is general agreement as to ghrelin's ability to affect both sleep and metabolism, in addition to inducing hunger. It is particularly interesting that, in the framework of the hunger-wake link, the effects of ghrelin and those of leptin are constantly in opposition [32]. These 2 peptides are believed to act reciprocally and in association with a chain of other neurosubstances whose composition is presently unknown.

Hypocretin-1 and hypocretin-2 (or orexin A and orexin B) play an important role in promotion of wakefulness [6] and probably a primary role in promoting the feeding-associated arousal at the right time of the nycthemeron [5]. The orexigenic action of the hypocretins, particularly hypocretin-1, appear more interesting than that of other orexigenic peptides because almost all of the other peptides and amines known for their effect on feeding and metabolism converge on its site of production and transmission. Thus, the hypocretinergic system could underlie the anatomofunctional structure of coordination of both vigilance and feeding with metabolic state. The problem is that the hypometabolic action of the hypocretins has always been hypothesized on the basis of indirect observations. We still need direct, calorimetric measurements, including that of background metabolism. The latter is indispensable because one of the effects of the hypocretins is to enhance locomotion and exploratory behavior—activities that necessarily increase the overall metabolic rate, thereby masking the expected (and proposed [7]) decrease of the metabolic rate in which we are interested [3,8].

3. Discussion

None of the numerous neurosubstances implicated in the control of sleep/wakefulness is indispensable for these states to take place; rather they promote, facilitate or inhibit one of the states of vigilance. It is proposed that the role of each of these molecules is to convey one of the factors, internal (stress, fullness or emptiness of the stomach, fever, estrus and, of course, level of metabolic activity) or external (photoperiod, temperature, danger), that modulate, but do not determine, the states of vigilance, so as to make them occur at the right time and last for the right duration.

The findings reviewed above led us to formulate a general principle applicable to neuroactive substances that affect sleep/wake on the one hand and hunger/satiety on the other hand. Whenever a neurosubstance is shown to induce satiety, it may also be somnogenic, and it should also increase the background metabolic rate. Conversely, whenever a neurosubstance is shown to be orexigenic, it should also promote wakefulness and, at the same time, decrease the background metabolic rate.

In terms of cause-and-effect relationships, if a neurosubstance acts on both vigilance and feeding, this effect could be attributed to its upstream action on metabolism. In other words, it can be hypothesized that a change in the background metabolic rate is the primary phenomenon, whereas changes in vigilance and feeding are consequences, operating via a cascade of neuroactive agents.

The most convincing recent observation in support of this principle has grown out of research on hypocretins-1 and -2 (particularly hypocretin-1). Their double action—affecting both feeding and sleep [1,4]—could have been suspected when these peptides were first identified and tested for their effect on feeding [5].

From all of the above observations it is clear that when an animal becomes depleted and its metabolic rate is reduced, the time is right for it to crave and seek for food, provided that prevailing circadian and ecological conditions permit. Once its nutritional needs are satisfied and a eumetabolic state is reestablished, it is appropriate that the animal spends a large part of the right period of the nycthemeron asleep.

New peptides and nonpeptidic neurosubstances implicated in the control of either sleep or feeding continue to be identified. When found active with respect to one of these two behaviors, they—sooner or later—reveal their property of also promoting the other behavior. Apart from its heuristic value, this concept, if further confirmed, would help advance our understanding of the overall mechanism by which these two competing and complementary behaviors are made to alternate—behaviors that occupy such a preponderant part of an animal's daily existence.

Acknowledgment

The author thanks Theodore B. VanItallie, MD, for his editorial help.

References

[1] Zepelin H, Rechtschaffen A. Mammalian sleep, longevity and energy metabolism. Brain Behav Evol 1974;10:425-70.
[2] Danguir J, Nicolaidis S. Dependence of sleep on nutrient's availability. Physiol Behav 1979;22:735-40.
[3] Nicolaidis S, Danguir J. Metabolic determinants of feeding and sleep. The ischymetric hypothesis. Exp Brain Res 1984;Suppl 8:173-87.
[4] de Saint-Hilaire Z, Nicolaidis S. Métabolic determinients of sleep and wakefulness: effect of metabolically active substances. Sleep Res 1991;20A:82-3.
[5] Sakurai T, Amemiya A, Ishi M, et al. Orexins and orexin receptors : a family of hypothalamic neuropeptides and G protein–coupled receptors that regulate feeding behaviour. Cell 1998;92:573-85.
[6] Hagan JJ, Leslie RA, Patel S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci U S A 1999;96:10911-6.

[7] Sakurai T. Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy balance. Sleep Med Rev 2005;9:231-41.
[8] Nicolaidis S, Even P. Physiological determinants of hunger, satiation and satiety. Am J Clin Nutr 1985;422:1083-92.
[9] Danguir J, Nicolaidis S, Gerard H. Relation between feeding and sleep patterns in the rat. J Comp Physiol Psychol 1979;93:820-30.
[10] Danguir J, Nicolaidis S. Sleep and feeding patterns in the ventromedial hypothalamus lesioned rat. Physiol Behav 1978;21:769-77.
[11] Danguir J, Nicolaidis S. Cortical activity and sleep in the rat lateral hypothalamic syndrome. Brain Res 1980;185:305-21.
[12] Danguir J, Nicolaidis S. Intravenous infusion of nutrients and sleep in the rat: an ischymetric sleep regulation hypothesis. Am J Physiol 1980;238:E307-12.
[13] Danguir J, Nicolaidis S. Circadian sleep and feeding patterns in the rat: possible dependence on lipogenesis and lipolysis. Am J Physiol 1980;228:E223-8.
[14] Mayer J. Regulation of energy intake and the body weight: the glucostatic theory and the lipostatic hypothesis. Ann N Y Acad Sci 1955;63:15-42.
[15] Nicolaidis S. Short term and long term regulation of energy balance. Proceedings of the XXVI International Congress of Physiological Sciences, IUPS, New Delhi, vol X, 1974. p. 122-3.
[16] Huston JP, Haas HL, Boix F, et al. Extracellular adenosine levels in neostriatum and hippocampus during rest and activity periods of rats. Neuroscience 1996;73:99-107.
[17] Niconova EV, Vijayasarathy C, Zang L, et al. Differences in activity of cytochrome *C* oxidase in brain between sleep and wakefulness. Sleep 2005;28:21-7.
[18] Cirelli C, Toroni G. Differences in brain gene expression between sleep and waking as revealed by mRNA differential display and cDNA microarray technology. J Sleep Res 1999;8(Suppl 1):44-52.
[19] Nicolaidis S, Even P. Metabolic rate and feeding balance. Ann N Y Acad Sci 1989;575:86-105.
[20] Oomura Y. Significance of glucose, insulin and free fatty acid on the hypothalamic feeding and satiety neurons. In: Novin D, et al, editors. Hunger. New York (NY): Raven; 1976. p. 145-57.
[21] Gousham A, Nicolaidis S. Feeding enhances extracellular lactate of local origin in the rostromedial hypothalamus but not in the cerebellum. Brain Res 1999;816:84-91.
[22] Kalinchuk AV, Urila AS, Alanko L, et al. Local energy depletion in the basal forebrain increases sleep. Eur J Neurosci 2003;17:863-9.
[23] Even P, Nicolaidis S. Dextrofenfluramine increases energy cost of muscular effort. Pharmacol Biochem Behav 1986;24:647-55.
[24] de Saint-Hilaire-Kafi Z, Gibbs J, Nicolaidis S. Satiety and sleep: the effects of bombesin. Brain Res 1989;478:152-5.
[25] Even P, De Saint Hilaire Z, Nicolaidis S. Peripheral administration of bombesin increases metabolism in the rat. Physiol Behav 1991;49:439-42.
[26] Nicolaidis S. Mecanisme nerveux de l'équilibre énergétique. Journ Annu Diabetol Hotel Dieu 1976;1:153-6.
[27] Woods SC, Lotter EC, Kay MC, Porte D. Chronic intracerebroventricular infusion of insulin reduced food intake and body weight in baboons. Nature 1979;282:503-5.
[28] Danguir J, Nicolaidis S. Chronic intracerebroventricular infusion of insulin causes selective increase of slow wave sleep in rats. Brain Res 1984;306:97-103.
[29] Orosco M, Gerozissis KC, Rouch C, Nicolaidis S. Feeding-related insulin changes in the PVN-VMH revealed by microdialysis. Brain Res 1995;671:149-58.
[30] Ruffin MP, Nicolaidis S. Intracerebroventricular injection of murine leptin enhances the postprandial metabolic rate in the rat. Brain Res 2000;874:30-6.
[31] Ruffin MP, Even PC, El-Ghissassi M, Nicolaidis S. Metabolic action of neuropeptide Y in relation to its effect on feeding. Physiol Behav 1997;62:1259-64.
[32] Wren AM, Small CJ, Ward HL. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. Endocrinology 2000;141:4325-8.