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Morphological and physiological base of appetite regulation in the hypothalamus. A review

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ABSTRACT

The neuroendocrine control of appetite has great importance in the maintenance of the homeostasis of an organism. The anatomic base of the appetite regulating system consists of the neurons localized in several hypothalamic nuclei i.e. the arcuate nucleus, paraventricular nucleus, ventromedial nucleus, dorsomedial nucleus, lateral hypothalamic areas, and suprachiasmatic nucleus. The functional elements of this system constitute the neuronal factors synthesized in these hypothalamic centres. Generally, they can be divided into two groups: orexigenic factors, which stimulate appetite and anorexigenic factors, which inhibit food intake. The orexigenic and anorexigenic systems in the hypothalamus are linked both morphologically and functionally. This information supports the hypothesis of the existence of the interconnected appetite-regulating network localized in the hypothalamus. The localization of orexigenic-producing nerves and their receptors overlaps with sites containing receptors for anorexigenic factors, therefore confirming their reciprocal interactions. To the most important components of the appetite-regulating network belongs the neuronal system of NPY, which integrates the final pathway regulating food intake. It seems that such numerous orexigenic and anorexigenic pathways are too redundant and their functions are often doubled. However, it is a characteristic feature of the biological mechanism regulating a key function of an organism, which works as "the security system" for it's continuously changing needs in the internal and external environment.

KEY WORDS: appetite regulation, hypothalamus, orexigenic factors, anorexigenic factors

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INTRODUCTION

In the homeothermic vertebrates, one of the most important problems of the organism is the maintenance of the homeostasis, which is the state of relative balance with respect to a continually changing number of environmental external and internal stimuli affecting an organism. Many regulating mechanisms responsible for maintenance of homeostasis evolved during the evolution. One of these mechanisms is the system regulating food intake, which consists of the neural centres localized in the hypothalamus and numerous neuronal factors acting in this area of the central nervous system (Morley et al., 1987; Kuenzel et al., 1994; Berthoud et al., 2002).

The anatomic base of the appetite regulating system consists of the neurons, which are localized in several hypothalamic nuclei. The most important of them are: the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventromedial nucleus (VMN), dorsomedial nucleus (DMN), lateral hypothalamic area (LHA), and suprachiasmatic nucleus (SCN) being master pacemaker (Kuenzel et al., 1994; Berthoud et al., 2002; Cassone and Stephan, 2002). The functional elements of this system constitute the various neuronal factors, which are synthesized in these hypothalamic areas. Generally, they can be divided into the two groups: orexigenic factors, which stimulate appetite and anorexigenic factors, which inhibit food intake. It has to be noted, that many of them are synthesized outside the hypothalamic areas, or even outside the brain, for example some of them originate from the digestive tract or adipocytes (Kalra et al., 1999; Berthoud et al., 2002).

THE HYPOTHALAMIC AREAS INVOLVED IN THE APPETITE REGULATION

One of the most important nuclei regulating appetite is the ARC. It is located at the base of the hypothalamus round of the bottom of the third ventricle of the brain (Figure 1) and extends rostrocaudally from the posterior border of the optic chiasm to the mamillary bodies (Welento et al., 1969; Kalra et al., 1999). This neuronal formation seems to be the most important among the sites associated with the hypothalamic regulation of energy balance. The lack of the brain-blood barrier in this centre facilitates the direct communication between the central nervous system and periphery stimuli. Moreover, the ARC contains a high density of neurons that produce the orexigenic peptides, which project into various hypothalamic sites including the PVN, VMN, DMN - other nuclei involved in the regulation of food intake. Morphological evidence demonstrates that a subpopulation of neurons in the ARC co-express neuropeptide Y (NPY) and γ-aminobutyric acid (GABA); NPY-producing neurons localized in this nucleus are synaptically linked with β-endorphin and galanin-producing neurons, creating the interconnected orexigenic network (Kalra et al., 1999; Berthoud et al., 2002).

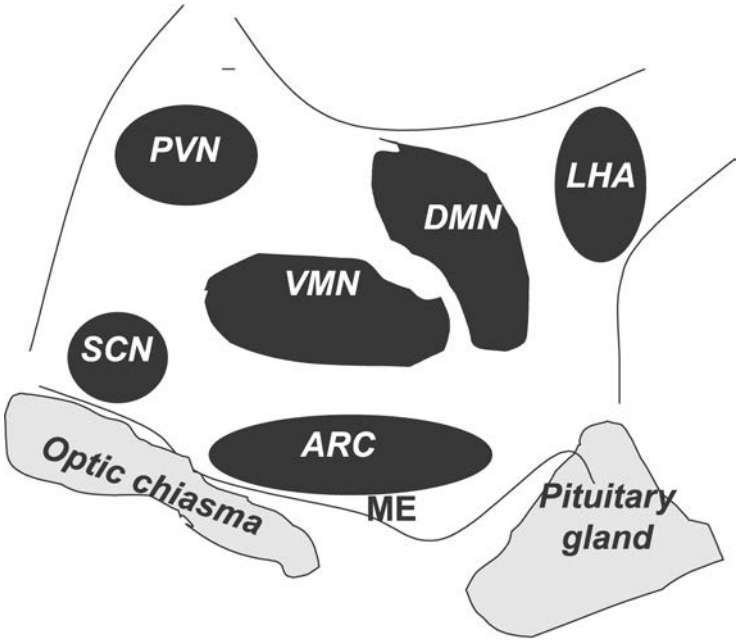

Figure 1. Hypothalamic nuclei involved in the appetite regulation ARC - arcuate nucleus; PVN - paraventricular nucleus; VMN - ventromedial nucleus; DMN - dorsomedial nucleus; LHA - lateral hypotalamic area; SCN - suprachiasmatic nucleus

The PVN, located on either side of the roof of the third ventricle in the hypothalamus, is one of the main centres regulating appetite (Sawchenko and Swanson 1983; Morley et al., 1987). Orexigenic factors injected into the PVN stimulate feeding, implying the existence of receptor sites for these factors (Morley et al., 1987). *In vivo* and *in vitro* experiments suggest that the PVN is a main place of NPY release (Kalra et al., 1991; Dube et al., 1992). It has been confirmed that in this area there are the receptive sites for both orexigenic and anorexigenic factors (Kalra et al., 1999). On the basis of many studies it could be assumed, that as well as being a crucial place where orexigenic factors are released, the PVN is also a place where interactions between neuromodulators inhibiting NPY release take place (Kuenzel, 1994; Berthoud et al., 2002).

The VMN is regarded as the satiety centre. The signals generated in the VMN are responsible for the tonic inhibition of food intake. Similarly to the ARC, this nucleus contains the morphological connections with other nuclei involved in appetite regulation (Morley et al., 1987; Kuenzel et al., 1994; Berthoud et al., 2002).

Another important area, concerning with food intake, is the DMN. A great number of neurons projecting from the ARC to the DMN, suggests that the DMN also can be an important site of NPY release. Probably it is the place of interaction

between NPY and leptin and thus being the integral component of the feedback loop between the periphery and the brain (Morley et al., 1987; Kuenzel et al., 1994; Berthoud et al., 2002).

The lateral hypothalamic area (LHA) is adjacent dorsally and laterally to the VMN (Welento et al., 1969). This area functions as passage for many neural fibres connecting hypothalamic nuclei with one another along with other structures of the brain. Some observations suggest that LHA acts as a "feeding centre", which generates orexigenic signals normally restrained by signals from the VMN (Morley et al., 1987; Kuenzel et al., 1994; Berthoud et al., 2002).

The pattern of ingestive behaviour is a highly regulated phenomenon in all-living organisms. The drive to eat evoked by appetite or the sensation of hunger, in most vertebrates, is neurally based and entrained to the light-dark cycle. Some experiments indicate that the timing mechanism is involves in generation of the sensation of hunger (Kalra, 1997). The SCN, being a master pacemaker, consists of two small round nuclei resting dorsally on the optic chiasma on either side of the third ventricle (van den Pol et al., 1979). The SCN exerts a restraining influence on ingestive behaviour through the release of anorexigenic signals and thus generates signals, which adjust food intake to the circadian rhythm. A circadian pattern in hypothalamic gene expression of the orexigenic signals is also consistent with the pattern of daily energy management. There is evidence suggesting the existence of two mechanisms emanating from the SCN: one for synthesis and the second for release of orexigenic signals. This nucleus has a neuronal link with the ARC; efferents from SCN innervate neurons producing NPY, galanin and POMC in the ARC. It has been shown that there are neuronal links with PVN, DMN, VMN and LHA, which make up the communication tract regulating the circadian rhythm of food intake (Morley et al., 1987; Kuenzel et al., 1994; Berthoud et al., 2002).

OREXIGENIC SIGNALS

One of the most important, best-known and powerful orexigenic factors is the neuropeptide Y. This 36-amino acid peptide belonging to the pancreatic polypeptide family is very abundant in the CNS, also within hypothalamus, and in the peripheral sympathetic nervous system (Tatemoto et al., 1982). In the hypothalamus, it is synthesized primarily in certain cell bodies of the ARC, from which it is transported *via* axonal projections through the LHA to the PVN, but also to the DMN and the VMN (Bai et al., 1985; Baker and Herkenham, 1995; Kalra and Kalra, 1996a; Kalra, 1997). Two NPY Y_1 and NPY Y_5 receptor subtypes, putative receptors mediating feeding, are localized in all nuclei involved in the regulation of food intake. Therefore, it is quite possible that the sphere of NPY action is

widespread in the hypothalamus. NPY is apparently the only messenger molecule that can be considered as a physiological appetite transducer in the brain. There is a lot of evidence, which support, this view (Kalra et al., 1999). Central administration of NPY stimulates feeding in satiated rats, and also rapidly enhances ongoing feeding (Clark et al., 1985). Such components of feeding behaviour as: cumulative food intake, number of feeding episodes, mean episode length, total time spent eating, eating rate and interepisode interval, are affected by exogenous NPY in a dose-dependent manner (Clark et al., 1987; Kalra et al., 1988). Fasting markedly augments NPY release in the PVN both *in vivo* and *in vitro* experiments (Dube et al., 1992; Kalra, 1997). NPY Y_1 receptor mRNA in the hypothalamus is also augmented by fasting and food restriction (Xu et al., 1998). Moreover, hyperphagia and obesity in several genetic and experimental models are associated with modifications in the NPY-ergic signaling (Dryden et al., 1995).

The regulation of NPY secretion in the hypothalamus in the daily management of ingestive behaviour is both under the neural and hormonal regulation and seems to have a complex and multifactorial character. There are data showing temporally correlated pattern between independent neural component, driven by the circadian clock, and changes occurred on hypothalamic NPY levels, in their synthesis and release (Kalra et al., 1999).

The NPY hypothalamic system due to its strategic distribution, communicates directly with majority of hormonal, circulating signals reaching the brain. For example, steroids originating from the gonads and adrenal cortex exert a modulatory influence on NPY synthesis and release (Hisano et al., 1988; Sar et al., 1990; Sahu et al., 1992, 1994). In addition, metabolic signals relayed by the circulating peptide hormones, insulin, leptin and cytokines can directly affect the NPY system and also are suspected to cross the blood-brain barrier (Schwartz et al., 1992; Zhang et al., 1994; Halaas et al., 1995).

It has been known for a long time that gonadal steroids modulate food intake and body weight gain in rodents and other mammals (Kalra and Kalra, 1996b). They promote NPY neuro-secretion in the hypothalamus (Sar et al., 1990; Sahu et al., 1992, 1994). It is supposed that, the anorectic effects of oestrogen can affect the NPY synthesis in the ARC and its release in the PVN through its receptors on NPY neurons (Sar et al., 1990; Bonavera et al., 1994). Evidently, an underlying role of oestrogen is to inhibit food intake *via* direct action on the NPY pathway in the ARC-PVN of female rats (Baskin et al., 1995).

Another one, powerful factor stimulating appetite is galanin - the 29 amino acid peptide (Tatemoto et al., 1983). Intracerebroventricular injection of galanin stimulates feeding in satiated rats (Kyrkouli et al., 1986, 1990; Schick et al., 1993). Galanin is synthesized in the ARC, DMN and PVN areas and it appears that galanin receptors may be widely distributed in the rat brain (Skofitsch and Jacobowitz, 1985; Howard et al., 1997; Mitchell et al., 1997). Close anatomical and functional

relationships exist between galanin and neurons producing other signals in the brain. Moreover, it has been shown the existence of the co-expression of galanin in NPY-producing neurons in the ARC and PVN areas (Horvath et al., 1996), and galanin receptors in the PVN, LHA and VMN. Galanin, may, in part, mediate NPY-induced feeding (Kalra et al., 1999). Moreover, galanin-immunopositive nerve terminals establish synaptic links with POMC containing dendrites and soma in the ARC. It raises the possibility that this peptide may stimulate the release of β-endorphin, which also augments ingestive behaviour (Horvath et al., 1995).

The representatives from all three families of endogenous opioid peptides like β-endorphin, dynorphin-A and enkephalin, also exhibit the orexigenic activity, however its action is weak and short-lived (Levine et al., 1985). The POMC-neurons precursor of the β-endorphin, appear in the great numbers in the ARC area. Their neuronal terminals innervate also the other nuclei involved in the regulation of food intake (Finley et al., 1981a). Neurons producing met-enkephalin and leu-enkephalin are more widely distributed in the hypothalamus and their perikarya have been visualized in feeding-relevant sites, such as the ARC, VMN, DMN and PVN. These sites are also richly innervated by enkephalin-immunopositive fibres (Finley et al., 1981b; Morley et al., 1987). Dynorphin-producing cells are also found in various regions of the hypothalamus, including the ARC and PVN (Morley et al., 1987). Just like other orexigenic factors, they have the morphological links between β-endorphin-producing neurons and NPY and Gal neurons. NPY immunopositive terminals established synaptic contacts with β-endorphin-containing perykaria, suggesting that NPY may induce feeding directly and also indirectly by stimulating β-endorphin in relevant sites such as the PVN (Horvath et al., 1992).

The glutamate and GABA there are amino acids acting as the neuro-transmitters, which stimulate food intake (Decavel et al., 1990; van den Pol et al., 1990). There are produced in majority of the hypothalamic nuclei, however their receptors taking part in the regulation of food intake are localized mainly in the LHA (Stanley et al., 1993a,b). It has been confirmed the presence of the synaptic contacts with β-endorphin-producing neurons and co-expression with NPY and galanin-producing neurons in the ARC (Blasquez et al., 1994; Horvath et al., 1997). Both glutamate and GABA act on the postsynaptic level (Kalra et al., 1999).

Recently discovered (1998), group of factors, which have very powerful orexigenic activity are orexins (Sakurai et al., 1998). Orexin A and B are synthesized mainly in the LHA and the DMN, and their receptors are localized in the LHA and the PVN (De Leca et al., 1998; Sakurai, 1999). Similarly to other orexigenic factors, orexin-producing neurons have synaptic contacts with neurons synthesized NPY and leptin localized in the ARC and the PVN (Horvath et al., 1999; Funahashi et al., 2000).

The more recently discovered peptide - ghrelin (1999) secreted mainly by the oxyntic glands of the stomach, was first identified as a powerful stimulator of growth hormone release (Kojima et al., 1999; Seoane et al., 2000; Takaya et al.,

2000). It works by signaling hunger and stimulating feeding, which manifests the orexigenic property (Nakazato et al., 2001). Their presence in the ARC area has been documented (Kojima et al., 1999), but up to now there has been no information confirming ghrelin synthesis in the hypothalamus. Ghrelin found in the hypothalamus are probably the peripheral origin. The expression of ghrelin receptors has also been demonstrated in the ARC (Willesen et al., 1999). It has been shown the existence of numerous ghrelin receptors on the NPY-producing neurons in the ARC; therefore ghrelin may promote feeding by stimulating the NPY neurons (Wren et al., 2000; Shintani et al., 2001). Recent studies show that, ghrelin interacts with leptin receptors in the ARC. The opposing effect of leptin and ghrelin on neurons in the ARC may serve also as a neurophysiological correlate of the orexigenic and anorexigenic networks (Traebert et al., 2002).

On the basis of above-mentioned information one could put forward the hypothesis, that neurons synthesizing the orexigenic factors, which are localized in the hypothalamic nuclei, create the reciprocally reinforced network, which integrates the processes connected with regulation of food intake.

ANOREXIGENIC SIGNALS

Another great group of neuronal factors involved in the appetite regulation consist of the anorexigenic factors i.e. factors inhibiting food intake. The best-known representative of this group is leptin, 167 - amino acids peptide, being the product of *ob* gene expression. This relatively recently discovered peptide (1994), is regarded as the satiety signal, integral component of the feedback loop between the periphery and the brain (Zhang et al., 1994; Pellymounter et al., 1995). Leptin, is synthesized mainly by the adipocytes but leptin mRNA and peptide have been also found in planceta, digestive tract, skeletal muscle and recently also in the hypothalamus and pituitary gland (Morash et al., 1999). *In situ* hybridization studies showed that the biologically active, long form of the leptin receptor is localized in various sites of the hypothalamus, among others, in the ARC, PVN, VMN and LHA (Mercer et al., 1996a; Schwartz et al., 1996a). The main place of leptin activity has been established in the ARC (Jacod et al., 1997; Satoh et al., 1997). In this nucleus, the subpopulation of the NPY- producing neurons expresses the leptin receptors localized on membrane (Hakansson et al., 1996; Mercer et al., 1996b). Leptin inhibits NPY gene expression and also decreases the release NPY acting on the postsynaptic level in the ARC, PVN and DMN (Schwartz et al., 1996b). By the same mechanism, leptin influences also the decrease of galanin and POMC release and the increase of neurotensin release (Kalra et al., 1999).

Glukagon like-peptide (GPL) exerts also the powerful anorexigenic activity (Shimizu et al., 1987). Injections of this peptide into the III ventricle inhibit food

intake even in the fasted animals (Lambert et al., 1993; Turton et al., 1996). GLP cells bodies have been found in hypothalamic sites that correspond with GLP binding sites in the ARC and PVN (Jin et al., 1988; Kreymann et al., 1989; Shughrue et al., 1996; Larsen et al., 1997). Exogenous GLP decreases food intake, acting on the postsynaptic level, inhibiting signals initiated by NPY in the PVN (Turton et al., 1996). Some recent reports suggest that the GLP may be one of the mediators of the anorectic effects of leptin (Goldstone et al., 1997).

Neurotensin was isolated and characterized in the 1970s (Mashford et al., 1978). This anorexigenic factor is released during the feeding and inhibits the spontaneous food intake (Hoebel et al., 1982; Levine et al., 1983). Neurotensin immunopositive neurons are localized in the ARC, PVN and DMN, and innervate hypothalamic nuclei taking part in the appetite regulation (Stanley et al., 1982; Hawkins, 1986).

Cocaine and amphetamine regulated transcript (CART) is a newly identified neuropeptide involved in the feeding behaviour and body weight regulation (Koylu et al., 1997). CART is the third most abundantly expressed factor in the hypothalamus (Gautvik et al., 1996). CART mRNA and the peptide are widely distributed in the ARC, PVN and VMN, and in the dorsomedial/lateral hypothalamic area (Koylu et al., 1998; Lambert et al., 1998; Broberger, 1999). Although CART receptors have not been described yet, CART positive-immunostaining has been observed in the PVN and DMN, indicating that these regions may be potential sites of CART action (Kristensen et al., 1998; Vrang et al., 1999). It has been established that cell bodies containing CART peptide have close appositions with NPY-immunoreactive nerve terminals in the ARC, DMN, LHA and PVN, suggesting interactions between CART and NPY (Lambert et al., 1998; Broberger, 1999).

Corticotropin-releasing hormone (CRH), 41-amino acids peptide, was isolated and sequenced in 1981 (Vale et al., 1981). Primarily this hypothalamic hormone stimulates the release of pituitary ACTH, which, in turn, stimulates corticosterone secretion from the adrenal glands (Brown et al., 1982). CRH-producing cells and CRH-immunoreactive terminals are localized in various regions in the hypothalamus, but primarily in the PVN (Palkovits, 1984; Sawchenko and Swanson, 1984). Experimental evidence suggests that, the sites of anorectic action of CRH within the PVN are possibly mediated by two types of receptors, CRH R1 and CRH R2 (Insel et al., 1984; Krahn et al., 1984; Monnikes et al., 1992). Other reports confirm that CRH released locally in the PVN, may tonically restrain the action of endogenous orexigenic signals.

Cholecystokinin (CCK) was isolated in 1968 as a 33-amino acid peptide from the porcine gastrointestinal tract (Mutt and Jorpes, 1968). The biologically active form of CCK consists of 8 amino acids and it is synthesizes in the whole hypothalamic area (Beinfield, 1983). CCK receptors appear to be distributed throughout the hypothalamus parallely with the distribution of endogenous CCK (Moran et al., 1986; Hill et al., 1987, 1990). There are two existing types of CCK receptors

(Moran et al., 1986; Pisegna et al., 1992), A and B, probably type A is involved in the regulation of food intake (Figlewicz et al., 1992). As well as restraining appetite, CCK-8 also elicits the complete behavioural sequence of the satiety in rats, including grooming and apparent sleep (Antin et al., 1978). CCK decreases food intake by diminishing the size of individual meals (Levine et al., 1986). It is possible that CCK acts synergistically with other orexigenic factors to produce the satiety effect (Kalra et al., 1999).

Somatostatin, another anorexigenic peptide, was isolated and characterized in 1973 (Brazeau et al., 1973). It is widely distributed in the hypothalamus exists mainly as a cyclic tetradecapeptide (Frohman et al., 1992). Somatostatin perikarya are localized in the periventricular region of the anterior hypothalamus (Krisch et al., 1978; Filby et al., 1983; Johansson et al., 1984). This region covers partly the SCN and the PVN (Polkowska et al., 1987; Tillet et al., 1989). Primarily somatostatin restrains release of growth hormone from the pituitary gland but is also well known for its anorexigenic action. Peripheral administration of somatostatin decrease feeding in animals *via* vagally mediated mechanism but its effect is short-lasting (Levine et al., 1982; Feifel and Vaccarino, 1994). It has been shown, that central administration of somatostatin produces the biphasic effect on food intake that may be related to the fed state of the animal organism or the dose used (Aponte et al., 1984; Feifel and Vaccarino, 1990).

In conclusion, the orexigenic and anorexigenic systems in the hypothalamus are linked both morphologically and functionally. This information supports the hypothesis of the existence of the interconnected appetite-regulating network localized in the hypothalamic nuclei. The localization of orexigenic-producing nerves and their receptors overlap with sites containing receptors for anorexigenic factors, which confirms their reciprocal interactions (Kalra et al., 1999). The hypothesis of the appetite-regulating network localized in the hypothalamus suggests the existence of four elements (Figure 2). One of them is the orexigenic network, which releases and transducers appetite stimulating signals. The second component - the anorexigenic network generates signals inhibiting food intake. These signals might have an indirect influence exerted by other orexigenic factors or a direct one exerted by NPY, most often on postsynaptic level. The third element, the DMN-VMN complex, generates tonic signals inhibiting the activity of the orexigenic signals during the inter-meal intervals. The fourth component is circadian clock acting in a parallel way with appetite regulating network and adjusting food intake to the circadian rhythm of an organism (Kalra et al., 1999; Berthoud, 2002). The most important key component of the appetite-regulating network is neuronal system of NPY, which integrates the common, final pathway regulating food intake. It seems that such numerous orexigenic and anorexigenic pathways are too redundant and their functions are often doubled. However, it is a characteristic feature of the biological mechanism regulating a key function of organism. It is a kind of “the

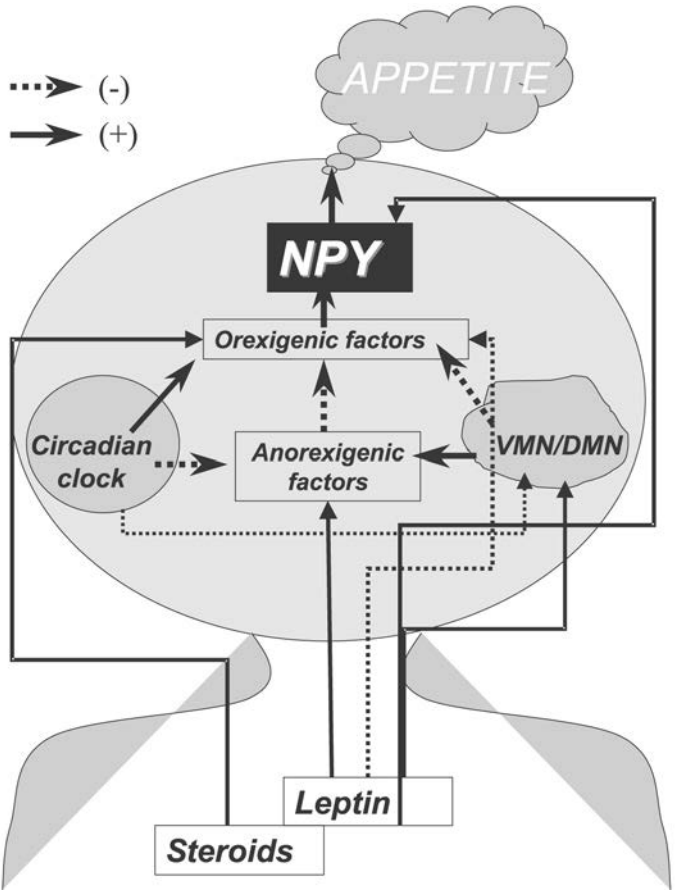

Figure 2. Appetite regulation network

security system" for continuously changing needs of organism in the internal and external environment (Kalra et al., 1999; Berthoud, 2002).

Recently appeared a many sophisticated and powerful methods to make further progress in the mechanism of the function of appetite regulating network. Techniques such as the immunochistochemistry and *in situ* hybridization methods allow to explain the function of the neural pathways in the hypothalamus. The production of loss-of function and gain function transgenic animals, together with the ability of localized rescue of function and selective toxin-induced ablation of specific neuron populations provides the tools to link specific neurons with specific behavioural, autonomic, and endocrine functions (Berthoud, 2002). In addition, recent progress in improving anatomical resolution makes the noninvasive neuroimaging methods excellent tools, particularly in humans, for understanding the neural control of food intake and energy balanced.

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STRESZCZENIE

Morfologiczne i fizjologiczne podstawy regulacji pobierania pokarmu w podwzgórzu

Wiadomo, że jednym z najważniejszych „problemów" organizmu, szczególnie stałocieplnych kręgowców, jest utrzymanie homeostazy, czyli stanu względnej równowagi wobec bezustannie zmieniającego się środowiska, zarówno zewnętrznego jak i wewnętrznego oraz dużej ilości bodźców do niego dochodzących. W toku ewolucji wykształciły się mechanizmy regulujące, obronne, transmitujące informacje, które są odpowiedzialne za utrzymanie tej homeostazy.

Jednym z mechanizmów odpowiadających za stan równowagi energetycznej organizmu jest system - układ regulujący pobieranie pokarmu, a jednym z elementów tego systemu są ośrodki nerwowe w podwzgórzu i działające w ich obrębie peptydy podwzgórzowe biorące udział w regulacji łaknienia. Anatomicznym podłożem układu regulującego łaknienie są neurony zlokalizowane w jądrach podwzgórza. Najważniejsze z nich to jądro łukowate, jądro przykomorowe, jądro brzuszno-przyśrodkowe, grzbietowo przyśrodkowe, obszar bocznego podwzgórza oraz jądro nadskrzyżowaniowe, będące nadrzędnym zegarem biologicznym także w regulacji rytmu pokarmowego. Funkcjonalnym elementem tego układu są rozmaite związki, peptydy, neurotransmitery syntetyzowane na obszarze podwzgórza. Można je podzielić na 2 grupy. Najogólniej są to związki oreksygeniczne, czyli pobudzające łaknienie oraz związki anoreksygeniczne, czyli hamujące pobieranie pokarmu. Należy zaznaczyć, że wiele z tych czynników syntetyzowanych jest poza obszarem podwzgórza i mózgu, także na obwodzie, na przykład wiele z nich jest obecnych w przewodzie pokarmowym. Podsumowując, można stwierdzić, że neuralne systemy, oreksygeniczny i anoreksygeniczny, są powiązane morfologicznie i funkcjonalnie. Potwierdza to hipotezę o istnieniu sieci nerwowej regulującej łaknienie, zlokalizowanej w ośrodkach nerwowych podwzgórza. Obszar receptorów i zakończeń nerwowych dla czynników oreksygenicznych pokrywa się z obszarem receptorów dla czynników anoreksygenicznych, co również świadczy o wzajemnym oddziaływaniu tych dwóch układów.

Liczba szlaków ORX i AORX robi wrażenie nadmiaru i wzajemnego dublowania funkcji. Jest to jednak cecha charakterystyczna dla mechanizmów regulujących kluczowe funkcje organizmu. Jest to rodzaj systemu zabezpieczającego wobec bezustannie zmieniających się potrzeb organizmu w środowisku.