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Research Article

Hypothalamic Mechanisms of Vegetative Function Homeostasis

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Abstract

Hypothalamic mechanisms of homeostatic reactions provide regulation of such vital physiological constants as osmotic pressure, ionic balance, humoral and hormonal activity of blood, sugar content and concentration of gases in blood, blood pressure, body temperature and etc. Numerous neurophysiological researches are devoted to the study of the role of the hypothalamus in the regulation of the cardiovascular system, respiration, digestion, endocrine system, in the regulation of sleep and wakefulness, emotional and motivational reactions, metabolism, thermoregulation, etc. The hypothalamic area is the highest subcortical center of integration of autonomic, emotional and motor components of complex reactions of adaptive behavior, the main central mechanism of homeostasis of the internal environment of the body, sympathetic and parasympathetic tone, ergotropic and trophotropic states of adaptive behavior

Key Words: hypothalamus; brain; mechanisms; vegetative function homeostasis

Introduction

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Morphofunctional Organization of The Hypothalamus

The hypothalamus, as a ventral part of the diencephalic region, is a complexly organized structure containing a complex of nuclear formations closely connected by a multichannel system of afferent and efferent connections with different levels of the central nervous system. Within the hypothalamus there are four main regions, each of which contains a number of topographically differentiated and functionally specialized nuclear formations. Thus, the medial and lateral preoptic nuclei are distinguished in the preoptic area. The anterior hypothalamic region contains the supraoptic, paraventricular, suprachiasmatic and anterior hypothalamic nuclei. The tuberal region includes the dorsomedial, ventromedial, arcuate, and lateral hypothalamic nuclei. The middle or infundibular group of nuclei also includes the periventricular nucleus.

The infundibular (INF) and paraventricular nuclei (PVN) are most susceptible to metabolic disruption, with the PVN being more sensitive to diabetes. In the INF, obesity results in reduced synaptic plasticity and energy sensing capability, whereas diabetes involves molecular reprogramming associated with impaired tanycytic barriers, activated microglia, and neuronal inflammatory response. In the PVN, cellular metabolism and neural activity are suppressed in diabetic macaques. Spatial transcriptomic data reveal microglia's preference for the parenchyma over the third ventricle in diabetes. [1]

Hypothalamic AMPK as a possible target for energy balance-related diseases Hypothalamic AMP-activated protein kinase (AMPK) is a canonical regulator of energy balance and metabolism at the whole-body level. This makes this enzyme an attractive target for treating energy balance-related diseases. However, targeting AMPK within the hypothalamus presents a challenge related to the specific cellular

biodistribution of the enzyme and the need to use clinically safe methods of administration. Current evidence has shown that targeting based on small extracellular vesicles (sEVs) might offer a realistic approach for regulating hypothalamic AMPK. This would allow modulation of both sides of the energy-balance equation, namely food intake and energy expenditure, and therefore of overall metabolism. Moreover, this strategy could provide treatment options not only for obesity but also for catabolic/wasting diseases such as hyperthyroidism, rheumatoid arthritis, and even cancer cachexia.[13] The posterior hypothalamic region includes the posterior hypothalamic nucleus, supramamillary, premamillary, lateral and medial mammillary nuclei. The posterior hypothalamic region includes the subthalamic nucleus of Luis.

The autonomic nervous system regulates internal organs and peripheral circulation, which enables the maintenance of homeostasis in vertebrate species. One of the brain regions involved in autonomic and endocrine homeostasis regulation is the paraventricular nucleus of the hypothalamus (PVN). The PVN is a unique site at which multiple input signals can be assessed and integrated. The regulation of the autonomic system by the PVN and, especially, the sympathetic flow, depends upon the integration of inhibitory and excitatory neurotransmitter action. The excitatory neurotransmitters such as glutamate and angiotensin II, and inhibitory neurotransmitters such as γ-aminobutyric acid and nitric oxide, play a key role in the physiological function of the PVN. Moreover, arginine-vasopressin (AVP) and oxytocin (OXT) are important in the regulation of sympathetic system activity. The PVN is also crucial for maintaining cardiovascular regulation, with its integrity being pivotal for blood pressure regulation. Studies have shown that pre-autonomic sympathetic PVN neurons increase blood pressure and the dysfunction of these neurons is directly related to elevated sympathetic nervous system activity under hypertension. Etiology of hypertension in patients is not fully known. Thus, understanding the role of PVN in the generation of hypertension may help to treat this cardiovascular disease. This review focuses on the PVN's inhibitory and excitatory neurotransmitter interactions that regulate sympathetic system activity in physiological conditions and hypertension. [7]

Taking into account the fact that sympathetic and parasympathetic reactions are registered at hypothalamic irritated, a number of authors classify hypothalamic structures as sympathetic and parasympathetic, thus transferring the idea of antagonism and reciprocal organization of peripheral mechanisms of the autonomic nervous system to hypothalamus as well. In a systematic study of autonomic and somatic reactions caused by irritation of various areas of the subbuglia, Hess concluded that there are two antagonistic zones in the intercerebral area - trophotropic or parasympathetic, and ergotropic or sympathetic. According to Hess, the ergotropic zone is located in the posterior hypothalamus and in the area of the circumventricular gray matter, and its irritation causes all signs of excitation of the sympathetic nervous system (increase in blood pressure, mydriasis, increased heart rate, increased respiration, increased motor activity, rage reaction). The trophotropic zone is located in the rostral parts of the hypothalamus, in the preoptic area, and it's irritation causes symptoms characteristic of an increase in the tone of the parasympathetic system (miosis, increased intestinal peristalsis, vasodilation, decreased heart rate and respiration, drowsiness, adynamia).

The notion that there are sympathetic and parasympathetic reciprocal mechanisms clearly localized in the nuclear structures of the hypothalamus is disputed by a number of researchers. Monnier notes that although ergotropic and trophotropic states are mediated through the sympathetic and parasympathetic systems, the rigid pattern of antagonistic sympatho-parasympathetic innervation is not adequate to characterize ergotropic and trophotropic adaptive responses. Monnier's ideas about the functions of ergotropic and trophotropic parts of the hypothalamus are in many respects consonant with the ideas developed in recent years about the absence of independent mechanisms of regulation of cardiovascular, respiratory or somatosensory reactions separately in the hypothalamus. The authors point out the presence of specific zones of integration of vegetative, emotional and motor components of various behavioral reactions of ergotropic and trophotropic types. However, in contrast to Goss, most researchers believe that hypothalamic mechanisms of integration of ergotropic and trophotropic reactions are located in all parts of the hypothalamus with some predominance of trophotropic zones within the anterior, and ergotropic - within the posterior hypothalamus. However, in contrast to Goss, most researchers believe that hypothalamic mechanisms of integration of ergotropic and trophotropic reactions are located in all parts of the hypothalamus with some predominance of trophotropic zones within the anterior, and ergotropic - within the posterior hypothalamus.

Physiological and pathophysiological roles of hypothalamic astrocytes in metabolism the role of glial cells, including astrocytes, in metabolic control has received increasing attention in recent years. Although the original interest in these macroglial cells was a result of astrogliosis being observed in the hypothalamus of diet-induced obese subjects, studies have also focused on how they participate in the physiological control of appetite and energy expenditure. Astrocytes express receptors for numerous hormones, growth factors and neuropeptides. Some functions of astrocytes include transport of nutrients and hormones from the circulation to the brain, storage of glycogen, participation in glucose sensing, synaptic plasticity, uptake and metabolism of neurotransmitters, release of substances to modify neurotransmission, and cytokine production, amongst others. In the hypothalamus, these physiological glial functions impact on neuronal circuits that control systemic metabolism to modify their outputs. The initial response of astrocytes to poor dietary habits and obesity involves activation of neuroprotective mechanisms but, with chronic exposure to these situations, hypothalamic astrocytes participate in the development of some of the damaging secondary effects. The present review discusses not only some of the physiological functions of hypothalamic astrocytes in metabolism, but also their role in the secondary complications of obesity, such as insulin resistance and cardiovascular affectations.[11]

When studying the neurochemical organization of different regions of the hypothalamus by methods of biochemical, histochemical, autoradiographic, immunochemical, electron microscopic, electrophysiological and neurophysiological analysis, the localization of a number of neurotransmitters and enzymes of their synthesis and decay in the hypothalamic region was established. In hypothalamic structures there is a high concentration of noradrenaline, dopamine, serotonin, histamine, as well as acetylcholinesterase, gamma-aminobutyric acid (GABA) and hormone peptides, which indicates the presence of noradrenergic, dopaminergic, serotoninergic, cholinergic, histaminergic, GABA-ergic, peptidergic structures in the hypothalamus.

Major depressive disorder ranks as a major burden of disease worldwide, yet the current antidepressant medications are limited by frequent non-responsiveness and significant side effects. The lateral septum (LS) is thought to control of depression; however, the cellular and circuit substrates are largely unknown. Here, we identified a subpopulation of LS GABAergic adenosine A2A receptors (A2AR)-positive neurons mediating depressive symptoms via direct projects to the lateral habenula (LHb) and the dorsomedial hypothalamus (DMH). Activation of A2AR in the LS augmented the spiking frequency of A2AR-positive neurons leading to a decreased activation of surrounding neurons and the bi-directional manipulation of LS-A2AR activity demonstrated that LS-A2ARs are necessary and sufficient to trigger depressive phenotypes. Thus, the optogenetic modulation (stimulation or inhibition) of LS-A2AR-positive neuronal activity or LS-A2AR-positive neurons projection terminals to the LHb or DMH, phenocopied depressive behaviors. Moreover, A2AR are upregulated in the LS in two male mouse models of repeated stress-induced depression. This identification that aberrantly increased A2AR signaling in the LS is a critical upstream regulator of repeated stress-induced depressive-like behaviors provides a

neurophysiological and circuit-based justification of the antidepressant potential of A2AR antagonists, prompting their clinical translation. [4]

By the method of surgical deafferentation of hypothalamus it is shown that after hypothalamic isolation in hypothalamic islet the concentration of dopamine and histamine does not decrease, the content of choline acetyltransferase (enzyme of acetylcholine synthesis) and glutamate decarboxylase (enzyme of GABA synthesis) slightly decreases and the level of noradrenaline and serotonin significantly decreases. These data suggest a dual hypothalamic and extrahypothalamic origin of some hypothalamus neurotransmitters. Histochemical studies by a number of authors have shown that the main pathway of noradrenergic, dopaminergic, serotoninergic, cholinergic, and histaminergic systems is in the region of the lateral hypothalamus within the medial bundle of the forebrain. Heterochemistry of hypothalamic cells, high sensitivity of individual neurons to two or more mediators was established during microiontophoretic application of pharmacological preparations to the area of an individual neuron and registration of its impulse activity. Details of the effects of microiontophoretic application of various neurotransmitters on the spiking activity of hypothalamic neurons are summarized in a review by Hayward.

Data on the polychemism of hypothalamic neurons indicate the presence of a large set of neurotransmitters in each nuclear region of the hypothalamus. Obviously, the set of mediators is characteristic not so much for separate brain regions as for whole functional systems, which may include neuronal groups of different regions united by a single system. The task of future researchers is to find out more precisely the chemical differentiation of biologically different reactions regulating the integrative activity of the hypothalamus.

Considering the peculiarities of neuronal organization of integrative activity of hypothalamus, it should be noted that in contrast to neurons of other parts of the central nervous system, neurons of some parts of hypothalamus have double sensitivity to the action of neurotransmitters released in the area of presynaptic terminals and to the action of physicochemical factors of neuronal environment (temperature, osmotic pressure, glucose, hormones, angiotensin, prostate-glandins and other biologically active substa Neural Functions of Hypothalamic Oxytocin and its Regulation Oxytocin (OT), a nonapeptide, has a variety of functions. Despite extensive studies on OT over past decades, our understanding of its neural functions and their regulation remains incomplete. OT is mainly produced in OT neurons in the supraoptic nucleus (SON), paraventricular nucleus (PVN) and accessory nuclei between the SON and PVN. OT exerts neuromodulatory effects in the brain and spinal cord. While magnocellular OT neurons in the SON and PVN mainly innervate the pituitary and forebrain regions, and parvocellular OT neurons in the PVN innervate brainstem and spinal cord, the two sets of OT neurons have close interactions histologically and functionally. OT expression occurs at early life to promote mental and physical development, while its subsequent decrease in expression in later life stage accompanies aging and diseases. Adaptive changes in this OT system, however, take place under different conditions and upon the maturation of OT release machinery. OT can modulate social recognition and behaviors, learning and memory, emotion, reward, and other higher brain functions. OT also regulates eating and drinking, sleep and wakefulness, nociception and analgesia, sexual behavior, parturition, lactation and other instinctive behaviors. OT regulates the autonomic nervous system, and somatic and specialized senses. Notably, OT can have different modulatory effects on the same function under different conditions. Such divergence may derive from different neural connections, OT receptor gene dimorphism and methylation, and complex interactions with other hormones. In this review, brain functions of OT and their underlying neural mechanisms as well as the perspectives of their clinical usage are presented). [16]

When studying the ultrastructural organization of adrenergic innervation of the hypothalamus, it was found that only a small fraction of adrenergic fibers form classical synaptic contacts on neurons of the paraventricular nucleus of the hypothalamus. Many varicosities of adrenergic fibers containing adrenergic microgranular vesicles do not form specialized synapses on neurons of this region of the hypothalamus. The authors conclude that noradrenaline or adrenaline is released from these varicosities into the interstitial fluid and has a “neurohumoral” effect on the cellular elements of a relatively large area. The type of functional adrenergic innervation without membrane specialization of synaptic contacts has also been described for adrenergic fibers of the neocortex and sympathetic fibers of skeletal muscles). Three possible mechanisms of adrenergic innervation of hypothalamic neurons are also allowed: hormonal effect of adrenergic mediators of blood (catecholamines of adrenal medulla), more localized neurohumoral action at release of neurotransmitters by varicosities of adrenergic fibers that do not have specialized synaptic contacts, and mediator local effect in the area of synaptic contact. Three possible mechanisms of adrenergic innervation of hypothalamic neurons are also allowed: hormonal effect of adrenergic mediators of blood (catecholamines of adrenal medulla), more localized neurohumoral action at release of neurotransmitters by varicosities of adrenergic fibers that do not have specialized synaptic contacts, and mediator local effect in the area of synaptic contact. Obviously, the second mechanism of action of biogenic amines is characteristic of integrative hypothalamic neurons.

Defensive behaviors are critical for animal's survival. Both the paraventricular nucleus of the hypothalamus (PVN) and the parabrachial nucleus (PBN) have been shown to be involved in defensive behaviors. However, whether there are direct connections between them to mediate defensive behaviors remains unclear. Here, by retrograde and anterograde tracing, we uncover that cholecystokinin (CCK)-expressing neurons in the lateral PBN (LPB^{CCK}) directly project to the PVN. By in vivo fiber photometry recording, we find that LPB^{CCK} neurons actively respond to various threat stimuli. Selective photoactivation of LPB^{CCK} neurons promotes aversion and defensive behaviors. Conversely, photoinhibition of LPB^{CCK} neurons attenuates rat or looming stimuli-induced flight responses. Optogenetic activation of LPB^{CCK} axon terminals within the PVN or PVN glutamatergic neurons promotes defensive behaviors. Whereas chemogenetic and pharmacological inhibition of local PVN neurons prevent LPB^{CCK}-PVN pathway activation-driven flight responses. These data suggest that LPB^{CCK} neurons recruit downstream PVN neurons to actively engage in flight responses. Our study identifies a previously unrecognized role for the LPB^{CCK}-PVN pathway in controlling defensive behaviors.[15]

The sensory properties of hypothalamic neurons have been studied in a number of electrophysiologic studies. Twenty years after the first microelectrophysiological studies by Cross and Green, devoted to the study of the properties of osmosensory hypothalamic neurons, our ideas about the structural and functional organization of hypothalamic afferent systems have been considerably deepened. It has been established that olfactory structures of the brain send a powerful flow of olfactory afferentation to neurons of the most ancient anterior hypothalamic section. Information about the direct projection of fibers of the optic tract to the area of the suprachiasmatic nucleus was obtained in studies using autoradiographic techniques. According to Bremer's data, light stimulation causes a sharp activation of neurons of the suprachiasmatic nucleus. Apparently, physiological mechanisms mediating the effect of light on neuroendocrine autonomic and behavioral reactions are localized in this region of the anterior hypothalamus. A number of electrophysiological studies have shown the predominant localization in the anterior hypothalamus of neurons with selective activity to visual afferentation. Taking into account the data on the wide convergence of somatic excitations (light, sound and somatosensory) on neurons of both posterior and anterior hypothalamus, the evoked activity of the majority of hypothalamic neurons during the excitation of somatic afferents is considered as a response of secondary, nonspecific type. Along with “sensory” neurons of nonspecific type, specific monosensory neurons

have been found in the hypothalamus. Specific localization of osmo-, thermo-, gluco-, and steroidreceptors within the hypothalamus has been described by a number of authors. The specific discriminative response of these neurons forms the mechanisms of functioning of hypothalamic thermostat, osmostat, glucostat and stereoidostat regulating homeostasis of temperature, osmotic pressure and glucose and steroid levels.

The hypothalamus is key in the control of energy balance. However, strategies targeting hypothalamic neurons have failed to provide viable options to treat most metabolic diseases. Conversely, the role of astrocytes in systemic metabolic control has remained largely unexplored. Here, we show that obesity promotes anatomically restricted remodeling of hypothalamic astrocyte activity. In the paraventricular nucleus (PVN) of the hypothalamus, chemogenetic manipulation of astrocytes results in bidirectional control of neighboring neuron activity, autonomic outflow, glucose metabolism, and energy balance. This process recruits a mechanism involving the astrocytic control of ambient glutamate levels, which becomes defective in obesity. Positive or negative chemogenetic manipulation of PVN astrocyte Ca^{2+} signals, respectively, worsens or improves metabolic status of diet-induced obese mice. Collectively, these findings highlight a yet unappreciated role for astrocytes in the direct control of systemic metabolism and suggest potential targets for anti-obesity strategy.[19]

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Energy expenditure and energy intake need to be balanced to maintain proper energy homeostasis. Energy homeostasis is tightly regulated by the central nervous system, and the hypothalamus is the primary center for the regulation of energy balance. The hypothalamus exerts its effect through both humoral and neuronal mechanisms, and each hypothalamic area has a distinct role in the regulation of energy expenditure. Recent studies have advanced the understanding of the molecular regulation of energy expenditure and thermogenesis in the hypothalamus with targeted manipulation techniques of the mouse genome and neuronal function. In this review, we elucidate recent progress in understanding the mechanism of how the hypothalamus affects basal metabolism, modulates physical activity, and adapts to environmental temperature and food intake changes.[20]

Since the hypothalamus is the main subcortical center for the regulation of autonomic functions, the question of the representation of visceral afferents in this area is of interest. When studying the response of neurons of the anterior and posterior regions of the hypothalamus to irritation of the phrenic and sciatic nerves and to light stimulation, a broad convergence of heterosensory excitation to neurons of both anterior and posterior hypothalamus was found. According to the results of studies by some authors, convergence of excitation of somatic and visceral afferents occurs already on the insertion neurons of the spinal cord (layers V- VII, according to Rexed).

Recent studies have shown that the hypothalamus functions as a control center of aging in mammals that counteracts age-associated physiological decline through inter-tissue communications. We have identified a key neuronal subpopulation in the dorsomedial hypothalamus (DMH), marked by Ppp1r17 expression (DMHPpp1r17 neurons), that regulates aging and longevity in mice. DMHPpp1r17 neurons regulate physical activity and WAT function, including the secretion of extracellular nicotinamide phosphoribosyltransferase (eNAMPT), through sympathetic nervous stimulation. Within DMHPpp1r17 neurons, the phosphorylation and subsequent nuclear-cytoplasmic translocation of Ppp1r17, regulated by cGMP-dependent protein kinase G (PKG; Prkg1), affect gene expression regulating synaptic function, causing synaptic transmission dysfunction and impaired WAT function. Both DMH-specific Prkg1 knockdown, which suppresses age-associated Ppp1r17 translocation, and the chemogenetic activation of DMHPpp1r17 neurons significantly ameliorate age-associated dysfunction in WAT, increase physical activity, and extend lifespan. Thus, these findings clearly demonstrate the importance of the inter-tissue communication between the hypothalamus and WAT in mammalian aging and longevity control. [8]

Hypothalamic neurons are closely related to the activity of vagus afferents carrying information about the functions of internal organs. When studying the response of anterior and posterior hypothalamic neurons to vagus and sciatic nerve stimulation, it was found that 78% of posterior hypothalamic neurons showed convergence of viscerosomatic excitations, while 62% of anterior hypothalamic neurons had bimodal viscerosomatic neurons of convergent type. The authors note that posterior hypothalamic neurons are more reactive than anterior hypothalamic neurons to vagus nerve stimulation. These data are somewhat unexpected, because based on Helgorn's concept of localization of parasympathetic centers in the anterior hypothalamus, one should have expected preferential reactions to stimulation of parasympathetic nerve afferents in the anterior hypothalamus. The data on the convergence of visceral afferent impulses on hypothalamic neurons under irritation of the vagus and phrenic nerves are noteworthy.According to the authors' data, most of the responding neurons of the posterior and anterior hypothalamus respond to stimulation of both vagus and phrenic nerves. Interestingly, the responses of polysensory hypothalamic neurons to the stimulation of visceral afferents of parasympathetic and sympathetic nerves are unambiguous, predominantly of excitatory type, which indicates nonspecific properties of the studied polysensory “convergent” neurons of the anterior and posterior hypothalamic region. When studying the sensory properties of hypothalamic neurons, the question of projection of specific cardiovascular afferents in the hypothalamus is also of special interest. Barosensitive neurons were found in the anterior medial and posterior sections of the hypothalamus.

Neurons responsive to right and left atrial stretch were also detected in the supraoptic, paraventricular, anterior, lateral, and mediodorsal regions of the hypothalamus. Based on the fact that neurons responding to atrial stretch are osmosensitive and also respond to the introduction of CaC1 into the left atrium and the carotid sinus region, Hayward believes that excitation of atrial stretch receptors modulates the activity of hypothalamic osmosensitive neurons, involved in the regulation of functions of the anterior (adrenocorticotropin) and posterior (antidiuretic hormone) pituitary gland, thus providing homeostasis regulation of osmotic pressure and ionic balance of the organism by a reflex feedback mechanism.

Hypothalamic regulation of homeostasis of autonomic functions is realized due to the interrelation of the hypothalamic region with many structures of the central nervous system. Functional interrelations of the hypothalamus with central links of the forebrain limbic system, with the hippocampus and with the nuclei of the amygdala complex play an important role in the integration of emotional-motivational and visceromotor reactions.

The hypothalamus regulates innate social behaviors, including mating and aggression. These behaviors can be evoked by optogenetic stimulation of specific neuronal subpopulations within MPOA and VMHvl, respectively. Here, we perform dynamical systems modeling of population neuronal activity in these nuclei during social behaviors. In VMHvl, unsupervised analysis identified a dominant dimension of neural activity with a large time constant (>50 s), generating an approximate line attractor in neural state space. Progression of the neural trajectory along this attractor was correlated with an escalation of agonistic behavior, suggesting that it may encode a scalable state of aggressiveness. Consistent with this, individual differences in the magnitude of the integration dimension time constant were strongly correlated with differences in aggressiveness. In contrast, approximate line attractors were not observed in MPOA during mating; instead, neurons with fast dynamics were tuned to specific actions. Thus, different hypothalamic nuclei employ distinct neural population codes to represent similar social behaviors. [2]

Functional relationships between hypothalamus and reticular formation of the midbrain are expressed in facilitatory and inhibitory mutual influences, in the realization of which a complex system of noradrenergic, dopaminergic, serotoninergic, cholinergic, and other neurochemical structures of the brainstem and hypothalamus takes part. Tonic inhibitory interactions between the activating system of the midbrain reticular formation and the hypnogenic zone of the preoptic area of the hypothalamus are one of the main mechanisms of circadian rhythm regulation. There is also evidence of a mutual facilitating influence of the hypothalamus and midbrain reticular formation. The mesencephalic reticular formation is an auxiliary activating system for desynchronizing mechanisms of the hypothalamus, and at the same time it is under the tonic activating influence of the hypothalamus itself.

Obviously, the positive feedback between these two components of the activating system plays an important role not only in maintaining the homeostasis of excitability of the central nervous system, but also in the regulation of viscerosomatic, neuroendocrine, and emotional-motivational reactions.

Functional relationships between the hypothalamus and the new cortex play an important role in the integration of vegetoendocrine, somatomotor, and affective components of complex behavioral reactions of adaptive behavior. A number of morphologic and electrophysiologic studies have shown the existence of a direct projection of the frontal, temporal, parietal, and orbitofrontal cortex into the hypothalamic region. Registration of antidromic discharges of sensorimotor and prefrontal cortex neurons at irritation of hypnogenic zones of the anterior hypothalamus and activating structures of the posterior hypothalamus also testifies to the direct projection of the neocortex to the hypothalamus. The data on the antidromic response of the neurocortex to irritation of both the posterior hypothalamus and the midbrain reticular formation are noteworthy. Apparently, such divergent-type cortical neurons provide cortical integration of hypothalamic and reticular formation activity.

The prefrontal cortex (PFC) enables mammals to respond to situations, including internal states, with appropriate actions. One such internal state could be 'tiredness'. Here, using activity tagging in the mouse PFC, identified particularly excitable, fast-spiking, somatostatin-expressing, γ-aminobutyric acid (GABA) (PFCSst-GABA) cells that responded to sleep deprivation. These cells projected to the lateral preoptic (LPO) hypothalamus and the lateral hypothalamus (LH). Stimulating PFCSst-GABA terminals in the LPO hypothalamus caused sleep-preparatory behavior (nesting, elevated theta power and elevated temperature), and stimulating PFCSst-GABA terminals in the LH mimicked recovery sleep (non-rapid eye-movement sleep with higher delta power and lower body temperature). PFCSst-GABA terminals had enhanced activity during nesting and sleep, inducing inhibitory postsynaptic currents on diverse cells in the LPO hypothalamus and the LH. The PFC also might feature in deciding sleep location in the absence of excessive fatigue. These findings suggest that the PFC instructs the hypothalamus to ensure that optimal sleep takes place in a suitable place. [3]

Cortico-hypothalamic relationships obey the principle of bilateral control. If corticofugal influences are decisive in hypothalamic activity, then ascending tonic and phasic influences coming from the hypothalamus are no less important for normal cortical functioning. The direct projection of diencephalic structures into the frontal cortex was also proved by the peroxidase method.

Neurons in the prefrontal cortex (PFC) can provide top-down regulation of sensory-affective experiences such as pain. Bottom-up modulation of sensory coding in the PFC, however, remains poorly understood. Here, we examined how oxytocin (OT) signaling from the hypothalamus regulates nociceptive coding in the PFC. In vivo time-lapse endoscopic calcium imaging in freely behaving rats showed that OT selectively enhanced population activity in the prelimbic PFC in response to nociceptive inputs. This population response resulted from the reduction of evoked GABAergic inhibition and manifested as elevated functional connectivity involving pain-responsive neurons. Direct inputs from OT-releasing neurons in the paraventricular nucleus (PVN) of the hypothalamus are crucial to maintaining this prefrontal nociceptive response. Activation of the prelimbic PFC by OT or direct optogenetic stimulation of oxytocinergic PVN projections reduced acute and chronic pain. These results suggest that oxytocinergic signaling in the PVN-PFC circuit constitutes a key mechanism to regulate cortical sensory processing. [10]

Histofluorescence and autoradiographic methods established that ascending noradrenergic and dopaminergic fibers of the medial bundle of the forebrain, passing through the lateral hypothalamus, end in the frontal cortex. The data on high convergence of ascending “nonspecific” impulses of reticular and hypothalamic origin on sensorimotor cortex neurons are of interest. Apparently, the ascending influences of the hypothalamus and reticular formation are specific in nature. There is evidence for a hypothalamic mechanism of cortical activation in the state of physiologic hunger and for a reticular genesis of cortical activation during painful stimulation.

Borderline personality disorder (BPD) is characterized by emotional instability, impulsivity and unstable interpersonal relationships. Patients experience discomforting levels of distress, inducing symptoms like dissociation, aggression or withdrawal. Social situations are particularly challenging, and acute social stress can reduce patients' cognitive and social functioning. In patients with Major Depressive Disorder or posttraumatic stress disorder, which show high comorbidity with BPD, the endocrine stress response is characterized by Hypothalamus-Pituitary-Adrenal (HPA) axis dysfunction, which affects cognitive functioning. Compared to these clinical groups, research on HPA-axis function in BPD is relatively scarce, but evidence points towards a blunted cortisol reactivity to acute stress. Since BPD patients are particularly prone to social stress and experience high subjective difficulties in these situations, it seems plausible that HPA-axis dysregulation might contribute to decreased social cognition in BPD. The present review summarizes findings on the HPA-axis function in BPD and its association with social cognition following acute social stress. We conclude that research on social cognition in BPD reveals heterogeneous results with no clear relationship between social functioning and HPA-axis response. More research is needed to better understand the psychophysiological underpinnings of impaired social cognition in BPD. [5]

What is the functional role of ascending hypothalamic-cortical pathways projecting to different regions of the neocortex? According to Makarchenko, hypothalamo-cortical influences are aimed at maintaining a certain optimal level of cortical activity. It has been shown that stimulation of the preoptic region of the hypothalamus restores the initial level of background activity of most neurons of the visual cortex, shifted to one side or another as a result of the action of the polarizing current,

which indicates a stabilizing homeostatic effect of the modulating (corrective) influence of hypothalamic structures on the cortex.

The multichannel ascending hypothalamic-cortical system, consisting of activating and inhibitory subsystems, plays an important role in the regulation of sleep and wakefulness. Numerous studies have shown that irritation of the posterior hypothalamus causes desynchronization in the EEG and the behavioral reaction of "waking up". The data on the preservation of synchronizing and desynchronizing influences of various hypothalamic structures on cortical activity after disconnection of the midbrain reticular formation indicate an independent role of the hypnogenic and activating mechanisms of the hypothalamus in the regulation of sleep and wakefulness processes. A number of chronophysiological studies have shown that the suprachiasmatic nucleus of the anterior hypothalamus acts as a central pacesetter or biological clock for the circadian (diurnal) rhythm of activity of neurons of the central nervous system.

Seasonal changes in food intake and adiposity in many animal species are triggered by changes in the photoperiod. These latter changes are faithfully transduced into a biochemical signal by melatonin secreted by the pineal gland. Seasonal variations, encoded by melatonin, are integrated by third ventricular tanycytes of the mediobasal hypothalamus through the detection of the thyroid-stimulating hormone (TSH) released from the pars tuberalis. The mediobasal hypothalamus is a critical brain region that maintains energy homeostasis by acting as an interface between the neural networks of the central nervous system and the periphery to control metabolic functions, including ingestive behavior, energy homeostasis, and reproduction. Among the cells involved in the regulation of energy balance and the blood-hypothalamus barrier (BHB) plasticity are tanycytes. Increasing evidence suggests that anterior pituitary hormones, specifically TSH, traditionally considered to have unitary functions in targeting single endocrine sites, display actions on multiple somatic tissues and central neurons. Notably, modulation of tanycytic TSH receptors seems critical for BHB plasticity in relation to energy homeostasis, but this needs to be proven. [6]

Salient cues, such as the rising sun or availability of food, entrain biological clocks for behavioral adaptation. The mechanisms underlying entrainment to food availability remain elusive. Using single-nucleus RNA sequencing during scheduled feeding, we identified a dorsomedial hypothalamus leptin receptor-expressing (DMHLepR) neuron population that up-regulates circadian entrainment genes and exhibits calcium activity before an anticipated meal. Exogenous leptin, silencing, or chemogenetic stimulation of DMHLepR neurons disrupts the development of molecular and behavioral food entrainment. Repetitive DMHLepR neuron activation leads to the partitioning of a secondary bout of circadian locomotor activity that is in phase with the stimulation and dependent on an intact suprachiasmatic nucleus (SCN). Last, we found a DMHLepR neuron subpopulation that projects to the SCN with the capacity to influence the phase of the circadian clock. This direct DMHLepR-SCN connection is well situated to integrate the metabolic and circadian systems, facilitating mealtime anticipation. [9]

The study of structural and functional relations of the hypothalamus with the structures of the rhombencephalon (bridge and medulla oblongata) is important for elucidating the mechanisms of hypothalamic regulation of autonomic functions. The method of autoradiography established bilateral projection of the hypothalamus into the medulla oblongata region. A number of electrophysiological data testify to the direct output of hypothalamic excitation to the medulla oblongata neurons. However, in all these studies the hypothalamic projection to functionally and electrophysiologically identified output reticulo-spinal sympatho-activating neurons of the medulla oblongata has not been studied. Only studies show projection of the posterolateral hypothalamic region to output reticulo-spinal sympatho-activating neurons identified antidromically. Oscillograms illustrate the responses of an antidromically identified reticulo-spinal sympatho-activating neuron to single and frequency stimulation of the posterior hypothalamus. The authors' data on the relatively short latent period of reticulo-spinal sympatho-activating neurons' responses to hypothalamic stimulation (among. 4.9 +0.3 ms), relative stability of the latent period, the fluctuations of which do not exceed +0.4 ms, and the ability to reproduce the frequency of stimulation up to 50-100 imp/s testify to the probable monosynaptic activation of neurons.

Hypothalamic connections with hindbrain structures are bilateral. Histofluorescence studies by a number of authors have shown the projection of monoaminergic neurons of the bridge and medulla oblongata into the hypothalamus. The method of autoradiography revealed ascending projections of the suture nuclei of the rostral region of the bridge into the lateral and paraventricular hypothalamus. Antidromic activation of rhombencephalon neurons at irritation of the basal forebrain region also testifies to direct projection of some structures of the bridge and medulla oblongata to the area of the lateral hypothalamus. The data on the ascending projection of the main bulbar collector of visceral afferents - the nucleus of the solitary tract - are controversial. The results of a number of histomorphologic and autoradiographic studies indicate a disynaptic projection of afferents of the visceral part of the solitary nucleus to the hypothalamus and other limbic structures of the forebrain through the structures of the pontine and midbrain. However, Sakumoto's studies show that when horseradish peroxidase is injected into the preoptic area and into the anterior hypothalamus, this enzyme is detected in noradrenergic neurons of the nucleus solitarii, indicating a direct upward projection of these neurons to the hypothalamus and to limbic structures of the forebrain. Evidence for direct upward projection of the caudal, visceroceptive portion of the nucleus solitarii tract into structures of the hypothalamus, amygdala, preoptic field, and periventricular nucleus of the thalamus was obtained by anterograde autoradiographic and retrograde peroxidase labeling techniques in studies by Ricardo and Co. Apparently, interoceptive information arrives to limbic forebrain structures via relatively direct pathways. Further studies of the neural organization of hypothalamic-rhombencephalic relationships are important for elucidating the central mechanisms of regulation of the body's vegetoandrocrine and affective reactions.

In the problem of hypothalamic regulation of autonomic mechanisms of the spinal cord, for a long time the idea that there is no direct connection between the hypothalamus and autonomic centers of the spinal cord prevailed. Only in separate works, carried out by the degeneration method, the data on direct projection of descending hypothalamic pathways to the spinal cord region are given. Convincing data on the presence of direct connections of the hypothalamus with autonomic centers of the spinal cord have been obtained in recent years using peroxidase and autoradiographic methods. When peroxidase was injected into the T7-T12 region of the spinal cord, retrograde transport of the enzyme marker was detected predominantly in the paraventricular, dorsal, lateral, dorsomedial, and posterior hypothalamic regions. In the same work, it was shown that when amino acid isotopes were injected into the region of the anterior hypothalamus, labeled fibers were detected autoradiographically in the intermediolateral region of the thoracic spinal cord. Peroxidase technique showed hypothalamic projection to the area of sympathetic preganglionic neurons of the spinal cord and in the studies of Kuipers and Maisky. There are also some electrophysiological data on direct projection of the hypothalamus into the spinal cord region.

When studying the characteristic of discharges in the lumbar white connective twigs caused by single or pack irritation of the hypothalamus, it was shown that when the pressor zones of both anterior and posterior hypothalamus are irritated, a hypothalamic-sympathetic discharge consisting of three waves is registered in them. The latency period of the first, the earliest wave of the hypothalamic-sympathetic discharge averages 19.7+4.5 ms. The first discovered early hypothalamic-sympathetic discharges with such a short latent period obviously indicate the existence of descending channels for rapid conduction of

hypothalamic impulsation to sympathetic preganglionic neurons of the spinal cord. The authors note that the early wave of hypothalamic-sympathetic evoked discharge, which is conducted through this fast-conducting pathway, is probably generated when sympathetic preganglionic neurons are excited by direct hypothalamic descending discharge. The generation of late components of the hypothalamic-sympathetic response, in all probability, occurs indirectly during hypothalamic excitation of output reticulo-spinal sympatho-activating neurons of the medulla oblongata. When studying the nature of modulating effect of high-frequency hypothalamic stimulation on the activity of the spinal cord, a number of authors noted an increase in the activity of sympathetic nerves. In a comparative electrophysiological study of the nature of the effect of tetanic stimulation of the pressor structures of the posterior tuberal and anterior hypothalamus, it was found that within the entire hypothalamus the system of descending facilitation of sympathetic nervous system activity dominates. In a number of works it has been shown that irritation of some points of the anterior hypothalamus and preoptic area causes generalized suppression of sympathetic activity with concomitant vagus bradycardia.

Sympatho-inhibitory zones of the hypothalamus are localized caudal and ventral to the anterior commissure. A comparative study of changes in the characteristics of tonic activity of various sympathetic nerves revealed that three types of modulation of electrical activity of vertebral, cardiac and renal postganglionic sympathetic nerves are most often observed during hypothalamic stimulation: generalized amplification of sympathetic nerve activity, generalized inhibition of sympathetic nerve activity, selective suppression of vertebral nerve activity, and amplification of cardiac and renal nerve activity. Opposite changes in sympathetic activity, most often visceral and muscular sympathetic nerves, have been established by other investigators. The data on the characterization of early and late components of hypothalamic-sympathetic evoked discharge and on differential hypothalamic modulation of the activity of neuronal populations of various sympathetic outputs indicate the existence of a multichannel system of descending hypothalamic control of the activity of sympathetic preganglionic neurons of the spinal cord.

There are not only direct projections of the hypothalamus to the structures of the spinal cord, but also direct projections of the ascending fibers of the spinal cord into the hypothalamus. The data of histomorphologic studies by a number of authors testify to the rostral projection of ascending afferents of the spinal cord into the posterolateral hypothalamus. The Fink-Heimer method revealed afferent terminals of the spinal-periventricular fiber system in the region of the posterior dorsal and posterolateral hypothalamus. Part of these fibers, diverging from the medial loop, passes ventral to the red nucleus and enters the posterior hypothalamus through Forel's field. There is also electrophysiological evidence of a possible direct projection of somatosensory afferents of the specific ascending lemniscus pathway to the posterior hypothalamus.

It is the heterogeneous changes of hypothalamic functions that determine the chronological sequence of aging in mammals. Recently, it was hypothesized by Cai the decrease in slow-wave sleep (SWS) resulting from skin aging as responsible for the degeneration of hypothalamic suprachiasmatic nucleus (SCN). It was soon hypothesized by the European people in television that the increase in body fat as responsible for the degeneration of male preoptic sexually dimorphic nucleus (SDN-POA), via the aromatase converting testosterone to estradiol as proposed by Cohen. It is the hypothalamic paraventricular nucleus (PVN) that remains unchanged in neuron number during aging for psychological stress. In this chapter, it is briefly reviewed more manifestations of hypothalamic related mammalian aging processes, including [1] the aging of ovary by lipid, estradiol and hypothalamus; [2] the aging of muscle, stomach, intestine, thymus, and the later aging of brain, regulated by growth hormone/insulin-like growth factor 1(GH/IGF1); [3] the cardiovascular hypertension from PVN activation, the bone and other peripheral aging by psychological stress, and that of kidney by vasopressin. It is classified these aging processes by the primary regulation from one of the three hypothalamic nuclei, although still necessary to investigate and supplement their secondary regulation by the hypothalamic nuclei in future. It is the hypothalamic structural changes that shift the functional balance among these three hypothalamic systems toward aging.[18]

Hypothalamic Menin regulates systemic aging and cognitive decline Aging is a systemic process, which is a risk factor for impaired physiological functions, and finally death. The molecular mechanisms driving aging process and the associated cognitive decline are not fully understood. The hypothalamus acts as the arbiter that orchestrates systemic aging through neuroinflammatory signaling. Our recent findings revealed that Menin plays important roles in neuroinflammation and brain development. Here, we found that the hypothalamic Menin signaling diminished in aged mice, which correlates with systemic aging and cognitive deficits. Restoring Menin expression in ventromedial nucleus of hypothalamus (VMH) of aged mice extended lifespan, improved learning and memory, and ameliorated aging biomarkers, while inhibiting Menin in VMH of middle-aged mice induced premature aging and accelerated cognitive decline. We further found that Menin epigenetically regulates neuroinflammatory and metabolic pathways, including D-serine metabolism. Aging-associated Menin reduction led to impaired D-serine release by VMH-hippocampus neural circuit, while D-serine supplement rescued cognitive decline in aged mice. Collectively, VMH Menin serves as a key regulator of systemic aging and aging-related cognitive decline.[17]

The Role of Hypothalamus in The Regulation of Autonomic Functions

Cardiovascular regulation. The first systematic studies of the role of hypothalamus in the regulation of cardiovascular function of the organism with the use of stereotactic experimental technique were carried out by Karplus and Kreidl at the dawn of our century. Topographic localization of pressor and depressor points in the hypothalamus was further studied in numerous studies. When elucidating the role of hypothalamic departments in the realization of phase shifts of arterial pressure, it was found that in cardiovascular effects of hypothalamic irritation, pressor reactions predominate and there is a diffuse distribution of pressor zones throughout the hypothalamus. A detailed study of the directionality of vasomotor reactions at different parameters of hypothalamic electrical stimulation showed that maximal pressor reactions occur at hypothalamic stimulation with a frequency of 100 imp/s. According to some authors, depressor reactions occur more easily when the hypothalamus is stimulated with low frequency stimuli. The mechanism of reversion of vasomotor reactions during low- and high-frequency hypothalamic stimulation is discussed in a number of works [21-22].

An important stage in studying the problem of hypothalamic regulation of cardiovascular functions is the study of the regional structure of systemic vasomotor reactions caused by irritation of various hypothalamic structures. Systematic studies on the peculiarities of hypothalamic regulation of regional blood circulation have been performed by Swedish authors. These studies established the existence of mechanisms of highly differentiated descending hypothalamic discharge causing selective change of various components of cardiovascular response. Thus, it has been shown that when the “protective” zone of the hypothalamus is irritated, sympathetic, cholinergic (atropine-sensitive) muscle vasodilation occurs along with vasoconstriction of skin and intestinal vessels, increased blood pressure, tachycardia, and pupil dilation. According to some authors, irritation of certain hypothalamic zones causes a noncholinergic vasodilatory response due to selective inhibition of vasoconstrictor fibers of muscle vessels. Apparently, selective depression of spinal nerve potentials with concomitant enhancement of tonic activity of the inferior cardiac and renal nerves, described during irritation of some points of the anterior hypothalamus, is

an electrophysiological expression of noncholinergic dilatation of muscle vessels as a result of selective inhibition of vasoconstrictor fibers [1-4].

Folkow's studies have established that the sympathetic cholinergic vasodilator zone is located in the vicinity of the hypothalamic structure, irritation of which causes generalized inhibition of sympathetic vasoconstrictor and cardiac accelerator tone. It is assumed that the "sympathoinhibitory depressor" zone of the anterior hypothalamus is a relay station of the cortical descending inhibitory pathway affecting the activity of the vasomotor center of the medulla oblongata. The authors also admit the possibility of direct transmission of the descending inhibitory discharge of the hypothalamus to sympathetic preganglionic neurons of the spinal cord. The cortical-hypothalamic system of inhibition of activity of sympathetic structures of the spinal cord is probably triggered by psychic stimuli and causes cardiovascular shifts during emotional experiences [5-10].

The study of regional blood circulation under irritation of various brainstem structures allowed to reveal a number of mechanisms of neurogenic vasodilatation, and nowadays, besides the mechanisms of passive (inhibitory) vasodilatation due to inhibition of sympathetic vasoconstrictor tone (irritation of depressor zones of cortex, hypothalamus and brainstem, baroreceptor depressor reflexes), active vasodilatation is also distinguished, which is carried out by excitation of efferent vascular fibers. Depending on the mediator released in the terminals of these fibers during their excitation, four types of active vasodilation have been identified at this stage of studying the mechanisms of neurogenic vasodilation: parasympathetic cholinergic, sympathetic cholinergic, beta-adrenergic, and histaminergic [19-22].

The hypothalamus is an important substrate for the integration of various emotional-behavioral reactions, and the main role of the hypothalamus in the regulation of hemodynamics is to coordinate cardiovascular shifts with emotional-behavioral reactions of various types. Studies on revealing the relationship between visceromotor and somatomotor manifestations of holistic somatovegetative reactions of emotional-behavioral type associated with various structures of the hypothalamus have been conducted in a number of laboratories. The data of all these studies indicate that autonomic, in particular, cardiovascular reactions arising from irritation of "pressor" and "depressor" zones of the hypothalamus cannot be considered in isolation from the somatomotor components of a holistic behavioral reaction; they are a component of these reactions, and therefore the old idea that each component of a holistic reaction has its independent representation in the hypothalamus is simplistic. Hilton notes that there is no separate center in the hypothalamus for the cardiovascular or any other system, but rather areas of integration of visceromotor and somatomotor components of various behavioral responses. While the medulla oblongata provides homeostasis of the main parameters vital for the whole organism (lung ventilation, blood pressure level), coordinating vasomotor regulation with respiratory regulation, hypothalamic mechanisms integrate autonomic and somatomotor manifestations of complex reactions of adaptive behavior [11-15].

Studies of the regional structure of pressor and depressor reactions caused by hypothalamic stimulation indicate a differentiated fractional organization of hypothalamic "vasomotor" centers. When performing a particular behavioral act, a generalized increase or decrease in vascular tone in all circulatory circles is not biologically appropriate. Vegetative shifts should provide an optimal mode of activity of those organs and systems, the activity of which is crucial at the moment for the implementation of adaptive behavior of the organism [17].

A number of authors attribute to diencephalic, in particular, hypothalamic structures the main role in the development of specific changes in regional blood circulation under stress stimuli. It has been established that suprapontine autonomic mechanisms play an important role in the development of specific changes in regional blood circulation under arterial hypoxia - vasoconstriction of portal and renal vessels and vasodilatation of muscular and skin vessels, since in "bridge" animal's autonomic reactions to hypoxia are less differentiated than in "thalamic" animals, i.e., with intact diencephalic structures [3-8].

The study of neural mechanisms of hypothalamic regulation of cardiovascular function revealed the presence of pressosensitive neurons in the posterior hypothalamus. According to Frazier, there are two populations of pressor neurons in the posterior hypothalamus: cells that are excited when blood pressure rises and cells whose background activity is suppressed when blood pressure rises. Hayward assumes the existence of pressor detectors in the posterior hypothalamus, which, when excited by an increase in blood pressure, have a reciprocal effect on the pressor neurons of the posterior hypothalamus, increasing the activity of vasodepressor neurons and suppressing the activity of vasopressor neurons. When blood pressure decreases, vasopressor neurons are excited. According to Spier's data, when intrasinus pressure increases, some neurons of the anterior hypothalamus become more active, some neurons react with discharge, and the activity of some neurons is suppressed. The author considers the zone of localization of baroreceptor neurons of the depressor field of the anterior hypothalamus as the rostral part of the integrative center of the baroreceptor reflex. Obviously, this zone corresponds to the sympathoinhibitory zone of the anterior hypothalamus [10-13].

Regulation of respiration. Hypothalamic mechanisms of respiratory regulation are necessary for the most perfect adaptation of respiration to the changing needs of the body in gas exchange and play an important role in the coordination of respiratory processes with thermoregulation, metabolism, with cardiovascular function and somatomotor activity. The hypothalamus exerts constant, tonic control over the activity of the neurons of the respiratory center. Coagulation of the posterior hypothalamus slows respiratory rate even under conditions of normal pulmonary ventilation (normopnea). Numerous studies have examined the nature of respiratory changes during electrical irritation of various hypothalamic structures. According to Hess, electrical irritation of the ergotropic, dynamogenic field of the posterior hypothalamus causes increased frequency and deepening of respiration along with other reactions of sympathetic nervous system activation. Irritation of the anterior hypothalamus causes various trophotropic reactions, including a decrease in respiratory activity. The results of the study by Gelgorn and Monnier are in agreement with Hess's data. The presence of reciprocal mechanisms of regulation of respiratory activity, clearly localized in the posterior and anterior regions of the hypothalamus, is disputed by the results of a number of authors. According to Wang's data, electrical irritation of medial structures of not only posterior but also anterior hypothalamus causes respiratory rate with a shift toward inspiration. At irritation of the posterior hypothalamus along with the increase in blood pressure in some experiments, a decrease in respiratory rate is observed [15].

The influence of hypothalamus on respiratory activity is connected with mechanisms of integration of vegetosomatic manifestations of emotional and behavioral reactions of the organism, and, obviously, there are no specific points in hypothalamus activating or suppressing the functional system of respiration. Change of breathing, apparently, is only a component of more complex integrated reactions, which have a certain localization in the structures of the hypothalamus. Thus, the increased respiratory rate during thermal or electrical stimulation of the preoptic area is a component of heat loss mechanisms, and hence should be regarded as thermal polypnoea. According to Evans, the region from the posterolateral hypothalamus to the ventral covering of the midbrain plays an important role in the integrated regulation of respiration. Respiratory effect during irritation of the "protective" hypothalamic zone is considered as emotional polypnea associated with stress. Respiration increases and mydriasis at irritation of the posterolateral hypothalamus area are obviously also components of ergotropic activity of the organism.

Some authors consider the change of respiration at irritation of the brainstem reticular formation as a manifestation of generalized reticular activation [6-11].

Under stressful condition, reproductive function is impaired due to the activation of various components of the hypothalamic-pituitaryadrenal (HPA) axis, which can suppress the activity of the hypothalamic-pituitary-gonadal (HPG) axis at multiple levels. A hypothalamic neuropeptide, gonadotropin-inhibitory hormone (GnIH) is a key negative regulator of reproduction that governs the HPG axis. Converging lines of evidence have suggested that different stress types and their duration, such as physical or psychological, and acute or chronic, can modulate the GnIH system. To clarify the sensitivity and reactivity of the GnIH system in response to stress, we summarize and critically review the available studies that investigated the effects of various stressors, such as restraint, nutritional/metabolic and social stress, on GnIH expression and/or its neuronal activity leading to altered HPG action. In this review, we focus on GnIH as the potential novel mediator responsible for stress-induced reproductive dysfunction.[14]

A number of studies have shown that hypothalamic irritation along with changes in respiration results in changes in blood pressure. In this connection the question arises about a possible secondary genesis of respiratory reactions at hypothalamic irritation as a result of hemodynamic changes. Despite the fact that there is no data on the occurrence of discharges of respiratory neurons of the medulla oblongata at a single hypothalamic stimulation, the lack of correlation between changes in respiratory activity and hemodynamics is considered as evidence of a direct influence of the hypothalamus on the activity of respiratory neurons. Under conditions of reduced excitability of the posterior hypothalamus, asphyxia leads to a decrease in respiratory responses, which may be accompanied by both pressor and depressor reactions. When studying the nature and severity of autonomic reactions arising from stimulation of various points of the hypothalamus, it was found that respiratory reactions have the lowest threshold; shifts in the initial level of blood pressure are detected only at higher stimulation intensity [4-9]. The localization in the hypothalamus of discrete mechanisms of control of respiratory activity is evidenced by the presence in the anterior hypothalamus of neurons whose activity is modulated by the phases of respiration. They are named respiratory neurons of the hypothalamus. Repeated pack irritation of various structures of the preoptic, anterior and posterior regions of the hypothalamus causes an increase in the animal's respiration in the rhythm of repetition of stimulus volleys, most often without accompanying changes in blood pressure, heart rate and motor activity.

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