



Spinal Mechanisms of Homeostasis

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Opinion Article

Autonomic Functions

Autonomic mechanisms of the spinal cord take part in the regulation of a number of visceral functions. There is evidence, for example, of the participation of thermosensitive neurons of the spinal cord in the maintenance of homeostasis of the organism. Since maintenance of blood pressure constancy is one of the most important manifestations of homeostasis of autonomic functions involving the spinal cord, let us consider this issue in more detail. The functional state of sympathetic preganglionic neurons (SPNs) of the spinal cord is of crucial importance in maintaining blood pressure homeostasis and regulation of vascular tone and cardiac activity. When studying the functional specialization of these neurons, it was shown that on vasomotor neurons of sympathetic ganglia responding antidromically to muscle nerve stimulation (sympathetic postganglionic fibers oriented only to blood vessels pass in muscle nerves), axons of only B2 and C-SPNs converge. The conclusion that B2 -SPNs are the main vasomotor output from the spinal cord is confirmed by the data obtained when studying the background activity of SPNs of the lateral horns [1]. Not only somato-visceral afferentation but also descending influences converge to vasomotor SPNs. Bulbo-spinal neurons of the lateral, reticular, small cell, paramedian, ventral reticular, gigantocellular nuclei of the reticular formation, and the central nucleus of the medulla oblongata participate in the descending transmission of suprasegmental influences on the sympathetic mechanisms of the spinal cord. According to Henry and Calaresu, at least five descending reticulo-spinal systems of the medulla oblongata, of which two are sympatho-activating and three sympathoinhibitory, are involved in the suprasynal regulation of cardioacceleratory SPNs. In studying the influence of bulbospinal monoaminergic

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pathways on sympathetic nerve activity, it has been shown that catecholaminergic pathways pass in the dorsolateral canaliculus of the medulla oblongata. Descending sympathoactivating pathways are also localized in this region. According to Coote and McLeod, there are both noradrenergic and serotonergic sympathoinhibitory pathways. The authors note the existence of three descending inhibitory systems: the noradrenergic sympathoinhibitory system of ventrolateral medulla oblongata neurons with axons in the dorsolateral canaliculus of the spinal cord, the serotonergic system of suture nuclei neurons with axons in the dorso- and ventrolateral canaliculi of the spinal cord, and the reticulo-spinal system of the ventromedial reticular formation of the medulla oblongata. When the ventromedial reticular formation, i.e., the classic depressor area of the medulla oblongata, is irritated, inhibition of the SPN occurs with a latency period of 5-30 ms, whereas the latency period of baroreflex inhibition of the sympathetic discharge of the spinal cord when the sinus nerve is irritated is 150-300 ms. Therefore, it is unlikely that the system of ventromedial reticular formation neurons with fast-conducting axons participates in the baroreflex inhibition of SPN. When dorso- and ventrolateral tubules are irritated in the area C3 -C4 of the spinal cord and sympathetic discharge is registered at the level of thoracic segments (distance of about 130 mm), inhibition of somatosympathetic discharge occurs with a latency period of 130 ms. Taking into account the localization of monoaminergic neurons of the medulla oblongata, whose axons form these bulbospinal inhibitory pathways, we can think that baroreflex inhibition is transmitted through descending channels from the ventrolateral reticular formation of the medulla oblongata and the caudal nucleus of the suture, which are characterized by a slow rate of conduction of inhibitory bulbospinal impulsion[2,3]. The

question of the level at which baroreflex inhibition of spinal cord SPN occurs is of interest. There is data on both the bulbar and spinal level of realization of baroreflex inhibition of SPN. The authors who adhere to the viewpoint about the bulbar level of closing the reflex arc of late somatosympathetic reflex responses, taking into account the barosensitivity of these responses and the absence of a pronounced barosensitivity of the early spinal response, believe that baroreceptor inhibition of sympathetic activity occurs at the bulbar level. However, a number of data contradicts the idea of the bulbar level of realization of baroreflex inhibition of SPN activity and testifies to the existence of spinal mechanisms of baroreceptor inhibition of sympathetic discharge. Thus, it was found that irritation of descending pathways at the level of lateral canaliculi of the spinal cord causes the same inhibition of sympathetic activity as baroreflex inhibition. It is shown that not only early but also partially late barosensitive components of somatosympathetic discharge are formed mainly at the level of the spinal cord. The data on some barosensitivity of the early, purely spinal component of somatosympathetic discharge are indicative of the spinal, not only bulbar, level of realization of baroreflex inhibition. Recently, convincing data have been obtained showing that baroreflex sympathoinhibitory influences are probably realized on the interneuronal apparatus of the spinal cord [4-6]. Multichannel transmission of suprasegmental influences on SPN is provided not only by the reticulospinal system of the medulla oblongata, but also by a number of other descending projection pathways (pontomesencephalic, hypothalamic, corticospinal), which are also important components of the mechanisms of central control of autonomic functions that maintain homeostasis of various physiological constants of the organism. The data on convergence of extero- and interoceptive afferent inflow and supraspinal modulating influences on SPN indicate some integration of supraspinal cardiovascular reflexes at the spinal level. This view differs from the classical concept of the organization of central mechanisms of regulation of cardiovascular functions, according to which afferent and suprabulbar activity is integrated in the medulla oblongata and transmitted to the spinal cord through common excitatory and inhibitory pathways [7,8]. The question of possible realization by the spinal cord of the reflex control of autonomic functions has long been disputed by many authors. However, to date, a number of convincing data on the contribution of spinal cord structures to the formation of the neurogenic component of vascular tone maintenance, to the realization of somatosympathetic reflexes and, ultimately, to the vasomotor regulation have been accumulated. Thus, a number of studies have shown the possibility of realization of reflex reactions of the cardiovascular system in spinal animals. In early terms after high atraumatic transection of the spinal cord, performed by ultrasound scalpel, a high level of blood pressure can be maintained and pressor reactions can be induced. All these data were the basis

for the assertion that spinal cord mechanisms can maintain arterial pressure at values peculiar to an animal with an intact central nervous system. A number of electrophysiological studies have shown the existence of tonically active sympathetic elements in the spinal cord even after chordotomy [9].

Stem Mechanisms of Homeostasis Autonomic Functions Cardiovascular Regulation

The brainstem reticular formation is involved in the regulation of cardiac activity, blood pressure and vascular tone, respiration, motor activity and other vital functions of the organism. Data on the role of the brainstem in providing homeostatic processes aimed at maintaining constant parameters of the cardiovascular system function were obtained in the last century. Ovsyannikov and Dittmar, studying changes in arterial pressure under irritation of peripheral nerves in conditions of brain stem transection at different levels, revealed the localization of the "vasomotor" center in the medulla oblongata. Subsequently, by means of methods of local destruction and electrical stimulation of various parts of the brainstem, numerous data confirming the concept of localization of the main vasomotor center in the medulla oblongata were obtained. The notion that the only structure that tonically and reflexively activates the cardiovascular system is the medulla oblongata center, and all other parts of the central nervous system play only an auxiliary conductive role, proved to be untenable. It has been established that the complex multilink system of central control of blood circulation consists of a constellation of "centers" of different order, which are in a certain hierarchical subordination, which is consistent with the general principles of organization of mechanisms of central control of various functional systems of the organism. Each link of the unified system of blood circulation regulation is characterized by its specific regulation circuit. What is the specific role of the bulbar level of the "cardiovascular center" in the regulation of the cardiovascular system? In a number of works it has been shown that cardiovascular responses arising from the excitation of "cardiovascular" neurons of the medulla oblongata are components of integrative reactions of adaptive behavior, in the manifestation of which a number of functional systems are involved. It is shown that the functioning of the bulbar "cardiovascular center" is inseparably connected with the regulation of respiration, and one of the biological values of the bulbar reticular formation is the conjugation of the functions of blood circulation and respiration. When studying the bulbar structures of homeostatic regulation of cardiovascular functions, the question of diffuse or zonal selective organization of the processes of regulation of the tone of various regional vessels deserves special attention. When studying the morphofunctional organization of the mechanisms of central regulation of regional blood circulation, it was found that bulbar vasomotor centers are

built according to the type of zonal representation, which provides selective changes in the tone of vessels of different regions of blood circulation. There is data on zonal regulation of vascular tone irrespective of changes in heart rhythm and cardiac output. When studying the effect of electrical and chemical stimulation of the brainstem on the main hemodynamic parameters (systemic arterial pressure, cardiac output, heart work, total peripheral vascular resistance, tissue blood flow), it was revealed that when different medulla oblongata formations are irritated, there is a significant difference in the hemodynamic structure of cardiovascular responses, which indicates heterogeneity and mosaicism of the bulbar level of regulation of the cardiovascular system. Of great interest is the question of whether there are specialized bulbar systems of descending modulation of individual functionally differentiated output neurons of the spinal cord (sympathetic preganglionic neurons, respiratory motoneurons, motoneurons of somatic reflex arcs, and parasympathetic neurons). When studying conduction velocities along descending reticulospinal sympathoactivating fibers of the dorsolateral canal, calculated at rostrocaudal displacement of the stimulus point, as well as the difference of latency periods of responses in T3 and T10 white connective twigs, caused by irritation of the dorsolateral canaliculus at the level C5 of the spinal cord, it is shown that descending fibers activating B2 -sympathetic preganglionic neurons are characterized by conduction velocity from 4 to 8.9 m/s. It was found that in experiments with rostro-caudal movement of the irritation point of the dorsolateral canaliculus the minimum conduction velocities of descending activating influences oriented to respiratory, somatic and parasympathetic motoneurons, calculated by the shift of the posterior front of electrical responses of diaphragmatic, T3 -segmental and pelvic nerves, are equal to 17.0, 10.1 and 15.9 m/s, respectively. Based on these data, the authors concluded that specialization of suprasegmental efferent neurons exists. The presence of independent descending channels does not exclude the interaction and integration of different functional systems at the bulbar level. Maintenance of blood pressure homeostasis is carried out by the interaction of two antagonistic mechanisms: in case of blood pressure increase the depressor influence increases and, on the contrary, in case of blood pressure decrease the central pressor mechanisms are activated. To study the localization of depressor and pressor areas of the brain, the stereotactic technique of detailed scanning of deep brain structures with an irritating electrode has been used in numerous studies. The obtained data indicate a complex heterogeneous character of morphofunctional organization of vasomotor structures of the brainstem [10]. Homeostatic mechanisms of maintaining a constant level of blood pressure are associated with the activity of baro- and chemoreceptors. Information about parameters vital for the whole organism (gas composition and pH of the blood, pumping function

of the heart, blood pressure level) is received by the central nervous system via afferent fibers of the vagus and uvula nerves. Specific cardiovascular afferentation from reflexogenic zones of the heart and vessels by negative feedback mechanism regulates the optimal level of activity of the spinal cord SPN. It is known that each pulse push is accompanied by powerful activation of baroreceptors and a volley of excitation of afferents of aortic depressor and carotid nerves is transmitted to neurons in the area of the nucleus of the solitary tract. According to some authors, baro- and chemoreceptor afferents monosynaptically excite also neurons of the depressor area of the paramedian reticular nucleus. When the sinus nerve is irritated, polysynaptic activation of neurons of the gigantocellular, small cell nuclei, central nucleus of the medulla oblongata, nuclei of the pontine suture, and medulla oblongata occurs. Intracellular recording indicates monosynaptic activation of these neurons. In the studies of Biscoe and Sampson it is shown that during electrical stimulation of nerves containing baro- and chemoreceptor afferents, evoked potentials and evoked discharges of individual neurons are registered in the gigantocellular, small cell, and lateral reticular nuclei. The data of some other authors concerning the sinus nerve projection testify to baroafferent monosynaptic activation of only neurons of the nucleus of the solitary tract. Only when this nucleus is irritated, antidromic potentials in the sinus nerve are registered. This probably explains the fact that, with the exception of the narrowly defined area of the solitary complex, an insignificant number of neurons discharging in the heart rhythm was detected in the other brainstem regions. Obviously, baroreflex inhibition of sympathetic nerve activity, synchronous with pulse fluctuations of arterial pressure, is realized mainly at the spinal level. This is also evidenced by Lebedev's data on the absence of inhibition of background evoked activity of antidromoid-identified reticulo-spinal sympathoactivating neurons of the medulla oblongata on irritation of the aortic and sinus nerves [10,11].

The complex of the bulbar vasomotor center includes a system of vasoconstrictor, sympathoactivating neurons localized in the pressor "points" of the medulla oblongata. Some of these neurons are output reticulospinal neurons, the axons of which form descending sympathoactivating pathways of the dorsolateral canaliculus of the spinal cord.

The depressor mechanisms of the bulbar vasomotor center are associated with the activity of two types of inhibitory systems. The source of one of them is the central structures of baroreflex inhibition of sympathetic activity, depressor zone "A", according to Scherrer. These structures, according to Coote and McLeod, include noradrenergic and serotonergic elements of the ventrolateral reticular formation of the medulla oblongata and the suture nuclei area. Neural elements of the second inhibitory system are localized in the classical depressor zone of the ventromedial reticular formation of the medulla oblongata. It is the bulbar link

of the inhibitory pathway that starts from the sympathoinhibitory zone of the anterior hypothalamus. Depressor effects during irritation of various structures of the medulla oblongata may result from the interaction of both different types of inhibitory neurons with pressor neurons at the bulbar level and inhibitory descending influences on cardiovascular sympathetic preganglionic neurons at the spinal level. Only the first steps are being made in the study of neural mechanisms of interactions between activating and inhibitory brainstem systems involved in the formation of both tonic and phasic influences of the medulla oblongata on sympathetic neurons of the spinal cord. Cardioinhibitory neurons of the vagus nuclei system play an important role in the bulbar regulation of the cardiovascular system. The system of vagus motor nuclei forms the basis of the central apparatus of cardiac regulation. Reflex regulation during excitation of cardiovascular afferents is realized both by changes in the activity of sympathetic neurons of the spinal cord and through cardioinhibitory neurons of the medulla oblongata. In a number of morphophysiological studies it has been shown that in cats the source of cardioinhibitory influences are neurons of the reciprocal nucleus of the vagus rather than the dorsal nucleus. Using the criterion of antidromic identification taking into account latent periods of antidromic discharges corresponding to conduction velocity along thin myelinated Bx -fibers of cardiac branches of vagus (conduction velocity 8.0-14.5 m/s), it is shown that in pigeons cardioinhibitory influences are transmitted along axons of dorsal motor nucleus of vagus nerve. Data on the localization of cardioinhibitory neurons in the dorsal nucleus were also obtained in rabbits. Udelnov's studies have shown that efferent neurons of the "cardiac parasympathetic center" localized both in the region of the dorsal and vagus nucleus play an important role in the adaptive regulation of heart activity in accordance with the general needs of the organism and with the state of intracardiac hemodynamics. The authors have established that in the implementation of adaptive self-regulation of the heart, the "cardiac parasympathetic center" of the medulla oblongata has the ability to exert multidirectional effects on cardiac activity, which can both enhance and inhibit cardiac function. Based on experimental data not only on inhibitory but also active accelerating influences of parasympathetic innervation on the heart, the authors believe that the central nervous system uses quantitative variations of nerve influences in the organization of reflex influences of the parasympathetic nervous system on the heart [11, 12]. A number of studies point to the participation of midbrain formations in vasomotor reactions. Irritation of the midbrain reticular formation area most often causes a pressor reaction, heart rate increase and strengthening of myocardial contractile force. Tetanic irritation of the mesencephalic reticular formation along with a pronounced pressor reaction causes a generalized increase in tonic activity of the lower cardiac, vertebral and renal postganglionic sympathetic nerves. Obviously, the

structures of the mesencephalic reticular formation itself form a massive activation of homeostatic mechanisms and provide generalized excitation of the sympathetic nervous system. Morphological studies have shown that hypothalamic pressor pathways pass in the area of the medial longitudinal fascicle, central gray matter as part of the longitudinal fascicle of Schütz and in the area of the reticular formation of the midbrain, giving collaterals to its own neurons of the reticular formation. The descending pathway of the sympathetic cholinergic muscle vasodilation system also passes through the midbrain region. When studying the role of the midbrain in the realization of somato-sympathetic reflexes, its depressing influence on the structures of the pontobulbar region of the brainstem was shown, tonically inhibiting reflex discharges of vasoconstrictor neurons caused by impulses of A- and C-afferents. These data elucidating the mechanisms of reversion of pressor reflexes to depressor reflexes during decerebration and anesthesia testify to the important role of tonic influences of suprabulbar brainstem sections for normal activity of bulbospinal mechanisms of blood circulation regulation.

Regulation of Respiration

Adequate supply of tissues with oxygen and removal of carbon dioxide from the body are realized by coordinated activity of stem mechanisms of blood circulation and respiration regulation. In case of various metabolic disorders and environmental changes, there are significant shifts in the intensity of tissue respiration, which are provided by corresponding changes in lung ventilation, cardiac output and regional blood flow. In this complex of adaptive reactions, the main importance of external respiration is to maintain an optimal, almost constant level of blood gas composition, partial pressure of oxygen (Rao) and carbon dioxide (Rao) in arterial blood. For more than a hundred years, the regulation of respiration, aimed at ensuring homeostasis of blood gas composition, is associated with the region of the rhomboid brain, where the so-called "bulbar respiratory center" is located. The topography of the respiratory center was established by Mislavsky as early as 1885. The use of stereotactic method of local electrical stimulation with immersed needle electrodes allowed to limit the zone of the respiratory center more precisely. According to Pitts et al. data, the zone, irritation of which causes inspiratory reactions, is located in the ventromedial and caudal parts of the bulbar reticular formation in the area of the gigantocellular, ventral and partly lateral reticular nuclei, while the expiratory zone is located in the dorsal and rostral parts of the gigantocellular reticular nucleus. Micro-electrophysiological studies of the localization and properties of respiratory neurons identified by discharge synchronous with respiratory phases contributed to further deepening of our understanding of the neural organization of the respiratory center [13]. A major role in the activity of the respiratory center is played by afferent impulses from mechanoreceptors of the lungs, which



are transmitted to the bulbar respiratory center via afferent fibers of the vagus nerve. Three types of mechanoreceptors have been described both in the lungs and in large parts of the extrapulmonary bronchi and trachea: slowly adapting stretch receptors, rapidly adapting stretch receptors, and spasm receptors. When they are excited, there are respectively three types of reflex reactions of the respiratory center: inhibition of inspiratory activity when lung volume increases and increase in respiratory rate and force of contraction of inspiratory muscles when lung volume decreases. During natural breathing, the receptors of the vagus nerve are irritated only when the lungs are distended. Inspiratory inhibition during lung volume expansion was first described by Gehring and Breuer, who found that increasing lung volume inhibited contraction of the inspiratory muscles. After transection of the vagus nerves, as a result of the elimination of vagal inhibition of inspiration, breathing becomes slowed and deep. The inhibitory reflex of Gehring-Breyer is one of the main mechanisms of reflex self-regulation of breathing. With each breath impulses of vagus afferents excite expiratory neurons of the respiratory center, which entails the emergence of exhalation. Lung mechanoreceptors with afferent fibers of the vagus nerve represent the main feedback of the respiratory periphery to the respiratory center, and afferentation of this system maintains the periodic activity of the respiratory center. After destruction of the pneumotaxis of the weighty mechanism of the variolian bridge vagotomy leads to respiratory arrest on inspiration or severe lengthening of breaths (apneic breathing) [14]. In addition to mechanoreceptors of the lungs, proprioceptors of the diaphragm, intercostal muscles and abdominal wall muscles participate in the regulation of respiration. Detailed information on the importance of reflexes from receptors of the lungs, respiratory muscles and upper respiratory tract in the regulation of respiration is given in the reviews by Glebowski and Felberbaum. In addition to mechanoreceptors of the lungs, airways and proprioceptors of respiratory muscles, respiratory reflexes from peripheral and central chemoreceptors play an important role in the regulation of breathing. The main function of respiratory chemoreceptors is to ensure a constant gas composition and acid-base balance of the internal environment of the body. At any deviations of blood gas composition chemoreceptor reflexes due to changes in alveolar ventilation provide elimination of these deviations. Increase of P_{aO_2} and decrease of P_{aO_2} , exciting chemoreceptors, cause a reflex increase in the minute volume of respiration, leading to a decrease in possible deviations in the blood gas composition. The mechanism of blood gas composition homeostasis maintenance in this case is realized by the principle of regulation by deviation by means of feedback. Deviation of regulated parameters (P_{aO_2} and P_{aCO_2}), acting reflexively on the respiratory center, and changes in external respiration contributes to the restoration of the optimal level of P_{aO_2} and P_{aCO_2} , at any level of tissue metabolism. The data of numerous experiments show that

along with regulation by deviation, the mechanism of regulation by perturbation is widely used in the respiration control system. The importance of the principle of regulation by perturbation for maintaining homeostasis of blood gas composition is clearly revealed in the study of respiration under conditions of muscular activity in the transient mode. In this case, at the beginning of muscular work, the work of respiratory muscles is intensified and the minute volume of respiration is increased due to proprioceptive signals about the perturbation before the appearance of deviation in P_{aO_2} , P_{aCO_2} , and pH. The change in external respiration at the very beginning of motor activity prevents the occurrence of a deviation in arterial blood gas composition. Considering the mechanisms of homeostasis regulation in this case, Marshak notes that this is a typical example of regulation not by deviation, but by perturbation. Receptors perceiving the gas composition of arterial blood are located in two areas: in the region of the aortic arch and in the carotid sinus. Afferent fibers of these receptors of the aortic and sinus nerves, respectively, enter the nucleus of the solitary tract, and from here chemoreceptor impulses are transmitted to respiratory neurons. Not only arterial chemoreceptors, the respiratory center itself, but also specialized chemosensitive areas of the brainstem are sensitive to changes in P_{aO_2} and pH. Discussing the role of various chemoreceptors in the system of respiratory regulation, Breslav believes that central chemosensitive zones located on the ventrolateral surface of the medulla oblongata act as sensitive sensors signaling the concentration of hydrogen ions and CO_2 tension in the cerebrospinal fluid. The author believes that aortic chemoreceptors located at the "gate" of the entire arterial system and sinocarotid chemoreceptors located at the "gate" of the cerebral vascular system serve as sensors responding to changes in CO_2 tension and blood pH. Integration and interaction of chemo- and mechanoreceptor impulses in neurons of the respiratory center contribute to the formation of rhythmic activity of respiratory neurons [15]. Impulsation from baroreceptor afferents also plays a role in the regulation of respiratory neuron activity. According to Richter and Seller, baroreceptor afferentation causes hyperpolarization of the membrane of inspiratory neurons either as a result of their direct inhibition or as a result of dysfasciculation due to baroreceptor inhibition of nonrespiratory neurons of the activating reticular formation causing tonic activation of respiratory neurons. Baroreflex depolarization of the membrane of expiratory neurons, occurring only during the period of spontaneous membrane hyperpolarization, may be the result of disinhibition during baroreflex hyperpolarization of inspiratory neurons. The bulbar respiratory center is always under the influence of impulsation coming to it from the higher parts of the brainstem. According to Monnier, the rhythmic activity of inspiratory neurons is formed under the influence of three inhibitory systems: the pneumotactic center of the Variolius Bridge, the expiratory center of the dorsolateral reticular formation

of the medulla oblongata, and the inhibitory component of the reflex system of the vagus nerve. Destruction of the anterior pontine region, especially after bilateral vagotomy, leads to inspiratory apnea, apneic breathing. Inspiratory apnea after transection of the varicose bridge anterior to the apneic center is eliminated by rhythmic irritation of the vagus nerve or inflating the lungs, i.e., prolonged discharge of mechanoreceptors of lung stretching. Neurons of the expiratory center, activated by the pneumotactic center or afferent vagus impulses, exert an inhibitory influence on the inspiratory neurons. Excitation of vagus afferents suppresses the inspiratory effect of the apneic center of the varicose bridge and the inspiratory center of the medulla oblongata. The activity of the pontobulbar structures of the respiratory center is influenced by the midbrain reticular formation. According to Hori's data, irritation of the medial region of the mesencephalic reticular formation results in nonreciprocal facilitation of the activity of inspiratory and expiratory neurons, while irritation of the lateral region results in nonreciprocal inhibition of their activity [16].

The brainstem reticular formation is also involved in the regulation of other autonomic functions. There are numerous data on the role of the brainstem reticular formation in the regulation of motor and secretory activity of the digestive and excretory organs, and in the realization of neuroendocrine functions. The brainstem reticular formation participates in the regulation and maintenance of homeostasis in the organism as a system integrating autonomic-endocrine-somatic functions, and the integrative activity of the brainstem reticular formation is carried out in interaction with the integrative mechanisms of the hypothalamus.

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