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REVIEWS

The Role of the Insular Cortex in the Control of Visceral Functions

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Abstract—The purpose of this review is to discuss the experimental evidence of the participation of the insular cortex in the regulation of visceral functions: respiratory, cardiovascular, and gastrointestinal ones. The data on the structure and connections of the insular cortex and the results of neurophysiological experiments and clinical observations are presented. We consider experimental evidence of viscerotopic organization of both sensory and motor projections of visceral systems in the insular cortex, which is why it is defined as the sensorimotor cortex. We present evidence that one of the mechanisms of the insular cortex effect on the regulation of the activity of internal organs is the modulation of reflex reactions at the bulbar level.

Keywords: insular cortex, visceral systems, respiration, Hering–Breuer reflexes, reflex relaxation of the stomach, antrofundal reflex, cardiovascular system

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The role of the cerebral cortex in regulation of functions of internal organs remains one of the central issues of the neurophysiology and physiology of visceral systems over the years. Pavlov, Bekhterev, Orbeli, Bykov, Chernigovskii, and many other outstanding Russian physiologists gave their answers to this question based on known experimental facts. Researchers have been interested in the problem of cortico-visceral interactions for many years [1–4]. As a result, the range of cortical areas directly involved in the regulation of the functions of internal organs is now determined. Their cellular structure and connections in the central nervous system have been described. Some studies are focused on patterns of interactions between these structures. It has become clear that areas of visceral or autonomic cortex function in the so-called autonomic neural network, which, in addition, includes various structures of the cerebral hemispheres and brain stem [5].

The cortical area should meet several specific criteria to be defined as a part of the system regulating autonomic functions [6]. First, adequate (electrical or chemical) stimulation, destruction, or removal of a certain area has to induce changes in the corresponding function. Impairments in the visceral functions have to be observed in patients with damage in the studied cortical area. Second, the electrical activity of the studied area should change in response to the stimulation of visceral afferents. Third, this part of the cortex should be connected to other structures of the central nervous system, which participate in the control of autonomic functions. Finally, activation of these cortical areas should be observed in awake subjects performing functional tests that increase the activity of visceral systems. At least three cortical areas meet these criteria. They include the sensorimotor cortex, medial prefrontal cortex, and insular cortex.

The aim of this review is to discuss experimental evidence of participation of the insular cortex in the control of visceral functions, in particular, the respiratory system. The data on its structure and connections, the results of neurophysiological experiments, and clinical observations are presented. On the basis of the literature and our own experimental data, we suggest a hypothesis of the structural and functional organization of visceral representation in the insular cortex and its role in the regulation of autonomic functions.

Anatomy and Cytoarchitecture of the Insular Cortex

The insular cortex in humans and primates has received its name from the specific anatomical structure where it is mainly located. The insula of the human cerebral cortex was first described in 1809 by the German anatomist and physiologist Reilly. In humans and other primates, it is indeed an island of cortex dipped in the lateral sulcus (sulcus lateralis Sylvii) at the bottom of the lateral cerebral fossa (fossa lateralis cerebri). It is covered with folds of the adjacent frontal, parietal, and temporal cortex and outlined by the deep circular sulcus (sulcus circularis insulae). At the bottom surface of the circular sulcus of insula is gradually disappearing, being replaced by the limen of insula (limen insulae). The deep central sulcus of insula (sulcus centralis insulae) divides the surface of the insula on the anterior and posterior parts. In other mammals, the cortex homologous to the insula does not form a particular anatomical structure, but is also located on the lateral surface of the hemi-

sphere. A characteristic feature of the insula is an adjacent structure, the claustrum, which is attached to it along its whole length. Therefore, insular cortex of all animal species is often defined as claustrocortex.

The insular cortex is characterized by heterogeneity of its cellular structure. The insular area includes granular, agranular, and dysgranular fields. Granular cortical areas are characterized by extensive five- or six-layered structure. Layers II and IV contain granule cells and are called the external and internal granular layers. The agranular cortex is characterized by the absence of granule cells and relatively simple organization of two or three layers. A typical cytoarchitectonic feature of the agranular areas is a high density of pyramidal neurons in layer V along with the lack of the internal granular layer. The dysgranular cortex is an intermediate type between the agranular and granular cortex. It can contain five or six layers, but with a small amount of granule neurons in layers II and IV. In some dysgranular fields, layer IV may contain clusters of granules without the clear laminar organization, whereas layer II generally lacks the granule cells. In other parts, layer IV can be relatively well-developed, but layer II remains rudimentary. In the insular region, the agranular fields are usually localized anteroventrally, and granular fields, posterodorsally [7–9].

Thus, the insular region is included in the mesocortex, i.e., the transition area between the three-layered allocortex and the developed six-layered neocortex. Many of these areas are called the paralimbic structures [7]. It is assumed that they take part in regulation of the activity of visceral systems. However, the heterogeneity of the laminar structure typical of the insular cortex and the presence of different cytoarchitectonic fields suggest that the function of different parts of the insular areas may significantly differ from each other. Apparently, some fields in the insular area are not directly related to the central control of autonomic functions.

Visceral Sensory Representation in the Insular Cortex

In 1938, Bailey and Bremer found that visceral sensory input into the central nervous system reaches the insular cortex. Stimulation of the central segment of the cut vagus nerve was shown to increase the frequency and amplitude of the EEG recorded from the orbito-insular region. More recent experiments with mapping of the evoked potentials in response to the stimulation of various cranial nerves clearly showed that the areas of representation of these nerves in the insular cortex are well-organized. The projection of the facial nerve has the most rostral location; then glossopharyngeal nerve; and, finally, the vagus nerve projection area is the most caudal. The experiments showed that the projection of the gustatory system is located in the rostral part of the insular region. The responses to the adequate stimulation of the tongue and electrical stimulation the gustatory nerves were recorded in the anterior insula [10, 11].

Recordings of single neuron activity in the insular cortex revealed that neurons responding to the gustatory stimuli were located in the rostral dysgranular insular cortex [10, 11]. The neurons that respond to interoceptors stimulation have more posterodorsal location in the granular insular region [11]. The cells responding to the stimulation of the stomach mechanoreceptors are located directly above and behind the gustatory area. Neural connections responsible for the conduction of afferent impulses from baroreceptors, chemoreceptors, and pulmonary stretch receptors to the insula have been identified [11–13]. Neurons responding to stimulation of cardiovascular baroreceptors were found in the posterior part of the studied insular cortex. The cells responsible for stimulation of arterial chemoreceptors, which are known to be directly related to the regulation of respiratory function, had an intermediate position. Most neurons in the insular cortex responding to interoceptive stimuli were monomodal, although in some cases there was a convergence of cardiovascular and respiratory inputs on a single neuron [11]. Later studies showed that respiratory discomfort and perception of dyspnea were also associated with the insular cortex. Enhanced activation of the insular cortex appeared during dyspnea [14–16], and, conversely, insular cortex damage reduced the feeling of dyspnea [17].

Thus, the so-called general visceral according to the cited authors, and in fact, visceral sensory area located within the insular cortex contains visceral representations of three systems: gastrointestinal, cardiovascular, and respiratory systems. It has viscerotopic organization. Interestingly, this visceral sensory area is located in close proximity to the somatic sensory area. In fact, the gustatory insular region is localized under the area receiving sensory input from the tongue, and the projections from the cardiovascular system are located along the border of the representation of the chest in the second somatosensory cortical area.

The results of morphological studies confirm the results of electrophysiological experiments. They suggest that information from interoceptors can reach the insular cortex via oligosynaptic pathways after a few switches in the autonomous centers of the brainstem: the nucleus of the solitary tract, parabrachial nuclei, and the hypothalamus [11, 18, 19].

On the basis of the results of neurophysiological and neuromorphological studies, the insular cortex is usually considered a visceral sensory area. According to other views, the insular cortex, along with some other areas of the cortex, is a part of the orbital network of the prefrontal cortex [20]. This network is assumed to provide the synthesis of sensory afferents of different modality, including visual, gustatory, olfactory, and visceral sensory, during implementation of feeding behavior. However, this does not exclude direct involvement of the insular cortex in the control

of visceral functions. In our opinion and according to some other authors [6, 21], the insular cortex is rather the sensorimotor visceral cortex than the sensory cortex, because it has both visceral afferent and efferent connections. This hypothesis is supported by the experiments showing that the stimulation of different parts of the insular cortex induces responses from different visceral systems.

Visceral Motor Effects of the Insular Cortex Stimulation

As mentioned above, one of the criteria which must be met by the cortex involved in the regulation of autonomic functions is the response of the visceral systems to its electrical stimulation. The electrical stimulation of the anteroventral insula causes changes in the motor activity of the gastrointestinal tract, the blood pressure, and heart rate in patients [22, 23]. Interestingly, these responses can be different depending on the stimulation of the left or right hemispheres. Thus, stimulation of the left insular cortex causes bradycardia and the depressor effects, while the stimulation of the right insular cortex mainly induced tachycardia and pressor responses [23]. These results suggest the involvement of the insular cortex in the control of visceral functions in humans; they are consistent with the data obtained in the experiments with electrical stimulation of the insular cortex in animals. In these studies, the electrical stimulation of the insular cortex was reported to induce respiratory arrest (apnea), changes in the respiratory rate, blood pressure, heart rate, the motor activity of the stomach, intestinal motility, salivation, and other parameters [22–29]. Chemical stimulation of neurons of the insular cortex also evokes responses from the visceral systems. For example, injection of L-glutamate in the insular cortex affects the respiratory function, producing apnea [30].

Summarizing these results, the experiments with electrical stimulation of the anterior insular cortex provide evidence of the existence of the effector representation of at least three visceral systems within this area: cardiovascular, respiratory, and gastrointestinal.

For a long time, there have been no experimental data that could answer the question about the spatial organization of the effector representation of certain visceral systems in the insular cortex. The method of repeated electrostimulation of the insular cortex via microelectrodes helped to conduct its mapping. These studies provided more accurate description of representations of the cardiovascular, respiratory, and gastrointestinal systems in the insular cortex [21, 28, 31–33]. Two types of responses to the local stimulation of the insular cortex have been found: an increase in blood pressure accompanied by tachycardia, or bradycardia and a decrease in the blood pressure. The pressor response has been induced by the stimulation of the rostral part of the posterior insular cortex; depressor response, by the stimulation of the caudal part.

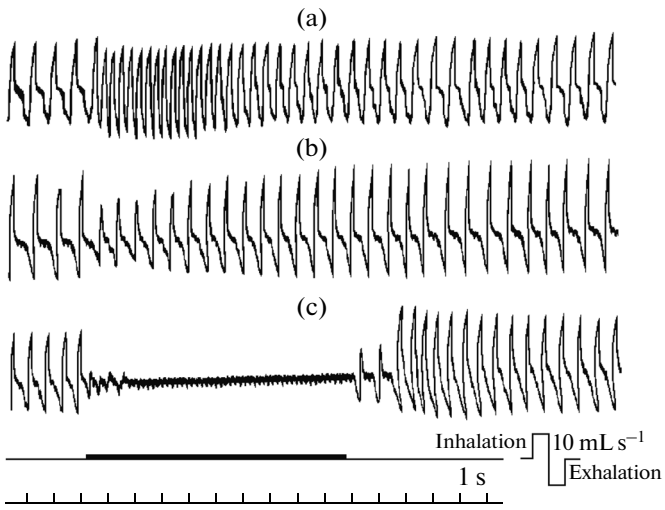

Fig. 1. The responses of the respiratory system to electrical stimulation of the insular cortex. The curves of the respiratory volume flow rate (pneumotachogram) is shown. (a) Excitatory response, (b) inhibitory response, (c) respiratory arrest. Lines below records mark the time of stimulation (1 s); calibration of the respiratory flow rate.

Regions, which stimulation resulted in the pressor and depressor responses were located in the agranular and dysgranular insular cortex. Gastrointestinal responses have been also registered after stimulation of the rostral insular area. Microinjections of an anterograde neuronal marker in the pressor and depressor regions revealed significant differences in the organization of their efferent projections [31]. In our experiments carried out on anesthetized spontaneously breathing rats, the cardiovascular system responded to a local microstimulation of the insular cortex mainly by a short-term increase in systemic blood pressure. Gastrointestinal responses appeared as diverted changes in the tone of the stomach and duodenum. The respiratory system responded by the changes in the volume–time parameters of breathing. Two adjacent zones were discovered in the insular cortex, which induced completely different responses of the respiratory system, inhibition and activation (Fig. 1) [28, 34]. Stimulation of the posterior visceral insular cortex caudal to the anterior commissure induced excitatory responses. They appeared as an increase in the inspiratory flow rate and respiratory rate. The total inspiratory effort and the tidal volume decreased; i.e., breathing became more frequent and less deep. Moving the stimulating electrode towards the rostral part caused a decrease in the inspiratory and expiratory flows, the total inspiratory effort, and respiratory volume. We considered these changes to be an inhibitory response. A typical feature of this response is the maximum response of the respiratory system takes place in the first cycle after initiation of respiratory stimulation. After that the respiratory system is gradually stops responding to the stimulus. A three- to fourfold increase in the current

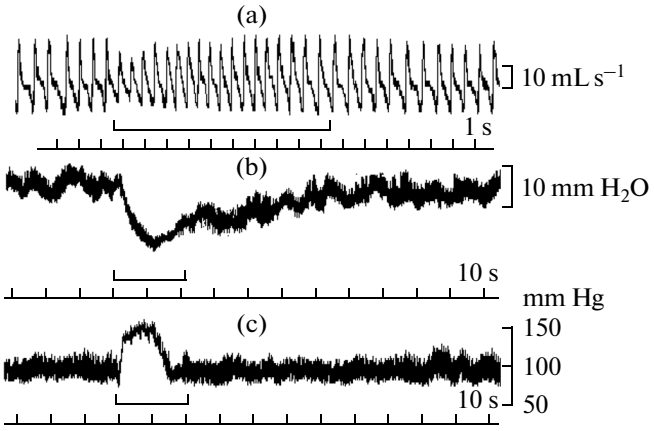

Fig. 2. Responses of the respiratory, gastrointestinal and cardiovascular systems: (a) pneumotachogram, (b) the pressure in the stomach, (c) blood pressure. Solid lines under the records mark stimulations; time is shown below.

strength compared to the threshold value leads to respiratory arrest. We should note that both the values of respiratory responses and their type depend only on the location of the electrode, but not on the phase of the respiratory cycle in which a stimulus was applied.

Systematic mapping of the insular cortex, which was held simultaneously with the recording of motor activity of the stomach, pneumotachogram, and systemic blood pressure, showed that the active spots are located in the insular region in organized manner. It has been found that the type and nature of the responses recorded during stimulation of the insular cortex depend on the location of the stimulating electrode. Gastrointestinal and inhibitory respiratory responses are recorded during stimulation of the most rostral insular area. When an electrode is moved caudal to the anterior commissure cardiovascular responses start to appear as a short-term rise of blood pressure along with inhibitory respiratory responses and responses of the gastrointestinal tract (Fig. 2). In the posterior part of the insular region, gastrointestinal responses disappear, and inhibitory respiratory responses are replaced with excitatory respiratory responses. In some cases, the stimulation of the posterior insular cortex induced cardiovascular depressor responses instead of pressor responses. The majority (94%) of the points where inhibitory respiratory responses were recorded are rostral to the anterior commissure (–0.3 mm from the bregma). These areas also included 80% of the stimulation points inducing changes in the motor activity of the stomach, and 65% of the points causing an increase in blood pressure. During stimulation of more caudal parts of the dysgranular, agranular, and insular cortices, 86% of all excitatory respiratory responses and 35% of cardiovascular responses were recorded.

The results have made it possible to draw a diagram showing the distribution of the areas and zones of effector representations of different visceral systems in the insular cortex of the rat [21]. According to this diagram, the effector representation of the gastrointestinal system is located in the middle of the insular cortex rostral to the anterior commissure. Representation of the cardiovascular system is located rostral and caudal to that level and occupies the part of the middle and posterior insular cortex. The representation of the respiratory system overlaps with the region representing the gastrointestinal and cardiovascular systems and consists of two areas: excitatory and inhibitory. The inhibitory zone is located in the middle insular cortex; the excitatory ome, in the posterior insular cortex. They overlap with the areas of the gastrointestinal and cardiovascular systems, respectively.

The results of mapping of efferent representation of visceral systems in the insular cortex lead to the conclusion that the representation of visceral motor systems in the insular cortex, as well as their sensory representation, has viscerotopic organization. Effector and sensory representations of different visceral systems are located in adjacent parts of the insular cortex and partially overlap occupying only part of the insular cortex. This area can be regarded as a specialized area, the visceral field of the insular cortex [21].

Participation of the Insular Cortex in the Reflex Regulation of Visceral Functions

The presence of direct and indirect projections from the visceral field of the insular cortex to the autonomous centers in the medulla oblongata suggests that the insular cortex is involved in the regulation of autonomic functions by modulating bulbar reflexes [31, 32, 35]. To test this hypothesis, we conducted experiments modeling regulation of some reflex mechanisms by stimuli from the insular cortex. We investigated the effects of the local electrical stimulation of the insular cortex on the reflex responses in rats playing an important role in the regulation of breathing pattern and motor activity of the gastrointestinal tract.

Hering–Breuer reflexes, inspiratory inhibitory and expiratory excitatory ones, are known to play an important role in the regulation of breathing. They carry out the vagal volume-dependent regulation of the duration of respiratory phases. During inspiration, increasing lung volume amplifies afferent impulses from slowly adapting pulmonary stretch receptors (SARs) via the fibers of the vagus nerve to the respiratory center. The inspiratory inhibitory reflex appears as inhibition of inspiratory neurons of the respiratory center and interruption of the inhalation. Simultaneously with inhibition of inspiratory neurons, activation of expiratory neurons takes place prolonging the exhalation and facilitates the expiratory excitatory reflex. Occlusion of the airway in the different phases of the respiratory cycle helps to test the activity of Hering–Breuer reflexes. The expiratory occlusion attenuates the inhibitory afferent

input from SARs and causes an increase in the duration of inhalation and the strength of inspiratory muscle contractions. The strength of inspiratory-inhibitory reflex is estimated by the degree of these changes. To test the expiratory-facilitating Hering–Breuer reflex, airway occlusion is applied at the maximum of inspiration, i.e., at the maximal stimulation of SARs causing elongation of subsequent exhalation. The vagal apnea is recorded in this case; its duration is used to evaluate the strength of the expiratory excitatory reflex. The experimental study of Hering–Breuer reflexes showed that stimulation of the anterior visceral field of the insular cortex caused strengthening of the inspiratory inhibitory reflex and attenuation of the expiratory excitatory reflex [36]. These findings are also supported by the increase in the normalized duration of the first breath after the inspiratory occlusion and reducing the length of exhalation after a terminal inspiratory occlusion, made against the backdrop of stimulating insular cortex (Fig. 3).

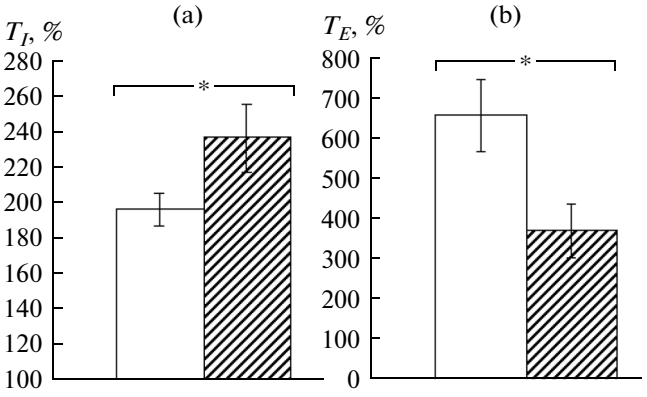

Fig. 3. Effect of stimulation of the insular cortex on the strength of Hering–Breuer reflexes: (a) inspiratory inhibitory reflex; (b) expiratory excitatory reflex. T_I % is the duration of the first breath during expiratory occlusion; data is shown as the percentage of the duration of the last pre-occlusion inhalation. T_E % is the duration of vagal apnea occurring due to the inspiratory occlusion, expressed as the percentage of the duration of the last pre-occlusion exhalation. White columns represent the control values, shaded columns represent the values obtained during electrical stimulation of the insular cortex. * Significant difference ($P < 0.05$).

The modulation of the bulbar reflex by impulses from the insular cortex was also confirmed by experiments with the registration of a reflex relaxation of the stomach. This vago-vagal reflex leads to relaxation of the stomach walls in response to their stretching. In experiments on animal models, it manifested as reduction of intragastric pressure during stimulation of the central segment of the vagus nerve and its subsequent slow recovery. We showed that microstimulation of the "stomach" area of the visceral insular cortical field led to prolongation of the recovery of gastral pressure to the initial level; i.e., it modulated the reflex response [37].

The results of chronic experiments on dogs on the effect of electrical stimulation of the insular cortex on the antro-fundic gastro-gastric reflex also support the putative modulation of reflex reesponses by cortical impulses from the insular region. Antro-fundic inhibitory reflex appears as inhibition of contractions of the fundus caused by stretching of the antrum. Electrical stimulation of the insular cortex in awake animals potentiated the inhibition of contractile activity of the fundus of the stomach in response to adequate stimulation of mechanoreceptors in its antral part [38].

Summarizing the results of these experiments, we may conclude that the insular cortex affects regulation of the activity of internal organs by modulation of reflex responses at the bulbar level. Apparently, this is one of the mechanisms of insular cortical neurons effect on the processes regulating current activity of the visceral systems.

Putative Pathways of Insular Effects on Visceral Functions

When considering the cardiovascular responses to stimulation of the insular cortex, direct experimental data on the pathways involved in the effect of the insular cortex on the function of the cardiovascular system can be discussed. The direct descending projections from the insular cortex to the lateral hypothalamic area, parabrachial nucleus, and the solitary tract nucleus have been found, which, in turn, are projected directly to groups of sympathetic preganglionic neurons [31, 35, 39]. On the other hand, it was found that the pressor responses to stimulation of the insular region are mediated via the sympathetic nervous system, since they were accompanied by an increase in the total activity of the sympathetic nerve trunks [40]. Administration of cobalt chloride, an inhibitor of synaptic transmission in the lateral hypothalamic area, dramatically reduces both the amplitude of pressor response and amplitude of the response to the insular cortex stimulation. The lateral hypothalamic area is involved in some other cardiovascular responses found in different studies [41–43]. Thus, it has been established that the structures of the lateral hypothalamus mediate the influence of the insular cortex on the cardiovascular system. However, how the cortical impulse spreads further? Apparently, the next switch is in the medulla oblongata, since the administration of cobalt chloride to the ventrolateral medulla eliminated renal sympathetic nerve responses to stimulation of the insular cortex and the hypothalamus [35].

It is necessary to mention another very important experimental fact. Polysynaptic pathways of cortical neuron activity in the regulation of sympathetic control of various internal organs have been investigated in experiments with introduction of pseudorabies virus to various sympathetic ganglia [44]. After the introduction of this marker in the stellate ganglion innervating the heart, the largest number of labeled insular cortical neurons were detected at levels close to the anterior commissure (–0.3 mm to bregma). Labeled neurons

were found in the posterior and middle insular cortex. However, their number decreases dramatically rostral to the +0.45 mm level; no labeled neurons have been found in the rostral part of the insular region. Therefore, the location of these neurons correlates well with the location of stimulation points in the insular region causing the pressor response of the cardiovascular system.

In the paper cited above [44], the transsynaptic neuronal marker was administered in the ciliary ganglion in addition to the stellate ganglion. The insular cortical neurons starting the polysynaptic corticosympathetic pathway regulating cortical sympathetic output to the gastrointestinal tract are also present in the insular cortex, but their number is smaller and distributed more evenly than neurons projecting to the stellate ganglion. Their location, in general, corresponds to the representation of the gastrointestinal system according the results of experiments with insular cortex stimulation. Gastrointestinal responses, specifically, a decline in the stomach tone, were often observed in our experiments and could be connected with the activity of the pyramidal neurons that send axons to "stomach" area of the nucleus of the solitary tract. We identified a compact group of these neurons in the middle of the insular cortex [32]. The mechanisms of the effect of the insular cortex on the gastrointestinal function are still not well understood. Our results suggest that one of these mechanisms is realized via direct insula-bulbar projections to the vagal-solitary complex and modulate the vago-vagal reflex responses [36, 37].

The representation of the respiratory system in the insular cortex should be considered to be a part of a wider cortical representation that modulates the activity of the respiratory center. Modification of the activity of the respiratory system by the descending effects of the insular cortex may be due to effects on the pontobulbar rhythm generator or directly on respiratory motor neurons bypassing the medullary respiratory center [45]. The presence of direct projections of the insular area to the nucleus of the solitary tract and, in particular, its projections to its ventrolateral (respiratory) part containing the neurons of the dorsal respiratory group was found [27, 32]. In addition, it is known that the insular cortex forms direct descending projections to the parabrachial nuclei of the pons and the fastigial nucleus which, in turn, is projected to the nucleus of the solitary tract. It is likely that the parabrachial nuclear complex acts as a relay mediating insular effects on other structures of the medulla and spinal cord involved in respiratory control. Thus, we can assume that the respiratory responses are evoked via the projections of the insular cortex and the nuclei to parabrachial vagal solitary complex. Another possibility is indicated by the presence of the projections, apparently polysynaptic, from the medial but not posterior insular region to the rostral part of the ventral respiratory group [12]. Inhibitory respiratory responses observed after stimulation of the medial insular cortex can be ultimately the result of the modulation of the inspiratory neurons located in this part of the ventral respiratory group. We should also bear in mind that the group of respiratory neurons in the dorsomedial and ventrolateral medulla are anatomically and functionally associated with the cardiovagal neurons in the same regions [46]. As we mentioned above, cardiovagal, respiratory, and sympathetic neurons of the vagal solitary complex and ventrolateral medulla have a variety of connections, interact with each other directly or through interneurons, and form the medullary cardiorespiratory network [47]. Apparently, the insular region may affect the operation of the cardiorespiratory network, but the investigation of the mechanisms underlying these effects is at its beginning.

Clinical Data

It is known that psychological factors may affect the visceral, neuroendocrine, and immune functions, aggravating many conditions and even causing their development [48]. The mechanisms of these phenomena are unclear. We assume that, at the cortical level, they are fulfilled by the areas of the cortex that, on the one hand, have no connection with the structures of the limbic system and, on the other hand, contain effector representations of the principal visceral systems. The experimental data discussed above indicate that the insular cortex may be one of such areas. The question arises, to what extent the data of clinical observations correspond, on the one hand, to the results of experimental studies and, on the other hand, to modern views on the role of insular cortex in the formation of integral behavioral acts. Here are some results of clinical observations.

Selective lesions of the orbital-medial prefrontal cortex cause numerous behavioral impairments, including changes in goal seeking, affective disorders, changes in motivation, aggression, short-term memory, and sexual responsiveness in neurological patients [49–51]. Stroke and brain infarction are accompanied by typical impairments in visceral systems if they affect the insula and adjacent prefrontal cortex. Cardiac arrhythmias, which can be the cause of some cases of sudden death of patients with a relatively favorable course of the disease, are the most common disorders [23, 52]. In addition to arrhythmias, strokes affecting the insular region or the temporal lobe can result in unilateral disruption of thermoregulation; and damage of the operculum causes temporary hyperhidrosis of the face and hands on the contralateral side [53].

Numerous data supporting the involvement of the insular cortex in the regulation of visceral functions were obtained when examining patients with epilepsy. It was found that seizure activity, which involved a group of neurons of the amygdalar–hippocampal, cingulate, opercular, frontal, and orbitofrontal cortical areas, can cause a variety of autonomic manifestations, including visceral sensory phenomena, vomiting, genitourinary

symptoms, and sexual arousal [54–56]. Cardiac arrhythmias are very common clinical manifestations of convulsive epileptiform activity [57, 58]. In patients with small seizures, the most common type of arrhythmia is a sinus tachycardia. However, almost all types of arrhythmias were described including atrioventricular block, sinus arrest, ventricular tachycardia, and fibrillation [58]. Arrhythmias can cause the death of many patients with epilepsy but without history of cardiovascular disease [23, 52]. Asystole and syncope rhythm caused by the vagus nerve impulses can accompany the unilateral temporal seizure activity. Simultaneous EEG and ECG recordings allowed differentiating seizure-dependent syncope from cardiogenic [59]. Various changes in the activity of the gastrointestinal tract, including vomiting and urge to defecate, appear during seizure activity involving insular cortical neurons [60, 61].

Functional mapping of the insular cortex in epileptic patients with implanted brain electrodes revealed the presence of four different functional areas of different type and topography, located in the posterior and medial insular cortex: somatosensory representation has been found in the most caudal part of the insula, thermal and nociceptive sensitivity was found during stimulation of the back upper region of the insula; visceral sensory sensations are recorded when stimulating electrodes are placed in front of the somatosensory area; taste—in the central part of the insula [62–64]. Responses were limited by the caudal and central part of the insular cortex, i.e., they were recorded only when dysgranular and granular cortices were stimulated, which emphasizes the connection between topography and heterogeneity of cytoarchitectonics of the insular cortex.

The comparison of clinical data with the results of experiments on the stimulation and destruction of the insular cortex draws attention to two points. First, the convulsive electrical activity in the insular region leads to changes in the activity of visceral systems that correspond to the effects of electrical stimulation. Second, the experimental destruction insular region and destruction during pathological processes leads to similar results.

In recent years, the use of modern neuroimaging (functional magnetic resonance and positron emission tomography) has made it possible to gather evidence of the involvement of the limbic and paralimbic structures including the insular cortex in the regulation of the respiratory and cardiovascular systems in awake humans. Dyspnea and coughing activate the insular cortex [14, 16, 65, 66–68]. Hypercapnia in hypoventilation syndrome, apnea, and hypoxia also alter the activity of the limbic and paralimbic cortices [69–71]. The neural circuits of the paralimbic and limbic cortex have been found to be involved in the cognitive and emotional modulation of spontaneous breathing in awake humans [72]. The functional and anatomical evidence of the participation of the insular cortex in the reflex control of the cardiovascular function have been described [73, 74].

CONCLUSIONS

The results of experimental studies and clinical observations discussed in this review convincingly show that the insular area of the cerebral cortex is involved in regulation of functions of visceral systems. The complex organization of the insular region and the heterogeneity of the cellular structure of its parts indicate its functional heterogeneity. The insular cortex is visceral sensory, integrates information, and has a descending modulating effect on the mechanisms underlying regulation of vegetative functions. The afferent and efferent representations of visceral systems in the insular areas of the cortex form its visceral field, which is a sensorimotor region with viscerotopic organization. The insular cortex affects the regulation of the activity of internal organs through the modulation of reflex reactions at the bulbar level. Apparently, this is one of the mechanisms underlying the effect of insular neurons on the processes regulating the current activity of the visceral systems. The regulation of visceral functions involves many cortical structures other than the insular cortex that are included in the group of paralimbic structures and are considered as a bridge between the limbic system and the neocortical associative fields. Along with the insular cortex, it includes the frontal limbic cortex, temporal cortex, and vast allocortical areas on the orbital surface of hemispheres. All of these areas of the cerebral cortex have similar cellular structures, connections, and, apparently, functions. The study of the specific role of each paralimbic cortical structure in the regulation of autonomic functions, mechanisms of their interactions with other structures forming the central autonomic network is the task of further research.

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