CURRENT PERSPECTIVES

Does vagus nerve constitute a self-organization complexity or a "hidden network"?

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Abstract

The vagus nerve provides wide visceromotor and viscerosensory innervation of internal organs. Findings accumulated in last years suggest that vagus nerve participates on regulation of much wider spectrum of functions than described previously. Many different studies provide plausible evidence that vagus nerve importantly participates not only in transmission of information from inflamed tissues, but also in efferent modulation of inflammatory processes. Moreover, there are some findings supporting the hypothesis that vagus nerve might participates in monitoring and modulation of tumorigenesis. Electrical stimulation of the vagus nerve is used as a treatment of epilepsy. Moreover, data also suggest a beneficial effect of electrical stimulation of the vagus nerve in patients with depression, anxiety, migraine and Alzheimer's disease.

We suggest, that the vagus nerve might constitute a highly differentiated complex system which modulates various functions. Moreover, we propose that the vagus nerve as a complex system might participate in constitution of a biological compartment of conscious. In this article we discuss findings and ideas supporting these hypotheses *(Ref. 73)*.

Key words: vagus nerve; tumorigenesis; inflammation, electrical stimulation, hemorrhagic shock, ischemia/reperfusion injury.

The autonomic nervous system is composed of huge amount of autonomic subsystems and elements constituting many levels of autonomic organization of organism. *Therefore the concept of the autonomic nervous system functions and structure might be different from today's view based on existing results of measurements and knowledge. The understanding of some functions of autonomic nervous system is difficult because of its complexity. A new view of autonomic nervous system might provide our understanding of changes in structure, composition, and conformation of molecules as a flow of information. However, detection of these processes might be limited by slow flow of information, its complexity or might be masked by other processes.*

For precise coordination of body functions by central nervous system (CNS), the internal environment is monitored and modulated with high precision (1). The vagus nerve with its wide visceromotor innervation of internal organs participates in the regulation of various body functions. Moreover, multiple visceral receptors localized on nerve endings of vagus nerve are able to monitor wide range of biological parameters (e.g. mechanical pressure; present of chemical compounds in tissues; oxygen content of inhaled air) (2–4).

The vagus nerve was traditionally accepted as a part of parasympathetic nervous system with classically described functions (e.g. regulation of heart, gut, respiration). However, data accumulating in last decades show some previously unrecognized functions of the vagus nerve. The vagus nerve transmits information from immune to the nervous system and vice versa, nervous system modulates immune functions via vagus nerve (5, 6).

Electrical stimulation of vagus nerve is used as a treatment of epilepsy (7). Data suggest also beneficial effect of electrical stimulation of vagus nerve on depression, anxiety, migraine and

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Alzheimer's disease (8, 9). Recent findings show an interesting and beneficial role of stimulation of vagus nerve efferent pathways during circulatory shock and myocardial ischemia (10, 11). Moreover, it is hypothesized that vagus nerve might participate also in monitoring and modulation of tumorigenesis (12).

All these facts suggest that vagus nerve might constitute a complex functional system (13) that is composed of many subsystems. The vagus nerve most probably performs more functions than described by recent physiology. This assumption can provide new view on vagus nerve that might change our understanding of regulatory processes modulated by autonomic nervous system.

Vagus nerve – fast pathway for communication between immune and nervous system

The CNS monitors the activity of the immune system through two principal pathways, humoral and neural (14–16). Whereas humoral pathways are relatively slow and don't bring information about the location of source of immune signals, contrary, neural pathways are fast and are location specific.

Role of afferent vagus nerve pathways in transmission of information from immune system to CNS

The role of the vagus in the transmission of information about peripheral inflammatory processes is well known, already cited also in medical books (e.g. 17). The findings indicate that capsaicin-sensitive afferent fibers of the hepatic vagus constitute a necessary component of the afferent mechanism of the first febrile phase (18). This is supported by data showing that vagal sensory neurons themselves express mRNA for IL-1 receptors, suggesting a direct reaction of afferent vagal fibers by IL-1 (19). IL-1 receptors appear also to be located on dendritic-like cells interdigitating in the vagus nerve parenchyma (20). Therefore, cytokines might activate the sensory afferents of the vagus nerve, which transmit signals from the immune system to the CNS, particularly to the nucleus of the solitarii tract and consequently to other brain areas (21, 22).

Important structures supporting transmission of information from the immune system to the brain via the vagus nerve represent paraganglia (23). Paraganglia, innervated by the vagus nerve, contain cells that posses receptors for IL-1. In paraganglia, immune cells are activated during inflammation and consequently might stimulate vagus nerve endings (15). This arrangement constitutes an important link between the immune and nervous systems (24, 25).

Role of efferent vagus nerve pathways in modulation of immune system functions

The CNS has the capacity to deliver neurotransmitters and neuropeptides to tissues in the body. For a long time, the immune system was considered as an exception to this rule. However, it is now evident that the thymus, spleen, and other lymphoid organs are innervated. Therefore the nervous system can stimulate or inhibit activities of the innate and adaptive immune system (26).

Whereas it was well established that afferent neural pathways in the vagus nerve participate in the brain-mediated response to inflammation (27), only recently was the executive function of the vagus nerve in inflammation described. This is mediated by acetylcholine, the principal vagus nerve neurotransmitter (28, 29). The findings show that both pharmacological and electrical stimulation of vagus nerve can attenuate the systemic inflammatory response via cholinergic anti-inflammatory pathways of vagus nerve (30). Recent data indicate, that anti-inflammatory pathways of vagus nerve might be activated by occupation of central melanocortin receptors (e.g. by ACTH, α-melanocyte-stimulating hormone) (10).

Relevance of vagus nerve anti-inflammatory pathways in hemorrhagic shock

In hemorrhagic shock, systemic inflammatory response plays a fundamental pathologic role. Recent findings show that activation of vagus efferent pathways by ACTH fragment reverses hemorrhagic shock in rats via suppression of NF-κB dependent systemic inflammatory response (10, 31).

Impact of vagus nerve anti-inflammatory pathways in ischemia/reperfusion injury

Ischemia/reperfusion is characterized by increased production of free radicals, activation of transcription factors (ie, $NF_{\kappa}B$), production of pro-inflammatory mediators (ie, tumor necrosis factor – TNF), induction of secondary inflammatory mediators (ie, chemokines and adhesion molecules) that participate in consequent damage of tissues (32). Findings demonstrated that both electrical and chemical stimulation of efferent vagal cholinergic pathways reduced the increase in free radical blood levels (11) and protected ischemia/reperfusion injury of heart and liver (33, 34).

The above data suggest a possible therapeutic use of stimulation of vagal cholinergic anti-inflammatory pathways. Stimulation of these pathways might represent new direction of a safe and nontoxic treatment able to rapidly improve cardiovascular functions and tissue perfusion for some hours in circulatory shock (10). Moreover, stimulation of vagal cholinergic anti-inflammatory pathways could provide the potential for development of a new class of drugs for a novel approach to management of ischemic heart disease (11).

We hypothesize that activation of anti-inflammatory processes by stimulation of the vagus nerve might represent a beneficial procedure in transplantation medicine. We speculate that this procedure might represent a potential new tool for reduction of ischemic/reperfusion injury of transplanted organs.

Vagus nerve – possible role in monitoring and modulation of tumorigenesis

The immune system plays an important role in the control of development of malignancy in the body and in elimination of tumors as they arise (35). Cell-mediated immune mechanisms together with humoral mechanism (including cytokines) are involved in the modulation of tumor tissue growth (36–38). Cytokines are powerful regulators of normal cell behavior and play an important role in the host immune response against cancer (39). Cytokines modulate tumor behavior by three important mechanisms: regulation of tumor-associated angiogenesis, activation of a host tumor-specific immunological response, and direct stimulation of tumor cell proliferation in an autonomic fashion (38, 40, 41).

Nervous system and tumorigenesis

Several lines of evidence indicate that psychological or behavioral factors can influence the incidence or progression of cancer (42, 43). These data suggest that the nervous system might potentially play a role in tumorigenesis via regulation of immune system activity (44). The bases for this hypothesis constitute rich and bi-directional interconnection between the CNS and immune system.

Therefore an interesting question arises: *Does a brain receive information about tumorigenesis and can modulate tumor progression?*

Blalock (45) suggests that the immune system might realize sensory functions that can monitor infections agents and also tumor cells. Whereas Blalock has only indirectly touched the problem of interconnection between tumor cells, immune system and brain, Gidron et al (12) articulated this idea more clearly. Gidron hypothesized that the brain is informed about tumorigenesis and modulates processes associated with cancer. He has focused on connection between inflammatory signals in tumorigenesis and consequent interaction between immune signals and brain. However, is the brain able to differentiate between inflammation and tumorigenesis? *Possibly the spectrum of cytokines and other chemical compounds synthesized during tumorigenesis might provide a sufficient amount of information necessary for brain to "detect" the presence of tumor in the organism.*

Gidron et al (12) had focused primary on the role of the vagus nerve in the proposed mechanisms of brain sensing of tumorigenesis. They paid attention to studies which described the finding, that patients with vagotomy as a therapy of gastric ulcers had a greater risk of lung and colorectal cancers (46–49).

Whereas data suggest an increased risk of cancer in patients after vagotomy, it is necessary to consider that also another factors might play a role in the increased incidence of tumorigenesis in these patients (for details see 47, 48). Moreover, controversial results are obtained from human and experimental studies in animals (50–54).

Whereas the above data seem to be ambiguous, we hypothesized that bi-directional interconnections between the nervous and immune systems might constitute a base for both sensing and modulation of tumorigenesis by CNS as originally predicted by Gidron et al (12). *In our opinion, the equivocal data from studies dealing with the effect of vagotomy in later cancer development might indicate that the vagus nerve represents only one route responsible for interaction between the brain and cancer. In addition to the vagus nerve, the sympathetic nervous system and humoral routes might be potentially involved in both monitoring and modulation of tumorigenesis and might therefore compensate for the elimination of the vagus nerve pathway.*

Monitoring and modulation of tumorigenesis by brain: practical implications

As mentioned above, the peripheral nerves and humoral pathways might represent one of the important routes for transmission of information about tumorigenesis to the CNS. *As tumorigenesis in general represents long-term process, it potentially might induce changes in activity in some brain regions. For example, the function of the nucleus of the solitarii tract (NTS) that plays a main role in the processing of visceral information transmitted by vagus nerve might be modulated. Another brain area with potentially modified activity might be the paraventricular hypothalamic nucleus (PVN) and the suprachiasmatic nucleus (SCHN).* The PVN represents the coordinating center of autonomic, endocrine, and immune systems. The SCHN is one of the key regulators of the circadian rhythm (literary data indicate that disruption of circadian rhythm might participate in tumorigenesis) (55, 56). According to these data, some interesting questions arise: *Can we observe altered responses (e.g. using functional techniques as fMRI, PET) of selected brain areas (e.g. NTS, PVN, SCHN) in patients with cancer in control conditions or exposed to any stimuli? Can possible alteration of NTS neuron activity also influence the processing of gustatory information and therefore to change quality or quantity of food intake in patients with cancer? How does cancer therapy interfere with processing of information in the above-mentioned and other brain regions?*

Focused experimental work is necessary to answer all these questions. The possibility that the brain is informed about tumors in the body is exciting and might open new research area. Cancer research focused in this new area might bring important data not only about etiopathogenesis, but also data that might improve diagnostics and therapy of cancer. The following paragraphs briefly describe some data that might provoke study of proposed interaction between tumorigenesis and CNS.

In last years it was observed that guanylhydrazone CNI-1493, with anti-inflammatory effect, acts trough the vagus nerve (28). CNI-1493 was already studied in the phase I trial in melanoma and renal cancer patients showing evidence of pharmacological activity as an inhibitor of TNF production (57). *It can therefore refer to possible therapeutic modulation of cancer progression via drugs that might act on CNS level and "stimulate brains defense reaction" against tumor cells.*

Accumulating data suggest that non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin, prevent cancer develop-

ment (58). Interestingly, it was proved, that NSAIDs modulate peripheral inflammation not only acting in region of inflammation, but also by action on CNS (59). *Therefore the preventive effect of NSAIDs on cancer development might be potentially mediated also by its action via CNS.*

Czura and Tracey (60) suggest that autonomic dysfunction of the cholinergic anti-inflammatory pathways may predispose some individuals to excessive inflammatory response. *Whether dysfunction of the neuroendocrine and immune interaction might predispose to cancer diseases needs to be investigated.*

Similarly, Shanks and Lightman (61) focused on the importance of the maternal-neonatal neuro-immune interactions. Some environmental stimuli might alter development of these interactions during intrauterine period. Shanks and Lightman (61) suggest that an altered neuro-immune developmental course might contribute to individual vulnerability to stress-related disease as well as inflammation in adulthood. *Whether intrauterine alternation of neuro-immune system interaction might potentially increase vulnerability to cancer remains to be investigated.*

Pavlov et al (16) suggest a role of alternative therapeutic approaches (hypnosis, meditation, prayer, biofeedback, acupuncture, and even Pavlovian conditioning) in modulation of inflammatory diseases. *On the basis of data reviewed in this article, it can be hypothesized that all of these methods can potentially modulate also processes connected with progression of cancer via modulation of interactions between CNS and tumor cells.*

Does vagus nerve monitor plasma catecholamine levels?

Release of catecholamines reflects activation of sympathoadrenal system. As catecholamines do not cross blood-brain barrier, nervous system is not informed directly about their plasmatic levels. *We hypothesize that the vagus nerve might participate in the transmission of information about catecholamine plasma levels to the CNS.*

Sensory neurons of vagus nerve possess receptors for catecholamines (62, 63). The data show that subdiaphragmatic vagotomy induces a significant increase of plasma epinephrine levels (64). Moreover, anatomical data show that the adrenal medulla, the main source of plasma epinephrine, is innervated by sensory neurons of vagus nerve (for review see 65). *We suggest that possible monitoring of plasma catecholamines and activity of adrenal medulla by vagus nerve might participate in a precise cooperation between the parasympathetic and sympathetic nervous system in modulating various functions. Our hypothesis is highly speculative and it is also possible that the vagus nerve might monitor another parameters that might reflect sympathoadrenal system activity.*

Vagus nerve electrical stimulation as therapeutic procedure in medicine

Electrical stimulation of vagus nerve (VNS) alters brain activity. These findings lead to the development of new technique for therapy of epilepsy by electrical VNS (7). It is suggested that beneficial influence of VNS in patients with epilepsy is caused by alternation of metabolic activity in specific brain areas (66). Recent data have shown that VNS also has antidepressant effects in adult patients with chronic or recurrent major depression (67). Beneficial effect of VNS has been observed also in patients with anxiety, migraine and Alzheimer's disease (8, 9). Moreover, studies shown that electrical VNS produce antinociceptive effect in both animals and man (68-70). VNS activated various brain areas that participate in the transmission and/or modulation of pain stimulation. Therefore it is most likely that antinociceptive effect is a result of activation of afferent pathways of vagus nerve (71).

The data above support suggestion that VNS might represent not only a new tool for brain research but also for new kind of therapy (7, 8, 72).

Conclusions

For a long time the vagus nerve was considered only as a part of parasympathetic nervous system with traditional spectrum of function, especially in regulation of heart, airways and gastrointestinal tract activities. However, data accumulated in last decades suggest that vagus nerve participates in regulation of much broader spectrum of functions.

Now it is well established that the vagus nerve represents a fast communication pathway between the immune and nervous systems (24, 21). Data suggest that anti-inflammatory activity of the vagus nerve modulates the response of the organism to hemorrhage or ischemia/reperfusion injury (10, 11, 31). Moreover, we hypothesized that the vagus nerve (together with the sympathetic nervous system, somatosensory fibers and humoral pathways) might participate in sensing and modulation of tumorigenesis as originally proposed by Gidron et al (12).

The data discussed support the hypothesis that the vagus nerve might constitute a special complex system with various functions that might participate in the regulation of body function in both physiological and pathological conditions and might form a "sixth sense" (73).

Autonomic systems, subsystems and their elements are importantly involved in the transmission and processing of information. We propose that the vagus nerve acts as a complex system of receptors, parts of cells as subsystems and a conformation of proteins as elements might participate in constitution of biological compartment of conscious. The vagus nerve does not only represent a connection between organs and central nervous system. It might be sophisticated receiver and processor of information, which produces decisions for the maintenance of internal harmony and homeostasis of organism.

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