COMMENTARIES

Vagus nerve as a complex system

Commentaries to Mravec and Hulin article "Does vagus nerve constitute a self-organization complexity or a "hidden network"? Bratisl Lek Listy 2006; 107 (1 – 2): 3 – 8."

Data accumulated in the past years indicate that the functions of the vagus nerve are immensely complex. Discussions, new ideas and hypotheses dealing with the newly identified vagus nerve functions may beneficially influence our knowledge on nervous system. Therefore the Editorial Office of Bratislava Medical Journal provides an opportunity of having the discussions and commentaries on vagus nerve functions published regularly.

Vagal Complexity: Substrate for Body-Mind Connections?

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The article by Mravec & Hulin (2006) points to recent discoveries of previously undocumented functions of the vagus nerve, notably its interactions with the immune system and its possible role in modulating mood and cognition. The authors suggest that the vagus may contribute to specialized brain functions not usually thought to be associated with autonomic systems, such as consciousness. I would like to elaborate on the idea that the vagus contributes significantly to affective states.

The idea that signals from the body (via the vagus and/or other viscerosensory pathways) contribute to affective states has been intermittently en vogue since at least the 19th century (e.g. 1). More generally, the association of bodily states with emotions or personality formed an important component of the "four humors" tradition in medicine dating from the time of Hippocrates (ca 400 BC), and indeed, the only surviving remnant of this teaching endures in our language, for instance the description of "phlegmatic behavior" or "choleric personality" (2). Assertions of this relationship were undermined eventually by an apparent overstatement of the role (e.g. emotion arising from the gut), and especially the state of knowledge regarding the central nervous (brain) systems to which vagal/viscerosensory input contributes. However, recent findings now implicate a role for the vagus in modulation of mood and arousal, based on electrical stimulation studies in humans (3), and combined with modern functional neuroanatomical procedures now strongly implicate vagal sensory drive in "bottom-up" modulation of mood and cognition, including memory, and perhaps even consciousness, via effects on arousal states.

Central projections of the vagus terminate in the nucleus of the solitary tract (NTS), a brainstem region with a well-established role in the integration of autonomic reflexes. In addition, ascending projections from the NTS contribute to stress-responsive brain circuits (4) and higher order processing of visceral information important to regulatory behaviors and neuroendocrine integration. Further, however, the NTS provides significant drive on brain arousal pathways including those associated with the locus coeruleus (5) and hypothalamus, as well as regions including the amygdala that are involved in memory (6). Indeed, the vagus, via the NTS, plays an important role in the facilitating effects of peripheral arousal (stress, fear, strong emotion) on memory (7,8). Similarly, the vagus mediates viscerosensory enhancement of anxiety, for instance the increase in anxiety-like behavior that can be observed during gastrointestinal infection or inflammation (9,10). In this way, vagal sensory pathways may convey the fact that "something is not right", impelling a sick animal to avoid potentially dangerous places or situations. This arrangement has implications for the affective symptoms, especially anxiety, that are so prevalent in inflammatory bowel disorders. Historically such symptoms have been believed to follow from "top down" psychological stress responses, or even act as causative factors for conditions such as gastric ulcer or irritable bowel syndrome. However, it is now clear that infection or inflammation per se contributes to anxiety, and thus intervention into the infection/inflammation (e.g. with anti-inflammatory medication) may be efficacious for the associated anxiety as well.

Why does the vagus modulate mood? At first glance vagal modulation of affective states seems incongruent with other, homeostatic functions that the vagus supports. However, influence on moods and arousal would constitute a powerful mechanism to influence behavior. In this way, signals from internal tissues indicating danger (e.g. pathogens, hypotension etc.) can provoke feelings of anxiety, or depression, which would bias an animal's behavior toward caution, or recuperation, etc. Thus it

can be said that the complexity of vagus nerve functions strongly supports a role for the vagus as "great wandering protector" (11).

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A response to Mravec and Hulin: Does the vagus nerve constitute a self-organization complexity or a "hidden network"?

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The article by B. Mravec and I. Hulin Does the vagus nerve constitute a self-organization complexity or a "hidden network"? (1) addresses a novel emerging scientific domain, namely the neuroscience of illness. It examines scientific evidence concerning how the central nervous system is "informed" about and may modulate tumourigenesis. In doing so, it expands a recently published model by Gidron et al. (2). The original model proposed that the vagus nerve may "inform" the brain about and modulate tumourigenesis. That model was based on converging evidence in which the vagus conveys information about peripheral inflammation to the brain (3), the crucial role of cytokines in early (4) and late (5) stages of tumourigenesis, and the effects of vagotomy (6, 7) on cancer incidence. Finally, given the effects of vagal activation on immunity (8) and the vagal reflex (9), activating this nerve may inhibit tumor-related inflammation, possibly slowing down tumor progression (2).

Mravec and Hulin are to be commended for extending the model by correctly suggesting that additional routes other than the vagus nerve may participate in tumor-to-brain communication and modulation. The other routes they propose are the sympathetic nervous system and humoral pathways. This is their major contribution to the previous model. While Gidron et al. (2) do not claim that only the vagal nerve takes part in this link, the original model fails to propose additional routes (beyond direct brain penetration and prostaglandin signaling near the blood-brain barrier). Mravec and Hulin's (2) expansion of the model helps to solve some inconsistencies about the role of the vagus in tumourigenesis. Since some studies did not show that vagotomy led to a greater incidence of cancer (10) while others did (6,7), it is important to consider alternative communicative and modulatory routes. This expansion not only has scientific importance, but could also have clinical implications for treating tumors via the additional routes, if proven to impact on their progression.

The second important contribution of Mravec and Hulin is in raising the question whether the brain can distinguish between peripheral inflammation and tumourigenesis. Gidron et al. also questioned whether the brain "knows"(via vagal input) that the inflammatory signals are tumor-related. The main issue is that the existence of this vagal homeostatic feedback system may work "in the service" of tumor modulation, taking advantage of the role of the vagus in informing about and in modulating peripheral inflammation.

A major contribution of their article is in the questions they raise. They ask for example what brain regions are active in patients with cancer. A study addressing this precise issue is currently underway by our research team. Mravec and Hulin specifi-

cally ask whether the nucleus of the solitary tract (NTS) plays a role in tumor-related and chemotherapy-related gustatory changes. This has clear implications for understanding cancer-related anorexia.

Beyond these important contributions, the article does not address a few important issues it may have aimed to address. First, its title appears to relate to a much broader topic than cancer alone. The title refers to the self-organizing nature of the vagus, yet the article hardly addresses this major issue. Does the vagus reflex work alone as a closed system? Which brain regions influence the communicative and modulatory roles of the vagus? A few studies have shown the role of other brain regions in immune-to-brain communication including the amygdala (11). Do the amygdala and „higher order“ cortical regions influence vagal modulation of inflammation? Furthermore, what are the relations between the ascending and descending vagal routes? A second important body of literature lacking in their article relates to the role of the sympathetic and beta-adrenergic system in tumourigenesis. This is important to their claim that the sympathetic nervous system influences tumourigenesis beyond the role of the vagus nerve. For example, Sood et al. (12) recently demonstrated that norepinephrine and epinephrine increased the invasive potential of ovarian cancer cells. These effects depended on beta-adrenergic receptors and were mediated by increasing the effects of matrix metalloproteineses. Finally, throughout the article, Mravec and Hulin attribute “decision making” capacities to the vagus nerve in its communicative and modulatory roles. However, this must only be seen as an allegory since such capacities may only be attributed to higher cortical regions such as the prefrontal cortex which governs executive functions. Future studies may need to examine whether preclinical tumors involve only sub-cortical regions such as the amygdala and the brain stem in addition to the vagus, while more established tumors (inducing patient awareness) may also involve cortical regions. Future studies need to address the effects of “decision making” brain regions on tumourigenesis.

The article by Mravec and Hulin extends the only explicit model so far suggested on this topic. Their article raises very important questions, suggests important additional pathways to the new subject of tumor-to-brain communication and modulation, and raises important clinical applications currently under investigation.

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Commentary to the article Does vagus nerve constitute a self-organization complexity or a “hidden network”? written by Mravec B. and Hulin I. in BMJ 2006.

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Extremely important article promoting scientific workers to take into consideration complexity of biological processes. Usually medical papers are analyzing some simple relations and we have till now an immense data base of separate facts. However some of these findings, especially in cytokines field are intricating as far as their effects. All these divergent knowledges need some-

where converge. Authors are indicating the possible pathway how to do it. Excellent illustration that autonomic nervous system on many levels has contact with a lot of subsystems, to central nervous system, to brain cortex – to cognition and to all relationships in environment in widest sense. With such convergent point of wiew not only acetylcholine but thinking at all, deeply influence the human body homeostasis. Infectologists, oncologists and psychiatrists can confirm these finding. Many thanks and congratulation to authors to their synthetic paper which can serve to young scientists as compass.

To the article of Mravec and Hulin

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New off-centre views and hypotheses about vital functions mechanisms are inevitably a source of the new targets setting and search of non-standard approaches and methodical ways for the purpose of argumentation of idea put forward. The article by Mravec B, Hulin I „Does vagus nerve constitute a self-organization complexity or a "hidden network" (Bratisl Lek Listy 2006; 107 (1 – 2): 3 – 8) is of such studies that are thought provoking and stimulate scientists to new researches and findings.

Notes of authors

The vagus nerve with its wideapread innervation of internal organs, various receptor types and a huge amount of efferent and afferent fibers represent a highway allowing fast bi-directional transmission of information between the brain and peripheral tissues. Even though we know some types of information transmitted via the vagus nerve, it is most likely that the spectrum of peripheral signals transmitted to the central nervous system via the latter nerve will be enlarged.

As discussed in our previous article, we suggest that the vagus nerve might transmit information of tumorigenesis and of plasma catecholamine levels to the brain. Moreover, we hypothesize that the vagus nerve might represent an important part of the system constituting the "biological compartment of consciousness". However, the information transmitted and processed by this compartment does not have to necessarily reach the highest level of consciousness. We suggest that the vagus nerve might detect a majority of changes in tissues innervated by it. It allows the brain to learn about the "status of cells" within the organism. The research focused on finding an answer to the question as to which diseases the brain might monitor via the vagus nerve, might open a new field in the science of etiopathogenesis of diseases.