

INSIGHT REVIEW

Complex intracardiac nervous system

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Abstract

The heart is an organ with continuous activity, which must satisfy demands of an organism on various conditions. Therefore, heart activity is modulated at many levels, including intrinsic regulatory mechanisms, humoral factors and autonomic nervous system. The regulation of heart activity by sympathetic and parasympathetic nervous system is well known. Accumulated evidence in recent decades indicates that intracardiac neurons can also significantly regulate heart activity. These neurons are concentrated in multiple heart ganglia. Interactions between neurons within intracardiac ganglia together with interconnections between individual ganglia provide anatomical and functional basis of complex nervous network of the heart. This complex intracardiac nervous system together with extracardiac autonomic neurons, innervating heart, provides modulation of heart activity during both physiological and pathological conditions.

This review article summarizes recent knowledge about the role of heart neurons in physiological conditions and in etiopathogenesis of selected diseases. Effect of pharmacological and surgical interventions on heart neurons is also discussed (*Fig. 2, Ref. 70*).

Key words: autonomic nervous system, cardiovascular diseases, heart ganglia, intracardiac nervous system, Parkinson's disease.

Heart activity, similarly as activities of other inner organs, is modulated at many levels, including intrinsic regulatory mechanisms, humoral factors and autonomic nervous system (1). The heart as an organ with continuous activity must precisely satisfy demands of an organism on various conditions. Control mechanisms regulating heart activity is very complex. The importance of descending regulation of the heart by sympathetic and parasympathetic nervous system is well known. Also, it was known for a long time that the heart possesses nerve cells. However, only data accumulated in the last decade show the complexity and functional importance of intracardiac neurons in modulating heart function (2, 3, 4).

Intracardiac neurons are concentrated in multiple heart ganglia (5). Interactions between neurons within intracardiac ganglia together with interconnections between individual ganglia provides anatomical and functional basis for complex nervous network of the heart, also called "heart brain" (6, 7). This complex intracardiac nervous system together with extracardiac autonomic neurons provides modulation of heart activity during both physiological and pathological conditions (8).

In this paper, we will first outline the role of intracardiac neurons in hierarchical organization of the heart control. In second part are discussed data indicating involvement of intracardiac neurons in heart diseases. Moreover, effect of pharmacological and surgical interventions on heart neurons is depicted.

Hierarchical organization of heart control

Two decades ago, Folkow (9) formulated three levels of the hierarchical organization of the heart: 1) Local level, involving myogenic activity of the heart. 2) Bulbar level, involving barore-

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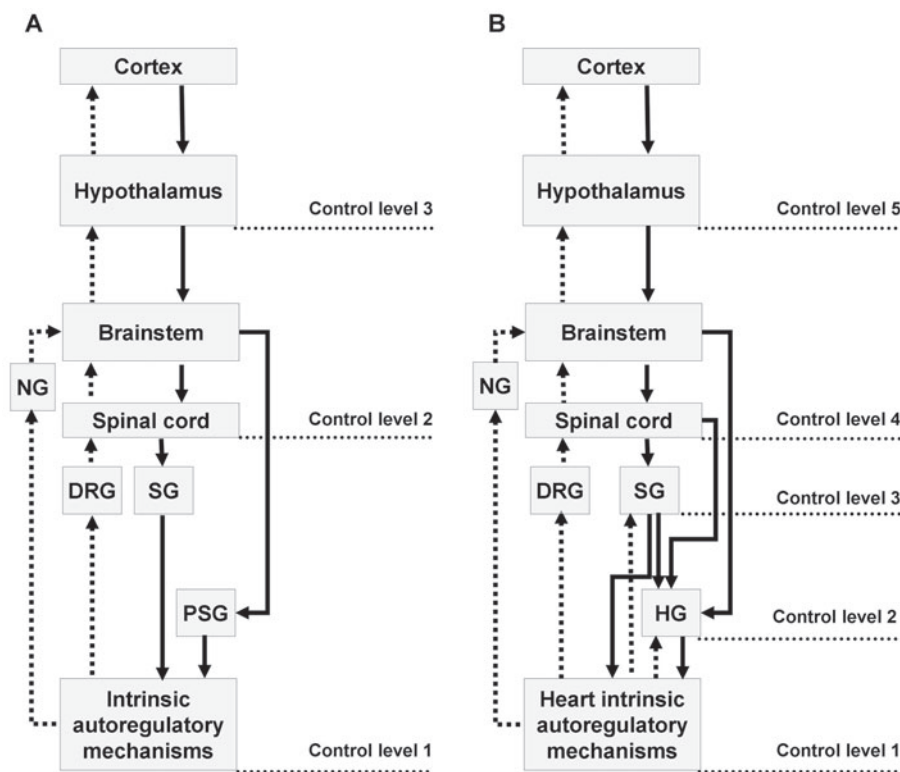


Fig. 1. A) Schema of classical view of hierarchical organization of inner organs regulation. B) New concept of hierarchical organization of heart regulation show more complex interconnections between heart ganglia and other structures of nervous system regulating heart activity. Efferent (motoric) pathways – solid lines; afferent (sensory) pathways – broken lines. DRG – dorsal root ganglia, HG – heart ganglia, NG – nodose ganglia, PSG – parasympathetic ganglia; SG – sympathetic ganglia (modified according 22, 69).

ceptor and chemoreceptor inputs to the brainstem and relatively simple homeostatic neurohumoral outputs to regulate cardiac output. 3) Higher central neural level, involving neocortical, limbic and hypothalamic expression of integrated behavioral, visceral and humoral patterns. This concept was later modified by Goldstein (1). He proposed that at the lowest level, heart structures possess intrinsic “tone”. At the next, simple homeostatic reflexes maintain appropriate “steady-state” cardiovascular heart performance. The operating characteristic of the homeostats reset as a part of hypothalamically elaborated patterns generated at the next higher level. Finally, at the highest level, limbic and frontal cortices interpret afferent signals about the internal and external environments to determine the occurrence and intensity of hypothalamically evoked patterns. This is the level of memory, learning and consciousness (Fig. 1A) (1).

Sympathetic and parasympathetic innervation of the heart

Autonomic nervous system provides bidirectional communication between the heart and the central nervous system (10). Autonomic innervation is richer in atria compared to ventricles, differs between right and left side of the heart and also between layers of myocardium. This differentiation is responsible for adequate modulation of heart activity (11, 12).

Sympathetic nerves originate in cervical and stellate ganglia. Neurons of these ganglia are under control of sympathetic preganglionic neurons located in intermediolateral nucleus of spinal cord segments from Th1 to Th5 (10, 13). Sympathetic nerves possess also sensory fibers that transmit information from nociceptors through dorsal root ganglia to the spinal cord and consequently to the brain (14).

Parasympathetic innervation of the heart by vagus nerve originate in neurons localized mainly in nucleus ambiguus, in lesser extent in dorsal vagal nucleus and in the region between these nuclei (15, 16, 17). Fibers originating in brainstem neurons innervate parasympathetic postganglionic neurons in heart ganglia. Axons of neurons localized in nodose ganglia transmit (via vagus nerve) sensory information to the nucleus of the solitary tract and consequently to other brain areas (18).

Intracardiac nervous system as local modulator of heart activity

In the old concept of neuronal control of inner organs were ganglia, which are localized in tissues of these organs, seen as simple relay stations that allow transmission of information between parasympathetic preganglionic and postganglionic neurons (19).

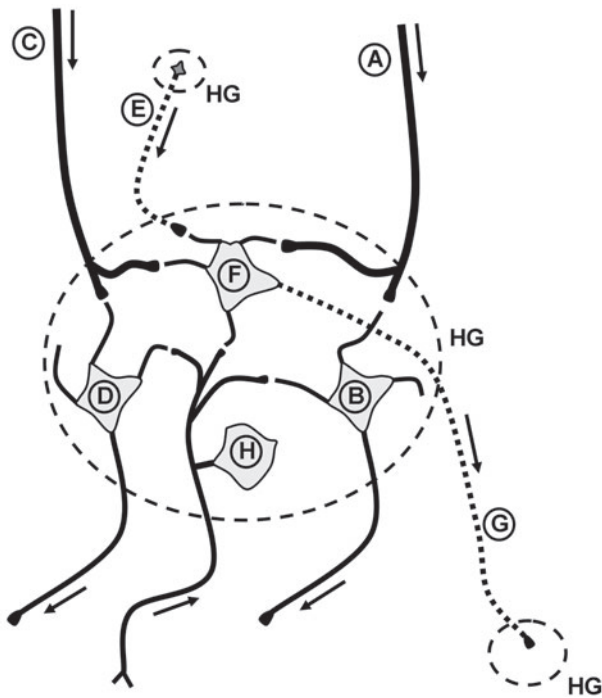


Fig. 2. Simplified drawing of neurons within heart ganglion and their projections. Arrows indicate direction of signals transmission. A – axon of parasympathetic preganglionic neuron; B – parasympathetic postganglionic neuron; C – axon of sympathetic preganglionic neuron; D – sympathetic neuron; E – axon from neuron localized in another heart ganglion; F – local circuits interneuron; G – axon innervating another heart ganglion; H – intracardiac sensory neuron; HG – heart ganglion; (modified according 8, 69, 70).

However, data accumulated in the last decade show that ganglia in the heart represent more complex structures. Indeed, neurons of heart ganglia process information and elaborate response that allows to modify heart activity “from beats to beats” (Fig. 1B; 20, 21, 22).

Different types of intracardiac neurons are accumulated in heart ganglia (e.g. parasympathetic and sympathetic postganglionic neurons, local sensory neurons, interneurons, Fig. 2). These neurons synthesize many different neurotransmitters. Besides acetylcholine, some neurons possess enzymes for biosynthesis of monoamines. Population of “small intensely fluorescent” cells synthesize most probably dopamine and serotonin, some magnocellular neurons synthesize norepinephrine and epinephrine (23). The presence of enzymes for histamine synthesis was also confirmed (24). Moreover, various neuropeptides (e.g. cocaine and amphetamine-regulated transcript, calcitonin gene-related peptide, neuropeptide Y, tachykinins, vasoactive intestinal polypeptide) were identified in heart neurons (25, 26, 27, 28). Nitric oxide synthase-immunoreactive neurons were also identified in the heart (29). Chemical diversity within intracardiac neurons may reflect functional specialization of intracardiac neurons (30).

Heart ganglia are localized in epicardiac fat in both atria and ventricles (31). Groups of intracardiac ganglia are accumulated in some heart regions constituting plexuses of ganglia. In human heart, five plexuses of ganglia in atria and five plexuses in ventricles were recognized (2).

Axons of neurons localized within heart ganglia innervate different heart regions, predominantly sinoatrial and atrioventricular nodes. This arrangement indicates that the intracardiac nervous system might significantly modulate functions of conduction system of the heart. However, the amount of axons of intracardiac neurons innervating heart is lower compared with axons of extracardiac origin (32).

Intracardiac neurons show spontaneous activity, which is modulated by extracardially localized neurons and is also influenced by local cardiovascular environment (4). Heart environment is monitored by mechanoreceptors and chemoreceptors of intracardiac neurons. Computation of these information together with interconnections between heart ganglia constitute complex intracardiac nervous system. Microcircuits of intracardiac nervous system allow to modulate heart activity also in conditions when influence of extracardiac neuronal control is eliminated (8).

Role of the intracardiac nervous system in hierarchy of the heart rhythmogenesis

Very recently, several authors hypothesized that along with the existence of an intracardiac pacemaker (the sinus node) extracardially localized generator of cardiac rhythm should exist. This generator is presumably localized in all structures of the cardiovascular center of the brainstem. Further, central rhythmogenesis commands may interact with cardiac pacemaker structures and therefore every heart beat is under neural command. Whereas intrinsic cardiac rhythm generator is a life-sustaining factor that maintains heart pumping when the central nervous system is shutdown, the brain generator may provide the heart with adaptive reactions to changes in the environment. This arrangement of the two duplicating levels of rhythmogenesis appears to provide functional perfection of the cardiac rhythm generation system in the whole organism (33, 34).

However, our working hypothesis is that there might be another heart rhythm generator. We feel that complex intracardiac nervous system might represent this second intracardiac rhythm generator. The importance of proposed second rhythm generator might increase during conditions when transmission of signals from the central nervous system is interrupted (e.g. in patients with transplanted heart).

Does intracardiac nervous system play a role in heart diseases?

Significance of interactions between intracardiac neurons and conduction system of the heart

In the heart, there are recognized also sinoatrial and atrioventricular ganglia, named according to their localization. Close anatomical relationship of these ganglia with sinoatrial and atrioventricular nodes suggest intimate functional interactions (19). Therefore heart neurons might represent a key element that pro-

cesses signals from the heart itself and from central nervous system and elaborate appropriate commands that modulate rhythmogenesis and conduction of heart activation.

Based on these facts, possible involvement of intracardiac ganglia in etiopathogenesis of arrhythmias was evaluated in last years. The obtained data show that some interventions terminating or evoking arrhythmias may produce their effect also via modification of intracardiac neuronal activity (35). Therapeutic interventions, which at first step localize heart ganglia and then produce specific radiofrequency ablation has already been described (36).

The role of intracardiac neurons in etiopathogenesis of arrhythmias supports observation of significant reduction of postoperative arrhythmias after coronary bypass operation in patients with preserved anterior epicardial fat (this region contains intracardiac ganglia, 37)

It was suggested that excessive release of catecholamines may participate in the formation of arrhythmias during myocardial infarct (38, 39). Since some intracardiac neurons also synthesize catecholamines, they may potentially participate in inducing arrhythmias during myocardial infarct.

Regulation of heart activity in conditions when extracardiac neuronal control is eliminated

Heart transplantation causes elimination of cardiac sympathetic and parasympathetic innervation (40). However, intracardiac nervous network remains relatively preserved. Therefore it was proposed to use a term posttransplantational *decentralization* instead of *denervation* of the heart (41). Data show that chronic decentralization of heart causes alteration of properties of intracardiac neurons. Intrinsic cardiac neurons in canine decentralized heart undergo changes in membrane properties that may lead to increased excitability while maintaining synaptic neurotransmission within the intrinsic cardiac ganglionated plexus (42).

We suggest that altered activity of intracardiac neurons in transplanted heart might reflex their endeavor to compensate a loss of modulatory influence of the central nervous system. However, regulation of heart activity is less precise because the central nervous system that processes information from variety of sensors and elaborates complex commands is disconnected with heart.

Do intracardiac neurons participate in modulation of pain during myocardial ischemia?

Myocardial ischemia is characterized by changes in intracardiac environment (e.g. concentration of bradykinin, prostaglandins, reactive oxygen species; 43). Intracardiac sensory neurons show sensitivity to these compounds and might therefore influence processing of information during myocardial ischemia (44, 45). This assumption is supported by effect of spinal cord electrical stimulation, which is used as a therapeutic procedure for termination of heart pain refractory to conventional pharmacotherapy. Whereas electrical stimulation of spinal cord did not alter cardiovascular parameters, activities of intracardiac neu-

rons were found to be inhibited (46, 47). These facts suggest important role of intracardiac neurons in modulation of transmission of nociceptive stimuli evoked by myocardial ischemia.

Is heart failure accompanied by altered function of intracardiac neurons?

In patients with heart failure it was observed positive correlation between mortality and plasma epinephrine levels (48). However, data show that epinephrine is not released only from sympathoadrenal system (49). Heart itself contains population of catecholamine synthesizing neurons, constituting an intrinsic adrenergic system (50). Whether catecholamines produced by these neurons might participate in etiopathogenesis of heart failure is unclear.

Findings in dogs with heart failure induced by tachycardia showed altered response of intracardiac neurons to activation of their nicotinic receptors (51). Moreover, it was observed in failed human hearts a significant reduction of number of intracardiac neurons (52). Thus, further studies of function of intracardiac neurons in heart failure may contribute to elucidation of its etiopathogenesis as well as to identify new targets for pharmacological interventions.

Modification of intracardiac neurons morphology and their number in some heart diseases and their loss associated with ageing

Cardiac neurons display various pathological changes during cardiac diseases. In patients with diabetic atrophy, it was observed a loss of Nissl's substance in intracardiac neurons. In ischemic hearts, one third of cardiac neurons displayed inclusions and were markedly enlarged. A severe loss of heart neurons was observed in Chagas's disease (52). These pathological changes of structure of intracardiac neurons may be responsible for altered regulation of heart by the intracardiac nervous system (53).

Interestingly, the number of intracardiac neurons decreases during life (5). It was hypothesized that remaining neurons undergo structural changes and reorganization (54). However, it is unclear whether any relationship does exist between ageing-related loss of intracardiac neurons and altered functions of the heart (55).

Is there a role of intracardiac neurons in cardiovascular dysfunctions in Parkinson's disease (PD)?

Variable dysfunctions of the autonomic system have been recognized in PD, including cardiovascular symptoms (56). It was believed that orthostatic hypotension, common in PD patients, is a consequence of chronic L-dopa treatment. However, several recent studies showed that orthostatic hypotension may be more likely the result of cardiac sympathetic denervation in PD (57, 58). Indeed, imaging techniques indicated a reduction of sympathetic terminals in the heart of patients with PD (59). Moreover, immunohistochemical studies showed the presence of Lewy bodies in heart neurons (60). It was suggested, that these intracardiac neuronal changes can, at least partially, lead to arrhythmias in PD (61, 62). Very recently we suggested, that similarly to the loss of dopaminergic neurons of substantia nigra,

catecholaminergic intracardiac neurons may be also affected in patients with PD (63).

Does pharmacological or surgical intervention modify heart functions via alteration of function of intracardiac neurons?

A variety of drugs can modify heart activity via different mechanisms. These drugs can either alter activity of heart tissue or modify activity of nervous structures responsible for control of heart activity (64, 65). Many of these drugs influence also functions of intracardiac neurons and consequently function of the heart (8, 66).

Also, surgical procedures (e.g. heart transplantation, repair of septal defect, valvular procedures, and congenital reconstructions) can alter activity of intracardiac nervous system. These procedures frequently involve incisions through areas densely populated with cardiac ganglia. Significant modification of function of the intracardiac nervous system with potential negative impact on the regulation of heart activity was ascribed to these interventions (40). Therefore, the use of appropriate operative techniques, which protect regions rich in ganglia of the heart, is highly recommended.

Conclusions

The old view of anatomical organization of autonomic innervation of inner organs cannot be further accepted (Fig. 1A). Actually, neuronal processing of information responsible for precise regulation of organs is performed not only in the central nervous system, but also in neuronal systems localized in these organs (Fig. 1B). Inner organs possess complex neuronal systems which are able to modulate their function also in circumstances when pathways transmitting signals from central nervous system are interrupted. A classical example represents the enteric nervous system where neurons constitute complex nerve nets with similar organization as appeared at the earliest stages of the evolution of nervous system (67). This nerve net represents additional control level in hierarchical structure of neural control of the gastrointestinal tract (68).

Arrangement of intracardiac nervous system discussed in this review represents another example of complex neuronal network in inner organ. This neuronal network is constituted by various populations of neurons condensed in heart ganglia. Neurons of these ganglia process information from central nervous system together with information from the heart. Therefore, intracardiac neurons may participate in the regulation of heart activity "from beat to beat".

The importance of the intracardiac nervous system may increase during some heart diseases (ischemia, heart failure) and also in circumstances when regulatory influence of the central nervous system is interrupted (heart transplantation). Moreover, it is necessary to take into consideration that pharmacological therapy and surgical interventions may also modify activity of intracardiac neurons.

We feel that cardiovascular research focused on better understanding of the complexity of the intracardiac nervous sys-

tem in health and disease in the next years may bring an important information into physiology and pathophysiology of humans and animals.

References

- Goldstein DS.** Control of sympathetic outflows and functions of central catecholamines. 164—233. In: Goldstein DS (Ed). Stress, Catecholamines, and Cardiovascular Disease. New York; Oxford university press, 1995.
- Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA.** Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec* 1997; 247 (2): 289—298.
- Baptista CA, Kirby ML.** The cardiac ganglia: cellular and molecular aspects. *Kaohsiung J Med Sci* 1997;13 (1): 42—54.
- Arora RC, Hirsch GM, Johnson Hirsch K, Hancock Friesen C, Armour JA.** Function of human intrinsic cardiac neurons in situ. *Amer J Physiol Regul Integr Comp Physiol* 2001; 280 (6): 1736—1740.
- Pauza DH, Skripka V, Pauziene N, Stropus R.** Morphology, distribution, and variability of the epicardiac neural ganglionated subplexuses in the human heart. *Anat Rec* 2000; 259 (4): 353—382.
- Randall CW, Wurster RD, Randall DC, Xi-Moy SX.** From cardio-accelerator and inhibitory nerves to a „heart brain“: an evolution of concepts. 173—199. In: Nervous control of the heart. Shepherd JT, Vatner SF (Eds.) UK: Harwood; Reading, 1996.
- Randall DC.** Towards an understanding of the function of the intrinsic cardiac ganglia. *J Physiol* 2000; 528 (Pt 3): 406.
- Armour JA.** Myocardial ischemia and the cardiac nervous system. *Cardiovasc Res* 1999; 41 (1): 41—54.
- Folkow B.** Physiology of behavior and blood pressure regulation in animals. 1—18. In: Julius S, Bassett DR (Eds.). Handbook of hypertension, Vol 9. Behavioral factors in hypertension. New York; Elsevier Science, 1987.
- Kawashima T.** The autonomic nervous system of the human heart with special reference to its origin, course, and peripheral distribution. *Anat Embryol* 2005; 209 (6): 425—438.
- Wittling W, Block A, Genzel S, Schweiger E.** Hemisphere asymmetry in parasympathetic control of the heart. *Neuropsychologia* 1998; 36 (5): 461—468.
- Kawano H, Okada R, Yano K.** Histological study on the distribution of autonomic nerves in the human heart. *Heart Vessels* 2003; 18 (1): 32—39.
- Hall WC** **The visceral motor system.** 469—500. In: Purves D, Augustine GJ, Fitzpatrick D, Hall WC, Lamantia AS, McNamara JO, Williams SM (Eds). Neuroscience. Sunderland; Sinauer Associated, 2004.
- Barr JA, Kiernan JA.** Visceral innervation. 364—376. In: Barr JA, Kirnan JA (Eds.). The Human Nervous System — An Anatomical Viewpoint. Philadelphia; J. B. Lippincott Company, 1993.
- Barr JA, Kiernan JA.** Cranial nerves. 122—147. In: Barr JA, Kirnan JA (Eds.). The Human Nervous System — An Anatomical Viewpoint. Philadelphia: J. B. Lippincott Company, 1993.
- Taylor EW, Jordan D, Coote JH.** Central control of the cardiovascular and respiratory systems and their interactions in vertebrates. *Physiol Rev* 1999; 79 (3): 855—916.

17. **Cheng Z, Zhang H, Guo SZ, Wurster R, Gozal D.** Differential control over postganglionic neurons in rat cardiac ganglia by NA and DmnX neurons: anatomical evidence. *Amer J Physiol Regul Integr Comp Physiol* 2004; 286 (4): 625–633.
18. **Xie Q, Itoh M, Miyamoto K, Li L, Takeuchi Y.** Cardiac afferents to the nucleus of the tractus solitarius: A WGA—HRP study in the rat. *Ann Thorac Cardiovasc Surg* 1999; 5 (6): 370–375.
19. **Gray AL, Johnson TA, Ardell JL, Massari VJ.** Parasympathetic control of the heart. II. A novel interganglionic intrinsic cardiac circuit mediates neural control of heart rate. *J Appl Physiol* 2004; 96 (6): 2273–2278.
20. **Horackova M, Armour JA.** Role of peripheral autonomic neurons in maintaining adequate cardiac function. *Cardiovasc Res* 1995; 30 (3): 326–335.
21. **Randall DC, Brown DR, McGuirt AS, Thompson GW, Armour JA, Ardell JL.** Interactions within the intrinsic cardiac nervous system contribute to chronotropic regulation. *Amer J Physiol Regul Integr Comp Physiol* 2003; 285 (5): 1066–1075.
22. **Armour JA.** Cardiac neuronal hierarchy in health and disease. *Amer J Physiol Regul Integr Comp Physiol* 2004; 287 (2): 262–271.
23. **Slavikova J, Kuncova J, Reischig J, Dvorakova M.** Catecholaminergic neurons in the rat intrinsic cardiac nervous system. *Neurochem Res* 2003; 28 (3–4): 593–598.
24. **Singh S, Johnson PI, Javed A, Gray TS, Lonchyna VA, Wurster RD.** Monoamine— and histamine—synthesizing enzymes and neurotransmitters within neurons of adult human cardiac ganglia. *Circulation* 1999; 99 (3): 411–419.
25. **Steele PA, Gibbins IL, Morris JL, Mayer B.** Multiple populations of neuropeptide—containing intrinsic neurons in the guinea—pig heart. *Neuroscience* 1994; 62 (1): 241–250.
26. **Slavikova J.** Distribution of peptide—containing neurons in the developing rat right atrium, studied using immunofluorescence and confocal laser scanning. *Neurochem Res* 1997; 22 (8): 1013–1021.
27. **Richardson RJ, Grkovic I, Anderson CR.** Cocaine- and amphetamine-related transcript peptide and somatostatin in rat intracardiac ganglia. *Cell Tissue Res* 2005; 23: 1–8.
28. **Slavikova J, Kuncova J, Chottova—Dvorakova M, Reischig J.** Nonadrenergic noncholinergic regulation of the cardiac performance: morphology and function of the peptidergic innervation of the mammalian heart. *Cesk fysiolog* 2005; 54 (2): 70–77.
29. **Tanaka K, Takanaga A, Hayakawa T, Maeda S, Seki M.** The intrinsic origin of nitric oxide synthase immunoreactive nerve fibers in the right atrium of the guinea pig. *Neurosci Lett* 2001; 305 (2): 111–114.
30. **Richardson RJ, Grkovic I, Anderson CR.** Immunohistochemical analysis of intracardiac ganglia of the rat heart. *Cell Tissue Res*. 2003; 314(3): 337–350.
31. **Johnson TA, Gray AL, Lauenstein JM, Newton SS, Massari VJ.** Parasympathetic control of the heart. I. An interventriculo—septal ganglion is the major source of the vagal intracardiac innervation of the ventricles. *J Appl Physiol* 2004; 96 (6): 2265–2272.
32. **Steele PA, Gibbins IL, Morris JL.** Projections of intrinsic cardiac neurons to different targets in the guinea—pig heart. *J Auton Nerv Syst* 1996; 56 (3): 191–200.
33. **Pokrovskii VM.** Integration of the heart rhythmogenesis levels: heart rhythm generator in the brain. *J Integr Neurosci* 2005; 4 (2): 161–168.
34. **Pokrovskii VM.** Hierarchy of the heart rhythmogenesis levels is a factor in increasing the reliability of cardiac activity. *Med Hypotheses* 2006; 66 (1): 158–164.
35. **Scherlag BJ, Yamanashi WS, Amin R, Lazzara R, Jackman WM.** Experimental model of inappropriate sinus tachycardia: initiation and ablation. *J Interv Card Electrophysiol* 2005; 13 (1): 21–29.
36. **Scherlag BJ, Nakagawa H, Jackman WM et al.** Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. *J Interv Card Electrophysiol* 2005; 13 (Suppl 1): 37–42.
37. **Cummings JE, Gill I, Akhrass R, Dery M, Biblo LA, Quan KJ.** Preservation of the anterior fat pad paradoxically decreases the incidence of postoperative atrial fibrillation in humans. *J Amer Coll Cardiol* 2004; 43 (6): 994–1000.
38. **Schomig A, Richardt G.** The role of catecholamines in ischemia. *J Cardiovasc Pharmacol* 1990; 16 (Suppl 5): 105–112.
39. **Schomig A, Haass M, Richardt G.** Catecholamine release and arrhythmias in acute myocardial ischemia. *Europ Heart J* 1991; 12 (Suppl F): 38–47.
40. **Singh S, Johnson PI, Lee RE et al.** Topography of cardiac ganglia in the adult human heart. *J Thorac Cardiovasc Surg* 1996; 112 (4): 943–953.
41. **Arora RC, Ardell JL, Armour JA.** Cardiac denervation and cardiac function. *Curr Interv Cardiol Rep* 2000; 2 (3): 188–195.
42. **Smith FM, McGuirt AS, Leger J, Armour JA, Ardell JL.** Effects of chronic cardiac decentralization on functional properties of canine intracardiac neurons in vitro. *Amer J Physiol Regul Integr Comp Physiol* 2001; 281 (5): R1474–R1482.
43. **Schultz HD.** Cardiac vagal chemosensory afferents. Function in pathophysiological states. *Ann NY Acad Sci* 2001; 940: 59–73.
44. **Syven C.** Neurophysiological aspects of angina pectoris. *Z Kardiol* 1997; 86 (Suppl 1): 95–105.
45. **Thompson GW, Horackova M, Armour JA.** Sensitivity of canine intrinsic cardiac neurons to H₂O₂ and hydroxyl radical. *Amer J Physiol*. 1998; 275 (4 Pt 2): H1434–1440.
46. **Foreman RD, Linderth B, Ardell JL et al.** Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovasc Res* 2000; 47 (2): 367–375.
47. **Armour JA, Linderth B, Arora RC et al.** Long-term modulation of the intrinsic cardiac nervous system by spinal cord neurons in normal and ischemic hearts. *Auton Neurosci* 2002; 95 (1–2): 71–79.
48. **Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L.** Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Consensus Trial Study Group. *Circulation* 1990; 82 (5): 1730–1736.
49. **Kaye DM, Lefkovits J, Cox H et al.** Regional epinephrine kinetics in human heart failure: evidence for extra—adrenal, nonneural release. *Amer J Physiol* 1995; 269 (1 Pt 2): 182–188.
50. **Huang MH, Friend DS, Sunday ME et al.** An intrinsic adrenergic system in mammalian heart. *J Clin Invest* 1996; 98 (6): 1298–1303.
51. **Arora RC, Cardinal R, Smith FM, Ardell JL, Dell'Italia LJ, Armour JA.** Intrinsic cardiac nervous system in tachycardia induced heart failure. *Amer J Physiol Regul Integr Comp Physiol* 2003; 285 (5): 1212–1223.
52. **Amorim DS, Olsen EG.** Assessment of heart neurons in dilated (congestive) cardiomyopathy. *Br Heart J* 1982; 47 (1): 11–18.

53. **Jurgaitiene R, Pauziene N, Azelis V, Zurauskas E.** Morphometric study of age—related changes in the human intracardiac ganglia. *Medicina (Kaunas)* 2004; 40 (6): 574—81.
54. **Akamatsu FE, De-Souza RR, Liberti EA.** Fall in the number of intracardiac neurons in aging rats. *Mech Ageing Dev* 1999; 109 (3): 153—161.
55. **Ferrari AU, Radaelli A, Centola M.** Invited review: aging and the cardiovascular system. *J Appl Physiol* 2003; 95 (6): 2591—2597.
56. **Micieli G, Tosi P, Marcheselli S, Cavallini A.** Autonomic dysfunction in Parkinson's disease. *Neurol Sci* 2003; 24 (Suppl 1): S32—S34.
57. **Li ST, Dendi R, Holmes C, Goldstein DS.** Progressive loss of cardiac sympathetic innervation in Parkinson's disease. *Ann Neurol* 2002; 52 (2): 220—223.
58. **Goldstein DS.** Dysautonomia in Parkinson's disease: neurocardiological abnormalities. *Lancet Neurol* 2003; 2 (11): 669—676.
59. **Goldstein DS, Holmes C, Li ST, Bruce S, Metman LV, Cannon RO.** Cardiac sympathetic denervation in Parkinson disease. *Ann Intern Med* 2000; 133 (5): 338—347.
60. **Wakabayashi K, Takahashi H.** Neuropathology of autonomic nervous system in Parkinson's disease. *Europ Neurol* 1997; 38 (Suppl 2): 2—7.
61. **Iwanaga K, Wakabayashi K, Yoshimoto M et al.** Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. *Neurology* 1999; 52 (6): 1269—1271.
62. **Okada Y, Ito Y, Aida J, Yasuhara M, Ohkawa S, Hirokawa K.** Lewy bodies in the sinoatrial nodal ganglion: clinicopathological studies. *Pathol Int* 2004; 54 (9): 682—687.
63. **Mravec B.** Salsolinol, a derivative of dopamine, is a possible modulator of catecholaminergic transmission: a review of recent developments. *Physiol Res.* 2005.
64. **Schorb W, Ertl G.** Angiotensin II type 1 receptor induced signal-transduction pathways as new targets for pharmacological treatment of the renin—angiotensin system. *Basic Res Cardiol* 1996; 91 (Suppl 2): 91—96.
65. **Krum H.** Sympathetic activation and the role of beta-blockers in chronic heart failure. *Aust N Z J Med* 1999; 29 (3): 418—427.
66. **Hogg RC, Trequatrini C, Catacuzzeno L, Petris A, Franciolini F, Adams DJ.** Mechanisms of verapamil inhibition of action potential firing in rat intracardiac ganglion neurons. *J Pharmacol Exp Ther* 1999; 289 (3): 1502—1508.
67. **Swanson LW (Ed).** Brain architecture. Understanding the basic plan. New York; Oxford University Press, 2003: 1—263.
68. **Wood JD, Alpers DH, Andrews PL.** Fundamentals of neurogastroenterology. *Gut* 1999; 45 (Suppl 2): II6—II16.
69. **Verrier RL, Antzelevitch C.** Autonomic aspects of arrhythmogenesis: the enduring and the new. *Curr Opin Cardiol* 2004; 19 (1): 2—11.
70. **Crick SJ, Sheppard MN, Anderson RH.** Nerve supply of the heart. 3—54. In: Ter Horst GJ (Ed.). *The nervous system and the heart.* New Jersey; Humana Press, 1999.

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