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Review Article

The Human Heart as the "Little Brain"—the Intrinsic Cardiac Nervous System (ICNS)

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Abstract

The heart is extensively supplied with nerves of the autonomic nervous system (ANS). These nerves allow the brain to have neural control of vital cardiac activity. The sympathetic and parasympathetic branches of ANS act antagonistically to regulate the mechanical and physiological functions of the heart, atrial and ventricular contractions, heartbeat, heart rhythm, blood flow, and blood pressure.

Nerves descending from the brain stem provide a continuous network of cardiac nerves and ganglia disseminated in the atrial and ventricular epicardial of the heart. This extensive system of nerves in the heart, termed the intrinsic cardiac nervous system (ICNS), controls local cardiac activity and is sometimes called the "little brain". However, the little brain is not solely responsible for the cardiac activity, as is evident in various cardiovascular diseases.

A brain injury can affect heart function, indicating that the brain plays a significant role in modulation heart physiology. A scientific quest that has been continuing for more than a century has unraveled some of the factors responsible for heart functions. In recent years, crosstalk between the little brain and the brain's central nervous system has become a crucial topic of research as scientists have realized its clinical implications.

The high number of deaths from cardiovascular disease has made it imperative to explore this interactive signaling network to develop appropriate therapeutic interventions. In this review, the role played by this second brain is explicated, leading to a greater understanding not only of its function within the heart but also its connection to the human brain.

Keywords: *Autonomic Nervous System; Intrinsic Cardiac Nervous System; Neural Crest Cells; Pulmonary; Sympathetic Nervous System*

Abbreviations

ANS: Autonomic Nervous System; AV: Atrioventricular; CANS: Cardiac Autonomic Nervous System; CCS: Cardiac Conduction System; CNS: Central Nervous System; CVD: Cardiovascular Disease; GP: Ganglionated Plexus; ICNS: Intrinsic Cardiac Nervous System; NCC: Neural Crest Cell; SA: Sinoatrial; RFCA: Radiofrequency Catheter Ablation

Introduction

Since antiquity, the human heart has been a physiologically complex organ that has fascinated philosophers, physicians, and scientists. Heart-related diseases that affect millions of people worldwide are the subject of intense physiological and clinical studies even today.

The heart is mainly composed of cardiac muscle tissue, fibrous, and neural tissue. Today, what is known about this organ has come from a series of studies by ancient philosophers to modern scientists. As a Greek philosopher, Aristotle (384–322 BCE) proclaimed the heart as a superior organ [1]. Even the first Egyptians mummified their dead by embalming only their heart within them [1]. They probably believed that the heart is needed to start the journey in the afterlife.

Galen initially wrote the foundation of scientific evidence on the heart's structure and function in the book *De usu Partium* [2]. Galen, born in 129 AD in Pergamon, Greece, was a philosopher, physician, and anatomist when science was significantly influenced by politics and religion [3].

As a physician of gladiators, Galen observed the heart beating in soldiers dying from chest wounds, and later based on his experiments on animals, he concluded that the heart is a muscle mass that functions as a pump [4]. He claimed that the arteries carry blood instead of air, as was believed at that time. Galen was first in describing and depicting human pulmonary circulation. However, he erroneously stated that the liver produced and distributed blood, which was then consumed by the body. In addition, he opined that the interventricular septum possessed pores so that blood moved from one side to the other of the ventricle [4]. Galen was was much repected for his views, which remained unchallenged for over one thousand years.

In his book *De Humani Corporis Fabrica* (published in 1543 ACE), Andreas Vesalius dispelled some of Galen's findings [2]. However, Michael Servetus, in his 1553 book publication, completely discarded the notion of the leaky nature of the septum dividing the ventricles. Instead, he proposed that blood movement from the right to the left side of the ventricle occurs through the pulmonary artery and the lungs [4].

A contemporary of Servetus, Realdo Colombo in 1559 CE, described the phases of contraction and relaxation in the heart in his book *Di re anatomica*l. He also described the heart valves and observed the unidirectional flow of blood in the heart chambers [4]. Girolamo Fabricius, who succeeded Colombo as an anatomist at Padua University, discovered valves in the veins [4].

William Harvey (1578–1657), much inspired by his teacher Fabricius, later summarized the function of these valves and the overall function of the heart in *Du Motu Cordis*, published in 1628 [5]. Harvey is credited with a highly detailed description of blood flowing in two separate directions from the heart, the pulmonary and the systemic circulation. Harvey was perplexed by Gallen's view that the liver is the factory of blood production and the total consumption of blood by the body. Harvey keenly observed the hearts in animals and reported that the heart beats about 72 times per minute, and around 540 pounds of blood is pumped out by the heart per hour. Thus, it is acknowledged to that he initiated the birth of physiology and, even more precisely, that of quantitative physiology [5].

In the 18th century, Albrecht von Haller observed an animal's heart beating even after its dissection and inferred that the nervous system plays no role in initiating a heartbeat [6]. However, the heart continued to be the subject of scientific discussion and study, and a definite interaction between the brain and cardiovascular function was known in the early 19th century.

Georges Romanes' work on jellyfish provided a fundamental understanding of the basis of the heartbeat. In 1839, Robert Remak discovered ganglion cells while studying the sinus venosus of the frog heart. In 1845, Eduard and Ernst Weber, German physiologists, proved the inhibitory effect of the vagus nerve on cardiac ganglia activity [6].

Thus, through the committed research of various physicians and scientists, the significance of cardiac mechanisms and functions became more thoroughly understood 20th century [7]. Further research in the 21st century should provide more answers to further the development of therapies and treatments for several cardiac diseases.

Discussion

The heart is a vital organ, fist-sized and securely lodged on the slightly left side of the breastbone. The heart is a pumping organ that starts its first beat at the end of the fourth week of gestation [8]. The brain only regulates the physiological function that includes the rhythm of the human heart, or so it was believed for a long time until more scientific data allowed physicians to concede the myogenic theory [4,9]. Scientific advancement has now revealed the role of the autonomic nervous system (ANS), part of the central nervous system (CNS), and an intrinsic cardiac nervous system (ICNS) that coordinate normal physiological cardiac functions [10].

Intrinsic cardiac nervous system (ICNS)

The heart is supplied by two types of nerves—extrinsic and intrinsic. The brain controls the heart through parasympathetic and sympathetic nerves that form the extrinsic system [11]. The sympathetic system connects to the heart through the intrathoracic ganglia [12]. The CNS regulates the activity of sympathetic nerves through the intrathoracic extracardiac ganglia [13] to positively affect heart functions, such as increasing heart rate, excitability, conduction velocity, and contraction of the heart ventricles.

The vagus nerve of the parasympathetic nervous system innervates the heart. Parasympathetic nerves act antagonistically to sympathetic nerves [12] and maintain balance and support normal organ functioning. However, they work jointly with an ICNS to fine-tune all cardiac functions.

Location and distribution of the ICNS

The ICNS is an extensive and complex nerve network in the heart—a telltale feature of the brain and is thus called the "mini brain" [14] or the "little brain" [13] located in the fat pads of the epicardium of the heart [10]. The intrinsic cardiac nervous system interacts with the extrinsic system for proper cardiac function [14].

The cardiac nerves are inundated with sensory ganglia. These cardiac ganglia are large and easily observed in other vertebrates, such as amphibians, reptiles, and birds. In contrast, the histological studies show that the human heart has varied sizes of ganglia, each with its unique number of neurons ranging from small to large [10,15], disseminated, and not easily detectable [9,15]. Human cardiac neurons have an average size of 39 μm [10].

Nerves connect these ganglia and together are called the ganglionated plexus (GP) [10]. These GPs are distributed in both the atrial and ventricular regions of the heart [10]. An extensive map of cardiac neurons and ganglia has been illustrated by Pauza., *et al.* (2000) [15]. The group worked with the hearts of fetuses and adults to locate the intrinsic ganglia of the heart [15]. Recently, a detailed 3D structure of the heart and the ICNSs in rats has been developed [16].

Embryology of the ICNS

During embryological development in mice, Hildreth., *et al.* (2008) [17] discovered that neural crest cells (NCCs) migrate, develop, and later form a large part of the parasympathetic nerves and a small part of sympathetic nerves that innervate the heart. Most research regarding the embryological origin of cardiac neurons has been recent.

Cells that contribute to the formation of cardiac neurons originate in the neural tube in the early stage of development [18], although these early NCCs differentiate distinctly. NCCs, also called cardiac neural crest cells [19], are multipotent stem cells that have been reported to be involved in the formation of the cardiac ganglion in the chick embryo [20].

The NCCs migrate from the neural tube during the fifth week of fetal development. The migration and accumulation of NCCs near the dorsal aorta are essential for their subsequent differentiation and development. These cells display a high degree of neuroplasticity at this stage. Further differentiation includes ganglia formation and terminal differentiation of neurons [18].

Nerve fibers of the ICNS

Thus far, ICNSs have been found in all mammals studied [21]. Different types of neurons are found within mammalian ICNSs [10]. In one early study, these neurons were reported to be sensory types. They showed various morphologies with an excentric nucleus [9]. However, with advanced technology, this investigative work has been simplified to some extent. Electron microscopy results have suggested that intrinsic cardiac neurons resemble autonomic neurons. The axodendritic synapses between neurons were more abundant than the axosomatic synapses, rarely seen in the human ICNS ganglia [10].

Heartful decisions: heart-brain communication

It is commonly imagined that the heart is the center of human emotions, including love, hate, anger, joy, sorrow, and fear—these feelings can be monitored by changes in heart rate and blood pressure [14]. The sympathetic and parasympathetic branches of the ANS act antagonistically and are responsible for maintaining physiological stasis of the heart. Thus, an injury to the brain can manifest itself in cardiovascular complications.

The brain controls emotions through the limbic system that the hypothalamus regulates [14,22]. The hypothalamus, in turn, manifests emotions due to various extrinsic and intrinsic stimuli [22]. Psychophysiology is the study of understanding this communication between the two major organs.

Brain and heart communication are not one-way channels. The CNS regulates cardiac activity, but the heart also communicates with the brain. John and Beatrice Lacey suggested this conversation between these two organs—through their various experiments on animals during the 1960s and 1970s. Afferent signals from the heart influence brain perceptions and thus behavior of animals [23].

Neurocardiology is a relatively new field of study that correlates the function of the heart with the brain. The nervous system can induce cardiac arrhythmias in response to cardiac damage [24]. An earlier study showed that the brain's cuneate nucleus is affected by vago-aortic afferent nerves in cats [25]. Numerous studies have indicated that there is crosstalk between the two organs.

ICNS functions

Sinoatrial (SA) and atrioventricular (AV) nodes and the His-Purkinje system comprise the cardiac conduction system (CCS) of the heart [26].The SA node is the initiation point for a heartbeat and, as such, is called the natural pacemaker of the heart. The conduction of the

action potential generated by cells at the SA node to the other cells of the heart maintains the heart's rhythm. The AV node modulates this signal before it is transmitted to the ventricles. The His-Purkinje system propagates the impulse towards the ventricle walls [27]. Thus, the ICNS plays a vital role in generating and conducting electrical impulses throughout the heart.

Cells of the sympathetic branches of the nervous system—through the ICNS—spread and contact cardiomyocytes. Cardiac cell contraction is regulated by norepinephrine released by adrenergic neurons of this system [28]. The neurotransmitter norepinephrine binds to β1 and β2 adrenergic receptors. Acetylcholine released from neurons extending from the parasympathetic branches of the ANS promotes the slowing of cardiomyocyte contractions [29]. Histological studies have shown that these two types of nerves, adrenergic and cholinergic, are characteristically colocalized in heart tissue [30].

The ICNS also plays a role in modulating cardiac operations, including atrial fibrillation. It has been suggested that the ICNS participates in regulating arrhythmogenesis [30]. The ICNS and ANS together form a complex called the cardiac autonomic nervous system (CANS) that modulates atrial fibrillation and can be targeted to treat arrhythmia [31].

Transplanted heart studies have been instrumental in deciphering the significance of ICNS function and its connection to the ANS. If nerves are severed during surgery, there is an imbalance in the system that regulates heart rhythm [32]. The current consensus is that the parasympathetic nervous system typcially has little effect on myocardial contractility [33]. However, denervation of sympathetic nerves influences the increase blood flow during stress or exercise [34]. Interestingly, the reinnervation of these nerves occurs in the transplanted heart even thirteen years after surgery [35]. It is suggested that the ICNS undergoes a process of neuromodulation to retain the heart's function [36].

ICNS' role in disease and pathology

Cardiovascular diseases (CVDs) are responsible for approximately 17.9 million deaths worldwide annually [37]. Hence, CVDs are the topic of intense clinical studies and research. A truncated list of cardiovascular diseases includes high blood pressure, myocardial infarction, cardiomyopathy, focal inflammation, congestive heart failure, atrial and ventricular arrhythmias, and sudden cardiac death [11,32,38].

Sympathetic dysfunction leads to cardiac anomalies, and studies on these diseased hearts lead to a better understanding of this connection. The adverse cardiac events that follow sympathetic nerve dysfunction are severe arrhythmias and sudden cardiac death [32]. One of the causes of for congestive heart failure is a decrease in the re-uptake of norepinephrine by neuronal transporters [39]. Increased sympathetic nerve activity has also been reported in chronic heart failure [40]. Studies on induced cardiac hypertrophy in rats have shown that its effect leads to localized hyperinnervation, adversely affecting soma functions [41]. Hyperactivation of an intrinsic cardiac ganglion can induce atrial and ventricular arrhythmias [13].

Interestingly, in a study in dogs, radiofrequency catheter ablation (RFCA)—resulting in vagal denervation of the SA and AV nodes—improves heart rate variability, and this ablation process did not adversely affect ventricular functions [42]. Cardiomyopathy in diabetic patients revealed that diabetes could also lead to cardiac neuropathy [43].

Myocardial infarction (MI) influences the myocardium and CANS function, especially the ICNS [44]. MI most often results in arrhythmia, sometimes leading to heart failure [11]. Also, there is an alteration in neuropeptide production in sympathetic cardiac nerve cells due to MI [45].

Hardwick., *et al.* (2014) observed physiological changes in the ganglion plexuses within four days after induced MIs in guineapigs. Futhermore, the researchers noted a higher response to norepinephrine up to a week after the induced MIs. This altered response may have been due to an immediate neuromodulation response, improving parasympathetic-signally function [46].

It has been suggested that CVD studies will provide a better understanding of the mechanism of heart regulation and, in turn, enable researchers to develop targeted therapeutics to treat various types of CVDs [38,47]. Ventricular ischemia therapy preposes targetting the signal input received by the ICNS from the extracardiac ganglia to prevent its hyperactivation [48].

Evolutionary significance of the ICNS

The regulation of the heart by the CNS is vital for cardiac functioning. This axis, commonly called the brain-heart axis, has existed for 500 million years in cartilaginous and bony fishes [49]. The inhibitory action of parasympathetic innervation on the heart is present throughout vertebrate evolution [50]. The parasympathetic nervous system controls heart function in cartilaginous fish, while both the parasympathetic and sympathetic systems control the same in bony fish [49].

Pauza., *et al.* (2000) reported that about 9316 neurons are present in each human epicardiac ganglion [15]. However, the number of neurons vary with age. An infant has about 94,000 neurons, which usually reduces to about 43,000 in the elderly [15].

Galen first observed that the heart could throb even when removed from the body, indicating that the heartbeat is not dependent solely on its nerve connection with the brain [3]. The brain controls heart function, but not entirely, strongly suggesting that the ICNS had evolved to play a more specific role in modulating cardiac rhythm.

The brain-heart complex is highly interconnected and interrelated—a hallmark of highly evolved multicellular organisms. Thus, it can be opined that this intricate network of nerves in the heart is evolutionarily significant as it takes up more complex functions along with its communication with the brain to perfect the modulation of heart function.

Conclusion

Although the ICNS is an extension of the sympathetic and parasympathetic branches of ANS and is under CNS control, there is sufficient evidence implying that the ICNS is a local cardiac modulation system. The extrinsic system of nerves (ANS) works closely and intimately with the ICNS.

The ganglia plexus on the three fat pads of the heart (two atrial and one ventricular)—interconnected by nerves—forms the ICNS. These nerves affect the SA node, the AV node, and ventricle contraction and together maintain the heart's rhythm. Thus, the ICNS in conjunction with the CNS, controls the chronotropic, dromotropic, ionotropic, and lusitropic functions of the heart through the feedback loops of the sympathetic and parasympathetic branches of the ANS.

Future research should reveal more detailed mechanisms regarding the "littel brain's" purpose, offering solutions for new drug development and clinical treatments. This increased understanding will enhance the quality of life for those affected by CVD.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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