Ivabradine modulates the autonomic nervous system by affecting the “little brain” of the heart: A hypothesis

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**ABSTRACT**

Ivabradine decreases heart rate by selective inhibition of the If current in the sinoatrial node. Ivabradine is declared to have no direct effect on the autonomic nervous system (ANS). However, there are some data suggesting an (at least indirect) effect of ivabradine on the ANS. The pathomechanism behind is unclear. Based on the complex ofplexuses and ganglia in the heart, the existence of the intrinsic cardiac nervous system (ICNS), also known as the “little brain” of the heart, has been suggested. The human ICNS consists of seven epicardic neural ganglionated plexuses that are extensions of mediastinal nerves penetrating the heart via its hilum. The right and left atrium is innervated by two and three plexuses, respectively. In the neural plexuses, there are 700–1500 intracardiac ganglia formed by a complex array of neurons and topographically placed around the cardiac conduction system. The free wall of right atrium and most of the ventricular myocardium appears to be ganglion-free. An intracardiac ganglion comprises 200–1000 neurons morphologically and functionally divided into four subtypes: (i) sympathetic postganglionic neurons connecting the heart with the sympathetic nervous system, (ii) parasympathetic postganglionic neurons connecting the heart with the parasympathetic nervous system, (iii) local circuit neurons receiving inputs from both sympathetic and parasympathetic preganglionic neurons and connecting with adjacent neurons in the same ganglion or projecting to neurons in other intracardiac ganglia, and (iv) afferent neurons transducing cardiac sensory information from the cardiac milieu and providing the central nervous system with these data. Setting a new autonomic balance by ivabradine might be of benefit in the treatment of autonomic dysfunction-related pathologies.

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Ivabradine decreases heart rate (HR) by selective inhibition of the If current in the sinoatrial node. The European Society of Cardiology recommends ivabradine for treatment of patients suffering from both heart failure with HR above 70 bpm to reduce the risk of the composite endpoint of cardiovascular death or hospital admission and for coronary artery disease (CAD) to relieve myocardial ischemia. Nonetheless, ivabradine has no effect on alpha- and beta-adrenoceptors or baroreflex and a direct effect on the central nervous system is improbable due to its inability to cross the blood-brain barrier; thus, the mechanism of how ivabradine induces a parasympathetic preponderance remains elusive.

The following insight into the intrinsic cardiac nervous regulation might shed more light on the pathomechanism of ivabradine’s interference with the ANS. The morphologic evidence of intrinsic cardiac nerve fibres creating a complex of plexuses and ganglia in the heart indicated the existence of the intrinsic cardiac nervous system (ICNS), commonly known as the “little brain” of the heart. The human ICNS consists of seven epicardic neural ganglionated plexuses that are extensions of mediastinal nerves penetrating the heart via its hilum. The right and left atrium is innervated by two and three plexuses, and the right and left ventricle gets one and three plexuses, respectively. In the neural plexuses, there are 700–1500 intracardiac ganglia formed by a complex array of neurons and topographically placed around the cardiac conduction system. The free wall of right atrium and most of the ventricular myocardium appears to be ganglion-free. An intracardiac ganglion comprises 200–1000 neurons morphologically and functionally divided into four subtypes: (i) sympathetic postganglionic neurons connecting the heart with the sympathetic nervous system, (ii) parasympathetic postganglionic neurons connecting the heart with the parasympathetic nervous system, (iii) local circuit neurons receiving inputs from both sympathetic and parasympathetic preganglionic neurons and connecting with adjacent neurons in the same ganglion or projecting to neurons in other intracardiac ganglia, and (iv) afferent neurons transducing cardiac sensory information from the cardiac milieu and providing the central nervous system with these data. Setting a new autonomic balance by ivabradine might be of benefit in the treatment of autonomic dysfunction-related pathologies.
the heart to the ganglion [9]. Interestingly, the majority (more than 75%) of the intracardiac neurons is cholinergic (parasympathetic) and only about 10% is adrenergic (sympathetic). Moreover, about 15% of intracardiac neurons has a dual cholinergic-adrenergic character [12,13]. The ICNS seems to be a complex integration site of the autonomic cardiac control with a cardio-cardiac feedback control loop [9]. Indeed, the ICNS is supposed to process information on the cardiac milieu and provide it to the central nervous system. This might explain the dominance of afferent fibres in the autonomic reflex arcs, e.g. nervus vagus [14]. Operating with its own memory, the ICNS offers a special input/output gating mechanism to keep a proper regulatory equilibrium in accordance with previous experiences [15].

We put forward the hypothesis that part of ivabradine’s protective effects might reside in the modulation of the ANS by affecting the ICNS. This insight is based on linking the following particular considerations: (i) ivabradine reduces HR selectively; (ii) ivabradine induces parasympathetic preponderance; (iii) the ICNS processes information regarding the cardiac hemodynamics and metabolism and provides it to brain centres; (iv) the central nervous system processes the afferent information and modulates the ANS accordingly (Fig. 1). The pathomechanism of ivabradine’s interference with the "little brain" of the heart is hypothetical. We suggest a participation of both metabolic and hemodynamic alterations. The former may be associated with the well-established fact that bradycardia induces an improvement of energy metabolism via prolongation of the diastolic coronary bed perfusion and subsequent reduction of the release of ATP-splitting products, such as adenosine, or attenuated lactate production, particularly in the heart [16]. Alteration of hemodynamics in terms of heart rate reduction, even in the healthy heart, results in prolongation of the left ventricular filling time in diastole related to the enlargement of the end-diastolic volume with increased wall tension and adjusted stroke volume [17]. These metabolic and hemodynamic changes may interfere with the plexuses and ganglia of the intrinsic cardiac nervous system in a complex manner, thus modulating the autonomic nervous system. Supposedly, the information processed by the ICNS and subsequently provided to the central nervous system might be influenced not only by a pharmacological trigger, e.g. ivabradine-induced I_{K1} current inhibition, but also by the particular physiological or pathological condition.

Setting a new autonomic balance by ivabradine might be of benefit in the treatment of autonomic dysfunction-related pathologies such as postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia [18,19]. Thus, ivabradine may become an alternative or complementary treatment to the alpha- and beta-adrenoceptor blockers and avoid or minimise their side effects.

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**Declaration of Competing Interest**

The authors declare no conflict of interest.

**References**


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