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Ion channel expression in intrinsic cardiac neurons: new players in cardiac channelopathies?☆

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A B S T R A C T

The autonomic nervous system is an important modulator of electrical disorders observed in cardiac pathologies through changes in the balance between sympathetic and parasympathetic tone. The final common pathway for cardiac neuronal autonomic control resides in the intrinsic cardiac nervous system (ICNS), composed of intracardiac neurons (ICN), and which allows sympathetic-parasympathetic efferent neuronal interactions at intracardiac sites. The ICNS is a complex system that plays a crucial role in the regulation of cardiac physiological parameters and has been shown to contribute to cardiac diseases, in particular cardiac arrhythmias. It is therefore crucial to understand the molecular determinants, such as ion channels, that control the excitability of the ICNS and their potential modulation in pathological conditions.

This review discusses several ion channels expressed by ICN, including potassium channels (e.g., inward rectifier, calcium-dependent, voltage-activated, muscarinic-sensitive), voltage-gated sodium channels (VGSC), voltage-gated calcium channels (VGCC), hyperpolarization-activated cyclic nucleotide–gated (HCN) channels and Transient Receptor Potential (TRP) Channels, and their potential involvement in cardiac pathologies. We highlight the need for further research on ICN ion channels, particularly under pathological conditions, to develop therapies for cardiac arrhythmias.

1. Introduction

Since Hodgkin and Huxley established the ionic basis of neuronal action potentials, the field of ion channel research has made considerable headway in neuroscience and cardiology. It took a giant step forward with the cloning of ion channel genes allowing the identification of a number of mutations that cause abnormal functions of these proteins leading to human diseases called channelopathies. To date, numerous inherited cardiac electrical disorders such as, Long QT Syndrome, Brugada Syndrome or catecholaminergic polymorphic ventricular tachycardia have been associated to the mutations of ion channels [1]. The cardiomyocyte being at the crossroads of cardiac automatic, contractile and conduction abilities, it has attracted main focus to address channelopathies. Although these studies have brought key information in the mechanistic knowledge of these pathologies, many parameters involved in the occurrence, the maintenance, the severity or the complexity of the pathologies remain to be elucidated. Apart from cardiomyocytes, the heart is composed of several cell types, also expressing ion channels, amongst which the intrinsic cardiac neuronal population is of growing interest for its pathophysiological implications.

The autonomic nervous system plays a pivotal role in regulating cardiac electrical disorders through alterations in the equilibrium between sympathetic and parasympathetic activity [2–4]. The final common pathway for cardiac neuronal autonomic control is situated within the intrinsic cardiac nervous system (ICNS), which is composed of intracardiac neurons (ICN). This system enables interactions between sympathetic and parasympathetic efferent neurons at intracardiac sites [5,6]. These ICN are organized as interconnected nodes thereby forming ganglion plexus localized within the epicardial adipose tissue [7–9]. Several classes of ICN have been identified based on their expression of several markers [6,10–13]. Indeed, while the vast majority of ICN express cholinergic markers, a subset of them also express tyrosine hydroxylase, a marker of catecholaminergic neurons. Furthermore, the phenotypic diversity of ICN is also characterized by the expression of additional markers, including the calcium-binding protein calbindin, the neuropeptide Y, the neuronal nitric oxide synthase, and the cocaine and amphetamine-regulated transcript peptide. On another hand, electrophysiological studies have demonstrated the existence of distinct neuronal populations based on their electrical properties [10,14–16]. The ICNS is therefore a complex system that plays a crucial role in the

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regulation of cardiac physiological parameters and has been shown to contribute to cardiac diseases and particularly to cardiac arrhythmias. For example, atrial fibrillation has been correlated with excessive activity of ICN [17]. The ablation of ganglionated plexus reduces AF and is one of the strategies used in therapy [18,19]. Apart from atrial electrical disorders, this system has also been related to ventricular arrhythmia susceptibility through its modulation of ventricular refractory periods [20]. In heart failure, structural remodeling of ICN as well as electrophysiological alterations of this system through changes in ionic channel expression, also increase ventricular arrhythmia susceptibility [21,22]. ICN remodeling is also observed in diabetes and is associated to cardiac arrhythmias [23]. As a consequence, ICN can be considered as a crucial cardiac cell type, playing a pivotal role in regulating cardiac physiology and pathophysiology. It is therefore crucial to advance our understanding of this system with regard to ionic channels in pathological conditions.

This review focuses on this cell type and questions the potential involvement of modulation of their ion channels in cardiac pathologies. Noteworthy, ligand-gated ion channels, while undoubtedly of high physiological significance, are not covered in this review. On another hand, this review is focused on ICN which are postganglionic parasympathetic neurons but the knowledge of ion channel expression in other structure of the autonomic nervous system constitutes important parameters as well.

2. ICNS ionic channels and physiopathological consequences

2.1. Potassium channels

Amongst all ion-transporting proteins, potassium channels stand out for their remarkable diversity in molecular structure and organization. In excitable cells, they play a critical role in establishing the negative resting membrane potential due to their inherent potassium permeability. Modulation of potassium channels, whether pharmacological or physio-pathological, profoundly influences the functional properties of most, if not all, biological tissues. This central role positions them at the heart of cellular behavior, making them essential targets for any investigation into cellular electrophysiology.

Within the central and peripheral nervous systems, all types of potassium channels have been identified and functionally characterized. Notably, most of these channels are also found within the ICNS. Here, we will review these channels based on the family they belong to (see Fig. 1 and Table 1).

2.1.1. Inwardly rectifying potassium channels

For decades, inward rectification of potassium currents has been described to account for underlying negative resting membrane potential in ICN. This phenomenon explains the distinct behavior observed in different ICN types [24]. Hogg et al. (2001) [25] characterized a Ba^{2+}-sensitive K_{IR} current present in approximately 33 % of adult rat ICN. During postnatal development, this channel expression increases, coinciding with a decrease in hyperpolarizing h-current density [25] (see next chapter). These changes contribute to the shift in neuronal excitability between neonatal and adult rat ICN. Indeed, the increase in K_{IR} and the decrease in Ih result in an increase in intraburst frequency of action potentials, a decrease in after-hyperpolarization amplitude (AHP) and a recovery of resting membrane potential after AHP. Consequently, in adult ICNs, neuronal excitability is decreased when compared to neonatal ones. Recently, KCNJ3 has been identified in pig ICN as a molecular candidate for K_{IR} Channels [26].

Other inward rectifier potassium channels, known as ATP-sensitive potassium channels, not only influence cell membrane potential but

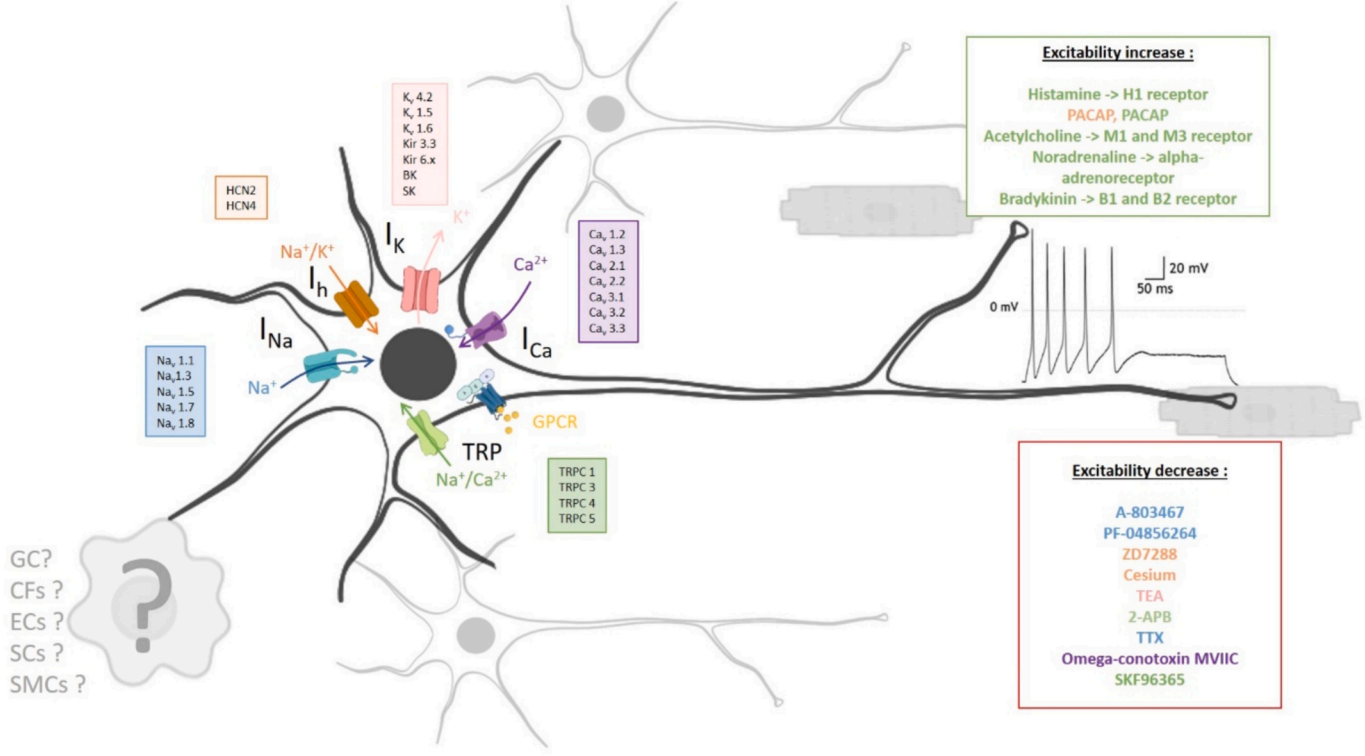

Fig. 1. Ion channels in interaction with ICNS. Overview of potential ion channels identified in ICN and the effect of their modulation on neuronal excitability. Cardiac cell types, other than ICNs, are represented in watermarks. Glial Cells (GC), Cardiac Fibroblasts (CFs), Endothelial cells (ECs), Stem cells (SCs), and Smooth muscle cells (SMCs). Pharmacological modulators of ion channels and their effects on ICN excitability are shown in the green box (increase in excitability) and the red box (decrease in excitability). The colors of the pharmacological modulators correspond to the colors of the ion channel families they target. Tetraethylammonium (TEA), Tetrodotoxin (TTX), Pituitary Adenylate Cyclase-Activation Polypeptide (PACAP), 2-aminoethoxyl-diphenyl borate (2-APB), and G Protein Coupled Receptors (GPCR). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Molecular identity of ion channels identified in intrinsic cardiac neurons. g-p: guinea pig; IHC: immunohistochemistry; TEA: tetraethylammonium; 4AP: 4-Aminopyridine; TTX: Tetrodotoxin, 2-APB: 2-Aminoethoxydiphenyl borate; FFA: Flufenamic acid.

Ion Channels	Current	Isoforms	Species	Molecular detection method/pharmacology	Current recorded	Ref
Potassium channels	Inward rectifier	K_{IR}	Ra	- / Voltage-dependence, Ba^{2+}	Yes	[25]
		$K_{IR}3.3$	pig	qRT-PCR/	no	[26]
	ATP-sensitive	$K_{IR}6.x/SUR2.X$	rat	- / sulfonylureas, levcromakalim	yes	[27]
	I_A	$K_v4.2$	rat, g-p	- / 4AP sensitive	yes	[28,31]
	Delayed rectifier	$K_v1.5/Kv1.6$		- / TEA sensitive	yes	[33]
	Calcium-dependent	BK	dog, rat	IHC / Charybdotoxin and TEA sensitive	yes	[38,41]
		SK	rat	- / Apamin	no	[39]
	Muscarinic	$K_v7.x$ (KCNQx)	rat, pig, g-p	- / Barium, muscarinic receptor agonists	no	[44,48]
HCN	Ih		g-p, rat	- / Cs^+	yes	[24,25,46]
	Ih		g-p	- / ZD7288, Cs^+ sensitive	no	[59]
	Ih		rat	- / ZD7288, Cs^+ sensitive	yes	[61]
VGSC		HCN2/4	Mouse, pig	Hybridation, qRT-PCR / -	no	[26,62]
	TTX-sensitive	$Na_v1.1$	pig	qRT-PCR /	no	[26]
		$Na_v1.3$	pig	RT-PCR / -	no	[31]
		$Na_v1.7$	pig	RT-PCR / PF-04856264	no	[31]
	TTX-resistant	$Na_v1.5$	dog	IHC, RT-PCR / TTX sensitivity,	yes	[72,73]
		Nav1.8	dog	IHC / A-803467	no	[73,78]
			mouse	IHC / A-803467	yes	[75]
VGCC	L-Type		rat	- / FPL 64176, Nifedipine	yes	[90,91]
		$Ca_v1.2$, 1.3	rat	RT-PCR, IHC / -	no	[92,93]
	P/Q-Type		rat	- / Ω-conotoxin MVIIC	yes	[91]
		$Ca_v2.1$	rat	RT-PCR, IHC / -	no	[92,93]
	N-Type		rat	- / Ω-conotoxin GVIA	yes	[90]
		$Ca_v2.2$	rat	RT-PCR, sh-RNA, IHC / Ω-conotoxin GVIA	yes	[93,98]
	R-Type		rat	- / NiCl2	yes	[91]
		$Ca_v2.3$	rat	RT-PCR, IHC / -	no	[92,93]
	T-Type	Ca_v 3.1, 3.2, 3.3	g-p	RT-qPCR / Nickel, Mibefradil	no	[94]
TRP	TRPC	TRPC?	g-p	- / ionic substitution	yes	[106]
		TRPC?	rat	- / $La3^+$, Gd^{3+}, SKF96365, Cd^{2+}	yes	[107]
		TRPC 1, 3, 4, 5	g-p	RT-qPCR / 2-APB, SKF96365, FFA	no	[109,111,112]
		TRPC?	rat	- / SKF96365, ML204	yes	[108]
		TRPC 4, 5	rat	- / ML204	no	[113]
		TRPC 1, 3, 5–7	rat	- / $Gd3^+$, ML204	yes	[114]

also establish a direct link between cellular metabolism and excitability. These channels which are known to be composed of Kir6.x subunits associated with sulfonylurea receptors (SURx), have been identified in 50 % of ICN isolated from rat [27]. They exhibit a pharmacological profile typical for ATP-sensitive potassium channels, including activation by micromolar concentrations of levcromakalim and inhibition by sulfonylureas like glibenclamide and tobutamide. As with these channels in other cell types, they are suspected to play a role in metabolic injury consequences in ICN, such as those occurring during ischemia-reperfusion episodes.

2.1.2. *Voltage-activated potassium channels*

Rat ICN display a total outward K^+ current upon membrane depolarization which comprises both Ca^{2+}-dependent and Ca^{2+}-independent components [28,29]. Ca^{2+}-dependent K^+ currents will be discussed in the next section.

Amongst the K+ currents activated by depolarization, A-type potassium currents with rapid activation and time- and voltage-dependent inactivation contribute to the early repolarization phase of the action potential in various excitable cells. While some studies have not detected a transient voltage-activated K+ current in rat ICN [29], others have reported an I_A-type current, inhibited by millimolar concentrations of 4-aminopyridine but insensitive to tetraethylammonium [28]. Recently, the presence of A-type potassium current was shown to depend on the species under study [30]. $K_v4.2$ channels, known to contribute to I_A currents, were identified in guinea-pig cardiac ganglia using semi-quantitative PCR. However, the role of I_A currents in ICNS excitability remains debated, as studies have shown them to be either ineffective [31] or to regulate firing rate through contribution to after-hyperpolarization (AHP) decay kinetics [28].

In addition to I_A-type channels, delayed rectifier K+ channels have also been described in rat ICN, the activation of which leading to action potential termination. These channels have been shown to be sensitive to verapamil or D600 [32] and their inhibition by tetraethylammonium (TEA) reduces AHP amplitude [28,29], indicating their involvement in controlling membrane voltage during the action potential. It has been proposed that $K_v1.5$ and $K_v1.6$ may contribute to the molecular identity of the channels responsible for these non-inactivating delayed rectifier potassium currents [33].

2.1.3. *Calcium-dependent potassium channels*

Three types of calcium-activated potassium (K^+) channels (BK, IK, and SK) have been described in neuronal cell populations for decades [34]. These voltage-dependent channels, activated by increase in intracellular calcium following neuronal action potentials, exhibit different sizes of calcium-dependent potassium conductance [35].

Using intracellular microelectrodes, calcium-activated K^+ channels have been shown to contribute to the electrophysiological properties of neurons within the ICNS [36]. Notably, these channels play a role in shaping action potential AHP. Also, $I_{K,Ca}$ channels contribute to resting membrane potential, as evidenced by membrane depolarization observed in rat ICN superfused with calcium-free solution [28,37].

In neonatal rat intracardiac neurons, Ca^{2+}-activated BK channels have been fully characterized and exhibit sensitivity to sub-millimolar concentrations of tetraethylammonium (TEA) but not 4-aminopyridine. These pharmacological properties have been used to demonstrate that calcium-dependent K^+ channels contribute to action potential and AHP durations in these neurons [38]. However, BK channels are not solely responsible for this modulation [38]. SK channels have been shown to be responsible for the postnatal increase in AHP in intracardiac rat neurons thanks to their apamin sensitivity [39]. SK channels similarly influence ICN excitability in mouse, pig and human [30]. In canine cardiac ganglia, Pérez et al. (2013) [40] confirmed the presence of BK calcium-activated K^+ channels. Further investigation revealed that the beta 4

regulatory subunit is the primary BK channel subunit expressed in this tissue, while multiple alpha subunit splice variants contribute to the complexity of the current observed in the ICN [41].

Perez et al., (2013) [40] identified two components in BK currents, both inhibited by paxillin and TEA and activated by calcium influx from the extracellular medium rather than intracellular stores. Interestingly, these channels exhibit rapid inactivation and have minimal impact on AHP amplitude. However, their inhibition leads to a decrease in spike firing, likely due to increased action potential duration and effective refractory period [40].

2.1.4. Muscarinic sensitive (M) potassium channels

Muscarinic receptors on cultured ICN can mediate both cellular excitation (depolarization) and inhibition (hyperpolarization) via M1 and M2 receptors, respectively. M2 and M3 muscarinic agonist bethanecol, for example, was shown to depress intracardiac neuronal activity [42]. Interestingly, both M1 and M2 receptors have been reported to inhibit the M-current [43]. K_v7 channels, belonging to the KCNQ gene family, underlie the M-current [44]. Inhibiting this current, which is partially active at resting membrane potential, can drastically enhance cell excitability.

Identified in rat ICN [28], this M-current is blocked by muscarine at micromolar (μM) concentrations, thereby eliciting or stimulating action potential firing. Barium, at millimolar (mM) concentrations, inhibits the M-current, while cesium has no effect. Besides, acetylcholine application to ICN decreases peak calcium channel amplitude through M4 muscarinic receptors [45].

Therefore, the muscarinic receptors and the M-current control ICN excitability. Inhibition of the M-current by muscarinic activators like acetylcholine contributes to increased ICN firing and can be considered a key modulator of discharge activity in these neurons [46].

Physiopathological injuries can influence ICN excitability by modulating the M-current. For example, oxidative stress [44] or reactive oxygen species [47] enhance the M-current, leading to cytoprotective neuron silencing. Conversely, [48] recently demonstrated an increased M-current in pathological conditions like myocardial infarction.

2.1.5. Conclusion

In conclusion, potassium channels play a pivotal role in regulating the electrophysiological properties of neurons within the ICNS. The diverse array of potassium channel families, including inwardly rectifying, voltage-activated, calcium-dependent, and muscarinic-sensitive channels, contributes to a complex interplay that shapes neuronal excitability. These channels influence resting membrane potential, action potential dynamics, and firing patterns, ultimately impacting the function of the ICN. Furthermore, the modulation of potassium channels by various factors, including neurotransmitters, pharmacological agents, and pathological conditions, highlights their critical role in both physiological and pathological processes. Understanding the intricacies of potassium channel function and regulation is essential for developing therapeutic strategies targeting neuronal excitability and related disorders. While potassium channels are well-established as critical players in cardiac channelopathies, with polymorphisms in their encoding genes clearly impacting cardiomyocyte excitability and contributing to cardiac pathologies, the role of altered intracardiac neuron (ICN) electrophysiological properties, specifically through neuronal potassium channel modulation (see Table 2), in overall heart pathology remains unclear. This area undoubtedly warrants further investigation.

2.2. Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels

The Hyperpolarization-activated cyclic nucleotide–gated current, abbreviated Ih or If, is distributed in many excitable cells. h-current is well-known to play an important role in the generation of spontaneous pacemaker activity in the heart and brain [49,50]. Besides controlling pacemaker activity, Ih also has various non-pacemaking functions such as determination and control of resting potential, alternation of membrane resistance, synaptic transmission and participation in perception [50]. In mammals, there are four different genes encoding four isoforms (HCN1–4) which contain six transmembrane segments (S1–S6) (including a positively charged S4 segment) and a cyclic nucleotide-binding domain (CNBD) located in the C-terminal region. It has been clearly demonstrated in cells from the sinus node of the heart that the pacemaker current is directly modulated by the intracellular level of cAMP [51–53]. HCN1 channels are predominantly expressed in the brain and to a limited extent in the heart and the adrenal glands. HCN2 and HCN3 are expressed in brain, heart, adrenal, testis and esophagus. HCN4 is predominantly expressed in testes and heart, less in brain and adrenals. Direct cAMP-dependent modulation is best observed with HCN2 and HCN4, whereas HCN1 is moderately modulated and HCN3 appears unmodulated [54,55]. All these isoforms are sensitive to cesium, ZD7288 and ivabradine [56,57].

Very little has been done to characterize and understand the role of this pacemaker current in ICN (see Fig. 1 and Table 1). Cardiac neurons show a depolarizing current that is activated by hyperpolarization and inhibited by cesium and ZD 7288, suggesting the presence of HCN channels in these neurons [24,38,46,58]. It is hypothesized that the h-current is involved in the increased excitability of ICN induced by pituitary adenylate cyclase-activating polypeptide peptides, which co-localize with acetylcholine in the preganglionic parasympathetic fibers innervating the guinea pig intracardiac ganglia. This increase in excitability is sensitive to cesium and ZD7288 [59]. Furthermore, in dissociated guinea pig ICN, α-amidated biologically active polypeptides (PACAP27) increase Ih by shifting the voltage dependence of activation. This effect would be mediated primarily by PAC1 receptor activation of adenylyl cyclase and generation of cAMP [60]. Conversely, the reduction in h-current density observed in adult intracardiac neurons in

Table 2
Cardiac channelopathies related to mutations of channels potentially expressed in ICN. LQT: Long QT, SQT: Short DT, PEPD: Paroxystic Extreme Pain Disorder, PCCD: progressive cardiac conduction defect.

Ion Channels	Isoforms	Cardiac channelopathies or Cardiac consequences of mutations	Ref
Potassium channels	K_{IR} (KCNJ2/ KCNJ3)	the Andersen-Tawil syndrome/ LQT7	[119,120]
		SQT3	[121]
		Atrial fibrillation	[122,123]
		Heart failure	[124]
		Adrenergic Atrial Fibrillation	[125]
	K_{IR}6.2	Ventricular fibrillation	[126]
		J-wave syndrome susceptibility	[127]
		Dilated cardiomyopathy	[128]
	K_v4.2	Ischemic/dilated cardiomyopathy	[129]
	K_v1.5	Atrial fibrillation	[130]
	KCNMA1 (BK)	Myocardial infarction/ Heart failure	[131]
	K_{Ca}2.x/ K_{Ca}3.1 (SK)	Atrial fibrillation	[132]
HCN	HCN4	Bradycardia, tachycardia	[64,65]
VGSC	Na_v1.3	Sinus and junctional bradycardia in epilepsia	[87]
	Na_v1.7	Syncope, bradycardia in PEPD	[84,85]
	Na_v1.5	Brugada syndrome, LQT3, Atrial Fibrillation, inherited sick sinus syndrome, PCCD	[74]
	Nav1.8	Brugada Syndrome	[80,81]
VGCC	Ca_v1.2	Timothy syndrome, the Brugada syndrome 3, and early repolarization syndrome	[96]
	Ca_v1.3	congenital sinus node dysfunction, heart block	[95,133]
	Ca_v2.1	familial Atrial Fibrilation	[97]
	Ca_v2.2	Severe cardiac arrhythmias in myoclonus-dystonia-like syndrome	[100]
	Ca_v 3.1	sinus node dysfunction, heart block	[95]

comparison to neonatal intracardiac neurons indicates that pacemaker current may be a contributing factor in the alterations in neuronal excitability control during development [25,61]. More recently, mRNAs encoding HCN2 and HCN4 subunits have been detected by in situ hybridization and PCR in mouse intracardiac ganglia [62]. This work suggests that the regulatory subunit tetratricopeptide repeat-containing Rab8b-interacting protein (TRIP8b) plays a role in modulating atrial electrophysiology beyond HCN-mediated sino-nodal control of the heart. HCN2 and HCN4 mRNA have also been identified in pig ICN by qRT-PCR [26].

2.2.1. Conclusion

Overall, in cardiac neurons, inhibition of the Ih current increases the amplitude and duration of the AHP and reduces the frequency of action potential discharge. The HCN channel may therefore play a role in promoting neuronal excitability by limiting the hyperpolarization phase following the action potential. Genetic screening for mutations in HCN channels clearly shows that these pacemaker channels may be associated with certain inherited cardiac arrhythmias and/or neurological disorders such as epilepsy [63]. For example, the mutations of the HCN4 channel, leading to either loss or gain of function were respectively associated with bradycardia and tachycardia [64,65]. In the brain, the correlation in various forms of epilepsy between epileptic activity and altered HCN expression and/or properties strongly suggests a causal relationship [66]. It is certainly likely that certain HCN mutations, depending on the isoform expressed in the ICNS, play a role in the intrinsic excitability and regulatory properties of the heart.

Given the paucity of data in this field, it would be essential to carry out an in-depth study of the consequences of these mutations, which have already been characterized, on the excitability of the intracardiac neuronal network and its development.

2.3. Voltage gated sodium channels

Voltage Gated Sodium Channel (VGSC) are transmembrane proteins which are essential determinant of cellular excitability through the control of the initiation and propagation of Action Potentials (AP). The canonical VGSC is generally composed of a pore forming alpha subunit associated to auxiliary beta subunits. To date, nine alpha subunits ($Na_v1.1$-$Na_v1.9$) and four beta subunits (β_{1-4}) have been identified in mammals. VGSC can be divided into two categories depending on their sensitivity to the Tetrodotoxin (TTX). $Na_v1.5$, $Na_v1.8$ and $Na_v1.9$ are considered resistant to TTX, being blocked by concentrations of the micromolar range, whereas other VGSC are sensitive and blocked by nanomolar concentrations of TTX. Amongst the VGSC family, at least seven isoforms are mainly found in the nervous system ($Na_v1.1$, $Na_v1.2$, Na_v 1.3, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$) while $Na_v1.4$ and $Na_v1.5$ are respectively the major skeletal and cardiac muscle isoforms [67–69].

Given the essential role of VGSC in the control of cell excitability, they have been extensively studied in the central and peripheral nervous system as well in cardiac and skeletal muscle cells in the physiological and physio-pathological context [67,70,71]. However, little is known about the identity and contribution of VGSC isoforms in the ICN (see Fig. 1 and Table 1). The few existing works report contradictory information concerning the TTX sensitivity of cardiac neurons, with some observing only TTX-sensitive channels and others both TTX-sensitive and TTX-resistant channels.

In guinea pig cardiac ganglia, 300 nM of TTX did not block AP generations excepted when extracellular calcium was lowered indicating that most of VGSC are TTX-sensitive and that calcium channels are potential contributors of AP initiation [36]. In dog, 300 nM TTX was shown to block tonic, but not phasic cardiac neuronal AP, when associated to a low extracellular concentration of calcium to limit calcium current [15]. In this work, 1 μM TTX was needed to block AP from phasic neurons. These results indicate that phasic and tonic neurons display different TTX sensitivity suggesting different isoforms and/or densities of VGSC depending on the neuronal types in dog.

2.3.1. TTX-resistant VGSCs in cardiac neurons

2.3.1.1. $Na_v1.5$. The presence of TTX-resistant VGSC involved in AP of canine cardiac neurons was confirmed by a study of Scornick et al. in 2006 [72]. They observed that around 90 % of the global voltage-gated sodium current was blocked by 300 nM of TTX in the absence of extracellular calcium. The 10 % of sodium current remaining exhibits a TTX IC_{50} of 1.2 μM, corresponding to a TTX-resistant current. Immunohistochemistry and RT-PCR experiments combined to the biophysical properties of the TTX-resistant current strongly suggest that $Na_v1.5$ voltage gated sodium channel is the TTX-resistant isoform expressed in canine cardiac neurons [72]. The presence of $Na_v1.5$ was also observed by immunohistochemistry in canine cardiac neurons in a study of Chen et al. in 2016 [73] and they also reported another TTX-resistant VGSC, $Na_v1.8$. The presence of $Na_v1.5$ in cardiac neurons is particularly interesting since this isoform is well known to be highly expressed in cardiomyocytes and has therefore been extensively studied in the context of cardiac channelopathies. Several distinct inherited cardiac arrythmia disorders such as Brugada Syndrome (BS) or long QT Syndrome type 3 (LQT3) are associated with heterozygous mutations in the SCN5A gene [74] encoding $Na_v1.5$ (Table 2). Interestingly, the autonomic nervous system has already been suggested to contribute to cardiac disorders associated with $Na_v1.5$ mutations. An imbalance between parasympathetic and sympathetic inputs is often observed in BS, LQT3 or AF, suggesting cross-relations between these pathologies, $Na_v1.5$ and the autonomic nervous system [2–4]. For example, BS patients can exhibit a high susceptibility to vasovagal syncope and vagal tone increase and consecutive bradycardia are also known to increase the risk of arrhythmias in LQT3 [2,4]. Since the final common pathway for cardiac neuronal control resides in the intrinsic cardiac nervous system, the question of the presence of $Na_v1.5$ and the consequences of its mutations in ICNS function is particularly interesting and deserves futher investigations.

2.3.1.2. $Na_v1.8$. In mouse cardiac neurons, a first study described that the sodium current was composed only by TTX-sensitive VGSC, a concentration of 300 nM being sufficient to block AP initiation [16]. In contrast, a study of Verkerk et al. in 2012 [75] has shown that the TTX-resistant isoform $Na_v1.8$ was functionally expressed in mouse cardiac neurons. This was supported by immunolabelling experiments in mouse embryonic tissue and adult isolated cardiac neurons. Electrophysiological experiments on isolated neurons indicates that 0.5 to 1 μM of A-803467, a selective blocker of $Na_v1.8$, block 20 % of the total VGSC current and reduces the firing rate of AP. Whereas these data suggest the presence of $Na_v1.8$ in mouse cardiac neurons, the concentrations used were high enough to potentially impact other VGSC. Indeed, A-803467 is a selective blocker of $Na_v1.8$ but this selectivity depends on the concentration as well as on the resting cell membrane potential [76] and concentrations of 1 μM have been shown to potentially impact $Na_v1.5$ for example [77]. Experiments performed in canine cardiac neurons also identified $Na_v1.8$ by immunohistochemistry [73,78]. In these studies, they tested the impact of local micro-perfusion of A-803467 into anterior right, inferior right and superior left ganglionated plexi of in situ canine hearts. They observed that 1 μM A-803467 reduced the incidence of atrial fibrillation. As a consequence, $Na_v1.8$ could be functionally expressed in ICN and could be a potential therapeutic target in cardiac arrhythmias. However, as mentioned previously, it is difficult to rule out that 1 μM of A-803467 doesn't impact any other VGSC. Besides, $Na_v1.8$ has also been proposed to be expressed in cardiomyocytes [79] and several mutations of SCN10A gene encoding Nav1.8 have been linked to cardiac pathologies such as the Brugada Syndrome [80,81] (Table 2). The presence of Nav1.8 in cardiomyocytes or in cardiac neurons is an ongoing matter of debate. Therefore, the functional expression of this

isoform needs to be further investigated as well as the impact of its mutations on ICNS function and associated cardiac regulation.

2.3.2. TTX-sensitive VGSC in cardiac neurons

The TTX-sensitive current represents the major component of global VGSC currents of cardiac neurons but very few studies have investigated to date the isoforms expressed in these cells.

2.3.2.1. $Na_v1.1$, $Na_v1.3$ and $Na_v1.7$. $Na_v1.1$ has recently been observed in pig at the RNA level [26]. Tompkins et al. (2016) identified transcripts encoding $Na_v1.3$ and $Na_v1.7$ in guinea pig cardiac neurons [31] whereas transcripts encoding $Na_v1.6$ and $Na_v1.2$ were absent. By using PF-04856264, a $Na_v1.7$ blocker, they state that $Na_v1.7$ is not involved in basal excitability but participates to the increase of excitability induced by Pituitary Adenylate Cyclase-Activation Polipeptide (PACAP) stimulation. Indeed, pretreatment with PF-04856264 suppressed the increase in action potential number induced by PACAP. They hypothesize that this regulation could involve Nav1.7 phosphorylation through the pERK1/2 pathway. From a physiopathological point of view, the presence of Na1.7 is very interesting since several mutations of this channel have been characterized, particularly in pain disorders [67,82]. Amongst these mutations, a gain of function mutation of Nav1.7 is the leading cause of Paroxysmal Extreme Pain Disorders [83,84]. This pathology is often coupled with dramatic syncope and bradycardia [84,85] compatible with a potential modification of cardiac neuron excitability (Table 2). Nav1.7 has also been observed in extracardiac sympathetic neurons and its mutations could also affect extracardiac catecholaminergic neurons [86].

The functional expression of $Na_v1.1$ and $Na_v1.3$ has never been investigated. These VGSC are widely expressed in brain. Recently, a mutation of $Na_v1.3$ (L247P) was characterized from a patient with childhood focal epilepsy [87]. In this study, a telemetry investigation of the 18-month-old female patient revealed several episodes of sinus and junctional bradycardia thought to correspond with vagal activity (Table 2). It is conceivable that these cardiac consequences could be related to the impact of Nav1.3 mutation on ICN function. However, epilepsy is well known to predispose patients to autonomic tone modifications and altered cardiac function independently of the identification of ion channel mutations [88]. Investigating in more details the impact of $Na_v1.3$ mutation on ICN function is therefore needed.

2.4. Voltage gated calcium channels

Voltage-gated calcium channels (VGCCs) also play a crucial role in the neuronal context, participating in the rising phase of the action potential, regulating neuronal excitability and neurotransmitter release. The VGCC family comprises 5 channel subfamilies (type L, P/Q, R, N and T) with a total of ten alpha subunits (Cav1.1 to Cav3.3) characterized by different biophysical and pharmacological properties. In particular, we distinguish between high-threshold calcium channels (L, P/Q, N and R) activated for relatively depolarized membrane potentials (~ -30 mV) and low-threshold calcium channels (T-type) activated for more negative potentials, close to the neuronal resting potential [89].

The first studies to investigate the nature of the VGCCs expressed by cardiac neurons were carried out in rats, reporting the existence of at least three different calcium currents, all belonging to the category of high-threshold channels. Xu and Adams reported the presence of L-type calcium channels, identified by their sensitivity to nifedipine, and N-type calcium channels, blocked by the omega-conotoxin GVIA. As the combination of these two pharmacological molecules was not associated with a total loss of calcium current, this group suggested the presence of at least one additional calcium channel [90]. This work was later completed by Jeong's group, who reported the presence of L-, N-, Q-, and R-type channels responsible for 11, 63, 19, and 7 % of the total calcium current, respectively, by combining several pharmacological molecules [91]. Completing this pharmacological approach, the expression of these different channels was subsequently confirmed by the detection of transcripts corresponding to the $Ca_v1.2$, $Ca_v1.3$ (L-type), $Ca_v2.1$ (Q-type), $Ca_v2.2$ (N-type) and $Ca_v2.3$ (R-type) subunits by RT-PCR [92,93]. Only Tompkins' group suggests the presence of low-threshold calcium channels. By RT-PCR, these authors indeed detected transcripts encoding $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$ subunits. Furthermore, infusion of two specific inhibitors of T-type calcium channels, nickel and mibefradil, is associated with mild membrane polarization suggesting that these channels are functionally expressed in cardiac neurons [94] (see Fig. 1 and Table 1). Amongst these different calcium channels, several of them has already been characterized as important actors of cardiac channelopathies (See Table 2). For example, $Ca_v1.3$ and $Ca_v3.1$ channelopathies lead to sinus node dysfunction and heart block (for review see [95]). $Ca_v1.2$ mutations lead to Timothy syndrome, BS and early repolarization syndrome (reviewed in [96]) and $Ca_v2.1$ mutation was identified in familial atrial fibrillation [97]. While most of these channels are expressed in cardiomyocytes, it would be important to assess the impact of their mutations on ICN function.

2.4.1. N-type calcium channels

The N-type calcium channel, carried by the $Ca_v2.2$ subunit, is the predominant calcium channel in cardiac neurons. Pharmacological inhibition of this current results in a significant increase in rheobase as well as in a decrease in action potential discharge frequency [92]. Similarly, decreased expression of this channel by shRNA also results in reduced intracardiac neuronal excitability [98]. Thus, this channel appears to be one of the key determinants of the excitability of intracardiac neurons. Interestingly, N-type calcium current has been correlated with several cardiac pathological remodeling and associated arrhythmia susceptibility by the group of Li Y-L. Indeed, in a rat model of chronic heart failure, cardiac neurons were shown to have reduced excitability, which was explained by reduced expression of the N-type calcium channel [93]. This electrical remodeling of intracardiac neurons has been associated with increased susceptibility to ventricular arrhythmias [22,98]. Similarly, in a rat model of type II diabetes, arrhythmia susceptibility was correlated with reduced expression of N-type calcium current resulting in a decreased neuronal excitability [92,99]. To our knowledge, only one mutation of the CACNA1B gene encoding Cav2.2 has been identified. This mutation was found in a family with myoclonus-dystonia-like syndrome associated with severe cardiac arrhythmias [100], suggesting that Cav2.2 of cardiac neurons may be involved in the cardiac effects observed with this mutation. However, no study has yet investigated the impact of such mutations on cardiac neurons and global cardiac function.

2.5. Transient Receptor Potential channels

Transient Receptor Potential (TRP) channels are multifunctional signaling molecules with many roles in cellular physiology, especially in sensory perception and are expressed in many tissues and cell types. The name comes from the discovery of a Drosophila mutant with defective light sensing showing a transient receptor potential (TRP) upon exposure to continuous light instead of the expected sustained response (the wild-type channel) [101].

Most of TRPs are polymodal channels activated by both physical (temperature, voltage, pressure and tension) and chemical stimuli, some of which are non-selective cation channels in the plasma membrane when others are able to regulate calcium release in intracellular organelles. The mammalian TRP channel family (28 members, 27 in humans) is composed on the basis of sequence homology of six subfamilies: canonical (also called short TRPs, TRPC1–7), vanilloid (TRP channel subfamily V, TRPV1–6), melastatin (TRP channel subfamily M, TRPM1–8), ankyrin (TRP channel subfamily A, TRPA1), mucolipins (TRPML1–3), polycystins (TRPP3 or PKD2L1 and TRPP2) [102,103]. Most TRP have restricted expression patterns, but the large distribution

indicate that the superfamily covers most cells, tissues and organs of the human body. As calcium is a major second messenger in cardiac cellular function, TRP channels have been proposed to be mediators of different physiological and pathophysiological processes regarding to their expression and their functional role for calcium homeostasis in various cardiac cell types [104]. TRP ion channels are also widely distributed in the brain, and their expression has been detected in the hippocampus, cortex, cerebellum, thalamus, amygdala, substantia nigra and striatum [105]. Similarly to cardiac physiology, calcium plays a crucial role in the regulation of cellular processes, and amongst calcium-dependent physiological events involving calcium influx through plasma membranes, TRPC channels appear to be actors of neuronal development, proliferation, or differentiation. Then, regarding to specific ICNS it's not really surprising to find this subtype of ionic channels (see Fig. 1 and Table 1).

2.5.1. Substance P pathway and TRP channels

The characterization of TRP channels in intracardiac neurons has been initiated by studies designed to demonstrate the cellular pathways involved in the physiological or pathophysiological effects of the main neuropeptides regulating ICN excitability. Amongst those, the substance P induces the depolarization of the parasympathetic ganglionic neurons of the cardiac ganglia. By electrophysiological recordings on adult guinea-pigs ICN and using specific agonists and antagonists of the 3 known receptor subtypes (NK1, NK2 and Nk3), Hardwick et al. (1997) [106] have shown that the NK3 receptor was involved in the SP-induced depolarization and that this depolarization was reduced by 50 % in amplitude when reducing Na + extracellular concentration. Consistent with these results, the authors have shown that such a reduction of extracellular Na + resulted in a 47 % reduction of the SP-induced inward current. As blockers of K^+ and Cl^- conductance had no significant effects, Hardwick et al. (1997) [106] concluded for the first time that substance P induced depolarization of guinea-pig cardiac neurons via the activation of NK3 receptors inducing the activation of a non-selective cation conductance.

2.5.2. Noradrenaline, muscarinic pathways and TRP channels

Ishibashi et al. (2003) [107] have investigated the hypothesis of the role of a Noradrenaline (NA)-induced cation current in isolated neurons from rat ICNS in current-clamp conditions. NA induced a membrane depolarization leading to repetitive action potential. They have demonstrated that NA elicited a small inward sodium current that was blocked by the cation channels blockers La^{3+}, Gd^{3+}, SK1F96365 and Cd^2 in a concentration-dependent manner. Moreover, Ishibashi et al. have demonstrated that the activation mechanism of the NA-current involved PLC pathway, IP_3 and release of Ca^{2+} from intracellular stores and calmodulin, a mechanism characteristic of TRP proteins activity.

A few years later, regarding to the input of parasympathetic preganglionic fibers, Hirayama et al. (2015) [108] have studied with the same experimental strategy the regulation of membrane excitability of rat parasympathetic ICN by muscarinic receptors. They have demonstrated that the activation of muscarinic receptor by oxotremorine-M (1 μM) depolarized the membrane with the genesis of repetitive action potentials, and induced inward currents that were increased by removal of extracellular calcium, and blocked by the cation channels antagonists SKF-96365 and ML-204. This indicates strongly the involvement of non-selective cation channels. By the use of classical specific tools to characterize the PLC pathway, Hirayama et al. have suggested also that the activation mechanism of TRP channels by M1 and M3 receptors involves release of Ca^{2+} from intracellular stores and calmodulin.

2.5.3. PACAP and bradykinin pathway and TRP channels

The same research to characterize the effects of neuropeptides have been followed by DeHaven and Cuevas (2004) [109] to demonstrate that pituitary adenyl cyclase activating polypeptide (PACAP) and the vasoactive intestinal polypeptide (VIP) co-localized with choline acyltransferase (ChAT) in the parasympathic preganglionic fibers innervating the ICNS. Calupca et al. (2000) [110] were able to depolarize neonatal rat ICN, and used PACAP to augment action potential firing. These authors have shown that these effects were dependent on activation of VPAC and PAC1 receptors and concomitant increases in intracellular calcium. Since the sustained $[Ca^{2+}]_i$ elevations were blocked by the TRP channel antagonist 2-aminoethoxyl-diphenyl borate (2-APB), they have suggested a possible role of store-operated channels. Tompkins et al. [111] have also shown in guinea pig intracardiac neurons that the PACAP-induced increase in excitability requires Ca^{2+} influx through Cd^{2+}-sensitive calcium permeable channels other than voltage-dependent channels. In the continuity of these data, Merriam et al. (2012) [112] have demonstrated that the pretreatment with putative nonselective cationic channel inhibitors (2-APB, SKF 96365, flufenamic acid) reduced the PACAP-induced excitability increase of ICN in guinea pigs ganglia. Moreover, by using semi-quantitative PCR on laser-captured cardiac ganglia neurons they identified the transcripts for TRPC 1, 3, 4 and 5. Arichi et al. [113] have shown that ML204, a specific inhibitor of TRPC4 and TRPC5, significantly inhibited the Bradykinin-induced depolarization of ICN, suggesting the involvement of these cation channels in the activation of rat intracardiac ganglion neurons by BK.

2.5.4. Histamin pathway and TRP channels

More recently, histamine has also been demonstrated to be a regulator of rat intracardiac ganglion neurons excitability. With the same experimental strategy presented above, Sato et al. (2020) [114] have shown that histamine depolarized isolated neurons, an effect blocked by the H1 receptor antagonist tripolidine, mimicked by the H1 agonist 2-pyridylethylamine, and that histamine induced an inward current with the characteristics of TRPC channels. These functional results were confirmed by RT-PCR analysis revealing the expression of several TRPC subtypes (TRPC1, TRPC3, TRPC5, TRPC6 and TRPC7) in rat intracardiac ganglia, TRP channels that could be the target of histamine speculated to be implicated in the pathogenesis of various cardiovascular diseases.

Mutations in TRP channels cause several different diseases, which is consistent with the involvement of TRP channels in a wide variety of physiological functions. Amongst the various organ systems affected by TRP mutations, the central nervous system and the heart are notably impacted (for review [115]), leading to neurodegenerative diseases (e.g., TRPML1, TRPM7, and TRPM2) and arrhythmias (e.g., TRPM4). However, to our knowledge, no TRP channel has been reported to be involved in ICN channelopathies. Given the role of the TRPC subtype in ICN excitability, it may be an interesting target to investigate potential TRP channelopathies in this context.

2.5.5. Conclusion

23 years of investigation on the potential effects of neurotransmitters and neuropeptides on ICN via TRP channels have shown that the TRPC subtype plays a central role in modulating the excitability of intracardiac neurons. This type of ion channel therefore represents an interesting field for the characterization of new pathways involved in pathophysiological conditions.

3. Conclusion

As mentioned in this review, several ion channels from the potassium, HCN, VGSC, VGCC and TRP channel families have already been identified in the ICN. However, our knowledge of the molecular identity of these proteins is sparse and far from complete. Comparatively, cardiomyocytes have been extensively studied and, although many questions remain to be clarified, the repertoire of ion channels expressed in these cells, as well as their involvement in cardiac channelopathies, is quite well understood. The emergence in recent decades of the pivotal role of ICNS in cardiac arrhythmia occurrence highlights the importance of such studies in ICN.

Several tools have been developed since the study of ion channels in

cardiac neuron began. Amongst them, the use of transgenic animals to reproduce mutations in ion channels observed in pathologies associated with cardiac arrhythmias and autonomic dysfunction could prove an interesting avenue of research into the potential consequences of mutations in ICN. This could shed light on the specific role of certain ion channels in ICN function. However, such studies could be complex and exploratory, as they require the selection of channel mutations that might be present in the ICN. Similarly, several promising approaches have emerged that could provide a springboard for these investigations. Single-cell RNAseq approaches are one of them and were recently performed on ICN [116]. This could be an exceptional tool to purpose an ion channel repertory in different ICN. Moreover, a recent paper leveraged single-cell transcriptomic data from ICN to model their electrophysiology [117]. However, it is still challenging to determine whether the transcripts lead to functional expression or not. In addition, parasympathetic neurons derived from human pluripotent stem cells have recently been developed to model human pathology [118]. A strategy using patient-derived IPS cells differentiated in ICN could be a great opportunity to study channelopathies, although this will require validation of the ion channel expression profile compared to native ICN. Overall, the combination of approaches of RNAseq, transgenic animal models and IPS cells, amongst others, will allow to advance our understanding of ion channels in ICN and open new avenues in the field of cardiac channelopathies that may involve the ICNS.

CRediT authorship contribution statement

J. Bescond: Writing – review & editing, Writing – original draft. **J.-F. Faivre:** Writing – review & editing, Writing – original draft. **A. Jean:** Writing – original draft. **P. Bois:** Writing – review & editing, Writing – original draft. **A. Chatelier:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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