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Ionic mechanisms of the action of anaesthetics on sinoatrial node automaticity

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ABSTRACT

Although various general anaesthetics affect the heart rate in clinical settings, their precise mechanisms remain to be fully elucidated. Because the heart rate is determined by automaticity of the cardiac pacemaker sinoatrial node and its regulation by autonomic nervous system, it is important to clarify the effect of anaesthetics on sinoatrial node automaticity. The spontaneous electrical activity of sinoatrial node is generated by a complex but coordinated interaction of multiple ionic currents, such as the hyperpolarisation-activated cation current (I_f), T-type and L-type Ca^{2+} currents ($I_{Ca,T}$ and $I_{Ca,L}$), Na^+/Ca^{2+} exchange current (I_{NCX}), and rapidly and slowly activating delayed rectifier K^+ currents (I_{Kr} and I_{Ks}). Patch-clamp studies have revealed the direct inhibitory effects of various anaesthetics on sinoatrial node automaticity and its underlying ionic mechanisms. Sevoflurane, desflurane and propofol directly suppress the sinoatrial node automaticity by inhibiting multiple ionic channels and transporter, such as I_f, $I_{Ca,T}$, $I_{Ca,L}$, I_{Ks} and I_{NCX}. By incorporating these inhibitory effects of anaesthetics on multiple ion channels and transporter into sinoatrial node model, suppression of sinoatrial node activity is well reproduced in computer simulation. The inhibitory effect of anaesthetics on sinoatrial node automaticity can be exaggerated under some pathophysiological conditions, such as aging, heart failure and arrhythmias, where the function and/or expression of ion channels involved in sinoatrial node automaticity are modulated. This review focuses on molecular, ionic and cellular mechanisms underlying the regulation of sinoatrial node automaticity by anaesthetics, which will provide an electrophysiological and molecular basis for understanding the changes in heart rate during perioperative period.

1. Introduction

The cardiac excitation is initiated by an electrical impulse that is generated within the primary cardiac pacemaker sinoatrial node located within the terminal groove of right atrium. The impulse then propagates through the atria, atrioventricular node and His-Purkinje system to the ventricles to evoke the heartbeat (Dobrzynski et al., 2013). The intrinsic rate of heartbeat is determined by rhythmic electrical activity of sinoatrial node, which occurs through a complex but coordinated interaction of multiple ionic currents. An inward current is primarily produced by the hyperpolarisation-activated, cyclic nucleotide-gated (HCN) cationic current (termed either I_f in heart cells or I_h in neuronal cells), T-type and L-type Ca^{2+} currents ($I_{Ca,T}$ and $I_{Ca,L}$, respectively) and forward mode of Na^+/Ca^{2+} exchange current (I_{NCX}), while the outward current is mainly generated by the rapidly and slowly activating delayed rectifier K^+ currents (I_{Kr} and I_{Ks}, respectively) and transient outward K^+ current (I_{to}) (DiFrancesco, 1993; Boyett et al., 2000; Hüser et al., 2000; Bogdanov et al., 2001; Dobrzynski et al., 2007, 2013; Mangoni and Nargeot, 2008). Some of these ionic currents involved in sinoatrial node automaticity receive sympathetic and/or parasympathetic influences and play a crucial role in mediating autonomic regulation of sinoatrial node automaticity and heart rate (Boyett et al., 2000; Mangoni and Nargeot, 2008). Heart rate *in vivo* is thus determined by sinoatrial node automaticity and its regulation by autonomic nervous system.

In recent decades, ion channels have been emerging as one of the primary molecular targets for the action of general anaesthetics in central nervous system. Evidence is increasing that volatile and intravenous anaesthetics directly interact with neuronal ion channel proteins, such as $GABA_A$ receptor channel, glycine receptor channel and HCN channel, and thereby suppress the excitability in neurons (Franks and Lieb, 1994; Campagna et al., 2003; Rudolph and Antkowiak, 2004; Hemmings et al., 2005; Franks, 2008). In the heart, a variety of anaesthetic agents modulate the activity of ion channels and transporters to regulate cardiac functions, such as excitability and contractility (Hüneke et al., 2004). Accumulating evidence has demonstrated that

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various anaesthetics, such as isoflurane, sevoflurane, desflurane, propofol and fentanyl, produce direct negative chronotropic effects on sinoatrial node automaticity by inhibiting multiple ion channels and transporter (Bosnjak and Kampine, 1983; Saeki et al., 1995; Kojima et al., 2012, 2013a, 2014, 2015). It is important to understand the molecular and ionic mechanisms underlying the regulation of sinoatrial node function by anaesthetics in order to control the heart rate appropriately in patients during perioperative period. In this article, we review the cellular and electrophysiological effects of various anaesthetics on function of ion channels and transporter involved in sinoatrial node automaticity, and propose that the direct chronotropic action of general anaesthetics on sinoatrial node contributes to the modulation of heart rate during general anaesthesia in clinical settings.

2. Ion channels and transporter involved in sinoatrial node automaticity and their modulation by volatile and intravenous anaesthetics

2.1. Ionic mechanisms for sinoatrial node automaticity

The sinoatrial node cells exhibit spontaneous action potential that characteristically has a slow diastolic depolarisation phase (phase 4) at voltages ranging between approximately −60 and −45 mV (Fig. 1).

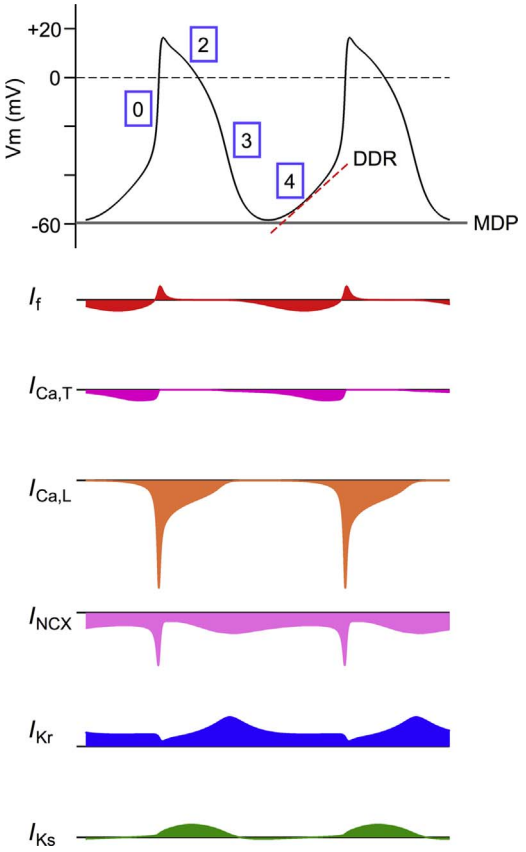

Fig. 1. Spontaneous action potential of sinoatrial node cell and its contributing ionic currents. Spontaneous activity is dependent upon the presence of a characteristic phase of slow diastolic depolarisation (phase 4). Diastolic depolarisation rate (DDR), indicated by dashed line (red), is slope of slow diastolic depolarisation and determines the firing rate. Numerals indicate the phases of spontaneous action potential: phase 0, upstroke; phase 2, plateau; phase 3, late repolarisation; phase 4, slow diastolic depolarisation (pacemaker potential). Zero-potential and maximum diastolic potential (MDP) are denoted by dashed (black) and straight (grey) lines, respectively. Time course of changes in major ionic currents (I_f, $I_{Ca,T}$, $I_{Ca,L}$, I_{NCX}, I_{Kr} and I_{Ks}) during spontaneous action potential is also shown. Spontaneous action potential and membrane currents are constructed from sinoatrial node model (Kurata model). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The slow diastolic depolarisation (pacemaker potential) brings the membrane potential toward the threshold for firing the subsequent action potential. Thus, the slope of this diastolic depolarisation, namely diastolic depolarisation rate (DDR), determines the firing rate of sinoatrial node automaticity by regulating the diastolic interval between action potentials. Activation of I_f, $I_{Ca,T}$, $I_{Ca,L}$ and forward mode of I_{NCX} as well as deactivation of I_{Kr} and I_{Ks} can lead to a gradual increase in net inward current during diastole, which underlies slow diastolic depolarisation of spontaneous action potential in sinoatrial node cells (Figs. 1 and 2) (DiFrancesco, 1993; Boyett et al., 2000; Hüser et al., 2000; Bogdanov et al., 2001; Dobrzynski et al., 2007, 2013; Mangoni and Nargeot, 2008).

The regulatory mechanism of sinoatrial node automaticity by sarcolemmal ion channels including I_f has been referred to as 'membrane clock' mechanism (DiFrancesco, 2010). In recent decades, experimental evidence has also been accumulating to indicate that spontaneous and cyclical local Ca^{2+} releases (LCRs) from the sarcoplasmic reticulum (SR) through type 2 ryanodine receptor (RyR2) occur during diastole and activate an inward I_{NCX} (forward mode) to drive pacemaker depolarisation in sinoatrial node cells (see also Fig. 2D) (Bogdanov et al., 2001; Vinogradova et al., 2006). This mechanism has been referred to as 'Ca^{2+} clock' mechanism (Lakatta et al., 2008). It is thus of great interest to elucidate how membrane clock and Ca^{2+} clock mechanisms interact to generate slow diastolic depolarisation that arises from small net inward current (Mangoni and Nargeot, 2008; Lakatta and DiFrancesco, 2009; Gao et al., 2010; Dobrzynski et al., 2013).

2.2. I_f and anaesthetics

I_f in sinoatrial node is generated by HCN channels, which are composed of four pore-forming subunits, each containing six transmembrane segments (S1 to S6 domains). Four isoforms with a high homology have been identified (HCN1-4), and HCN4 is a predominant isoform in sinoatrial node of many species, including humans (Dobrzynski et al., 2007; Chandler et al., 2009). I_f is activated upon hyperpolarisation, unlike other voltage-gated ionic currents, such as $I_{Ca,T}$, $I_{Ca,L}$, I_{Kr} and I_{Ks}. I_f produces an inward current that can initiate slow diastolic depolarisation. Spontaneous firing rate is reduced by pharmacological blockade of I_f in sinoatrial node cells of guinea-pig and rabbit hearts (Fig. 2A) (Nikmaram et al., 1997; Kojima et al., 2012). HCN channels, including HCN4, have a cyclic nucleotide-binding domain (CNBD) in the carboxyl terminal region. During β-adrenergic stimulation, cAMP directly binds to CNBD and causes a depolarising shift of voltage dependence of current activation, resulting in an increase in inward current in pacemaker potential range, especially at around maximum diastolic potential (MDP, Fig. 1) (Postea and Biel, 2011; Roubille and Tardif, 2013). This potentiation of I_f leads to an increase in DDR and is involved in mediating sympathetic acceleration of sinoatrial node automaticity (DiFrancesco, 1993, 2010).

It should be noted that viable sinoatrial node cells is scarcely available from human heart for functional analysis, because sinoatrial node tissue is usually left in the recipient chest during heart transplantation (Sharpe, 1996; Drouin, 1997) and intramural structure of sinoatrial node is complex (Li et al., 2015). At present, only a few laboratories have successfully conducted functional analysis on ionic mechanisms of sinoatrial node automaticity obtained from the human heart. Patch-clamp experiments have revealed that I_f is present and contributes to pacemaking activity in human sinoatrial node cells (Verkerk et al., 2007).

Several loss-of-function mutations in the gene encoding HCN4 channel have been linked to congenital sinoatrial node dysfunction and sinus bradycardia. The mechanisms for dysfunction of HCN4 channel include insensitivity to increased cAMP levels (Schulze-Bahr et al., 2003), reduced membranous expression (Ueda et al., 2004), and negative shift of voltage dependent activation (Milanesi et al., 2006; Nof et al., 2007). On the other hand, a gain-of-function mutation (R524Q)