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EPS and Arrhythmia

Electrophysiological Effects of Dexmedetomidine on Sinoatrial Nodes of Rabbits

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Background: The purpose of this study was to investigate the electrophysiological effects of dexmedetomidine on pacemaker cells in sinoatrial nodes of rabbits.

Methods: Healthy rabbits were anesthetized intravenously with sodium pentobarbital, and the hearts were quickly dissected and mounted in a tissue bath. Machine-pulled glass capillary microelectrodes which were connected to a high input impedance amplifier and impaled in dominant pacemaker cells. Thereafter, an intracellular microelectrode technique was used to record action potential.

Results: The amplitude of action potential, velocity of diastolic (phase 4) depolarization, and rate of pacemaker firing in normal pacemaker cells in sinoatrial node were decreased by use of dexmedetomidine (0.5 ng/ml, 5 ng/ml, 50 ng/ml) in a concentration-dependent manner. Pretreatment with yohimbine (1 μM), did not alter the effects of dexmedetomidine (5 ng/ml) on sinoatrial node pacemaker cells. Pretreatment with CsCl (2 mmol/L), dexmedetomidine (5 ng/ml) decreased the amplitude of action potential, but had no significant effect on other parameters of action potential.

Conclusions: Dexmedetomidine exerts inhibitory electrophysiological effects on pacemaker cells in sinoatrial nodes of rabbits in a concentration-dependent manner, which may not be mediated by alpha 2- adrenoreceptor.

Key Words: Action potential • Cardiology • Dexmedetomidine • Pacemaker activity • Sinoatrial node

INTRODUCTION

Dexmedetomidine (DEX), is a potent and highly selective alpha 2-adrenoreceptor agonist that possesses sedative, hypnogenetic, analgesic and sympatholytic properties.[1] Pre-clinical application showed that DEX can reduce the incidence of myocardial ischemia and myocardial infarction and other cardiovascular events, and decrease the perioperative mortality of patients undergoing non-cardiac surgery.[2-5] Adverse events such as bradycardia and hypotension did occur as a result of the infusion of DEX. However, clinical trials confirmed that DEX can reduce the incidence of intraoperative tachycardia and hypertension for patients who undergo coronary artery bypass grafting with severe coronary artery disease. An earlier animal study showed that DEX can prevent certain types of atrioventricular tachycardia. DEX may also have a potential therapeutic role in the acute phase of perioperative atrial and junctional tachyarrhythmias for congenital cardiac surgery.[6] However, DEX cannot be effective on sinoatrial nodes (SAN) through the alpha 2-adrenoreceptor because of SAN's absence of alpha 2-adrenoreceptors.[7-9] The hemodynamic effects of DEX result from both a peripheral and central mechanism. The fact that bradycardia occurred after the administration of DEX may be due to the central sympatholytic action and partly by baroceptor reflex and en-

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hanced vagal activity.[10,11] Inhibition of sympathetic nervous system activity and reduction of the plasma catecholamine concentrations were considered to be the cause of a reduced heart rate after infusion of the DEX. However, whether DEX has a direct effect on SAN is unknown. This experiment isolated the local (that is the cardiac) effects, and excluded the central sympathetic effects. In this manner, out study is beneficial in its attempt to further clarify and understand the specific effect of DEX on SAN.

The aim of the present study was to investigate the effects of DEX on SAN. We examined the following hypotheses: the effect of DEX on SAN is not only by way of the neuronal and humoral systems, but also through the ion channels of pacemaker cells. Therefore, we hope to further determine the prospect of this drug for optimum application during the perioperative period.

MATERIALS AND METHODS

Preparation of tissues

Healthy adult New Zealand white rabbits of either sex, weighing 1.5-2 kg, provided by the Experiment Animal Center of Wuhan University (Wuhan, China), were anesthetized with sodium pentobarbital (30 mg/kg) intravenously and the hearts were quickly dissected in cool, oxygenated Tyrode's solution. Tissue containing the SAN pacemaker cells and adjacent segments of the crista terminalis and atrial appendage was dissected free from the heart and mounted in a tissue bath.

Drugs and solutions

The composition of Tyrode's solution was 136.9 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 1.05 mM $Mgcl_2$, 0.42 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, and 5.55 mM glucose. DEX (production batch number 09081232) was purchased from Jiangsu Hengrui Medicine Company Ltd. (China). Yohimbine hydrochloride (Y3125-1G) and CsCl (289329-25G) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). NaCl, KCl, $CaCl_2$, NaH_2PO_4, $MgCl_2$, Glucose, NaOH, and KOH are domestic products with the analytical grade.

Electrophysiological recordings

For most of the experiments, the preparation was allowed to beat spontaneously during superfusion with Tyrode's solution maintained at 36 °C, saturated with 95% O_2 and 5% CO_2, and pumped to the tissue bath at a rate of 4 ml/min. The pH was adjusted to 7.35 ± 0.03 with HCl. In order to keep the concentrations of the various types of ions and drugs constant, we strictly controlled the perfusion rate by using the perfusion device BPS-4 (ALA Scientific Instruments, Inc., Westbury, NY, USA) and a constant-flow pump. After the preparation of SAN had been allowed to equilibrate for 30 min, machine-pulled glass capillary microelectrodes filled with 3 M KCl (resistance, 20 to 50 MΩ) which were connected to a high input impedance amplifier (Dua 773, World Precision Instruments, Sarasota, FL, USA), were impaled in dominant pacemaker cells. The signal was digitalized and collected using specific software (Acqknowledge 4.1, BIOPAC Systems, England). The variables measured were velocity of diastolic (phase 4) depolarization (VDD), maximal rate of depolarization (Vmax), amplitude of action potential (APA), action potential duration at 50% and 90% repolarization (APD50 and APD90), and rate of pacemaker firing (RPF). Subsequently, parameters were determined at the end of the exposure to the drug.

Effects of DEX on SAN pacemaker cells

Effects of different concentrations of DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) were examined respectively after a control period of 30 min in a non-cumulative manner. The preparation was washed with the normal Tyrode's solution to observe the recovery of action potential.

Effects of yohimbine on DEX-induced changes in action potential in SAN pacemaker cells

After superfusion with the Tyrode's solution containing yohimbine (1 μM), an alpha 2-adrenoreceptor antagonist, for 20 min, the preparation was perfused with Tyrode's solution containing yohimbine (1 μM) and DEX (5 ng/ml) for another 20 min, whereafter action potentials were recorded. Then, the preparation was washed with the normal Tyrode's solution to observe the recovery of action potential.

Effects of CsCl on DEX-induced changes in action potential in SAN pacemaker cells

After superfusion with the Tyrode's solution containing Cscl (2 mmol/l), a blocker of I_f, for 20 min, the

preparation was perfused with Tyrode's solution containing CsCl (2 mmol/l) and DEX (5 ng/ml) for another 20 min. Action potentials were recorded. Then the preparation was washed with the normal Tyrode's solution to observe the recovery of action potential.

Date analysis

All data were stored on the computer hard disk and analyzed off-line using Acq knowledge 4.1 (BIOPAC Systems, England) and SPSS 17.0 (Chicago, IL, USA).

All results were presented as mean ± SD for *n* experiments. The paired Student's t-test was employed to evaluate the statistical significance between pre- and post-application of reagents. Repeated measure ANOVA followed by the SNK (Student-Newman-Keuls)-q test was used to compare the effects between groups. $p < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Effects of DEX on SAN action potential

APA, VDD, and RPF in normal pacemaker cells in SAN were decreased by DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) in a concentration-dependent manner ($n = 10$, $p < 0.05$), but not the Vmax, APD50 and APD90 ($n = 10$, $p > 0.05$) (Figure 1). DEX decreased APA (mV) from 58.1 ± 6.2, 57.3 ± 6.0, 58.7 ± 5.0 to 48.6 ± 4.7, 41.9 ± 4.1, 36.8 ± 6.1; decreased VDD (mV/s) from 50.9 ± 8.3, 50.7 ± 5.4, 50.5 ± 9.0 to 42.6 ± 7.2, 36.3 ± 5.8, 30.4 ± 5.3; decreased RPF (beats/min) from 148.5 ± 10.8, 147.0 ± 9.0, 150.8 ± 5.6 to 141.6 ± 10.8, 132.6 ± 8.1, 123.9 ± 6.6, respectively. Action potential recordings in the absence (control) and presence of DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) are presented respectively in Table 1.

Effects of yohimbine on DEX-induced changes in action potential

Yohimbine (1 μM) had no significant effect on action potential ($n = 10$, $p > 0.05$). The Tyrode's solution contained yohimbine and DEX (5 ng/ml) decreased the VDD, APA and RPF from 50.3 ± 4.5 mV/s, 56.1 ± 5.9 mV and 145.9 ± 8.1 bpm/min to 36.5 ± 7.1 mV/s, 46.3 ± 4.5 mV and 133.7 ± 9.0 bpm/min ($n = 10$, $p < 0.05$), respectively. Pretreatment with yohimbine (1 μM) did not affect the effects of DEX (5 ng/ml) on SAN pacemaker cells (Table 2).

Effects of CsCl on DEX-induced changes in action potential

CsCl (2 mmol/l) alone decreased the VDD and RPF from 50.9 ± 6.2 mV/s and 147.2 ± 5.7 bpm/min to 39.1 ± 6.9 mV/s and 137.2 ± 4.0 bpm/min ($n = 10$, $p < 0.05$),

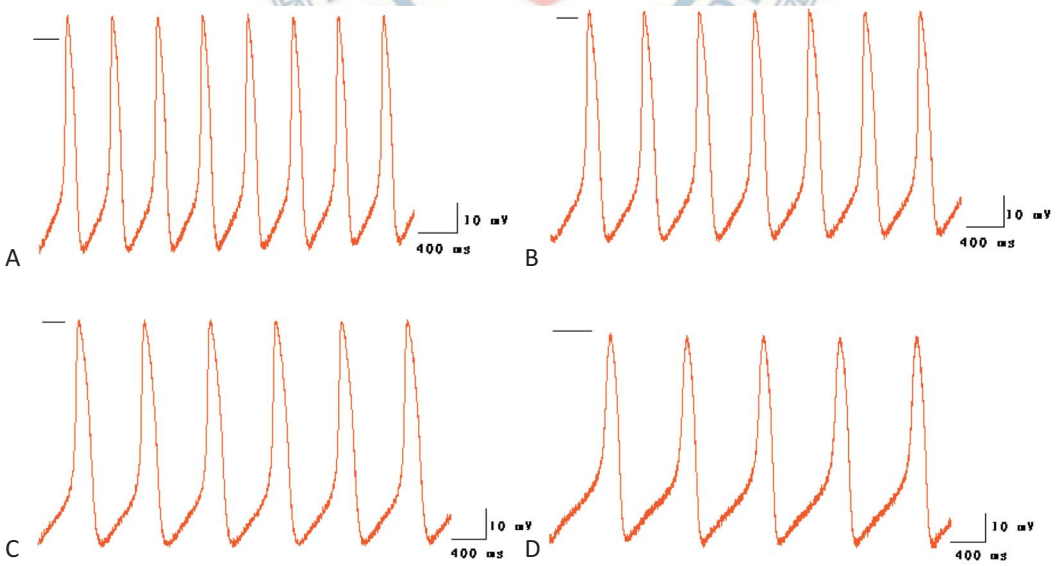

Figure 1. *Effects of DEX on transmembrane action potential in rabbit sinoatrial node pacemaker cells. Note: Effects of different concentrations of DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) were examined after a control period of 30 min in a non-cumulative manner. Short line before the action potential recordings indicates 0 mV. (A) Control. (B) 0.5 ng/ml DEX. (C) 5 ng/ml DEX. (D) 50 ng/ml DEX. DEX, dexmedetomidine.*

respectively. The Tyrode's solution contained CsCl (2 mmol/l) and DEX (5 ng/ml) decreased the APA from 54.0 ± 4.5 mV to 46.3 ± 5.5 mV (n = 10, $p < 0.05$), but had no significant effect on other parameters of action potential (n = 10, $p > 0.05$) (Table 3).

DISCUSSION

The most common manifestation of the negative effects of DEX is sinus bradycardia and hypotension.[10-12] Increasing plasma concentrations of DEX (0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 ng/m) resulted in decreases in heart rate, progressive decreases in cardiac output (CO), and no decrease in stroke volume.[11]

SAN is the impulse-generating (pacemaker) tissue located at the junction of the crista terminalis, a thick band of atrial muscle at the border of the atrial appendage, and the superior vena cava. SAN action potential is divided into three phases. Phase 4 is the spontaneous

Table 1. Effects of DEX on transmembrane action potential in rabbit sinoatrial node pacemaker cells

DEX	VDD (mV/s)	Vmax (v/s)	APD50 (ms)	APD90 (ms)	APA (mV)	RPF (beats/min)
control	50.9 ± 8.3	5.2 ± 1.1	128.3 ± 10.7	188.7 ± 19.7	58.1 ± 6.2	148.5 ± 10.8
0.5 ng/ml	42.6 ± 7.2*	4.5 ± 1.8	139.3 ± 12.7	205.1 ± 21.8	48.6 ± 4.7*	141.6 ± 10.8*
control	50.7 ± 5.4	5.5 ± 1.1	126 ± 9.1	180.6 ± 14.6	57.3 ± 6.0	147.0 ± 9.0
5 ng/ml	36.3 ± 5.8*#	5.3 ± 1.5	130 ± 9.8	189.0 ± 19.7	41.9 ± 4.1*#	132.6 ± 8.1*#
control	50.5 ± 9.0	5.2 ± 1.3	125.3 ± 17.8	181.8 ± 16.4	58.7 ± 5.0	150.8 ± 5.6
50 ng/ml	30.4 ± 5.3*#†	5.4 ± 1.7	135.0 ± 9.0	189.8 ± 14.2	36.8 ± 6.1*#†	123.9 ± 6.6*#†

The effects of different concentrations of DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) were examined after a control period of 30 min in a non-cumulative manner.
Mean ± SD, n = 10 * $p < 0.05$ vs. Control; # $p < 0.05$ vs. 0.5 ng/ml; † $p < 0.05$ vs. 5 ng/ml; APA, amplitude of action potential; APD50, action potential duration at 50% repolarization; APD90, action potential duration at 90% repolarization; DEX, dexmedetomidine; RPF, rate of pacemaker firing; Vmax, maximal rate of depolarization; VDD, velocity of diastolic (phase 4) depolarization.

Table 2. Effects of yohimbine (1 μM) on DEX-induced (5 ng/ml) changes in action potential

Group	VDD (mV/s)	Vmax (v/s)	APD50 (ms)	APD90 (ms)	APA (mV)	RPF (beats/min)
Control	50.9 ± 5.3	5.1 ± 1.0	127.8 ± 5.8	183.0 ± 9.1	55.8 ± 7.5	146.5 ± 8.1
Yohimbine	50.3 ± 4.5	5.3 ± 0.8	128.2 ± 4.3	184.4 ± 13.3	56.1 ± 5.9	145.9 ± 8.1
Yohimbine+DEX	36.5 ± 7.1*#	4.8 ± 0.8	132.7 ± 12.0	188.2 ± 4.7	46.3 ± 4.5*#	133.7 ± 9.0*#

After superfusion for 20 min with the Tyrode's solution containing yohimbine (1 μM), an alpha 2-adrenoreceptor antagonist, the preparation was perfused with Tyrode's solution containing yohimbine (1 μM) and DEX (5 ng/ml) for another 20 min. Action potential was recorded.
Mean ± SD, n = 10 * $p < 0.05$ vs. control; # $p < 0.05$ vs. yohimbine; APA, amplitude of action potential; APD50, action potential duration at 50% repolarization; APD90, action potential duration at 90% repolarization; RPF, rate of pacemaker firing; VDD, velocity of diastolic (phase 4) depolarization; Vmax, maximal rate of depolarization.

Table 3. Effects of Cscl (2 mmol/l) on DEX-induced (5 ng/ml) changes in action potential

Group	VDD (mV/s)	Vmax (v/s)	APD50 (ms)	APD90 (ms)	APA (mV)	RPF (beats/min)
Control	50.9 ± 6.2	5.5 ± 1.0	125.0 ± 9.0	180.0 ± 1.0	54.7 ± 5.8	147.2 ± 5.7
Cscl	39.1 ± 6.9*	5.2 ± 0.9	128.4 ± 10.7	184.2 ± 10.1	54.0 ± 4.5	137.2 ± 4.0*
Cscl+DEX	38.7 ± 6.4*	5.1 ± 0.8	130.7 ± 6.1	188.7 ± 10.9	46.3 ± 5.5*#	135.5 ± 5.7*

After superfusion for 20 min with the Tyrode's solution containing Cscl (2 mmol/l), a blocker of I_f, the preparation was perfused with Tyrode's solution containing Cscl (2 mmol/l) and DEX (5 ng/ml) for another 20 min. Action potentials were recorded.
Mean ± SD, n = 10 * $p < 0.05$ vs. control; # $p < 0.05$ vs. Cscl; APA, amplitude of action potential; APD50, action potential duration at 50% repolarization; APD90, action potential duration at 90% repolarization; RPF, rate of pacemaker firing; VDD, velocity of diastolic (phase 4) depolarization; Vmax, maximal rate of depolarization.

depolarization (pacemaker potential) that triggers the action potential. Phase 0 is the depolarization phase of the action potential. This is followed by phase 3 repolarization.

Phase 0 depolarization is primarily caused by increased Ca^{2+} conductance (gCa^{2+}) through the L-type Ca^{2+} channels, the voltage-dependent slow channels, which begin to open toward the end of phase 4. The speed and amplitude of phase 0 depolarization is dependent on the traits of Ca^{2+} channels in the SAN cells. The APA in normal pacemaker cells in SAN were decreased by DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml) in a concentration-dependent manner, which indicates that DEX may work on the inhibition of Ca^{2+} channels. The whole cell patch clamp technique was used in our previous study, which investigated the effects of DEX on $I_{Ca\text{-}L}$ in rat ventricular myocytes. The data suggest that DEX can attenuate $I_{Ca\text{-}L}$ in a concentration-dependent manner, which is consistent with this experiment.[13] Ning et al. reported that nifedipine reduced the amplitude of sinus node action potentials and the Vmax of phase 0.[14] Haruko Masumiya et al. observed that nifedipine, nisoldipine, verapamil, diltiazem and clentiazem all decreased the Vmax, APA, maximum diastolic potential (MDP), prolonged the cycle length (CL), action potential duration and slope, and shifted the threshold potential (TP) to the positive direction. CD-349, a novel 1,4-dihydropyridine, 10 mol/L significantly decreased the Vmax and prolonged APD and the CL without affecting APA and MDP.[15] In addition, APA, Vmax, MDP, VDD, RPF, APD_{90} of rabbit SAN were reduced by verepamil (inhibitor of $I_{Ca\text{-}L}$).[16] Regulation of inactivation of $I_{Ca\text{-}L}$ in SAN would decrease duration, cycle and interval of pacemaker activity.[17] $I_{Ca\text{-}L}$ is regulated by PKA (protein kinase A) and CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II).[18,19] The regulation of $I_{Ca\text{-}L}$ activation and reactivation kinetics by CaMKII can be one reason for the necessity of CaMKII in automaticity.[19] Therefore, it is possible that the inhibitory effect of DEX on $I_{Ca\text{-}L}$ in rabbit SAN might be partially and/or derived from specific kinetic changes of $I_{Ca\text{-}L}$. However, further study is necessary to demonstrate the inhibitory effect of DEX on $I_{Ca\text{-}L}$.

MDP, TP, and VDD are those factors that influence the autorhythmicity of SAN cells. This study indicates that VDD and RPF in normal pacemaker cells in SAN were decreased by DEX (0.5 ng/ml, 5 ng/ml, 50 ng/ml), which suggests that DEX can decrease the autorhythmicity of SAN cells through reducing the VDD and increasing the TP. The classic electrophysiological theory holds that diastolic (phase 4) depolarization of SAN cells is due to the increased net inward current as time passes, which consists of one outward current (potassium ions) and two inward currents (I_f and T-type calcium current). At the end of repolarization, ion channels open and conduct I_f. As the membrane potential reaches approximately -50 mV, $I_{Ca\text{-}T}$ open and Ca^{2+} enters the cell. At the end of phase 4, $I_{Ca\text{-}L}$ open as the membrane depolarizes to about -40 mV. As additional Ca^{2+} enters, the cells are further depolarized and reach an action potential threshold. The most important current of diastolic depolarization is I_f which is indispensable in initiating diastolic depolarization.[20] I_f is essential in the onset and control of the heart rate. The duration of the diastolic depolarization of SAN cells depending on the characteristics of the I_f is primarily responsible for the cardiac rate.[21] The unique property of reverse voltage dependence, together with the inward nature of the current at diastolic potentials, make this current adapted to initiate and support the diastolic depolarization.[22] The cardiac I_f is determined by the HCN (hyperpolarization-activated cyclic nucleotide-gated cation channel) ion channels. In vertebrates, the HCN channel family comprises four members (HCN1-4). In SAN tissues of lower mammals and humans, the predominant molecular constituent of the f channel is the HCN4 isoform; however, HCN1 and HCN2 have also been detected.[23] HCN3 seems to be absent from the SAN and specifically expressed in neurons.[24] The determination of resting membrane properties by HCN2 constitutes an important factor in the control of physiological pacemaking.[25] But further study is necessary to evaluate the effects of DEX on I_f by researching the effects of DEX on HCN1,2,4. The result that VDD was reduced by the DEX indicates DEX may inhibit the I_f and/or $I_{Ca\text{-}T}$ and/or $I_{Ca\text{-}L}$, or increase the outward diffusion of potassium. CsCl that is a blocker of I_f decreased VDD and RPF, which was consistent with the findings of Sohn et al.[26] and Zhang et al.[16] After pretreatment with CsCl (2 mmol/l), the electrophysiological effects of DEX (5 ng/ml) were not changed significantly ($n = 10$, $p > 0.05$) except APA ($n = 10$, $p < 0.05$), which indicates that DEX may decrease VDD through inhibiting the I_f, and increase the threshold potential through in-

hibiting $I_{Ca\text{-}L}$. Yohimbine can effectively inhibit the effect of DEX. Our previous study[13] showed that inhibition of $I_{Ca\text{-}L}$ by DEX can be weakened by Yohimbine (1 μM). However, no significant changes were shown before and after perfusion with the extracellular fluid containing 1 μM yohimbine alone. After pretreatment with yohimbine (1 μM), the electrophysiological effects of DEX (5 ng/ml) were inhibited, which suggests that the inhibitory effects of DEX may be via ion channels. Moreover, DEX cannot work on SAN through the alpha 2-adrenoreceptor because of the absence of alpha 2-adrenoreceptor on SAN.[7-9] Therefore, this indicates that in SAN of rabbits, action potentials can be influenced by DEX through ion channels.

CONCLUSIONS

In summary, our study observed the electrophysiological effects of DEX on pacemaker cells in SAN of rabbits. The results suggest that DEX exert inhibitory electrophysiological effects on pacemaker cells in SAN of rabbits in a concentration-dependent manner, which may not be mediated by alpha 2-adrenoreceptor agonist.

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