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粉防己碱对分离大鼠神经垂体末梢及 Y1 小鼠肾上腺皮质瘤细胞离子通道作用之比较

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王 钢，江明性，Mary D COYNE，José R LEMOS (*Worcester Foundation for Experimental Biology, Shrewsbury MA 01545, USA*)

摘要 本文采用标准及穿孔膜片钳技术研究了粉防己碱对分离大鼠神经垂体末梢及 Y1 小鼠肾上腺皮质瘤细胞的电压控门的钙道、钾道及钠道的作用. 细胞外的低浓度粉防己碱(13 μmol·L^{-1})可强抑制 Y1 细胞株上的 T 型钙道电流 52.9%. 粉防己碱 33 μmol·L^{-1} 细胞外使用时亦可强抑制分离的神经垂体末梢 L 型钙道电流 54.2%，但对其 N-型钙道电流无明显影响. 1 μmol·L^{-1} 粉防己碱在细胞外可阻断神经垂体末梢的慢控门、大电导、钙激活的钾道，使其开放概率降低 84.4%. 同一剂量的粉防己碱不影响快瞬时的钾道. 本文结论为(1) 离子通道对粉防己碱敏感性的顺序是：钙激活钾道 > T 型钙道 > L 型钙道 > N 型钙道 > 钠道；(2) 粉防己碱可为一慢控门的钙激活钾道的特异性阻断剂.

关键词 粉防己碱；后叶垂体；培养的肿瘤细胞；钙通道；钾通道；钠通道；膜片钳技术；神经末梢；电生理学

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Relation of age to effects of phentolamine and phenylephrine on heart

XU Hui (*Department of Pediatrics, China Medical University, Shenyang 110001, China*) Henry GELBAND, Jorge McCORMACK (*Department of Pediatrics, University of Miami, Miami FL 33101, USA*) Arthur S PICKOFF, Adrienne STOLFI (*Department of Pediatrics, Tulane University Medical Center, New Orleans LA 70112–2699, USA*)

ABSTRACT In the present study, the responses of neonatal and adult dog hearts to phenylephrine (PE) and phentolaminie (PA) were investigated in order to determine the influence of age factors. PA resulted in the slowing of the heart rate, the prolongation of corrected sinus node recovery time, atrial refractory period (ARP), ventricular effective refractory period (VERP), and ventricular functional refractory period (VFRP), and a significant inhibition of conducting tissues in neonatal dogs. In contrast, no such effects were seen in adult dogs. PE had a positive chronotropic effect in neonatal dogs but no such effect in adult dogs. In conclusion, α-adrenoceptors played an important excitatory role in the neonatal dog heart.

KEY WORDS phentolamine; phenylephrine; propranolol; heart rate; blood pressure; electrocardiography

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There has been an increasing interest in the understanding of the functional significance of neonatal myocardial α-adrenoceptors. Most investigators focused their attention to chronotropic effects of α-adrenocepors on *in vivo* myocardium. They suggested that α-adrenergic stimulation in immature cardiomyocytes results in a positive chronotropic effect. In contrast, α-adrenergic stimulation may result in a decrease of spontaneous HR in adult myocardium[1–3]. The conversion of a positive chronotropic effect is related to the postnatal increase in autonomic innervation[4] specifically, the adrenergic system.

Due to the potential physiological and clinical importance of these observations, we performed the following studies in order to elucidate the function of α-adrenoceptors in the immature hearts and to assess the role of maturation in determining the α-adrenoceptor function. This was accomplished by studying the effects of phentolamine (PA) and phenylephrine (PE) in the intact neonatal and adult dog hearts.

METHODS

Dog preparation Mongrel puppies, aged 3–7 or 8–15 d (weighing 704± *s* 150 g) and adult mongrel dogs of either sex were used. All dogs were anesthetized with sodium pentobarbital (30 mg·kg^{-1}) and mechanically ventilated. Arterial blood gases were monitored to assure acid–base balance and adequate oxygenation. All dogs were subjected to a combined propranolol (Pro) 0.6 mg·kg^{-1} iv and bilateral cervical vagotomies[4,5].

α-Blockade and stimulation α-Blockade was achieved with PA (0.5 mg·kg^{-1} iv in neonates and 5.0 mg·kg^{-1} iv in adults). PE infusions were used to stimulate α-receptors.

Recordings Electrocardiograph (ECG) from lead II and femoral artery BP were constantly monitored. Catheter electrodes were placed in atrium, right ventricular apex and noncoronary cusp. Electric stimulation was performed utilizing a programmable digital stimulator. Electric impulses were delivered at twice diastolic threshold with a pulse duration of 1.9 ms. The paper speed was 100 m·s^{-1}.

Measurements Electrophysiological measurements of sinus node recovery time (SNRT), corrected sinus node recovery time (CSNRT), atrial functional refractory period (AFRP), atrial effective refractory period (AERP), A–V node functional refractory period (AVNFRP), VERP, VFRP, and resting conduction intervals (PA, AH, HV) were performed according to standard procedures.

Statistical analyses Paired *t* tests were performed on the data obtained before and after a specific manipulation was completed. Results are presented as $\bar{x}\pm s$.

RESULTS

HR responses of neonatal and adult dogs to adrenergic drugs

1 Group I (3–7 d) Five out of 12 neonates exhibited a type A response. PE resulted in a slight tendency to increase HR. Inducing a type A response, in this group, Pro 1.0 mg·kg^{-1} resulted in only a little decrease (PE, 201± 43 bpm; Pro, 188 ± 32 bpm) and remained 12% faster than that prior to PE infusion. It suggested an α-mediated positive chronotropic effect.

Four out of 12 neonates had a type B response. The second dose of Pro, however, completely abolished the PE-induced acceleration (PE, 166± 25 bpm; Pro, 148± 24 bpm; $P<0.05$). In these puppies, the PA caused a further 24% reduction of mean HR (Pro 148± 24 bpm; PA, 116± 19 bpm; $P<0.01$). The PE induced cardioacceleration was likely to have been mediated via β-receptor stimulation. α-blockade with PA still resulted in a decrease in sinus rate, suggesting a tonic, α-mediated positive chronotropic effect.

Three out of 12 neonates had a type C response. Both α-receptor agonist and α-receptor antagonist drugs resulted in a decrease in HR.

2 Group II (8–15 d) In contrast to group I, all of the responses were type A, where a positive chronotropic effect due to α-receptor stimulation was seen.

3 Group III (adult dogs) Four out of 7 adult dogs exhibited a type B response and 3 had a type C one. In contrast to the neonates, a positive chronotropic effect due to α-adrenergic stimulation had never been seen in adult dogs.

BP responses of neonatal and adult dogs (Tab 1) The observed changes in BP were similar within each group regardless of the type of HR response.

BP responses were similar to those in groups I and II. Specifically no change in systolic and diastolic BP was seen following the combined Pro iv and bilateral vagotomies.

In group III, small and variable changes were seen following the combined Pro iv and bilateral vagotomies.

Tab 1. Heart rate (HR) and blood pressure (BP) responses of neonatal and adult dogs to iv adrenergic drugs. $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

		n	Control	Propranolol / mg·kg^{-1}		Phenylephrine / mg·kg^{-1}·min^{-1}			Phentolamine / mg
				0.6	1.0	0.5	1.0	10.0	Nanonate 0.5 Adult 5.0
3–7 d puppies		12							
HR / bpm	Type A	5	176± 24	169± 27*	188± 32*	173± 30*	178± 36*	201± 43*	138± 18**
	Type B	4	172± 30	152± 25*	148± 24***	155± 22*	158± 20*	166± 25**	116± 19***
	Type C	3	165± 13	180± 21*	148± 9*	168± 18*	159± 10*	164± 3*	117± 3*
BP / kPa	Systolic		7.3± 1.2	7.6± 0.9*	13.7± 1.9*	9.9± 1.9***	11.7± 2.3***	15.1± 2.4***	5.6± 1.2***
	Diastolic		3.6± 0.7	3.6± 0.4*	7.9± 1.6***	4.5± 0.9***	5.2± 1.2***	8.5± 1.7***	2.5± 0.4***
8–15 d puppies		12							
HR / bpm	Type A		164± 18	163± 19*	182± 20*	166± 21*	170± 21*	187± 17**	156± 21***
BP / kPa	Systolic		9.2± 1.3	8.5± 0.8*	13.9± 2.8***	7.9± 1.3**	10.5± 1.9**	15.3± 2.3***	8.1± 2.3***
	Diastolic		4.3± 9.7	4.0± 0.4*	7.9± 2.4*	4.4± 0.8*	4.8± 1.1*	8.5± 2.5***	3.7± 1.2*
Adult dogs		7							
	Type B	4	146± 6	117± 14*	107± 10***	116± 17**	112± 13**	128± 18*	105± 4***
	Type C	3	157± 22	118± 3***	113± 15**	116± 5***	113± 5***	116± 6***	109± 4***
BP / kPa	Systolic		18.8± 2.5	19.1± 2.7*	20.5± 5.6**	21.0± 2.5***	23.7± 4.7***	29.2± 2.9***	14.5± 3.7***
	Diastolic		14.1± 1.5	13.5± 1.7*	16.3± 4.7*	14.9± 2.8*	17.5± 4.0**	22.9± 2.9***	10.1± 2.7**

Type A: PE induced an increase in sinus rate which was not reversed to baseline by second dose of Pro, indicating that PE induced accelearion is α–mediated. Type B: PE induced an increase in sinus rate which was completely reversed by second dose of Pro, suggesting that the PE–induced cardioacceleration is a beta effect. Type C: PE resulted in a decrease in sinus rate, suggesting that this is an α–mediated cardiodeceleration.

The PE–induced increase in BP was substantially greater in the neonatal than in the adult group.

Effects of α–blockade on cardiac electrophysiological parameters (Tab 2) In order to ascertain whether age factor is related to the differences of electrophysiologic (EP) effects of PA *in vivo*, 9 neonatal puppies aged 8–14 d and 6 adult doges were used. The PA had significant effect on neonatal conducting tissues and only minor effect on adult hearts, suggesting that α–adrenoceptors show a marked excitatory effect on the neonatal hearts.

DISCUSSION

The autonomic nervous system has not been fully developed at birth[6,7], the extent and significance of this immaturity remain poorly understood. In our

Tab 2. Cardiac electrophysiological parameters of neonatal and adult dogs after α–adrenergic blockade. $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

	8–14 d old (n=9)		Adult 1–2 a (n=6)	
	Control	Phentolamine	Control	Phentolamine
Corrected sinus node recovery time	79± 55	183± 90**	96± 28	118± 38*
Atrial effective refractory period	66± 10	88± 18***	132± 15	155± 14**
Atrial functional refractory period	103± 13	128± 15**	166± 13	193± 12**
Ventricular effective refractory period	142± 13	166± 26**	150± 6	168± 8*
Ventricular functional refractory period	164± 14	197± 32**	181± 9	202± 14*

studies, PA resulted in a significant decrease of neonatal HR while the adult HR remained unaffected. This suggested that α-adrenoceptor plays a significant excitatory role in the neonatal sinus node while their effect on the adults is relatively minor.

Concerning the effects of PA on myocardial refractoriness, the magnitude of the prolongation of atrial refractoriness was significantly greater in neonates than in adults.

The chronotropic effects of α-adrenergic stimulation in the immature heart, however, have not been extensively studied[1,8,9]. The most important observation in our study was that an α-mediated positive chronotropic response was demonstrated in the intact neonatal canine while this had never been observed in the adult canine heart.

In summary, our study of the effects of PA and PE in the neonatal and adult hearts suggested a significant age related differences in the α-adrenergic regulation of the electrophysiological properties of the canine hearts. Our data also suggested that postnatal maturation of the autonomic nervous system are characterized not only by an increase in sympathetic innervation as reported in other studies, but also by changes in α-adrenoceptor function. Thus, α-adrenoceptors do play a significant excitatory role in the neonatal myocardium.

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年龄与酚妥拉明和苯福林心脏效应的关系

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徐 惠 (中国医科大学儿科, 沈阳 110001, 中国)

Henry GELBAND, Jorge McCORMACK (*Department of Pediatrics, Universtiy of Miami, Miami FL 33101, USA*)

Arthur S PICKOFF, Adrienne STOLFI (*Department of Pediatrics, Tulane University Medical Center, New Orleans LA 70112-2699, USA*)

摘要 本实验研究了新生和成年犬心脏对苯福林(PE)和酚妥拉明(PA)的反应以确定年龄因素的影响. PA使新生犬心率减慢, 校准窦房结恢复时间、心房不应期、心室有效不应期及心室功能不应期均被延长, 对传导组织有明显的抑制作用. 而成年犬则无. PE对新生犬产生正性频率作用, 但成年犬则无. 结论是: α-受体在新生犬心脏起重要的兴奋作用.

关键词 酚妥拉明; 苯福林; 普萘洛尔; 心率; 血压; 心电描记术