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Comparative Effects of Verapamil, Nifedipine, and Diltiazem on Contractile Function in the Isolated Immature and Adult Rabbit Heart

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Summary

The effects of postnatal development on the systolic and diastolic responses to pharmacologic blockade of the slow inward calcium current were investigated in blood-perfused hearts isolated from immature (14–21-day-old) and adult rabbits. Isovolumic left ventricular developed pressure, resting pressure, and maximal rate of pressure development ($+dP/dt$) at cumulative doses of either verapamil, nifedipine, or diltiazem were determined by means of an intracavitary balloon. Myocardial contractile function in the immature heart was more sensitive to pharmacologic blockade of the slow inward calcium current than is the adult heart. Doses of verapamil, or nifedipine, that comparably reduced pretreatment developed pressure and $+dP/dt$ were approximately 10-fold less in immature as compared to the adult heart. The dose of diltiazem which reduced developed pressure and dP/dt by 50% was 3-fold less in immature as compared to the adult heart. Verapamil and nifedipine decreased resting pressure in the adult but not in the immature heart. Conversely, diltiazem decreased resting pressure in the immature while not affecting resting pressure in adult hearts. Thus, postnatal cardiac development affects both the systolic and diastolic responses to

calcium channel blockade. In addition, diltiazem appears to be qualitatively and quantitatively different from verapamil and nifedipine with respect to the age-related cardiac effects of calcium channel blockade.

Abbreviations

SR, sarcoplasmic reticulum
SL, sarcolemma
LV, left ventricular

In the mammalian heart, excitation is coupled to contraction by intracellular Ca cycling mediated by the concerted functions of the SR and SL (5). Several lines of evidence suggest that the relationship between SL and SR in the regulation of excitation-contraction coupling may undergo significant changes during postnatal development.

Ultrastructural evidence suggests significant postnatal development of the SR and T-tubule network (13, 16, 24, 25). Ca-"triggered" Ca release by SR can first be demonstrated in skinned cardiac fibers 48 h after birth (3, 4). There is also suggestive evidence that the Ca reuptake properties of SR, important in relaxation, also develops after birth (16, 22, 28). Postnatal differences in cardiac contractile responses to extracellular Ca (23, 26), lanthanum (7), manganese (7), and caffeine (13), tension development under voltage-clamp conditions (16) suggest that: (a) a new source of "activator" Ca develops with the postnatal development of the SR and T-tubule system; and (b) trans-sarcolem-

mal Ca influx may be the primary source of Ca for activation of the contractile elements prior to develoment of the SR and T-tubule network.

To determine if Ca delivery to the contractile elements in the immature heart is more dependent on the trans-sarcolemmal influx of Ca via the Ca channel than in the adult heart, we investigated the dose-response relationship of three blockers of the slow inward Ca current, verapamil, nifedipine, and diltiazem, on contractile force development by isolated immature and adult rabbit hearts. All three agents reduce contractile force and the slow inward Ca current in the adult heart (1, 12, 19). If contraction in the immature heart is more dependent on trans-sarcolemmal Ca influx than in the adult heart, myocardial contractile force in the immature heart should be more sensitive than the adult heart to the negative ionotropic effects of these agents.

MATERIALS AND METHODS

Experimental model. Rabbit hearts were isolated and perfused in this study using methods similar to that described by Henry *et al.* (11) modified to permit recirculating perfusion with blood. Hearts were removed from either adult (2–3 kg) or 13–26-day-old (200–400 g) New Zealand White rabbits after administration of intravenous heparin (200 units/kg) and sodium pentobarbital (approximately 30 mg/kg). Each heart was suspended by a cannula and continuously perfused with whole heparinized blood (31°C) obtained from a donor adult rabbit. Blood was recirculated, bubble-oxygenated with 97% O_2/3% CO_2 ($Po_2 > 120$ mm Hg), and filtered (Pall Ultipor; 45 μ). Each heart was electrically stimulated (Grass Model 588 stimulator) at a rate 10% faster than the spontaneous rate by means of wires attached to the epicardial surface of the left atrium. In preliminary experiments, coronary perfusion flow rates that sustained maximal LV-developed pressures routinely resulted in coronary perfusion pressures which approximated the mean aortic pressure *in vivo.* Therefore, mean coronary flow was adjusted upward in each experiment to optimize LV-developed pressure without exceeding coronary perfusion pressures of 75 mm Hg in the immature and 100 mm Hg in the adult heart. This perfusion flow rate was then maintained constant for the duration of each experiment.

A compliant fluid-filled latex balloon affixed to a catheter was inserted through the left atrial appendage into the left ventricular cavity. The proximal end of the catheter was connected to a Statham pressure transducer. The balloon volume was slowly increased by saline infusion to a resting pressure that optimized developed pressure, approximately 10 mm Hg. Developed and resting pressures (mm Hg), electrically differentiated maximal rate of pressure development ($+dP/dt$; mm Hg/sec), and perfusion pressures (mm Hg) were continuously monitored. Resting pressure at end-diastole was corrected for balloon compliance by subtracting the balloon pressure, or the measured pressure obtained when the balloon is inflated outside of the heart with a measured volume of saline equal to the volume of saline previously used to inflate the balloon positioned in the left ventricular cavity.

All dose-response experiments were performed with hearts isovolumically contracting at constant rate with constant coronary flow, and resting end-diastolic volume. Hearts were perfused at constant flow during the dose-response experiments, rather than constant pressure, to ensure that the recognized coronary vasodilator effects of the calcium channel blockers would not alter coronary flow and thereby alter contractile function or resting pressure. The pH, Pco_2, and Po_2 of the perfusate were monitored throughout the experimental period with a Corning Model 165 blood gas analyzer.

Experimental protocols. Aqueous verapamil and diltiazem stock solutions were prepared and shielded from light. The nifedipine stock solution was prepared in 15% (v/v) ethanol and shielded from light. Because of the negative inotropic effects of ethanol vehicle alone (data not shown), the maximum concentration of nifedipine was limited to 0.2 μM.

Calcium channel blocker dose-response. After a stabilization period of approximately 30 min, adult or neonatal hearts received cumulative doses of the calcium channel blockers (±) verapamil (Knoll), nifedipine (Bayer), or diltiazem (Marion). The developed pressure, $+dP/dt$, and perfusion pressure were recorded after stabilization at each dose of the calcium channel blocker, usually within 10 min after addition, and expressed as the percentage of the pretreatment "control" values. The cumulative dose-response curve was completed in less than 3 h. Suitable control experiments have not shown significant changes in the contractility indices or coronary resistance during the 3-h experimental period.

Statistical analyses. The cumulative doses of calcium channel blocker which reduced baseline (control) developed pressure or $+dP/dt$ by 20 and 50% were defined as the ID_{20} and ID_{50}, respectively. The ID_{20} and ID_{50} were determined for each individual heart and the mean ± SE was calculated for each treatment and age group. All comparisons between the immature and adult groups were made by unpaired t test using two-tailed Student's t distribution. Comparisons of baseline developed and resting pressures and dP/dt of those hearts treated with verapamil, nifedipine, or diltiazem within an age group were made by one-way analysis of variance using Duncan's procedure for equal sample size. Differences between groups were considered statistically significant if the p value was less than 0.01.

RESULTS

Control values. The baseline control values for left ventricular developed pressure and $+dP/dt$ in the immature groups of immature hearts receiving either verapamil, nifedipine, or diltiazem were not significantly different. Similarly, the mean control values for developed pressure and $+dP/dt$ in the groups of adult hearts receiving either verapamil, nifedipine, or diltiazem were
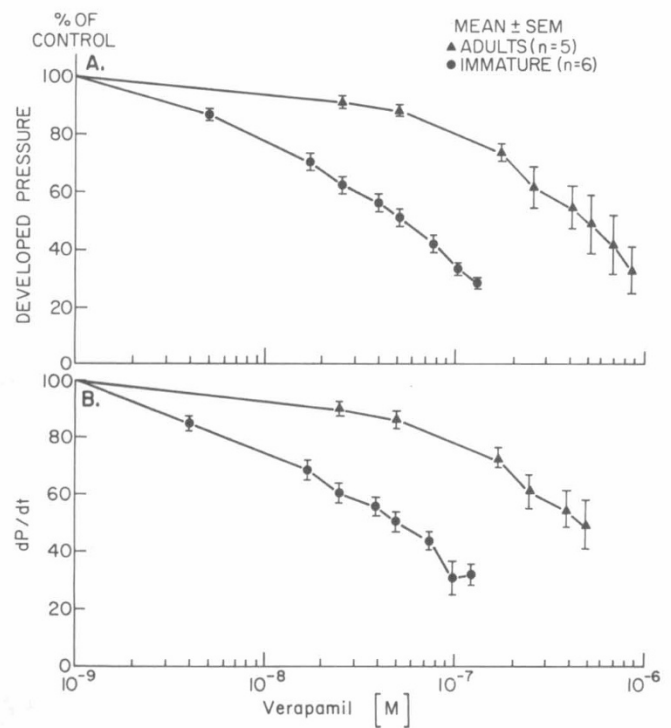

Fig. 1. The effect of verapamil on isovolumic LV-developed pressure and $+dP/dt$ in isolated perfused adult (▲) and immature (●) rabbit heart. Developed pressures (*upper panel*) and $+dP/dt$ (*lower panel*), expressed as percentage of the pretreatment control value, are shown as a function of the molar concentration of verapamil, plotted on a logarithmic scale. The mean ± SE control developed pressure and $+dP/dt$ were: immature = 67 ± 9 mm Hg and 979 ± 150 mm Hg/sec; adult = 99 ± 9 mm Hg and 1150 ± 121 mm Hg/sec.

not different. Stimulation rates were not significantly different between immature and adult hearts in either the verapamil (176 ± 9 *versus* 148 ± 11 min⁻¹) or the diltiazem (137 ± 9 *versus* 139 ± 8 min⁻¹) treatment groups. The mean stimulation rate of the immature group treated with nifedipine was higher than that in the adult group treated with nifedipine (167 ± 10 *versus* 120 ± 9 min⁻¹; $p < 0.05$).

Verapamil, nifedipine, and diltiazem dose-response. Both developed pressure and $+dP/dt$ were significantly reduced in the immature rabbit hearts by cumulative doses of verapamil (Fig. 1) and nifedipine (Fig. 2) which did not affect developed pressure and $+dP/dt$ in the adult hearts. The mean concentrations required to reduced control developed pressure and $+dP/dt$ by 20 and 50% for verapamil and 20% for nifedipine were significantly

different between the immature and adult hearts ($p < 0.005$; Table 1).

In contrast to the age-related difference in contractile response to all doses of verapamil and nifedipine, the diltiazem concentration required to produce a similar reduction in developed pressures was 1–4-fold less for immature hearts than adult hearts (Fig. 3). There were no statistically significant differences in the concentration required to reduce control developed pressure from 5 to 25% for the immature compared to the adult hearts (Fig. 3; Table 1). However, the mean concentration of diltiazem which reduced control developed pressure in the immature hearts by 50% was significantly less ($p < 0.005$) than the mean concentration which reduced developed pressure by 50% in the adult hearts (Table 1).

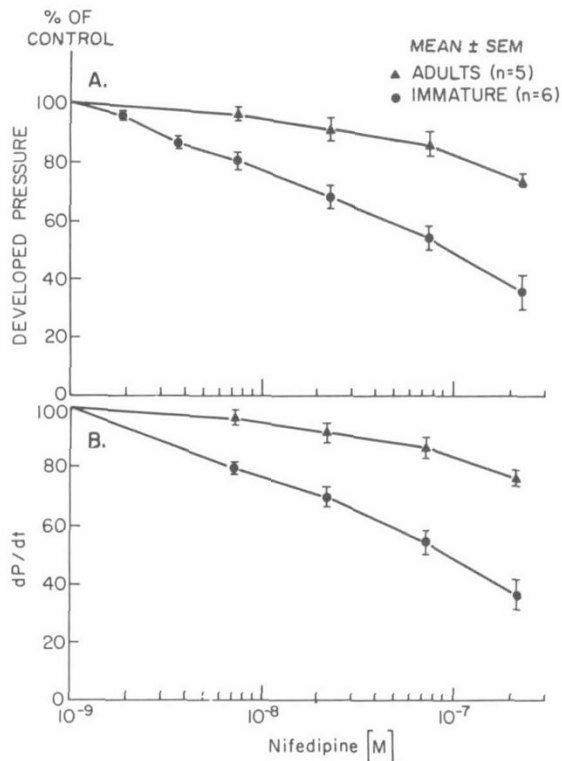*Bioassay of perfusate concentration of verapamil.* Verapamil

Fig. 2. The effect of nifedipine on isovolumic LV-developed pressure and $+dP/dt$ in adult (▲) and immature (●) rabbit heart. Developed pressures (*upper panel*) and $+dP/dt$ (*lower panel*), expressed as percentage of the pretreatment control value, are shown as a function of the molar concentration of nifedipine, plotted on a logarithmic scale. The mean ± SE control developed pressure and $+dP/dt$ were: immature = 87 ± 6 mm Hg and 1055 ± 130 mm Hg/sec; adult = 111 ± 7 mm Hg and 1336 ± 125 mm Hg/sec.
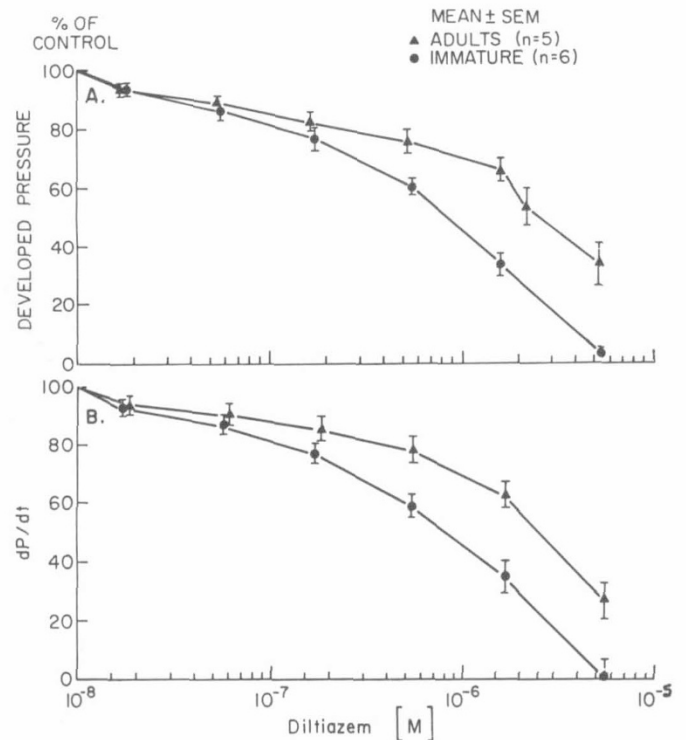
Fig. 3. The effect of diltiazem and isovolumic developed pressure (*upper panel*) and $+dP/dt$ in adult (▲) and immature (●) rabbit heart. Developed pressure (*upper panel*) and $+dP/dt$ (*lower panel*), expressed as percentage of the pretreatment control value are shown as a function of the molar concentration of diltiazem, plotted on a logarithmic scale. The mean control developed pressure and $+dP/dt$ were: immature = 81 ± 7 mm Hg and 1024 ± 97 mm Hg/sec; adult = 95 ± 1 mm Hg and 1074 ± 94 mm Hg/sec.

Table 1. *Inhibitory doses for Ca channel-blocking drugs in immature and adult rabbit heart**

Calcium channel blocker		n	Isovolumic LV-developed pressure†		$+dP/dt$	
			ID_{20}	ID_{50}	ID_{20}	ID_{50}
Verapamil	Immature	6	9.2 ± 1.8‡	52.0 ± 5.8‡	9.0 ± 2.3‡	54.0 ± 8‡
	Adult	5	110.0 ± 20‡	510.0 ± 140‡	110.0 ± 30‡	470.0 ± 130‡
Nifedipine	Immature	6	9.0 ± 1.7‡		11.0 ± 3.5‡	
	Adult	5	140.0 ± 34‡		130.0 ± 3.3‡	
Diltiazem	Immature	6	130.0 ± 35	880.0 ± 90‡	130.0 ± 28	990.0 ± 250§
	Adult	5	520.0 ± 250	3200.0 ± 700‡	550.0 ± 180	2800.0 ± 560§

* All inhibitory doses are mean (±SE) 10⁻⁹ M concentrations.

† ID_{20} and ID_{50} are the cumulative inhibitory doses of calcium channel blocker which reduced the contractile response by 20 or 50%, respectively.

‡ $p < 0.005$ immature *versus* adult.

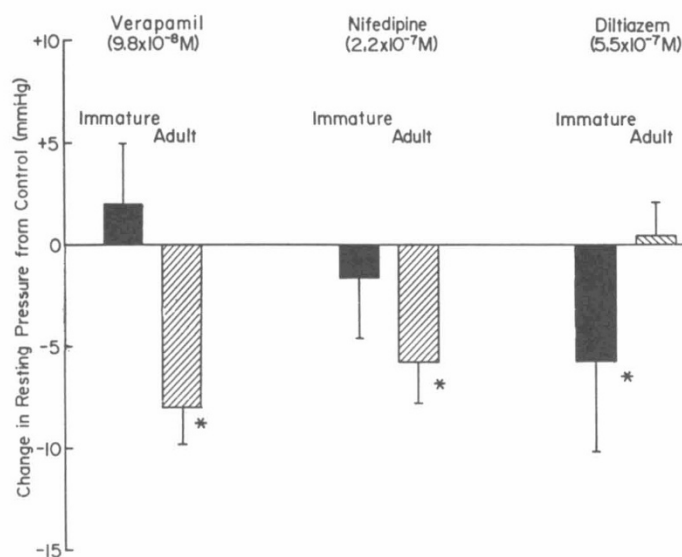§ $p < 0.01$ immature *versus* adult.

Fig. 4. The effect of selected concentrations of verapamil (98 nM), nifedipine (220 nM), and diltiazem (550 nM) on the resting pressure of immature (■) and adult (▨) rabbit hearts. * $p < 0.05$.

$(6.4 \times 10^{-8}$ M) when added to the perfusate of the adult heart reduced developed pressure ≤25% of the control developed pressure at equilibrium. When this perfusate containing verapamil was switched to perfuse the immature heart previously stabilized with verapamil-free perfusate, control developed pressure was reduced ≤90% in the immature hearts. This concentration of verapamil would have been predicted to reduce developed pressure in the immature heart by greater than 50% (Fig. 1). Thus, the greater tissue mass of the adult heart did not significantly reduce the verapamil concentration in the perfusate as evidenced by the appropriate depression in developed pressure exhibited in the cross-perfused immature heart.

Resting pressure. Verapamil and nifedipine, but not diltiazem, resulted in a dose-dependent reduction in resting pressures at end-diastole in adult hearts. Verapamil and nifedipine did not affect resting pressures at any dose in immature hearts. The effect of selected concentrations of verapamil (98 nM), nifedipine (220 nM), and diltiazem (550 nM) which resulted in a greater than 20% decrease in developed pressure in immature and adult hearts on resting pressure is illustrated in Figure 4. Resting pressure in adult hearts was significantly reduced by both verapamil and nifedipine (Fig. 4). Resting pressure in immature hearts was not significantly affected by either verapamil or nifedipine (Fig. 4). In contrast, resting pressure was significantly reduced by diltiazem in the immature heart whereas resting pressure was unchanged by diltiazem in the adult heart (Fig. 4).

DISCUSSION

In this study, we have demonstrated that verapamil, nifedipine, and diltiazem reduced developed pressure and $+dP/dt$ of the isolated immature rabbit heart at significantly lower concentrations than required to comparably reduce developed pressure and $+dP/dt$ in the adult. This is the first report of the effect of postnatal development on the inotropic response to three commonly used Ca channel blockers. Recent reports support our findings of significant age-related differences in the inotropic response to verapamil but differ with regard to whether the inotropic response of the adult or the newborn heart is more sensitive to the calcium channel-blocking agents. Gibson *et al.* (9) reported that cardiac output in the immature dog (ages 2–12 days) was more depressed by verapamil as compared with the adult dog. In contrast, George *et al.* (8) preliminarily reported that verapamil (10^{-7} M) reduced developed tension less in the perfused septal preparation from the newborn rabbit heart as compared to the adult. The reason for this apparent discrepancy

is unclear, though it is possible that the slower stimulation frequency (36/min) used in the study of George *et al.* (8) may have affected the sensitivity to verapamil since inhibition of slow channel-mediated Ca influx by verapamil is frequency dependent at rates less than 100 min^{-1} (10, 17). The stimulation frequencies used in this study were: (a) not different between age groups treated with either verapamil or diltiazem; (b) in a more physiologic range than used in the study of George *et al.* (8); and (c) in a range that has little effect on the inotropic sensitivity to verapamil (10, 17).

The greater inotropic sensitivity in immature rabbit hearts to the Ca channel blockers suggest a greater dependency of contraction in the immature heart on Ca channel-mediated trans-sarcolemmal Ca influx. This greater dependency of the immature heart may reflect the greater external cell surface area of the immature myocardial cells (13), developmental differences in sarcolemmal Ca regulation (2, 6, 14, 15), and/or the relative immaturity of the SR in the developing heart (4, 13, 16, 22, 25). This hypothesis is entirely consistent with the age-related difference in the contractile response to the inorganic calcium channel blocker manganese (7) and further supported by the rightward shift of the contractile response *versus* extracellular [Ca] relationship in newborn compared with adult hearts (23, 26).

The subcellular mechanism whereby dependency of contractile force on Ca channel-mediated Ca influx changes during postnatal development is still speculative. Ca channel-mediated Ca influx may: (a) directly initiate mechanical contraction; (b) replenish the intracellular stores of releasable Ca in the SR; and/or (c) trigger the release of Ca from SR stores for the contractile event (18). Thus, there may be age-related differences either in the relative contributions of SL and SR Ca delivered to the contractile elements and/or in the loading and release of SR Ca.

Indirect evidence, based on measurement of action potentials in neonatal and adult canine Purkinje fibers, indicates a greater inward Ca current during early postnatal development as compared to that in the adult (27). In addition, the amplitude of the slow response (Ca-dependent) action potential became progressively more sensitive to inhibition by verapamil with increasing age (27). In voltage-clamped feline papillary muscles, contractility of the neonatal papillary muscle was "more directly controlled by membrane potential" as compared to the adult (16). These observations suggest a decrease in Ca channel-mediated Ca influx with postnatal cardiac development but this conclusion must await confirmation using cellular voltage-clamp technques. It should be ponted out, however, that if the rightward shift in the contractility *versus* Ca channel blocker dose-response relationship (Figs. 1–3) associated with postnatal development was due solely to age-related differences in Ca current, then a smaller (not larger) Ca current would be predicted in the immature as compared to the adult.

Perinatal development of the SR is suggested by morphologic and functional evidence (13, 16, 20, 22, 24, 25, 27, 28). If developmental differences in SR Ca release are invoked to account for the rightward shift of the Ca channel blocker dose-response relationship (Figs. 1–3) during postnatal development, then Ca release from immature SR would be predicted to be more depressed by equivalent pharmacologic blockade of the Ca "trigger" as compared with the adult SR (29). In skinned rat heart fibers, the maximum myoplasmic [free Ca] and the [Ca] for "optimum" triggering of Ca release reached adult values between 2 and 10 days after birth (4). Although SR Ca release has not been evaluated in the rabbit heart, SR Ca release in the 14–21-day-old rabbit heart may not be fully developed. Further studies will be required to elucidate the role of the SR and T-tubule development on excitation-contraction coupling in the developing heart.

Alternative mechanistic explanations for the greater inotropic sensitivity to the calcium channel blockers in the immature heart (Table 1) include: (a) a different Ca sensitivity of the contractile elements (3, 4); and (b) a greater drug-"receptor" interaction or

affinity constant or a smaller number of receptors resulting in a greater reduction in the Ca current at any given drug dose.

A greater Ca sensitivity of the contractile proteins has been reported for skinned fetal and adult rat heart fibers (3, 4). Comparable studies have not been carried out during postnatal development. The Ca sensitivities of the myofibrillar ATPase from immature and adult rabbit heart, however, have been found to be equivalent (21). Thus, the observed age-related differences in the inotropic sensitivity to the calcium channel blockers may be due to differences in the relationship between contractile force and the calcium concentration of the contractile elements but experimental evidence for this postulate is still conflicting and incomplete.

Another possible mechanism of these age-related differences in inotropic sensitivity to the calcium channel blockers is related to myocardial binding affinity of these compounds with resultant differences in drug-receptor interaction. Because of the structural dissimilarities among the three blockers (1) as well as the suggested differences in site(s) of action (12, 19), this mechanism seems unlikely. Furthermore, preliminary results suggest comparable high affinity binding constants for [^{3}H]nitrendipine in membrane vesicles from the immature and adult rabbit heart (2).

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