EXPRESSION OF LDH mRNA IN VASCULAR SMOOTH MUSCLE CELLS: DIFFERENTIAL EFFECTS OF PLATELET-DERIVED GROWTH FACTOR AND ANGIOTENSIN II

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Growth of vascular smooth muscle cells (VSMC) is an important feature of atherosclerosis and hypertension. Mitogens (e.g., platelet-derived growth factor; PDGF) and vasoactive hormones (e.g., angiotensin II; ANG II) activate many of the same transmembrane signals and early growth-related genes. However, in cultured VSMC from normal adult rats, PDGF is hyperplastic (stimulating both protein synthesis and cell division) whereas ANG II is hypertrophic (stimulating protein synthesis and increasing cell size without cell division). In order to identify molecular events that might distinguish the responses of VSMC to PDGF and ANG II, a cDNA library was constructed from rat aortic VSMC and differentially screened with mRNA from cells treated for 3 hrs with either 10^{-6}M ANG II or 20 ng/ml PDGF (BB). One clone, hybridizing to PDGF mRNA with an intensity 10-fold greater than that of ANG II mRNA, was identified as encoding the lactate dehydrogenase (LDH) M isoform. LDH mRNA was constitutively expressed at low levels in VSMC made quiescent by a 72 hr incubation in 0.5% calf serum. PDGF or 10% calf serum caused a marked induction of LDH mRNA, beginning at 2 hrs and increasing for up to 24 hrs. In contrast, 10^{-6}M ANG II had no effect on LDH mRNA levels during the same 24 hr period. These results suggest that induction of LDH mRNA may be a marker for VSMC hyperplasia but not necessarily for hypertrophy. Analysis of differentially expressed genes, such as LDH, may provide important insights into the factors regulating VSMC growth.

HEMODYNAMIC AND PHARMACOKINETIC INTERACTION BETWEEN ORAL VERAPAMIL AND METOPROLOL: EVIDENCE OF ALTERED PRESYSTEMIC EXTRACTION

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Combination of beta-adrenoceptor blockers and calcium channel antagonists can give rise to both immediate and delayed serious adverse effects and rarely even a fatal outcome when prescribed concurrently in man, raising the possibility that pharmacokinetic interaction may contribute.

The effects (if any) of oral verapamil (n=6) and placebo (n=6) on hemodynamic parameters, plasma metoprolol, hepatic extraction of metoprolol and hepatic blood flow were studied in 12 anaesthetized cross-bred dogs during steady state portal metoprolol infusion. Studies conformed to national animal research guidelines and ethical approval was obtained. Jejunal administration of verapamil 1-2mg/kg resulted in marked falls in mean arterial blood pressure compared with placebo (67±4 versus 120±11mm Hg at 180min, $p<0.002$), and in heart rate, together with progressive atrio-ventricular conduction delay (PR interval 136±15 versus 81±5msec, $p<0.02$). A progressive rise in plasma metoprolol levels after verapamil was observed (147±18 versus 55±16ng/ml, $p<0.005$), and a fall in hepatic extraction of metoprolol (0.62±0.07 versus 0.86±0.04, $p<0.02$) without initial decline in hepatic blood flow.

Conclusions
The additive effects of beta-adrenoceptor blockade and calcium channel antagonists are generally beneficial in the treatment of angina pectoris, but can have serious hemodynamic and electrophysiologic consequences when excessive. An inhibition of metoprolol clearance, by verapamil, through reduced hepatic metoprolol extraction appears to contribute to this phenomenon.

Comparative Effects of ULFS-49 and Verapamil on Heart Rate and Contractility in Isolated Hearts

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ULFS-49 is a new drug believed to selectively block sinoatrial node Ca++ channels. We compared the effects of ULFS-49 to its structural analog, verapamil (VERAP), in isolated, blood perfused pig hearts with an isovolumic left ventricle (LV). LV function was evaluated by changes in peak systolic pressure (PLVP, mmHg) and maximum dP/dt normalized by PLVP ((dP/dt)/P, sec^{-1}). After control (CONT) measurements, doses of ULFS-49 or VERAP were increased cumulatively until either a 30% decrease in heart rate (HR, beats/min) or a 50% decrease in PLVP was achieved. Hearts remained in sinus rhythm throughout.

	Group I (n=6)		Group II (n=6)	
	CONT	ULFS-49	CONT	VERAPAMIL
HR	143±8	99±4*	136±7	120±7*
PLVP	104±5	95±4	100±3	45±4*
(dP/dt)/P	8.5±.9	7.3±.9	8.1±.5	4.9±.2*

*p<.05 vs control; mean ± S.E.

These results indicate that that ULFS-49 decreases HR to a much greater extent than VERAP, with minor effects on LV inotropy in the isolated, blood perfused pig heart. Conclusion: ULFS-49 is a highly selective bradycardic agent and may prove useful in the treatment of ischemic heart disease and congestive heart failure.

5-AMINO-IMIDAZOLE CARBOXAMIDE RIBOSIDE (AICA-R) PREVENTS CUMULATIVE CARDIAC DYSFUNCTION WITH REPEATED PACING IN DOGS: POTENTIAL ANTIANGINAL EFFECT.

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The effects of repeated episodes of demand ischemia on cardiac function and coronary blood flow distribution are not well characterized. We developed a canine model of coronary stenosis with repeated episodes of ischemia induced by pacing, and studied the effects of AICAr, which enhances endogenous adenosine release. Chloralose anesthetized dogs were instrumented to measure posterior (POST) cardiac wall thickening (WT), coronary blood flow (CBF) with microspheres, and endocardial ECG. A stenosis was placed on the left circumflex coronary artery and ischemia was induced with six 5 min periods of right atrial pacing separated by 15 min recovery periods. Vehicle (n=13) or AICAr (n=7; 1 mg/kg/min) or nitroglycerin (NTG, n=4; 3μg/kg/min) was administered as a constant infusion, I.v., beginning after Pace 1. Results are shown below. *p < 0.05 vs. Vehicle (Veh).

		Control	Pace 1	Pace 6
POST-WT (% of control)	Veh	100	49±6	2±5
	AICAr	100	50±7	35±7*
	NTG	100	56±4	62±8*
S-T segment (mV)	Veh	2.2±0.3	7.7±0.8	10.1±0.9*
	AICAr	2.3±0.4	7.2±1.1	4.2±0.7*
	NTG	2.0±0.3	7.4±0.8	4.9±0.3*
Endocardial CBF (ml/min/gm)	Veh	0.70±0.04	0.59±0.08	0.49±0.09
	AICAr	0.82±0.11	0.69±0.07	0.90±0.11*
	NTG	0.77±0.11	0.62±0.08	0.84±0.10*

In Veh. treated dogs, repeated periods of pacing elicited a progressive decline in WT and endocardial CBF, and an increase in S-T segment elevation. AICAr and NTG attenuated these changes. The beneficial effects of AICAr were prevented by intra-coronary infusions of adenosine deaminase to degrade local adenosine. These results suggest that the anti-ischemic properties of AICAr may be mediated by an adenosine-induced preservation of endocardial CBF.