ENALAPRIL AND COUGH: A POSSIBLE NEURAL MECHANISM. M. Hargreaves, M.B. Ch.B., K.Ravi,Ph.D., M.P.J. Senaratne, M.B.B.S.,Ph.D.and C.T. Kappagoda, M.B.B.S.,F.A.C.C. Div. of Cardiology, Univ. of Alberta, Edmonton, Canada.

Cough is an adverse effect of angiotensin converting enzyme (ACE) inhibitors and is believed to be secondary to the effect of ACE inhibitors on bradykinin (B) breakdown. The purpose of the present study was to identify a potential vagal sensory mechanism for this cough response. The rapidly adapting receptors (RAR) of the airways are activated by changes in extra-vascular lung water. Since B is an inflammatory mediator which increases vascular permeability, experiments were performed in anesthetized, artificially ventilated and open-chested rabbits to examine whether 1) the RAR were stimulated by B and 2) the sensitivity of RAR to B was enhanced by the ACE inhibitor enalapril maleate (E). RAR activity (n=8) was recorded from the cervical vagus. A dose-response relationship between B and RAR activity was elicited by administering graded doses of B (0.25-1.0 ug/kg,i.v.). After the activity had returned to the control state, E (2mg) was injected i.v. When the dose-response relationship between B and RAR was repeated five min later, it was found to be shifted significantly upwards. The RAR activity did not return to the control state after the second dose-response curve was elicited.

		Bradykinin (ug/kg)			
		Control	0.25	0.5	1.0
RAR	Before E	273±50	281±58	315±37	404±76
(imp/min)	After E	345±46	549±88	694±152	885±174*

*Analysis of covariance, slope significantly different from before E ($p<0.01$).

RAR are stimulated by B and this effect is enhanced by E. It is concluded that the cough observed after administration of E is due to stimulation of RAR.

THE MESSENGER RNA FOR THE LDL-RECEPTOR IS INCREASED BY VERAPAMIL

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To see if the Ca^{++}entry blocker induced stimulation of LDL-receptor synthesis is correlated with a selective increase in the amount of LDL-receptor specific mRNA human skin fibroblasts were incubated in the absence or presence of Verapamil. Trifluoperazine, which we recently had shown to increase LDL-receptor mRNA and 25-Hydroxycholesterol, which is known to supress the synthesis of LDL-receptor were used as (+) & (-)control. RNA was subjected to Northern blot analysis. It was probed sequentially with ^{32}P-labelled LDL-receptor cDNA and β-actin pseudogene DNA fragments.

LDL-receptor cDNA hybridized to a RNA that by criterion of size corresponded to human LDL-receptor mRNA The intensities of the hybridization signals indicated that RNA isolated from cells pretreated with verapamil contained more LDL-receptor mRNA than did RNA isolated from control cells. From semiquantitative estimations of LDL-receptor mRNA by dot blot hybridization it was concluded that pretreatment with 75μM Verapamil enhanced the relative concentration of LDL-receptor mRNA 2-fold and the pretreatment with nifedipine had no effect. The maximum verapamil effect was reached after 4 hours of preincubation.

The present data show that the verapamil induced increase in LDL-receptor activity is correlated with a corresponding increase in LDL receptor mRNA. These results indicate that verapamil selectively enhance the amount of LDL-receptor in cultured human fibroblasts.

PRESYSTEMIC ACETYLATION OF PLATELET CYCLOOXYGENASE: SELECTIVE INHIBITION BY CONTROLLED RELEASE-LOW DOSE ASPIRIN.

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Inhibition of platelet thromboxane (Tx) by aspirin (ASA) may be limited by coincidental inhibition of vascular prostacyclin (PGI_2). Volunteers received intra-duodenal ASA (50mg) as a bolus (A), or an infusion of 10mg/hr (B) or 5mg/hr (C) or vehicle for 4 days. Despite a reduction ($p<0.01$) in mean maximal plasma ASA (Cmax) from 1256 (A) to 52.1 (B) and 21.4 ng/ml (C), inhibition of both serum TxB_2 - mean 83% (B); 75% (C) - and urinary 11-dehydro-TxB_2, the major endogenous Tx metabolite, was substantial ($p<0.001$), but incomplete by the final day of the infusions. Inhibition of the prostacyclin metabolite, urinary 2,3-dinor-6-keto-$PGF_{1\alpha}$ (PGI-M), relative to control values was minimal during B and C (p=NS), but significant (mean 55%) during A ($p<0.05$).

Based on these results, a controlled release (CR) 75mg ASA tablet was formulated, designed to release ASA at a rate which would maximize Tx inhibition. Compared with 75mg regular ASA, mean Cmax was reduced from 939 to 62 ng/ml ($p<0.001$) after 75mg ASA CR p.o.. Based on plasma salicylate, the oral bioavailability of ASA CR was approximately 90% and was unaffected by food. While inhibition of serum TxB_2 and platelet-derived urinary 11-dehydro-TxB_2 was complete, inhibition of PGI-M was minimized after 1 month's dosing. ASA-CR has high selectivity for inhibition of platelet Tx; this may enhance the antithrombotic efficacy and reduce the side effects of ASA.

INHIBITION OF ATHEROSCLEROSIS BY LOVASTATIN IN CHOLESTEROL-FED RABBITS

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To evaluate the effects of Lovastatin on cholesterol-induced atherosclerosis, 50 New Zealand rabbits in five groups were fed a 0.3% cholesterol diet for 10 weeks. Groups L10 and L20 received 10 and 20 mg/day of Lovastatin respectively. The % endothelial surface covered with lipid lesions was determined by planimetry.

	Groups		
% Lesions	Control	L10	L20
Aorta	25±16	8±7**	9±4*
Pul. Art.	24±16	10±6*	4±5**

* Significantly different from control group.

No statistical differences were found in the bleeding time. Groups L10 and L20 had lower levels of serum cholesterol and LDL-cholesterol than those in the control group (715, 832 vs 879; 681, 734 vs 846 mg/dl) at 10 weeks. Another control group had a high lipid diet for 10 weeks and a normal diet for 10 weeks. A treatment group had the same diet sequence, but also had 20 mg/day of Lovastatin the last 10 weeks. No regression of atherosclerosis was seen in the treatment group.

This study shows that Lovastatin can suppress the development of aortic and pulmonary atherosclerosis in cholesterol-fed rabbits, but, did not regress established atherosclerosis.