Pancreatic lipase activity (IU/1000 ml) in duodenal lymph and arterial blood plasma of dogs prior to and during stimulated exocrine pancreatic secretion

Initial values (Saline$^+$: 0–60 min)		Stimulation of pancreatic secretion (4 U/kg b.wt secretin + pancreozymin$^+$: 0–60 min)					
Duodenal lymph	Arterial blood plasma	Duodenal lymph	Arterial blood plasma				Pancreatic juice
0–90 min	60 min	0–120 min	20 min	40 min	60 min	120 min	120 min
671 ± 103 (15)	279 ± 31 (15)	2391 ± 394 (15)	1141 ± 241 (15)	1460 ± 248 (15)	1569 ± 288 (15)	1578 ± 325 (15)	$433 \times 10^3 \pm 61 \times 10^3$ (15)

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The mean $\pm$ SE lipase activity in arterial blood plasma of 5 dogs collected in the 90th min of the pancreatic stimulation period was 1405 ± 184 IU/1000 ml ($p < 0.01$ compared to the second lymph sample).

duodenal lymph and venous plasma[12]. The results presented do not exclude that part of the pancreatic lipase in arterial blood plasma had originated from enzyme absorbed from the intestinal lumen into their blood and lymph vessels[11,12]. Maintenance of the serum lipase level by the intestines for a short period after pancreatectomy[13] might be due to the same mechanism.

Pancreatic lipase activity in duodenal lymph can originate from arterial blood plasma due to diffusion of the enzyme from blood capillaries into the duodenal interstitium and from there into the lymphatics, or also by direct absorption from the duodenal lumen into the lymphatics. A fact pointing to lipase absorption from duodenum into lymphatics was its significantly higher activity in duodenal lymph than in the corresponding arterial plasma samples, both under basal conditions and stimulated pancreatic secretion. It cannot be excluded that the lipase originating from the duodenum, as well as from the pancreas, might take part in the intralymphatic breakdown of triglycerides absorbed from the intestines.

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Reduction of bovine pulmonary hypertension by normoxia, verapamil and hexaprenaline[1]

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Summary. In calves with hypoxic pulmonary hypertension, resistance was reduced by $40 \pm 3\%$ with normoxia, $19 \pm 4\%$ with verapamil, and $60 \pm 1\%$ with hexoprenaline. It is possible that the increased resistance during normoxia is due partly to vasoconstriction rather than solely to vascular thickening, and that the vasoconstriction is due to an abnormality in calcium metabolism by the hypertensive vasculature.

Acute administration of oxygen to man or cattle with chronic, hypoxia-induced pulmonary hypertension results in only partial reduction of pulmonary arterial pressure[2–4]. Complete reversal of the hypertension requires prolonged exposure to alveolar normoxia[3,5]. The persistent elevation of pulmonary vascular resistance is generally considered to reflect luminal encroachment by vascular hypertrophy[6,7]. However, it has been suggested that a contractile abnormality of the vascular smooth muscle might also be involved[8,9]. If augmented smooth muscle tone accounts for part of the persistent hypertension, then potent pharmacologic vasodilators might elicit more smooth muscle relaxation and pulmonary vasodilation than does oxygen. The purpose of this study was to determine in cattle if either of the spasmolytics, verapamil, a calcium antagonist[10–13], or hexoprenaline, a β-adrenergic agonist[14,15], reduced chronic, hypoxia-induced pulmonary hypertension to a greater extent than did acute alveolar normoxia.

Methods. Cardiopulmonary variables were measured in 8, 4-month-old, unanesthetized, Hereford calves following catheterization as described previously[16]. Baseline measurements were made at the resident altitude of 1520 m ($P_B = 630$ mm Hg). The calves were then exposed in a hypobaric chamber to a simulated altitude of 4270 m ($P_B = 440$ mm Hg). After 2 weeks, the calves were re-

Cardiovascular responses to acute normoxia, verapamil, and hexoprenaline in cattle with chronic, hypoxia-induced pulmonary hypertension. Cardiovascular variables were measured before exposure to high altitude (baseline at 1520 m) and after 2 weeks at 4270 m during brief return to 1520 m (acute normoxia) and at high altitude before (chronic hypoxia) and after injection of verapamil and hexoprenaline

Variable	Baseline at 1520 m	After 2 weeks at 4270 m				
		Acute normoxia[a]	Chronic hypoxia$_1$	Verapamil[b] 1–5′	Chronic hypoxia$_2$	Hexoprenaline[c] 1–5′
PaO_2, mm Hg	68 ± 2	66 ± 1*	34 ± 1	38 ± 2*	37 ± 1	36 ± 1
$PaCO_2$, mm Hg	36 ± 1	35 ± 1	34 ± 1	33 ± 1	35 ± 1	35 ± 1
pHa	7.46 ± 0.01	7.43 ± 0.01	7.45 ± 0.01	7.45 ± 0.01	7.44 ± 0.01	7.43 ± 0.01
$\dot{Q}$, ml/min kg	130 ± 5	133 ± 12	133 ± 12	136 ± 14	126 ± 9	193 ± 17*
HR, min^{-1}	95 ± 4	98 ± 6*	117 ± 9	134 ± 9*	107 ± 5	178 ± 14*
SV, ml/kg	1.39 ± 0.08	1.39 ± 0.07*	1.14 ± 0.07	1.0 ± 0.1	1.17 ± 0.06	1.06 ± 0.09
$\bar{P}pa$, mm Hg	30 ± 3	54 ± 9*	88 ± 12	68 ± 8*	83 ± 11	54 ± 8*
TPR, mm Hg/ml/min kg	0.24 ± 0.02	0.40 ± 0.10*	0.73 ± 0.15	0.57 ± 0.10*	0.71 ± 0.12	0.28 ± 0.04*
$\bar{P}ao$, mm Hg	100 ± 4	106 ± 4	110 ± 4	89 ± 6*	108 ± 2	59 ± 4*
TSR, mm Hg/ml/min kg	0.78 ± 0.05	0.83 ± 0.10	0.87 ± 0.08	0.68 ± 0.06*	0.90 ± 0.08	0.34 ± 0.03*

Data are expressed as mean ± SEM of 8 cattle except for baseline TSR and $\bar{P}ao$ which were measured in 6 animals. * Difference ($p < 0.05$) as determined by paired t-test between; [a] acute normoxia and chronic hypoxia$_1$; [b] verapamil and chronic hypoxia$_1$; [c] hexoprenaline and chronic hypoxia$_2$.

turned to 1520 m for 1 h where they were recatheterized and cardiopulmonary measurements were made (acute normoxia). The calves were then re-exposed to 4270 m for 30 min to restore the conditions of chronic hypoxia, and the measurements were repeated (chronic hypoxia$_1$). While the animals remained at high altitude, verapamil (0.1 mg/kg) was administered as a bolus in saline through a right atrial catheter and cardiovascular responses were monitored. 30 min later, measurements were repeated before (chronic hypoxia$_2$) and after i.v. hexoprenaline (0.025 mg/kg). Data are expressed as mean ± SEM. Statistical analysis was performed with a paired t-test.

Results. The results are shown in the table. Chronic hypoxia increased mean pulmonary arterial pressure and total pulmonary resistance. Acute alveolar normoxia reduced mean pulmonary arterial pressure by 39 ± 2% and total pulmonary resistance by 40 ± 3%. Verapamil reduced mean pulmonary arterial (20 ± 2%) and aortic (19 ± 2%) pressures and total pulmonary (19 ± 4%) and systemic (21 ± 2%) resistances. Pulmonary arterial and aortic pressures reached a minimum at 1 to 5 min post-injection. Arterial oxygen tension was increased slightly, but carbon dioxide tension and pH were not changed. All cardiovascular variables except arterial oxygen tension were at their pre-verapamil levels by 30 min post-injection. Hexoprenaline reduced mean pulmonary arterial (36 ± 5%) and aortic (46 ± 3%) pressures and total pulmonary (60 ± 1%) and systemic (62 ± 3%) resistances. The reductions were maximal at 1 to 5 min post-injection. Total pulmonary resistance was decreased almost to its baseline level. Heart rate and cardiac output were increased. There was no correlation between percentage decrease in total pulmonary resistance and percentage increase in cardiac output ($r = -0.68$, $n = 8$, $p > 0.05$). By 15 min post-hexoprenaline, pulmonary arterial pressure and total pulmonary resistance were 73 ± 12 mm Hg and 0.35 ± 0.07 mm Hg/ml min kg, while cardiac output was 220 ± 17 ml/min kg.

Discussion. The chronically hypoxic cattle developed pulmonary hypertension that was only partially reversed by acute alveolar normoxia. However, hexoprenaline nearly reduced total pulmonary resistance to its pre-hypertensive level. This vasodilatory effect of hexoprenaline cannot be attributed to increased alveolar ventilation because there was no change in arterial blood gases. Nor did it seem likely that increased blood flow was responsible for the fall in resistance. In man with hypoxic pulmonary hypertension, exercise-induced elevation of blood flow increased rather than decreased pulmonary pressure and resistance[3]. Similarly, exercise was accompanied by increased pulmonary arterial pressure in neonatal calves[17]. In dogs with normotensive pulmonary circulations, increased cardiac output after hexoprenaline was accom-

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panied by increased pulmonary arterial pressure[15]. Thus, the concomitant reduction of pulmonary pressure and resistance elicited by hexoprenaline in the present study was probably due to active vasodilation rather than to passive, flow-induced distension of the hypertensive vessels. The excessive vasodilatory response to hexoprenaline suggested that the sustained vascular resistance during acute normoxia was due partly to persistent smooth muscle tone rather than solely to morphological thickening of the vessel wall. Although this concept has been stated[8,9], there is little data to support it, and it is not widely appreciated. The concept is compatible with a study of a calf with pulmonary hypertension in which 24 h of alveolar normoxia reduced pulmonary arterial pressure considerably more than did 10 min of oxygen breathing[18].

If it could be shown that the response to acute normoxia was not indicative of the total potential for relaxation of the hypertensive pulmonary vessels, then a secondary aim of this study was to gain some insight into the cause of the sustained smooth muscle tone. Free cytoplasmic calcium is a determinant of smooth muscle tone[19], and increased levels of calcium have been observed in the pulmonary smooth muscle of chronically hypoxic animals[20]. Thus, pharmacologic agents that alter the concentration of activator calcium were used as pulmonary vasodilators. Verapamil was chosen because it reduces transmembrane calcium influx that accompanies membrane depolarization[10,11], does not have adrenergic activity or act as a competitive inhibitor of any humoral mediator[12,13] and blocks the pulmonary pressor response to acute alveolar hypoxia[21,22]. The vasodilatory response to verapamil in the present study suggests that the transmembrane influx of extracellular calcium plays a role in the mechanism of chronic, hypoxia-induced pulmonary hypertension. Hexoprenaline was used because it is a β-adrenergic agonist that acts on β-2 (vasodilatory) type receptors[14,15], the spasmolytic effect of β-adrenergic activation is possibly related to both enhanced cellular sequestration and extrusion of free calcium[19,23,24] and reduction of calcium influx via hyperpolarization of the plasma membrane[24], and orciprenaline, another β-agonist, reverses the pulmonary pressor response to acute alveolar hypoxia[25,26]. Hexoprenaline was more effective than either normoxia or verapamil in reducing total pulmonary resistance in the chronically hypoxic calves. Speculatively, the greater effectiveness of hexoprenaline might have been due to enhanced intracellular sequestration and extrusion of activator calcium. It seems warrented to explore further the possibility that persistent elevation of activator calcium contributes to the sustained pulmonary vascular resistance in animals with chronic, hypoxia-induced pulmonary hypertension.

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Liver enzyme induction by the anion exchanger resin, Dowex 1 x 2, in the rat

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Summary. Peroral treatment of rats with the anion exchanger resin, Dowex 1 x 2, for 8 days leads to liver enlargement and increase of alkaline and acid phosphatases, glucose-6-phosphate dehydrogenase, malic enzyme, catalase, and the enzymes of microsomal drug metabolism in the liver. The sequestration of bile acids by this treatment mimics the biochemical effects of clofibrate- and phenobarbital-like drugs in the liver.

An interesting way for treating hypercholesterolemia is to administer to the patient a non-resorbable, macromolecular anion exchanger resin[2] which binds the intestinal bile acids during its passage through the gut and takes them out in the feces. Thus, more bile acids are excreted than normally[3-5] and the enterohepatic circulation of the bile acids is interrupted. Because the biosynthesis of bile acids from cholesterol is under negative feedback control by the bile acids reabsorbed from the gut[6,7], cholesterol catabolism is stimulated under anion exchanger resin treatment. The activity of cholesterol 7α-hydroxylase, a cytochrome-P-450-dependent mixed-function oxygenase in liver microsomes which determines the velocity of bile acid formation, is increased[8]. So more cholesterol is metabolized[9] and cholesterol blood level decreases[2,4,5]. Enhancement of bile acid biosynthesis is seen during bile drainage[8] when the enterohepatic circulation of bile acids is interrupted too. The inverse effect, i.e. decrease of bile acid formation, is seen when bile flow out of the liver is stopped either by bile duct ligation[10] or by α-naphthylisothiocyanate-induced cholestasis[11], so that the bile acids cannot leave the liver cell but inhibit their own biosynthesis.

Drug-metabolizing liver microsomal enzymes also depend on cytochrome P-450, and so bile duct ligation[10] and α-naphthylisothiocyanate treatment[11] diminish drug metabolism. Phenobarbital treatment stimulates both cholesterol catabolism[12] and drug metabolism[13]. So we did the following experiment in order to learn whether administration of the anion exchanger resin, Dowex 1x2®, to rats induces the biosynthesis of microsomal drug metabolizing liver enzymes.

Experimental. The experimental animals, male Wistar rats which had free access to food and drinking water, received Dowex 1x2 (chloride form, air-dried) for 8 days by stomach-tube in a daily dose of 500 mg/kg suspended in Tylose® solution; control rats received Tylose solution only. Each group consisted of 10 animals. 20 h after the