Glucagon and Aminophylline as Pulmonary Vasodilators in the Calf with Hypoxic Pulmonary Hypertension

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The cardiovascular actions of glucagon and aminophylline have been related to increasing intracellular levels of 3'5' cyclic adenosine monophosphate (cAMP). The mode of activity of the 2 agents differs: glucagon increases cAMP by increasing the activity of adenylcyclase, while aminophylline and other methyl xanthines increase cAMP by inhibiting phosphodiesterase which is the enzyme which breaks down cAMP to 5' AMP. Some of the effects of increasing intracellular cAMP are potentially beneficial in certain cardiovascular diseases. These effects would include a positive inotropic and chronotropic activity along with relaxation of contracted vascular smooth muscle.

We wished to test the hypothesis that these 2 agents, glucagon and aminophylline, operating by separate mechanisms to increase cAMP, will reduce hypoxic pulmonary vasoconstriction. Calves were selected for this study because chronic airway hypoxia produces sustained pulmonary hypertension which may lead to cor pulmonale (Brisket disease). Furthermore, pulmonary hypertension is due to pulmonary vasoconstriction, and this is a reversible process as demonstrated by the fact that when chronic hypoxia is relieved, the vasoconstriction disappears and there is reversal of the pulmonary hypertension. Thus, cattle at high altitude provide an ideal situation for testing the action of potential pulmonary vasodilators. One additional advantage of the calf is that one may study these animals in the awake, undisturbed state, thus eliminating the effects of anesthesia on results obtained.

Five calves were studied after 4 weeks of exposure at an altitude of 3,400 m (P0 = 510 mm Hg). At this time, all calves had developed hypoxic pulmonary hypertension. At different times the calves were given either a single intravenous injection of aminophylline (5 mg/kg) or a single intravenous injection of glucagon (3 mg).

Figure 1. Data from bolus intravenous injection of 3 mg of glucagon. Solid circles and lines represent the data from 5 calves at 3,400 m. Vertical bars are ± 1 SEM. Open circles and dashed lines are data from 2 calves studied at sea level. C designates control prior to drug injection. HR = heart rate, P0 = mean aortic blood pressure, PR = mean pulmonary arterial pressure, TPvR = total pulmonary vascular resistance, CI = cardiac index.

Glucagon (Fig 1) caused a significant fall in total pulmonary vascular resistance (TPvR) brought about by both an increase in cardiac output (CI) and a fall in mean pulmonary arterial pressure (Ppa) which were sustained for at least 20 minutes (control PR = 84 mm Hg, minimum P0 = 45 mm Hg, P < 0.05). Total peripheral resistance (TPeR) and mean aortic pressure (PAr) were also reduced while heart rate was significantly elevated by the bolus injection of glucagon. The pattern of response was similar at sea level except that TPvR and P0 were not altered.
Aminophylline (Fig 2) injection caused a transient rise in heart rate and P50, while P20 fell (control P20 = 68 mm Hg, minimum P20 = 51 mm Hg, P < 0.05). Maximal effects of pressures and heart rate occurred within the first minute of infusion of aminophylline and the reduction in P20 was sustained for only 10 minutes after infusion. TPuR decreased by a fall in P50 with little change in CI. No changes in blood gases or acid-base balance were induced by either drug.

In a second set of experiments 6 calves were studied at sea level and after 4 to 6 weeks on 3,400 m prior to and during a 3 hour infusion of glucagon at the rate of 0.10 to 0.15 mg kg\(^{-1}\) hr (Fig 3 and 4). Significant increases in heart rate occurred in both sea level and altitude studies; however, in the chronically hypoxic calves the increase in heart rate was significantly less than in sea level calves (mean maximum heart rate at sea level = 160 beats per minute, vs 134 beats per minute at high altitude) and was not sustained throughout infusion as it was in sea level studies. The increase in CI and decreases in P20 were comparable in sea level and high altitude studies.

In the sea level study no change in P20 occurred, while there was a large decrease in the chronically hypoxic calves (control P20 = 83 mm Hg, average infusion P20 = 46 mm Hg, P < 0.01). Accordingly, TPuR was reduced by a larger magnitude in studies at 3,400 m as compared to sea level. There were no changes in arterial blood gases or acid-base balance induced by glucagon.

With the exception of heart rate changes in the altitude calves actions of glucagon were sustained throughout the period of infusion.

In summary both glucagon and aminophylline caused reductions in TPuR, but with glucagon this was brought about by both an increase in CI and a fall in P50, while with aminophylline this occurred primarily by a reduction in P50. Our data support our hypothesis that both glucagon and aminophylline are vasodilators in the presence of chronic hypoxic pulmonary vasoconstriction.

The increased CI with glucagon in these calves was probably related to the known positive inotropic and chronotropic effects of this agent. The comparable increases in CI between sea level and high altitude indicates that chronic hypoxia does not depress the inotropic effect of glucagon. However, the reduction in maximum heart rate and failure to sustain a rapid heart rate during glucagon infusion in the chronically hypoxic calves suggests that chronotropic effects of glucagon may be par-
Role of the Autonomic Nervous System and Pulmonary Artery Receptors in Production of Experimental Pulmonary Hypertension

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Recently, we published evidence which demonstrates that acute or chronic balloon distention of the main pulmonary artery results in a significant elevation in the pulmonary artery pressure measured distal to the balloon. This pulmonary hypertension can occur in the absence of significant change in right ventricular end-diastolic pressure, aortic pressure and cardiac output. Since balloon occlusion of one major branch of the pulmonary artery did not elevate pulmonary artery pressure, a reflex mechanism was postulated to be responsible for the observed pulmonary hypertension. The purpose of this study was to investigate the role of the autonomic nervous system in the production of the proposed experimental pulmonary hypertension reflex.

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These studies were conducted in 28 adult mongrel dogs of both sexes weighing between 18 and 24 kg. Dogs were prepared with aortic catheters and pulmonary artery triple lumen balloon catheters and either studied immediately while still anesthetized with sodium pentobarbital (30 mg/kg) or allowed a recovery period of 8 to 14 days before being studied in the conscious state. The specially designed triple lumen balloon catheter and the technique for this animal preparation have been previously described.1,4 Briefly, the catheter was inserted through the jugular vein and the tip wedged under fluoroscopic control in a small branch of the pulmonary artery. Wedging the tip of the catheter in a small pulmonary artery gave stability to the balloon in the main pulmonary artery during repeated inflation and deflation. From side lumens in this catheter, pressures were measured proximal to the pulmonary arterial balloon in the right common carotid artery and distal to the balloon in the main pulmonary artery. We have demonstrated angiographically that during balloon inflation, the pulmonary artery is distended by blood flowing around the partially inflated balloon.

Afferent nerve pathways were evaluated by surgical denervation of the pulmonary artery wall, chemical blockade by lidocaine infiltration of the pulmonary artery wall, and bilateral cervical vagotomy. Surgical denervation of the pulmonary artery was accomplished by the following technique. Following left thoracotomy, the pulmonary artery and its major branches were isolated and mobilized free from surrounding tissues. The subsequent removal of deep adventitial

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**Figure 1.** Glucagon is infused at 10.0, 0.10, and 0.01 mg/kg/hr of the drug to a total of 5 ml/kg/hr of saline in 6 calves with chronic hypertension. After 12 hours of infusion, the calves were studied in the same manner as described above. The effect of infusion of glucagon on blood pressure is shown in the graph. The following values are shown for control prior to infusion (C1), after 3 hours of infusion and 0.5 hour (P1) after the end of infusion.

**Figure 2.** The effect of infusion of glucagon on heart rate is shown in the graph. The following values are shown for control prior to infusion (C1), after 3 hours of infusion and 0.5 hour (P1) after the end of infusion.

**Figure 3.** The effect of infusion of glucagon on cardiac output is shown in the graph. The following values are shown for control prior to infusion (C1), after 3 hours of infusion and 0.5 hour (P1) after the end of infusion.

**Figure 4.** The effect of infusion of glucagon on pulmonary artery pressure is shown in the graph. The following values are shown for control prior to infusion (C1), after 3 hours of infusion and 0.5 hour (P1) after the end of infusion.