Table 1 Effects of ICI 66082 on the responses to stimulation of the right ansa subclavia of the dog

Cumulative dose of ICI 66082 (mg/kg)	*No. of experiments*	*Reduction in response of increase in heart rate to stimulation at:*	
		0.5-3 Hz	*7-15 Hz*
		% Reduction compared to control	*% Reduction compared to control*
0.5	10	98 ± 0.6	72 ± 9.9
1.0	7	97 ± 0.8	80 ± 7.9
2.0	5	99 ± 0.7	89 ± 2.2
5.0	14	99 ± 0.4	92 ± 3.1
10.0	8	99 ± 0.4	93 ± 2.5

The results are the reduction (mean: ±s.e. mean) in response of an increase in heart rate to stimulation after giving ICI 66082, expressed as a percentage of the response before ICI 66082.

blocking effect, which was sometimes not complete, was achieved with 2.0 mg/kg ICI 66082.

It is concluded that it is not always possible to achieve complete blockade of the effects of maximal stimulation of sympathetic nerves to the heart even with very high doses of ICI 66082.

M.F. Knapp is an ICI Research Fellow.

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2-2′ Pyridylisatogen tosylate: an antagonist of the inhibitory effects of ATP on smooth muscle

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Taenia caeci preparations were obtained from female guinea-pigs in the weight range 250-600 g. The preparations were arranged in 10 ml isolated organ baths filled with McEwen's solution maintained at 35 ± 1°C and oxygenated with 95% O_2 : 5% CO_2. After an equilibration period of 30 min, drug-induced relaxations were recorded on a smoked drum using an isotonic frontal-writing

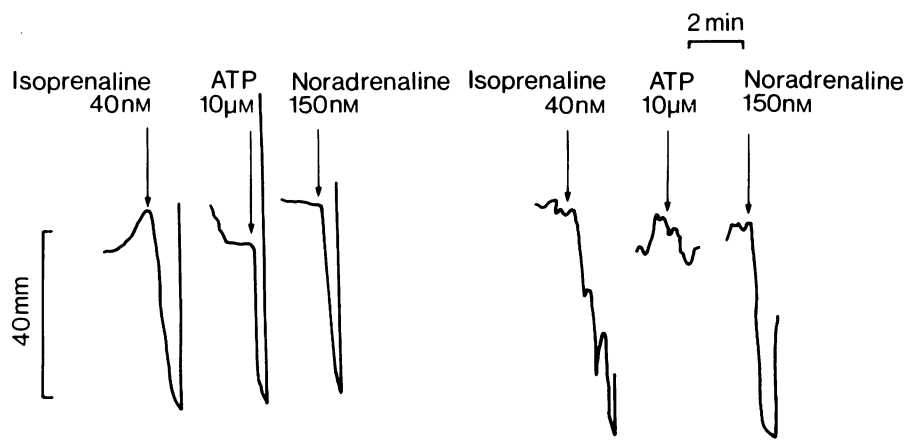

Fig. 1 Blockade of the ATP-induced relaxation of the taenia caeci by 2-2′pyridylisatogen. The drugs were administered on a 5 min cycle. Between panels (a) and (b) the preparation was exposed to 2-2′pyridylisatogen (50 μM for 25 min) which relaxed the tissue: the tone was restored with histamine (70 nM).

lever (magnification x4, load on the tissue 1.5 g).

2-2'pyridylisatogen (Patterson & Wibberley, 1965) exerted two actions on the taenia caeci. Concentrations above 2.5 μM gradually relaxed the smooth muscle over a 30 min contact period; this effect was accompanied by an increase in the frequency of the spontaneous contractions (78 experiments). The second effect, seen after the tone of the smooth muscle had been restored with either histamine or acetylcholine, was a reduction in the submaximal responses to ATP (2-600 μM) after 15-30 min contact of the tissue with 2-2'pyridylisatogen (20-50 μM, 28 experiments). The blockade was specific for ATP (Figure 1). Under these conditions, cumulative concentration-response curves to ATP were displaced to the right in parallel (six experiments).

High concentrations of 2-2'pyridylisatogen ($>$100 μM for 30 min or longer) caused a general antagonism of ATP, isoprenaline and noradrenaline. These non-specific effects were not reversed by washing the tissue with 3 l McEwen's solution over 3 h (four experiments).

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Increased inactivation of prostaglandin E_2 by the rabbit lung during pregnancy

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It is well established that the lungs are extremely efficient at removing prostaglandins E and F from the circulation (Ferreira & Vane, 1967; Horton & Jones, 1969). However, during parturition these prostaglandins appear in the venous blood, and their levels fluctuate in parallel with the uterine contractions (Karim, 1968; Hertelendy, Woods & Jaffe, 1973). This raises the possibility that these prostaglandins survive passage through the lungs during late pregnancy and might therefore act as circulating hormones during parturition. Accordingly, we have estimated the lung inactivation of prostaglandin E_2 in pregnant and non-pregnant rabbits. Our results suggest that this is actually enhanced during pregnancy and immediately postpartum.

Mature Dutch female rabbits were anaesthetized with pentobarbitone sodium given intravenously. Blood pressure was recorded from a femoral artery. Intra-arterial injections of PGE_2 were given through a catheter which had been inserted into the right carotid artery and advanced into the ascending aorta. Intravenous injections were given through a catheter advanced via the femoral vein into the vena cava.

Two doses which gave clearly defined but submaximal depressor responses were selected for both the intravenous and the intra-arterial routes, the ratio between these doses being the same. These four doses were given repeatedly following a Latin square design and a dose cycle of 10 minutes. The dose required to give a 20 mmHg (1 mmHg = 1.333 mbar) fall in diastolic blood pressure was measured graphically for each route. The ratio between these doses (i.v. dose/i.a. dose) was calculated and this was taken as a measure of the apparent degree of inactivation of the prostaglandin by the lung.

In non-pregnant rabbits the ratio was 14.4 $\pm$ 2.9 (mean $\pm$ s.e., $n = 7$) whereas in pregant rabbits (days 22-28) it was 68.8 $\pm$ 3.4 ($n = 5$). These ratios are significantly different ($P < 0.001$) suggesting that the lung inactivation was greater in the pregnant rabbits than in the non-pregnant controls. During the immediate post-partum period (days 1-4) the ratio was also significantly higher than in the non-pregnant animals (39.7 $\pm$ 8.6, $n = 7$, $P < 0.02$). Thus it is unlikely that lung inactivation declines to the non-pregnant state at the time of parturition. These results also show that the increased dose ratio seeen during pregnancy is unlikely to be related to any haemodynamic changes occurring as a direct result of the presence of foetuses in utero.

We have been unable to obtain as large an effect as that found in pregnancy by treating non-pregnant rabbits for 12 days with progesterone (10 mg/kg)/day, oestradiol monobenzoate (10 μg/kg)/day or a mixture of progesterone (5 mg/kg)/day and oestradiol monobenzoate (5 μg/kg/day. However, the results of these experiments indicated that there is a connection between elevated progesterone levels and enhanced lung inactivation of PGE_2.

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