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RELEASE OF PROSTAGLANDINS DURING CONTRACTION OF THE HUMAN UMBILICAL VEIN ON REDUCTION OF TEMPERATURE

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Flow rate was measured through the vein of the human isolated umbilical cord perfused at constant pressure (40 mmHg) at 37.5°C and 20°C. At the latter temperature the flow was decreased by 50.9% when compared with a mean of 201 ml/min at 37.5°C indicating venospasm. Indomethacin (10 μg/g) effected a highly significant reduction in the venous spasm caused by lowering the temperature. After indomethacin pretreatment, changing the cord temperature from 37.5°C to 20°C caused a mean decrease in flow of only 3.1%. When the effluent from the vein was passed over rat isolated stomach fundus and colonic strips, cooling of the cord was accompanied by contractions of the isolated tissues characteristic of prostaglandins. These results suggest that prostaglandins are involved in temperature-induced closure of the human umbilical vein after birth.

Introduction Constriction of the umbilical arteries and vein occurs immediately after birth to prevent foetal blood loss. This increase in vascular tone is unlikely to be mediated by neurogenic mechanisms as nerve endings have not been demonstrated in the umbilical cord (Roach, 1976). Locally released autacoids are more likely to be involved of which prostaglandins and thromboxanes may be of some importance. Prostaglandin E_1 (PGE_1), PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ have been detected in the human umbilical cord (Karim, 1967) and their intramural synthesis in human umbilical arteries has been postulated (Hillier & Karim, 1968; Jonsson, Tuvemo & Hamberg, 1976). There is also evidence that PGG_2, PGH_2 and perhaps thromboxane A_2 (TxA_2) may be concerned in umbilical artery closure (Tuvemo, Strandberg, Hamberg and Samuelsson, 1976).

It was therefore decided to seek additional evidence that prostaglandins play a role in closure of the human umbilical vein and specifically to determine whether the fall in cord temperature which occurs immediately after birth could be a stimulus for their production. Synthesis and release of vasoconstrictor agents may be caused by a reduction in cord temperature (Haselhorst, 1929).

Methods Umbilical cord segments were obtained from the hospital labour ward. A 20 cm segment of the cord was taken immediately after delivery. It was immediately placed in amniotic fluid-like Krebs solution (Fuchs & Wagner, 1963) at 37°C and perfusion of the vein commenced within 3 h.

The umbilical vein was cannulated, placed in an organ bath and perfused at 37.5°C with amniotic fluid-like Krebs solution saturated with carbogen at a constant pressure (40 mmHg) by means of a pump (Harvard, Model 1405) set at the foetal heart rate (140/min). The vein was perfused for 1 h to allow equilibration, after which the flow rate was measured. The bath temperature was then reduced to 20°C within 2 min and the perfusion flow recorded again 30 min later. In further experiments the umbilical cord was first treated with indomethacin solution, by injection at several points into the Wharton's jelly (10 μg/g tissue) and flow rate determinations carried out as described above.

The prostaglandin content of the perfusate from the umbilical vein was monitored by cascade superfusion (Vane, 1969). The apparatus was similar to that already described, except that perfusion was carried out by means of a constant flow pump and a heating coil was interposed between the vein and the isolated tissues to ensure that during reduction of temperature of the cord the cascade tissues remained at 37.5°C. The perfusate was superfused (6 ml/min) over segments of the descending colon and stomach fundus of the rat. A mixture of antagonists was pumped over the tissue cascade at 0.1 ml/min to make the responses specific for prostaglandins. This consisted of indomethacin 20 μg/ml, phenoxybenzamine hydrochloride 1 μg/ml, methysergide maleate 0.1 μg/ml, hyoscine hydrochloride 10 μg/ml, mepyramine maleate 1 μg/ml and propranolol hydrochloride 20 μg/ml.

Statistical examination of the results was carried out by a one way analysis of variance (Freund, 1962).

Results Reduction of the vein temperature from 37.5°C to 20°C in 10 cords was accompanied by a statistically significant ($P < 0.01$) reduction in perfusion rate from 201 ± 15 to 98 ± 7 ml/min (mean ± s.e. mean) indicating the occurrence of venospasm. In 5 cords pretreated with indomethacin the mean perfusion rate of 227 ± 23 ml/min did not

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differ significantly ($P > 0.05$) from that of the untreated cords. When the latter were cooled a significant reduction ($P < 0.01$) in flow to 221 ± 23 ml/min occurred but the mean fall was markedly less than that which occurred in the non-indomethacin treated cords. In a further six experiments, in which the umbilical vein was perfused with a constant flow and the effluent examined for prostaglandin-like activity, during cooling of the cord the cascade tissues showed contractile responses characteristic of prostaglandins. In five of these experiments the magnitude of the contraction of the fundus strip was greater than that of the colon. In the 6th the two responses were similar.

Discussion These results demonstrate that spasm is induced in the umbilical vein by reducing its temperature. This effect was blocked by indomethacin in a concentration that inhibits biosynthesis of prostaglandins (Vane, 1971). The venous spasm caused by cooling was accompanied by the appearance in the venous effluent of substances causing prostaglandin-like effects on the cascade tissues but release of other autacoids including thromboxanes cannot be ruled out. The antagonist mixture would have inhibited responses of the test tissues to noradrenaline, 5-hydroxytryptamine, acetylcholine and histamine but the large reduction in the venous spasm caused by indomethacin indicates that it is unlikely that they make an important direct contribution. Karim (1967) reported that bradykinin and angiotensin were not responsible for the vasoactive properties of umbilical cord extracts. It is unlikely that patency of the vein at body temperature requires continuous production of a venodilator prostaglandin because indomethacin did not reduce the flow rate at 37.5°C.

Identification of the type of prostaglandin involved was not carried out in this preliminary study but PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGG_2 and PGH_2 have each been reported to cause vasoconstriction in human isolated umbilical arteries or veins (Hillier & Karim, 1968; Park, Rishor & Dyer, 1972; Tuvemo *et al.*, 1976).

At birth the umbilical cord is influenced by a number of factors. Temperature is reduced, oxygen saturation of the foetal blood increases and manipulation and traumatic cord severence may occur. Venospasm could result from all these stimuli. Present results indicate that maintenance of the umbilical cord temperature close to that of the body is vital for venous patency and that temperature reduction and prostaglandin release in the cord at birth probably make a substantial contribution to closure.

The mechanism whereby cooling of the umbilical cord causes prostaglandin release is unknown. However, a reduction in temperature has been shown to lead to a phase change in membrane lipids and alter the activity of membrane-bound enzymes (Zakim & Vessey, 1974). Changes in temperature may be expected to cause not only changes in the rate of prostaglandin synthesis but also catabolism. Sensitivity changes in the vein to the contractile effects of prostaglandins may also contribute. Qualitative and quantitative studies are in progress to elucidate their relative importance.

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