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EVIDENCE FOR A PHYSIOLOGICAL ROLE FOR FETAL ANGIOTENSIN IN THE REGULATION OF THE UMBILICO-PLACENTAL VASCULATURE

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The mechanism(s) controlling fetal umbilico placental blood flow is largely unknown. Since this vasculature is non-innervated, neurogenic mechanisms may be ruled out altogether. This leaves either hormonal (humoral) or local mechanisms as alternatives. Recent quantitative *in vitro* studies from this laboratory on isolated human villous stem vasculature demonstrate that these vessels (lumen dia. 50-200 μ) are very sensitive to the constrictor action of angiotensin (All), bradykinin (BK) and serotonin (5-HT). Based upon the effective concentration required to elicit 50% maximal response (EC_{50}), the order of potency is All ($EC_{50} 2 \times 10^{-8}M$) > BK ($2.5 \times 10^{-8}M$) > 5-HT ($1 \times 10^{-7}M$) while angiotensin contracted all vascular strips studied, BK contracted only 65% and 5-HT only 50%. In addition to these agents, the prostaglandins (A_1 , E_2 and F_2 alpha) also contracted these vascular strips. While the doses required for this activity were relatively large ($>10^{-6}M$), their action, unlike the other agents studied, was slow to develop and long lasting, suggesting an intracellular mode of action.

Marked differences exist in the distribution of drug sensitivity throughout the umbilico-placental vascular unit. Umbilical Cord arteries were most sensitive to 5-HT and BK, but quite insensitive to All (i.e., 5-HT > BK >>> All), while the arteries of the chorionic plate were quite sensitive to all three agents, but yielded a similar order of potency. Since the villous stem arterioles demonstrated the greatest responses to All, the order of potency being All > BK > 5-HT, there appears to be an increasing sensitivity to All from cord arteries to villous arterioles. These findings reflect that the villous component of this vascular bed is uniquely sensitive to angiotensin II.

Acute studies in the instrumented fetal lamb preparation *in utero* tend to support the above findings. Angiotensin injection (fetal I.V. 10 nmoles) resulted in a 22% reduction (from 900 to 700 ml/min) in placental blood flow, with no change in uterine arterial perfusion pressure. Serotonin (25 nmoles), on the other hand, had no effect on placental blood flow directly, but did induce strong uterine contractions which, in turn, reduced placental blood flow. This flow response was temporally related to the uterine contractions. Injection of the angiotensin antagonist saralisin into the umbilical artery (5 μ moles) under steady-state conditions resulted in a slight (7.7%) but definite increase in umbilical placental blood flow (780-840 ml/min). Injections of angiotensin after saralisin were without effect.

While none of the above evidence constitutes an *a priori* proof of a relationship between fetal angiotensin levels and umbilico-placental vascular regulation, taken in the light of findings from other laboratories, a strong case can be made for this relationship. For instance, a role for the fetal renin-angiotensin system in the maintenance of the fetal hemodynamic state has been suggested by Trimper and Lumbers (1972) studying the fetal renal response to natriuretic challenge. A similar suggestion has been made by Mott (1976) studying factors influencing renin release in fetal lambs. Mott (1969) has also shown that nephrectomy greatly impairs the ability of the fetal rabbit to tolerate a hemorrhagic challenge and even in simply maintaining a steady-state hemodynamic status. In the fetal lamb, hemorrhage ($\leq 3\%$ blood volume) elevate plasma renin and angiotensin levels (Broughton-Pipkins, 1974). With respect to the placental vasculature, hypotension (Rudolph and Heymann, 1974) and hypoxia (Assali and Brinkman, 1973) result in a decrease in umbilico-placental blood flow in the fetal lamb studied *in utero*.

These above studies suggest a role for the fetal kidney in preserving fetal cardiovascular homeostasis. Since the fetal baroreceptor reflex is still hypodynamic in late gestation (Shineborne *et al.*, 1972), a hormonal mechanism to assist in regulation of fetal peripheral vascular resistance would seem desirable. Several lines of evidence support a renin-angiotensin component in fetal cardiovascular homeostasis in general, and, particularly in regulating placental vascular tone, which must maintain a low constant vascular resistance. An attractive hypothesis for the regulation of the placental blood flow involves the fetal renin-angiotensin system regulating the "bias" or background resistance (tone) of this vasculature which may be modulated locally by increase or decrease in prostaglandin synthesis in the placental arterial wall.

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