LIPOPHILICITY IS THE MAJOR DETERMINANT OF PERMEABILITY TO A RANGE OF BETA-ADRENOCEPTOR ANTAGONISTS IN THE FETALLY-PERFUSED GUINEA-PIG PLACENTA

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Beta-adrenoceptor antagonists are being used increasingly for the therapeutic management of hypertension in the last trimester of pregnancy. This study examines the relation between the differing degrees of lipophilicity of several of the beta-adrenoceptor antagonists and their placental permeabilities. The experimental model was the anaesthetised (pentobarbitone IV) pregnant guinea-pig with the fetal circulation of the placenta perfused in-situ with tissue culture medium containing bovine serum albumin. An indicator dilution method (^{14}C-drug + ^{3}H-sucrose) was used to estimate first-pass extraction of drug in the fetal circulation (extraction = $(1-(^{14}C/^{3}H_{out})/(^{14}C/^{3}H_{in}))$) (Day et al 1982).

The experiments involved comparison of several drugs within the same animal to make a comparative assessment of placental transport under the same conditions. All the experiments used concentrations of 10^{-5} mol.dm^{-3}. The first-pass extraction of atenolol was the lowest of the drugs so far studied, with an extraction of 0.0647 ±0.0218 (mean ±s.d.). Acebutolol showed an intermediate extraction of 0.433 ±0.080, whilst the remaining drugs all showed a much higher extraction, with a much lower coefficient of variation; labetalol (0.864 ±0.082), timolol (0.933 ±0.049), metoprolol (0.940 ±0.004), oxprenolol (0.979 ±0.002) and propranolol (0.983 ±0.004). This closely reflects the order of lipophilicity of the drugs as measured by their octanol-water partition coefficients at pH 7.40 and 37°C (Woods & Robinson 1981) (Kendall rank correlation coefficient τ =0.619, p=0.035). The greater variance in the poorly-extracted drugs was probably due to the effect of small changes in utero-placental blood flow and perfusate flow; highly-extracted drugs were relatively unaffected.

It would be expected that a drug such as atenolol which has low protein binding (5%) (Ritschel 1980), would be highly extracted, whereas a drug such as propranolol which is highly protein bound (90%), would be poorly extracted. From the data presented this is not true. All the drugs with the exception of labetalol (49%) are more than 99% ionized at pH 7.40; it would therefore be expected that labetalol would have an enhanced extraction, but although it has the second highest lipophilicity, it is fifth in the order of extraction.

We therefore conclude that the equilibria involved in protein binding and ionization can be established at a rate that does not affect the first-pass extraction of beta-adrenoceptor antagonists in the fetally-perfused guinea-pig placenta; under such conditions, lipophilicity is the major factor in determining the degree of extraction.

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