DEMONSTRATIONS

Effect of chlorpromazine on hexose penetration in the human erythrocyte

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It has been previously shown that chlorpromazine both accelerates and inhibits glucose exit from erythrocytes pre-loaded with glucose at 36° C depending upon the drug concentration (Baker & Rogers, 1972). The entry of sorbose, a hexose which obeys diffusion kinetics when penetrating the erythrocyte but which in fact is transported on the hexose system for which it has a very low affinity (Widdas, 1954) has been studied using the Ørskov photoelectric technique. Chlorpromazine produces a similar biphasic type of inhibition in the case of this sugar but, unlike glucose exit, sorbose entry is not accelerated. Glucose exit flux measured by optical techniques at 17° C resembles that seen at 36° C but glucose exchange flux determined by isotopic methods at this temperature does not show a biphasic response. The exchange flux is only minimally decreased over the concentration range which produces a two-fold inhibition of exit rate. At drug concentrations corresponding to the second phase of exit inhibition some small decrease in the rate of exchange is seen but this is not comparable in magnitude with the change in exit rate. This suggests a fundamental difference between these two processes and places limitations upon the kinetic models which may attempt to describe such fluxes. Simple carrier models (Widdas, 1954) or the more complex conformational models (Lieb & Stein, 1972) which do not contain separate terms in their kinetics for net and exchange fluxes cannot meet this criterion. Any model to describe these phenomena adequately must contain an exchange rate term which is separate from the net rate. These effects of chlorpromazine may be contrasted with the smooth acceleration of ethylidene glucose (4,6-0-ethylidene glucopyranose) entry, a sugar entering the cell by diffusion, which has been previously described (Baker & Rogers, 1972). It is concluded that changes produced by chlorpromazine on glucose permeation are effective upon the carrier itself rather than a generalized membrane effect.

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Use of the guinea-pig foetal placenta, perfused *in situ*, as a model to study the placental transfer of pharmacological substances

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Perfusion of the placenta *in situ*, via the umbilical arteries with the foetus removed, was introduced by Money & Dancis (1960) using the guinea-pig. The method has been used to study the placental transfer of metabolites and hormones (Dancis, 1971); the transfer of electrolytes has been investigated in the perfused rabbit placenta *in situ* (Faber, 1970; Tucker, 1970). The preparation which will be demonstrated, has not so far been used to study the placental transfer of pharmacological agents and their metabolites, or their effect on the transfer of physiological substances or other drugs.

Details of a simple modification of Money & Dancis' preparation have been described (Reynolds & Young, 1971). Briefly, the near term mother was anaesthetized with pentobarbitone sodium (Nembutal, 20–30 mg/kg) and supported in a saline bath at 38° C. The foetus was exteriorized by Caesarian section, the umbilical arteries and vein cannulated and the foetus removed; the maternal circulation to the placenta remained intact. The placenta was perfused with a physiological solution containing 6·5% dextran (Lomodex) at 2 ml/min and at a pressure of 34–40 mmHg which is equal to that measured in the umbilical artery of the intact foetus.

Maternal acid base balance and carotid arterial blood pressure were monitored throughout each experiment. Constant infusions were maintained, via the maternal jugular vein, of: (1) metaraminol (Aramine) to maintain and steady the maternal arterial pressure and placental circulation, and (2) of antipyrine (Phenazone) to monitor changes in the maternal placental blood flow. When the maternal arterial pressure and acid base balance were within the normal ranges, there was close agreement between the perfusate and maternal plasma concentrations of antipyrine; in a poor preparation or following maternal haemorrhage, there was a reduction in the antipyrine transfer (Reynolds & Young, 1971). Therefore, the transfer of antipyrine may be used as an index of maternal placental blood flow, and to determine whether the pharmacological effect of a drug on the transfer of another substance is direct, or mediated by changes in the maternal placental circulation. Antipyrine transfer itself is an example of the rapid diffusion of an antipyretic drug across the placenta. The net transfer and bi-directional flux of a pharmacological substance may be studied since the composition of the perfusion fluid is readily changed and a new steady state established.

The structure of the placental membrane separating the maternal and foetal blood in the guinea-pig is similar to that in the human (Enders, 1965). As an experimental animal, the guinea-pig is comparatively cheap and readily available in the pregnant state, though the gestation is 67 days. The small blood volume also allows economic use of the pharmacological agent being studied.

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Kinetic analysis of amino acid uptake by the rat retina *in vitro*

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Amino acids are actively taken up into brain tissue, as into other tissues, by several relatively non-specific uptake processes (Blasberg, 1967). Recently, it has been demonstrated that central nervous tissues also possess specific, high affinity, uptake processes for certain amino acids (e.g. GABA, glutamate, taurine, glycine) and it has been suggested that the presence of such an uptake process could be associated with a neurotransmitter role of the amino acid (Logan & Snyder, 1972).

In the present study, we have examined the retinal uptake of various amino acids, over wide concentration ranges, and have subjected the results to kinetic analysis using several different procedures.