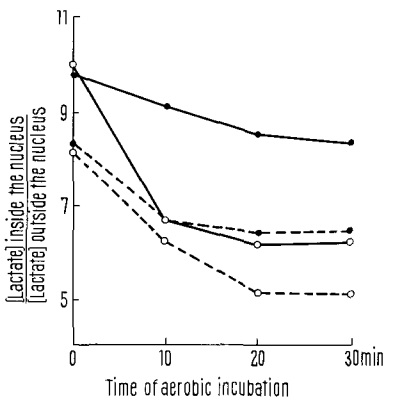
On the Effect of Insulin on Lactate Permeability through the Nuclear Membrane

This communication reports a phenomenon observed during a study on the effect of insulin in vitro on energy metabolism in isolated rat thymus nuclei. From these experiments it is concluded that insulin has no significant effect on oxygen consumption, ATP synthesis, glucose uptake, hexose monophosphate pathway activity and lactate production. A clear effect, however, was found on membrane permeability towards lactate. All methods used were exactly as described elsewhere[1-4]. From earlier[4] experiments it is known that endogenous lactate which is formed under anaerobic conditions is partly metabolized during a subsequent aerobic incubation and partly leaks out from the nucleus into the medium.

In the Figure it is demonstrated that leakage during aerobic incubation can be partly prevented by adding insulin. The ratio of lactate concentrations was influenced in the same direction when glucose was added. As can be seen in these experiments insulin had no effect on the lactate ratio during the anaerobic period. A more or less stable equilibrium of lactate inside and outside the nucleus was reached after 20 min of aerobic incubation. No information is available in literature on the influence of insulin on lactate permeability through the nuclear membrane. DANCHEVA[5] reported a slight stimulation of nuclear oxidative phosphorylation in isolated thymus nuclei by insulin in the presence of glucose and galactose and contributed this to an accelerated transport of the hexoses through the nuclear membrane. In our opinion it is unlikely that glucose entry is rate-limiting for its metabolic conversion because the nuclear membrane is extremely permeable for glucose[6]. Moreover, added glucose is rapidly catabolized to lactate by isolated thymus nuclei, while its further breakdown via the citric acid cycle is limited[2,3].



Influence of insulin on the ratio of lactate concentrations inside and outside the nucleus after anaerobic incubation. The anaerobic incubation was performed for 15 min at 30 °C and the subsequent aerobic incubation for 30 min at 22 °C. The basic medium consisted of 0.25 *M* sucrose. 3 m*M* $CaCl_2$. Broken lines illustrate experiments on endogenous substrate; solid lines experiments with 5 m*M* glucose. Open circles represent experiments without insulin; solid circles illustrate experiments in which 100 μunits insulin per ml were added.

Résumé. L'addition d'insuline aux noyaux isolés du thymus de rat peut prévenir les pertes de lactate endogène se produisant à travers de la membrane nucléaire.

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[1] H. M. KLOUWEN and I. BETEL, Int. J. Radiat. Biol. *6*, 441 (1963).
[2] A. W. T. KONINGS, Biochim. biophys. Acta *189*, 125 (1969).
[3] A. W. T. KONINGS, Life Sci. *8*, 1009 (1969).
[4] A. W. T. KONINGS, Experientia *25*, 809 (1969).
[5] K. I. DANCHEVA, Nature *212*, 1361 (1966).
[6] B. S. MCEWEN, V. G. ALLFREY and A. E. MIRSKY, J. biol. Chem. *238*, 2579 (1963).
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Testosterone Metabolism by Homogenates of Human and Rat Placenta

It now appears to be accepted that testosterone and its 16-hydroxylated derivative are intermediates in the placental biosynthesis of estrogens from the fetal precursors, dehydroepiandrosterone and 16-hydroxydehydroepiandrosterone, respectively[1-3]. The abundantly occurring human placental aromatase[4-7] effects a rapid conversion of these 19 carbon intermediates to the 18 carbon estrogens by a series of reactions which apparently includes oxidation of the methyl group at carbon 19 prior to its elimination[8].

In the rat, however, in vivo evidence suggests that the placenta produces little, if any, estrogen[9]; also, rat placental tissue does not appear capable of converting testosterone to estrogens in vitro[10].

Human and rat placenta appear to differ in yet another aspect. While rat tissue is capable of metabolizing testosterone to an androstane product such as 5α-androstane-3α,17β-diol[10] and thus appears to possess Δ4-reductase activity, evidence for this activity could not be found in midterm human placenta perfused in situ[11]. Recently, however, the Δ5-reduction of dehydroepiandrosterone by minced premature human placental tissue has been reported[12].

The present study compares the metabolism of 4-C^{14}-testosterone by homogenate preparations of human and rat placental tissue (both term and premature) incubated under identical experimental conditions.

Materials and methods. Human placentas were obtained at the time of delivery and processed immediately. Rat placentas were removed after sacrifice of the animals by concussion and also used immediately. Details of the methods used are reported elsewhere[13]. In brief, all