Nucleic Acid Precursor Uptake into Normal and Regenerating Rat Liver

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Growth-promoting hormones may alter precursor uptake into their target tissues (Tata, 1970), and in cell cultures uptake may be promoted by factors from serum (Cunningham & Pardee, 1969). In regenerating rat liver UTP concentrations are increased by 50% within 3 h after partial hepatectomy (Bucher & Swaffield, 1969). Experiments with [^3H]-orotate, -thymidine and -uridine, with [$\text{carboxy-}^{14}\text{C}$]inulin as marker for extracellular space, indicate twofold increases in intracellular acid-soluble ^3H radioactivity in the residual livers 1 h after partial hepatectomy. This response was not found in pancreas, thymus, salivary gland or muscle, which also differ from liver by their failure, with [^3H]orotate, to concentrate ^3H radioactivity intracellularly with respect to plasma. Actinomycin D (0.55 mg/kg body wt.) decreased total nuclear RNA synthesis in the livers of partially hepatectomized rats by 50%, but did not prevent the increased precursor uptake at 1 h. [^3H]Adenine distribution between liver and plasma did not alter after partial hepatectomy. Liver is sensitive to surgical stress (Moolten *et al.*, 1970), but neither unilateral nephrectomies nor sham operations affected [^3H]-orotate uptake.

The peak of DNA synthesis after partial hepatectomy in our rats occurs at 21–22 h. [^3H]Thymidine uptake into the intracellular acid-soluble compartment in liver at this time is still doubled, although that for [^3H]orotate is now only 30% above values for sham-operated animals.

Work with cell cultures indicates that uridine transport shows saturation kinetics and that permeation is the rate-limiting step for the incorporation of uridine into the intracellular pool (Plagemann & Roth, 1969). The uptake of [^3H]orotate into intact livers is linearly related to the administered dose up to about 2 mg/kg body wt., and the ratio of intracellular acid-soluble ^3H radioactivity to that of plasma did not exceed 6.8:1, in contrast with the ratio 10–12:1 for the partially hepatectomized animals. These findings are consistent with a carrier-mediated mechanism for the transport of orotate. The possibilities that this mechanism may be promoted by a humoral factor, which is increased by partial hepatectomy, and that the increased penetration of precursors plays a role in the initial stages of liver regeneration will be discussed.

Bucher, N. L. R. & Swaffield, M. N. (1969) *Biochim. Biophys. Acta* **174**, 491–502

Cunningham, D. S. & Pardee, A. B. (1969) *Proc. Nat. Acad. Sci. U.S.A.* **64**, 1049–1056
Moolten, F. L., Oakman, N. J. & Bucher, N. L. R. (1970) *Cancer Res.* **30**, 2353–2357
Plagemann, P. G. W. & Roth, M. F. (1969) *Biochemistry* **8**, 4782–4789
Tata, J. R. (1970) in *Biochemical Actions of Hormones* (Litwak, G., ed.), vol. 1, pp. 89–133, Academic Press New York and London

α -Adrenergic Blockers and Early Stages in Liver Regeneration

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Adrenalectomy does not prevent liver regeneration in partially hepatectomized rats (Ferrari & Harkness, 1954), but both catecholamines and glucocorticoids are known to facilitate the induction of some liver enzymes, including ornithine decarboxylase (Panko & Kenney, 1971), which is markedly increased early in liver regeneration (Jänne & Raina, 1968; Russell & Snyder, 1968).

Preliminary experiments in this laboratory established that propranolol, a β -adrenergic blocker, did not affect regeneration, but that phenoxybenzamine, an α -adrenergic blocker, did. A dose of 5 mg of phenoxybenzamine/kg body wt. given immediately before operation prevented the normal induction of ornithine decarboxylase; the effect, which was transient, delayed the peak of induction by 2 h. Under these conditions no effects were detected on DNA synthesis. Adrenalectomized rats behaved similarly to phenoxybenzamine-treated animals, showing only 26% of the usual decarboxylase activity at 4 h but no change in thymidine incorporation into DNA at 21–24 h.

If phenoxybenzamine was given 5–10 h after operation, after decarboxylase induction had taken place, the peak of DNA synthesis was affected. A dose of 5 mg of phenoxybenzamine/kg body wt. given 9 h after operation shifted the peak from 21.5 to 24.5 h. Administration of the drug 1 h before the peak had no effect, indicating that phenoxybenzamine does not act directly on the enzymes involved in DNA synthesis. Nuclear histone phosphokinase (Siebert *et al.*, 1971) is typical of the enzymes induced 12–15 h after partial hepatectomy; this induction was delayed by a dose of 5 mg of phenoxybenzamine/kg body wt. given at 9 h, suggesting that catecholamines facilitate not only the early wave of enzyme induction in regenerating liver but also that of enzymes, particularly those concerned with replication, that are induced later in G_1 phase.

Phenoxybenzamine did not alter the increased pyrimidine uptake detected 1 h after partial hepatectomy