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Regulation of Glycolysis and Gluconeogenesis at the Enzyme Level

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In contrast with the very wide occurrence of glycolysis as a major metabolic pathway, gluconeogenesis is restricted to certain types of cells. In most cases where capacity for gluconeogenesis does occur, it coexists with that for glycolysis. In fact, the former shares many reversible steps with the latter. The precise number and kind of physiologically irreversible steps to be by-passed by antagonistic enzymes can vary among different tissues and organisms, particularly at the initial and final steps.

The understanding at the enzyme level of the mechanisms involved in the regulation of each of these major metabolic pathways has recently made great progress in the case of glycolysis (Sols, 1967a). This has led to a coherent interpretation of the mechanism of the Pasteur effect as the result of the integration of several feedback allosteric mechanisms operating in series (Sols, 1967a,b). In contrast with this progress, the interpretation of the regulation of gluconeogenesis is still largely unsolved.

The study of the potentially key enzymes involved at the metabolic 'cross-roads' in cells that can oscillate between glycolysis and gluconeogenesis according to circumstances is a challenging problem in itself, and can also help towards a better understanding of the intrinsic regulation of each of these potentially antagonistic pathways. This dual purpose is involved in recent and current work in the author's Laboratory with two types of cells, those of liver and yeast, that have in common a noted ability to carry on readily either glycolysis or gluconeogenesis according to circumstances. Occasional comparison of the occurrence of certain key enzymes or isoenzymes in related tissues is proving to be of considerable help for a deeper physiological understanding of potentially regulatory mechanisms. A clear case is the identification of the

allosteric activation of certain pyruvate kinases as a control mechanism related to the potential switch-over to gluconeogenesis rather than intrinsic to the regulation of glycolysis (Gancedo, Gancedo & Sols, 1967b).

Adaptive changes involving the amount or the activity of certain key enzymes in liver (Sillero, Sillero & Sols, 1968) and yeast (Gancedo, Gancedo & Sols, 1967a) will be shown, and their likely physiological significance will be discussed. In both systems it has been found that the concentrations of irreversible enzymes at the initial and final stages of the glycolytic and gluconeogenic pathways can be controlled independently of each other, a fact that affords a valuable metabolic flexibility. Moreover, it will be shown that in liver some of the reported changes in the activities of irreversible enzymes are irrelevant in terms of the switch-over from glycolysis to gluconeogenesis.

Emphasis will be placed in the discussion on the enzyme-regulation problems in the key metabolic triangle involving the oxaloacetate-phosphoenolpyruvate-pyruvate 'cross-roads' in rat liver (Marco, Pestaña, Pérez-Díaz & Sols, 1968), currently under study in the author's Laboratory. The fact that at this level carbohydrate, lipid, protein and energy metabolisms are variously interconnected in liver, gives a very wide significance to the understanding of the regulation of this metabolic triangle.

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The Control of Glycolysis in Rat Epididymal Adipose Tissue

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The mechanisms of glycolytic regulation in adipose tissue may not necessarily be similar to those in muscle and brain. Glycolysis in adipose tissue is primarily involved in the provision of L-glycerol 3-phosphate and acetyl-CoA for lipid

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