TRANSPORT AND EXCHANGE DIFFUSION OF AMINO ACIDS BY IN VITRO PREPARATIONS OF PANCREAS FROM NORMAL, TUMOR-BEARING AND ALCOHOL-TREATED MICE

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When labelled amino acids are injected into mice they are extensively accumulated in the pancreas (Wheeler, Luckens and György, 1949; Hansson and Ullberg, 1959; Berlinguet, Bégin and Babineau, 1962). Studies of thin sections of mouse pancreas under in vitro conditions have shown that this is due to a remarkable ability of mouse pancreas to transport and accumulate amino acids (Bégin and Scholefield, 1964; Bégin and Scholefield, 1965 a, b). The movement is energy dependent, sodium and potassium dependent and is inhibited by the presence of other amino acids. More recently it has been shown that amino acids accumulated by the pancreatic tissue may undergo exchange diffusion with extracellular amino acids (Scholefield and Clayman, 1967). We have now examined the ability of pancreas taken from tumor-bearing animals or from animals which have received an injection of ethanol at least twelve hours beforehand to transport and accumulate amino acids and to bring about exchange diffusion of these amino acids. In the pancreas from the tumor-bearing or from the alcohol-treated mice much of the amino acid transport system has been lost while the ability to bring about exchange diffusion remains unaltered. Experimental results establishing these facts are presented in Figs. 1a and 1b. Thin sections of mouse pancreas prepared and incubated as previously described (Bégin and Scholefield, 1964), were studied under standard experimental conditions. It is apparent from the results

presented in Fig. 1a that the steady state level of methionine attained in the pancreas from tumor-bearing animals under these experimental conditions is only about 40 percent of that attained in pancreas from normal mice. Alternatively, it may be stated that in order to attain the same steady state level of methionine in the pancreas for studies of exchange diffusion, the incubations had to be carried out in the presence of two to three times as much amino acid in the incubation medium when tissue from host animals is studied (Fig. 1a). The efflux of accumulated methionine in the presence or absence of extracellular 1-aminocyclopentane-carboxylic acid (ACPC) is proportional to the intracellular amino acid concentration. The proportionality constant is the same whether the tissue is taken from normal or tumor-bearing animals. This result is portrayed in Fig. 1b. It establishes that despite the marked decrease in the ability of the host tissue to accumulate amino acids, its ability to cause exchange diffusion remains unaltered if care is taken to study the exchange diffusion process at the same extra- and intracellular concentrations of the amino acids under study.

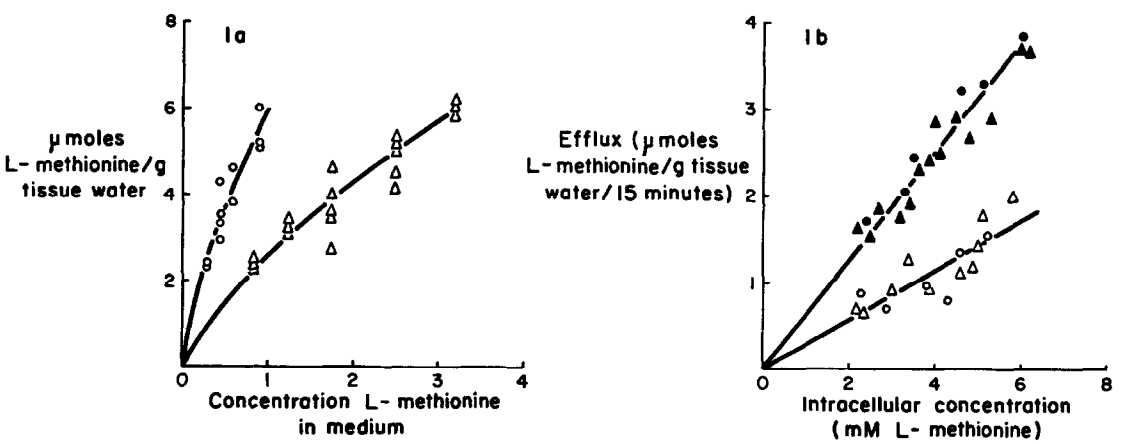

Fig. 1 (a) The steady state level of L-methionine in slices of pancreas from normal (○) and tumor-bearing (△) mice after incubation in vitro at 37° in the presence of methionine at various concentrations.

(b) The efflux of methionine at 15° from slices of pancreas from normal (○,●) and tumor-bearing (△,▲) mice during incubation in the absence (○,△) or presence (●,▲) of 5 mM ACPC.

A decrease in the ability to accumulate amino acids is also observed in the pancreas taken from mice treated more than twelve hours previously with alcohol (0.2 ml 50% ethanol in saline injected intraperitoneally) and it is apparent from the results presented in Table I that the responses of certain

TABLE I

The effects of Ehrlich ascites tumor or prior treatment with ethanol on amino acid uptake by mouse pancreas *in vitro*.

Amino Acid	Treatment		
	Nil	Ehrlich ascites tumor	Alcohol
Lysine	5.1 (6)*	2.4 (3)	3.7 (3)
Proline	12.2 (11)	5.4 (5)	4.4 (2)
Methionine	7.7 (8)	2.8 (4)	3.7 (3)

* All values refer to the concentration gradient calculated from μmoles amino acid accumulated/g cell water after incubation for 60 mins. (lysine and methionine) or 90 mins. (proline) at 37° under oxygen in a Krebs-Ringer phosphate medium containing 2 mM amino acid (Bégin and Scholefield, 1964). Mean values are quoted and the number of experiments is in parenthesis.

amino acids to these two forms of stress varies with the amino acid but is of similar magnitude for both. As shown in this Table the accumulation of amino acids such as methionine and proline is markedly altered whereas the accumulation of lysine is less changed in the pancreas from tumor-bearing or alcohol-treated mice.

If a "carrier protein" is involved in the transport of amino acids and if the same protein is also involved in exchange diffusion then a loss of this protein from the cell membrane would lead to a loss in the transport capacity of the cell and to a corresponding loss in the ability of the membrane to catalyze exchange diffusion. On this basis it must be concluded that there is no significant loss of the transport carrier from the membrane of the pancreatic cells under the present experimental conditions and the observed changes must be regarded as consequences of a loss of pumping capacity rather than loss of a carrier. The observed

decrease is not due to any lack of energy supply since no evidence could be obtained for a decreased incorporation of labelled amino acid into protein in these experiments. Previous results have shown that, as in other tissues, the movements of various amino acids into pancreas can exhibit varying degrees of sensitivity to the presence of sodium ions (Clayman, 1968) although changes in the concentration of these ions have previously been shown to be without effect on the process of exchange diffusion (Johnstone and Scholefield, 1965). It is therefore suggested that the present results are compatible with the hypothesis that the induction of tumors or the treatment of animals with alcohol leads to a decreased sodium flux in the pancreas and that this in turn leads to a decrease in amino acid transport but is without affect on exchange diffusion. Experiments are now in progress to determine (i) whether various forms of stress lead to changes in the sodium transport systems and (ii) the nature of the agent or agents which eventually lead to the decreased amino acid transport in the pancreas.

Summary Exposure of mice to alcohol or the presence of a tumor leads to a decreased amino acid transport by the host pancreas under *in vitro* conditions. There is no decrease in the capacity to catalyse exchange diffusion and it is suggested that the primary action is associated with sodium transport.

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