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Fasting and refeeding modulate neutral amino acid transport activity in the basolateral membrane of the rat exocrine pancreatic epithelium: fasting-induced insulin insensitivity

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The effects of fasting and refeeding on amino acid transport in the perfused rat exocrine pancreas were investigated using a rapid dual tracer dilution technique. Unidirectional amino acid influx (15 s) was quantified (relative to the extracellular tracer D-mannitol) over a wide range of perfusate concentrations in pancreata isolated frm fed and 24 h, 48 h, and 72 h fasted and 72 h fasted and refed (24 h) animals. In fed animals transport of phenylalanine (1–24 mM) and L-serine (1–50 mM) was saturable and weighted non-linear regression analyses of the overall transport indicated an apparent $K_t = 10 \pm 3$ mM and $V_{max} = 7.0 \pm 1.0$ μmol/min per g ($n = 7$) for phenylalanine and $K_t = 16 \pm 3$ mM and $V_{max} = 20.6 \pm 2.1$ μmol/min per g ($n = 5$) for serine. Fasting animals for 24 h or 48 h did not change the kinetics of either phenylalanine or serine transport. After a 72 h fast the rate of phenylalanine transport ($V_{max} = 15.9 \pm 2.9$ μmol/min per g, $n = 5$) was enhanced whereas the transport affinity ($K_t = 11 \pm 3$ mM) remained unaltered. L-Serine transport was essentially unaltered. When 72 h fasted animals were refed for 24 h the V_{max} for phenylalanine transport was reduced to values observed in fed animals. In parallel experiments refeeding had no significant effect on serine transport. Perfusion of pancreata isolated from 72 h fasted animals with bovine insulin (1 mU/ml or 1 μU/ml) did not stimulate either phenylalanine or serine transport. The fasting-induced stimulation of transport may provide a mechanism by which the extracellular supply of essential amino acids as phenylalanine is increased to meet the demands of continued proteolytic and lipolytic enzyme synthesis.

Introduction

The mechanisms by which fasting, refeeding and dietary composition modulate the synthesis and secretion of pancreatic digestive enzymes has been the subject of numerous investigations. The mammalian exocrine pancreas secretes approximately twenty proteins [1], and fasting and dietary manipulations have been reported to induce both coordinate and anticoordinate changes in individual pancreatic enzyme levels [2,3]. In adult rats fasting is generally associated with decreased rates of pancreatic amylase synthesis [4–6] and elevated pancreatic concentrations of lipase but unaltered levels of trypsinogen [7].

Incorporation of amino acids into exocrine pancreatic proteins appears to be regulated by the supply of extracellular amino acids, even at high concentrations [8,9]. In an earlier study Cheneval and Johnstone [9] reported that a 48 h fast reduced the uptake of glycine and 2-aminoisobutyric acid by adult rat pancreata incubated in vitro for

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90 min. Refeeding for 3 h stimulated amino acid transport activity, although the effect of refeeding was more pronounced on 2-aminoisobutyric acid uptake than on glycine uptake. Aminoisobutyric acid is often not a system selective analogue, and moreover previous studies of amino acid transport specificity in the intact perfused rat pancreas revealed only a low unidirectional uptake for glycine but markedly higher uptakes for L-phenylalanine and L-serine [10]. Kinetic analysis indicated that the high transport rates measured for these substrates in the perfused pancreas were largely mediated by two parallel Na^+-independent membrane carriers. In preliminary experiments we reported that L-phenylalanine transport was significantly elevated following a 72 h fast, and that refeeding for 24 h reduced L-phenylalanine transport to levels observed in fed animals [11]. We have now investigated in detail the effects of feeding, fasting, refeeding and perfusion with exogenous insulin on the kinetics of unidirectional L-phenylalanine and L-serine influx (15 s) in perfused pancreata isolated from 24 h, 48 h and 72 h fasted rats.

Methods

Animals and perfusion techniques

Male Wistar rats were housed in wire-bottomed cages and allowed free access to water and standard laboratory cubes (No. 491, Grain Harvesters Ltd., Kent, U.K.) or were deprived of food alone for periods of 24 h, 48 h or 72 h. Animals weighing between 160 and 250 g were anaesthetized with sodium pentobarbitone (60 mg/kg, Sagatal, I.P.) and supplementary anaesthetic was administered through a cannula in the external jugular vein. As previously described [10,12] the isolated pancreas was perfused in situ at constant flow (approx. 1.8 ml/min) via the aorta with a Krebs-Henseleit bicarbonate medium, and the pancreatic venous effluent either passed to waste or was collected sequentially from the cannulated portal vein. The preparation was maintained in a heated (38°C) Perspex perfusion cabinet and the perfusion rate, monitored using a photoelectric drop recorder, and perfusion pressure were continuously displayed on a Lectromed chart recorder. At the above flow rate perfusion pressures ranged between 20 and 40 mmHg.

The composition of the Krebs-Henseleit solution was (mM): NaCl, 118; KCl, 4.8; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 25; $CaCl_2$, 2.5; D-glucose, 3.3 and bovine serum albumin (2% w/v, Cohen Fraction V, Sigma Chemical Co., Dorset, U.K.). The perfusates contained different concentrations of unlabelled L-phenylalanine (1–24 mM, Sigma) or L-serine (1–50 mM, Sigma) and were continually gassed at 38°C with 95% O_2 and 5% CO_2 to a pH between 7.3 and 7.4. When the regulatory effects of insulin were examined, 100 μU/ml or 1 mU/ml bovine insulin (Wellcome, U.K.) was added to the perfusates. Pancreata were pre-perfused with the insulin containing solutions for 30 min before measuring amino acid influx in the continued presence of bovine insulin.

Epithelial amino acid influx and efflux measurements

The kinetics of unidirectional L-phenylalanine and L-serine influx across the basolateral plasma membrane of the pancreatic exocrine epithelium were examined using a rapid dual isotope dilution technique [13], previously applied to perfused pancreas [10–14]. Tracer amino acid uptake was quantified by directly comparing portal vein concentration-time profiles for a tritiated L-amino acid and D-[^{14}C]mannitol (extracellular reference) following an intra-arterial injection (100 μl in 2 s) of perfusate containing both tracers (see Fig. 1). Generally 20–30 (100-μl) venous samples were collected sequentially from the portal vein during 45–60 s. In addition a final venous sample was accumulated for a further 4 min to assess tracer recoveries and efflux from the pancreatic epithelium. Tracer amino acid uptake was quantified in successive venous samples from

$$\text{uptake} = 1 - (\text{L-[}^3\text{H]amino acid/D-[}^{14}\text{C]mannitol})$$

Unidirectional amino acid influx was calculated from the maximal fraction tracer uptake (U_{max}), the perfusion rate (F, ml/min per g) and the perfusate concentration of unlabelled amino acid (C_a, mM)

$$\text{influx} = -F \cdot \ln(1 - U_{max}) \cdot C_a$$

Efflux of the transported amino acid was estimated from

$$\text{efflux}\ (\%) = (1 - U_T/U_{max}) \cdot 100$$

where U_T is the overall amino acid uptake relative to D-[^{14}C]mannitol determined from the integrated recoveries of both tracers during a total 6 min venous collection period [10,12].

Radioactive molecules and counting procedures

The radioactive molecules L-[4-^{3}H]phenylalanine (23.5 Ci/mmol), L-[^{3}H]serine (29 Ci/mmol) and D-[^{14}C]mannitol (50–60 mCi/mmol) were obtained from Amersham International p.l.c., U.K. The paired-tracer injectates normally contained 1.4 μCi of ^{14}C and 7 μCi of ^{3}H, and each was made up to a 100 μl volume with a specific perfusate. All samples and the appropriate isotope standards were counted concurrently on a Beckman LS7500 liquid scintillation counter interfaced to a CBM microcomputer.

Kinetic analysis

The influx data obtained in the present experiments have been analyzed by weighted non-linear regression analysis [15]. In an earlier study in pancreata obtained from Sprague-Dawley rats [10], we concluded on the basis of kinetic modelling that a single Michaelis-Menten analysis of phenylalanine influx revealed the lowest weighted standard deviation of residuals. Serine influx was extremely difficult to fit and we presented kinetic constants derived from both single and double Michaelis-Menten analyses (see Table II in Ref. 10). The present kinetic study in Wistar rats did not provide the statistical resolution for selecting a double Michaelis-Menten fit for L-serine influx. In light of recent preliminary findings from this laboratory that serine influx may be mediated by at least three carriers, we chose to evaluate the effects of fasting and refeeding on the overall transport. As in our earlier study [10] the kinetics of L-phenylalanine influx were assessed using a single Michaelis-Menten equation.

Results

Transport of amino acids at the basolateral plasma membrane

The left inset in Fig. 1A illustrates portal vein dilution profiles obtained for D-[^{14}C]mannitol (extracellular tracer) and L-[^{3}H]phenylalanine following a bolus intra-arterial injection of both tracers into the circulation of a pancreas perfused with 0.05 mM unlabelled L-phenylalanine. In the right inset of Fig. 1A these dilution profiles are analyzed to assess the time-course of L-[^{3}H]phenylalanine uptake relative to D-[^{14}C]mannitol (uptake (%) = (1 − ([^{3}H]phenylalanine/ D-[^{14}C]mannitol)) · 100) in the 30 sequentially collected venous samples. A maximum uptake value (U_{max}) was measured approx. 15 s after the injection of tracers, and self-inhibition of maximal L-[^{3}H]phenylalanine uptake was more pronounced at higher substrate concentrations (Fig. 1). At a perfusate concentration of 24 mM phenylalanine L-[^{3}H]phenylalanine uptake was reduced to 23 ± 3% (mean ± S.E., n = 4), whereas a perfusate concentration of 50 mM serine (data not shown) was required to reduce L-[^{3}H]serine uptake to 23 ± 4% (n = 4).

As previously reported [10], unidirectional amino acid uptake in the present experiments was always accompanied by a concentration dependent tracer efflux from the pancreatic epithelium. The data in Fig. 1B indicate that, as previously observed in 24-h fasted animals [10], L[^{3}H]phenylalanine tracer efflux was enhanced in fed animals from 65 ± 5% at 1 mM to approx. 100% at 16 mM. Similar experiments with L-[^{3}H]serine revealed that tracer efflux was increased from 59 ± 4% (n = 5) at 1 mM to 93 ± 4% (n = 5) at 30 mM. Previous thin-layer chromatographic analyses have revealed that during the time-course of these experiments the tritium activity recovered in the pancreatic venous effluent was associated with the native amino acid [14].

Effects of fasting on the kinetics of amino acid influx

Unidirectional influx kinetics for the essential amino acid L-phenylalanine and the non-essential but insulin-sensitive [12] amino acid L-serine were examined in pancreata isolated from fed, fasted (24 h, 48 h and 72 h) and refed (72 h fasted and 24 h refed) Wistar rats. Fig. 2 illustrates kinetic saturation curves obtained for L-phenylalanine in perfused pancreata isolated from fed and fasted (48 h and 72 h) animals. Although phenylalanine transport was not altered following fasting for 24

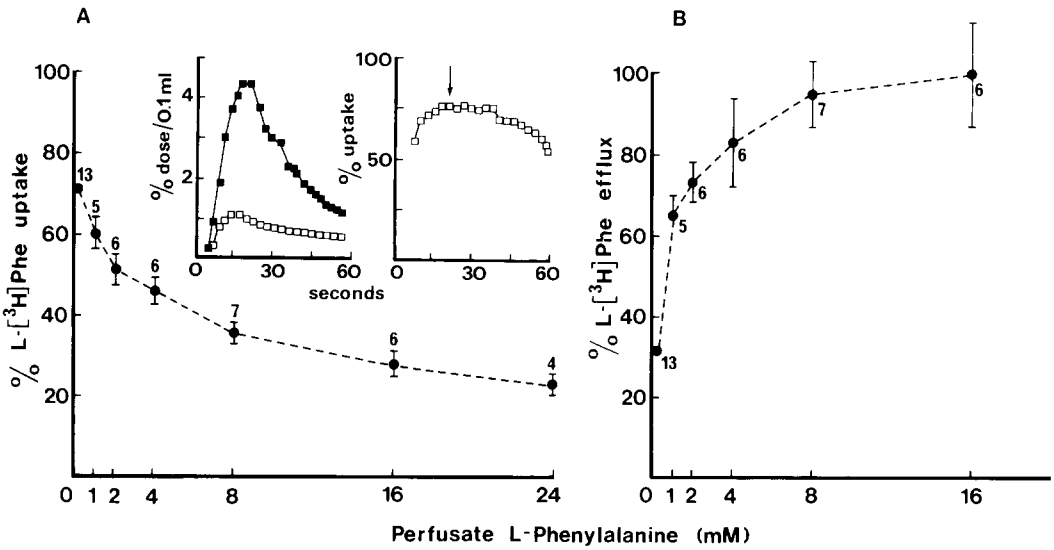

Fig. 1. Analysis of L-phenylalanine uptake and efflux across the basolateral membrane of exocrine pancreatic epithelium. The left inset in panel A shows paired portal vein dilution curves obtained for the extracellular tracer D-[^{14}C]mannitol (■) and L-[4-^{3}H]phenylalanine (□) following a bolus injection (100 μl in 1–2 s) of these tracers into the arterial perfusate supplying the isolated pancreas. The right inset in panel A depicts the time-course of L-[^{3}H]phenylalanine uptake relative to L-[^{14}C]mannitol and the arrow denotes the time point at which the venous concentration of D-[^{14}C]mannitol was maximal. (A) Self-inhibition of L-[^{3}H]phenylalanine uptake was tested by perfusing pancreata, isolated from fed animals, successively with different concentrations of unlabelled L-phenylalanine. Each preparation was pre-perfused with a given phenylalanine concentration for 4-min before measuring L-[^{3}H]phenylalanine uptake. (B) Concentration-dependent efflux of transported L-[^{3}H]phenylalanine. Tracer efflux was assessed simultaneously in all of the uptake studies and the results indicate that efflux was accelerated by increasing perfusate concentrations of L-phenylalanine. Values denote the mean ± S.E. of means of 4–13 perfused pancreata.

h or 48 h, fasting for 72 h increased the V_{max} for phenylalanine from a fed value of 7.0 ± 1.0 μmol/min per g to 15.9 ± 2.9 μmol/min per g and doubled the V_{max}/K_t ratio (Table I). Moreover, L-[^{3}H]phenylalanine uptake was increased at each concentration. This fasting-induced stimulation of

TABLE I

EFFECTS OF FASTING, INSULIN AND REFEEDING ON THE KINETICS OF L-PHENYLALANINE TRANSPORT

Michaelis-Menten saturation kinetics were investigated in pancreata isolated from fed, fasted (24 h, 48 h, 72 h) and refed (72-h fasted and 24-h refed) animals. Moreover, the sensitivity of L-phenylalanine transport to exogenous bovine insulin (Wellcome, U.K.) was tested at a perfusate concentration of 1 mU/ml in pancreata isolated fro 72-h fasted animals. Values denote the mean ± S.E. of means in 5–7 perfused pancreata. The final column lists the V_{max}/K_t ratio calculated for each of the experimental conditions.

	n [a]	K_t (mM)	V_{max} (μmol/min per g)	V_{max}/K_t
Fed	7	10.1 ± 2.7	7.0 ± 1.0	0.69
Fasted 24 h	5	9.9 ± 1.5	8.5 ± 0.7	0.86
Fasted 48 h	5	9.0 ± 0.8	7.8 ± 0.4	0.87
Fasted 72 h	5	11.2 ± 3.5	15.9 ± 2.9	1.42
Fasted 72 h + 24 h refeeding	5	7.1 ± 1.7	8.2 ± 0.8	1.16
Fasted 72 h + 1 mU/ml insulin	6	11.9 ± 2.1	12.1 ± 1.3	1.02

[a] Between 26 and 34 kinetic measurements were obtained in each protocol.

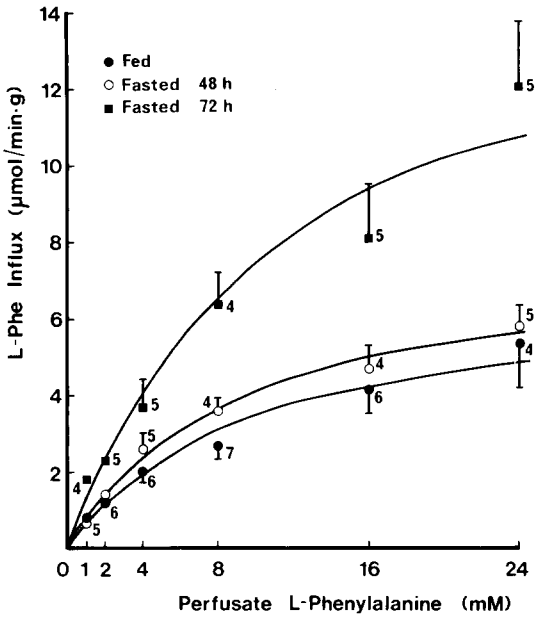

Fig. 2. Effects of fasting on the kinetics of L-phenylalanine transport in the exocrine pancreas. Pancreata, isolated from fed and fasted (24 h, 48 h and 72 h) rats, were perfused in situ and L-phenylalanine (L-Phe) influx was measured successively at different L-phenylalanine concentrations (1–24 mM). The kinetic curves illustrated represent single rectangular hyperbolas obtained by a direct fit to the three sets of mean influx values. For each curve the mean influx values were weighted for the reciprocal of their respective standard errors and the vertical lines denote the S.E. of n measurements in 5–7 pancreata. The kinetic curve obtained in pancreata isolated from 24-h fasted rats was virtually superimposed on the fed curve and hence has not been plotted.

phenylalanine transport appears to be a V_{max} phenomenon, since the fed K_t value of 10.1 ± 2.7 mM remained unchanged.

When we investigated the effects of fasting on L-serine transport, influx saturated at perfusate concentrations between 25 and 50 mM. Recent preliminary evidence from this laboratory indicates that serine transport may be mediated by at least three different carrier systems. In light of these findings and the difficulty in fitting a double Michaelis-Menten equation, we selected to estimate only the overall transport using a single Michaelis-Menten analysis. In pancreata from fed animals overall L-serine transport revealed a $K_t = 16.4 \pm 3.5$ mM and $V_{max} = 20.6 \pm 2.1$ μmol/min per g (Table II). The kinetics of serine influx were not significantly altered following fasting for 48 h or 72 h. The V_{max}/K_t ratio of 1.29 determined for serine in pancreata from fed animals was 1.9-fold higher than that estimated for L-phenylalanine (Table I).

The average weight loss of $23.0 \pm 0.004\%$ recorded for 72-h fasted rats is in concordance with data from previous studies [5]. In our fed animals the pancreas wet weight was $0.55 \pm 0.06\%$ (mean ± S.E., $n = 7$) of the total rat weight. Following 72 h fasting this percentage remained unchanged ($0.46 \pm 0.04\%$, $n = 5$), suggesting an average pancreatic weight loss of 23%.

Effects of refeeding and exogenous insulin

To evaluate whether the fasting-induced stimu-

TABLE II

EFFECTS OF FASTING, INSULIN AND REFEEDING ON THE KINETICS OF L-SERINE TRANSPORT

As with phenylalanine (Table I), the kinetics of L-serine influx were measured in pancreata isolated from fed, fasted (48 h, 72 h) and refed (72-h fasted and 24-h refed) animals. In these experiments the effects of exogenous insulting on L-serine transport were tested at 100 μU/ml, since this concentration was previously reported to stimulate L-serine transport in 24-h fasted rats [12]. Values denote the mean ± S.E. of means in 5–7 perfused pancreata. Details as in legend to Table I.

	n [a]	K_t (mM)	V_{max} (μmol/min per g)	V_{max}/K_t
Fed	5	16.4 ± 3.5	20.6 ± 2.1	1.29
Fasted 48 h	6	21.8 ± 3.6	23.6 ± 1.9	1.08
Fasted 72 h	7	24.6 ± 7.8	27.6 ± 4.4	1.12
Fasted 72 h + 24 h refeeding	6	25.6 ± 4.7	22.2 ± 2.1	0.87
Fasted 72 h + 100 μU/ml insulin	5	27.9 ± 7.0	28.3 ± 3.5	1.01

[a] Between 28 and 40 kinetic measurements were obtained in each protocol.

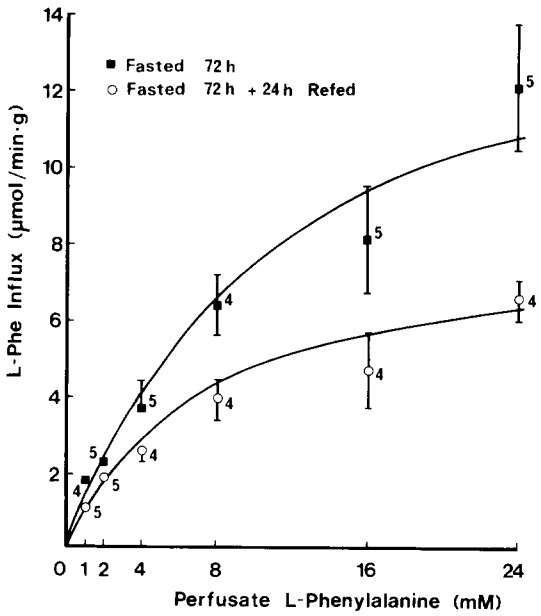

Fig. 3. Effects of refeeding on L-phenylalanine transport in the exocrine pancreas. The kinetic data obtained in pancreata isolated from 72-h fasted rats has been replotted from Fig. 2 for comparison with the influx kinetics determined in pancreata from 72-h fasted rats which had been refed for 24 h. The V_{max} for L-phenylalanine transport was markedly reduced after 24 h refeeding. Details as in the legend to Fig. 2.

lation in L-phenylalanine transport could be modified by refeeding, 72-h fasted rats were allowed free access to laboratory pellets for 24 h. When transport was measured in pancreata isolated from these animals, the V_{max} for phenylalanine was decreased to 8.2 ± 0.8 μmol/min per g (Fig. 3), a value quite similar to that measured in the fed state (Table I). Moreover, the K_t estimated for phenylalanine transport (7.1 ± 1.7 mM) was slightly lower than that determined in the fed state (Table I). In contrast, the kinetic constants for serine transport were essentially unaltered, although the V_{max}/K_t ratio was reduced from 1.12 in the 72 h fasted state to 0.87 following refeeding for 24 h (Table II). In these refeeding experiments animals regained approx. 89% of their original body weight, and when measured the pancreas wet weight was 0.48 ± 0.05% (mean ± S.E., $n = 5$) of the total rat weight.

Since caloric deprivation has been reported to be accompanied by an increased tissue binding of insulin but a decreased cellular responsiveness to the islet hormone [16], we examined the regulatory role of insulin in pancreata obtained from 72-h fasted rats. We had assumed that transport of phenylalanine via System L [10] would be relatively insensitive to regulation by insulin, and therefore perfused preparations with 1 mU/ml bovine insulin for 30 min before measuring the kinetics of influx in the continued presence of exogenous insulin. As shown in Table I the K_t and V_{max} values for phenylalanine influx were quite similar to those estimated in the 72-h fasted state. Moreover, in the presence of insulin the V_{max}/K_t ratio for phenylalanine was still 1.5-fold higher than that observed in fed animals. When pancreata from 72-h fasted animals were perfused with 100 μU/ml insulin, a concentration known to stimulate serine transport in 24-h fasted rats [12], no significant change in L-serine influx was observed (Table II).

Discussion

In the perfused rat exocrine pancreas L-phenylalanine is transported by a single Na^+-independent carrier resembling System L, whereas L-serine is largely transported by a Na^+-independent carrier [10] resembling the novel Na^+-independent System asc recently identified in erythrocytes [17,18].

Fasting-induced changes in neutral amino acid transport

Fasting for 24 h or 48 h had a negligible effect on the transport of either substrate, whereas after 72 h starvation L-phenylalanine transport was selectively increased (see Fig. 2, Tables I and II). A fasting-induced derepression of System L transport, which in the presence of nutrient (fed state) may have been partially repressed [19], could account for the enhanced V_{max} measured for phenylalanine (Fig. 2 and Table I). We also considered the possibility that L-phenylalanine transport measured in fed and 72-h fasted rats may have been influenced by different intracellular concentrations of phenylalanine. When in a parallel study the free amino acid concentrations in the exocrine pancreas obtained from fed and fasted animals were examined chromatographically, we found that

intracellular levels of L-leucine, L-isoleucine and L-phenylalanine were significantly increased after 72 h starvation [20]. Elevated intracellular concentrations of large neutral amino acids may have trans-stimulated L-phenylalanine influx by exchange transport via System L. Such exchange diffusion has previously been observed in the mouse pancreas in vitro [21], and Christensen [22] has stressed that the Na^+-independent System L participates intensely in trans-stimulation. Supply of extracellular phenylalanine could be elevated in exchange for intracellular substrate utilizing Systems asc, ASC or A for efflux. Although intracellular levels of L-serine were elevated by 72 h starvation (Mann, G.E., Smith, S.A. and Emery, P.W., unpublished data), inward transport of serine was not stimulated (Table II).

The observed decrease in pancreatic weight (−23%) induced by 72 h fasting may have increased the effective surface area for epithelial transport, however, our transport experiments clearly reveal a 129% increase in L-phenylalanine influx after 72 h fasting (see Fig. 2 and Table I). Since overall L-serine transport was unaltered by starvation (Table II), it seems unlikely that the present findings could be explained solely on the basis of changes in exchange surface area.

An insensitivity to exogenous bovine insulin was detected in pancreata isolated from 72-h fasted rats (Tables I and II). As anticipated transport of L-phenylalanine via the hormone-insensitive System L was unaffected by insulin, whereas a 72-h fast abolished the stimulatory effect of insulin on L-serine transport originallly observed in 24-h fasted animals [12]. In the pancreas insulin's stimulation of L-serine transport is dependent on extracellular calcium [23] and may involve the recruitment of additional carriers to the basolateral membrane. In fasted and diabetic animals rapid adaptative changes in the insulin receptor population occur inversely to plasma insulin levels, which in both conditions are significantly decreased [24]. The mechanisms of a fasting-induced dissociation of insulin binding (enhanced by fasting) from insulin's well established stimulatory action (decreased by fasting) on glucose and amino acid transport may reflect receptor and post-receptor defects, changes in cellular metabolism and altered membrane fluidity and phospholipid composition [16]. Further studies are necessary to resolve the fasting-induced insulin insensitivity in the pancreas.

Reversal of transport stimulation by refeeding

When 72-h fasted animals were refed for 24 h L-phenylalanine transport was reduced to rates observed in fed animals (Fig. 3, Table I). This period of refeeding also resulted in a decrease in intracellular phenylalanine concentrations from 0.66 ± 0.07 mM ($n = 5$) to 0.12 ± 0.02 mM ($n = 5$), a level measured in fed animals. Tissue concentrations of L-leucine and L-isoleucine were similarly reduced by 24 h refeeding but the 72-h fasted intracellular concentration of L-serine remained unaltered. Furthermore, L-serine transport was unaffected by refeeding (Table II). In this context it is important to consider that, as with amino acid transport, different adaptative changes occur in the synthesis rates of amylase, chymotrypsinogen and trypsinogen within 2 h of refeeding fasted rats [25].

Our findings with L-phenylalanine differ from those of Cheneval and Johnstone [9], who reported that starvation decreases (and refeeding stimulates) pancreatic uptake of glycine and 2-aminoisobutyric acid. The different transport systems under study, different experimental preparations or actual differences in the resolution of the techniques used could account for the apparent discrepancy. In our experiments amino acid influx kinetics were determined in the order of 15 s over a wide concentration range, whereas Cheneval and Johnstone [9] assessed net uptake at low concentrations after 90-min incubation.

Most modifications of amino acid transport induced by substrate deprivation have been ascribed to the Na^+-dependent transport System A, although in hepatocytes the Na^+-dependent System A, System ASC and System Gly (glycine, sarcosine) are all stimulated by amino acid starvation (see review in Ref. 22). Starvation of Chinese hamster ovary (CHO-K1) cells for leucine results in a 3–4-fold increase in the transport activity of the Na^+-independent System L, and moreover the enhanced transport rate is fully reversed within 1 h of refeeding with leucine [19]. These authors observed similar changes in transport for other System L substrates including L-phenylalanine.

Our present findings suggest that amino acid transport systems in the exocrine pancreas may be regulated differentially during starvation and refeeding. Increasing the influx of certain extracellular amino acids by derepression of a transport system and/or by exchange for other intracellular substrates has important implications for the maintained or increased synthesis of pancreatic enzymes during starvation.

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