Dear Editor:

There has been considerable interest in the metabolism of small peptides by the lactating mammary gland since the discovery that plasma-derived peptides may be an important source of amino nitrogen for milk protein synthesis (1). The uptake of certain essential amino acids is less than their output in milk protein, and evidence suggests that the shortfall is made up from peptide-derived amino acids (2). In this regard, Yang et al. (3) have recently reported that methionyl-methionine enhances α,1 casein synthesis by cultured bovine mammary explants. The authors conclude that methionyl-methionine stimulates milk protein synthesis due to enhanced substrate availability and the activation of intracellular signaling pathways such as Janus kinase 2 (JAK2), signal transducer and activator of transcription 5 (STAT5), and the mammalian target of rapamycin (mTOR). One major question which arises is the following: Can the mammary gland transport plasma-derived peptides intact or does extracellular hydrolysis occur followed by uptake of the free amino acids? In this connection, Yang et al. (3) made the interesting discovery that methionyl-methionine increases the expression of a peptide transporter, namely, peptide transporter 2 (PepT2), suggesting that the transport of intact dipeptides may in part account for the increase in α,1 casein synthesis. It is reasonable to assume that a peptide transporter would have to be situated on the basolateral membrane of mammary secretory cells to allow plasma-derived peptides to make a significant contribution to milk protein synthesis (4). However, immunohistochemistry has shown that PepT2 expression is confined to the apical aspect of rat mammary epithelial cells; thus, the proton-driven peptide transporter may play a role in the uptake of peptides from milk into mammary epithelial cells (5). Perhaps the function of PepT2 in the mammary gland is to transport the products of milk protein hydrolysis back into the mammary epithelium. Apropos, a favorable pH gradient exists across the apical pole of mammary epithelial cells for this to occur (4).

Examination of hydrolysis-resistant dipeptide transport by the in-situ perfused lactating mammary gland with the use of a rapid paired-tracer dilution technique, an experimental approach that allows transport to be studied semiquantitatively across the blood-facing aspect of the mammary epithelium, found dipeptide uptake to be negligible (6). This is consistent with the absence of PepT2 on the basolateral membrane of mammary epithelial cells (4). Therefore, under physiologic conditions, it is likely that plasma-derived peptides are hydrolyzed by mammary secretory cells extracellularly followed by uptake of the constituent amino acids via specific amino acid transporters. Indeed, there is functional evidence to support this hypothesis. Substrates in the form of aminoacyl-p-nitroanilides presented to mammary tissue are hydrolyzed followed by uptake of the liberated amino acids (7).

There is of course a possibility that the distribution of PepT2 in the bovine mammary gland differs from that of the rat mammary epithelium, but presently there is no evidence to support this. In light of this, the physiologic relevance of the effect of methionyl-methionine on PepT2 expression in the context of milk protein synthesis is called into question (3). It is probable that the effect of methionyl-methionine on PepT2 expression reflects events occurring at the apical aspect of the mammary epithelium. Prolonged incubation (24 h) of cultured explants would allow the concentration of methionyl-methionine to rise within the milk space, which in turn could increase the expression of PepT2 mRNA and protein.

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References

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Reply to DB Shennan

Dear Editor:

We appreciate the interest of David B Shennan in our recent article (1) and the remarks in his letter entitled “Peptide Transport and Metabolism by the Lactating Mammary Gland.” Shennan raised a valid question about the subcellular localization of peptide...