Introduction: Glutamate transport, metabolism, and physiological responses

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Hediger, M. A., and T. C. Welbourne. Introduction: Glutamate transport, metabolism, and physiological responses. Am. J. Physiol. 277 (Renal Physiol. 46): F477–F480, 1999.—The material covered in this set of articles was originally presented at Experimental Biology '98, in San Francisco, CA, on April 20, 1998. Here, the participants recount important elements of current research on the role of glutamate transporter activity in cellular signaling, metabolism, and organ function. W. A. Fairman and S. G. Amara discuss the five subtypes of human excitatory amino acid transporters, with emphasis on the EAAT4 subtype. M. A. Hediger discusses the expression and action of EAAC1 subtype of the human excitatory amino acid transporter. I. Nissim provides an overview of the significant role of pH in regulating Gln/Glu metabolism in the kidney, liver, and brain. J. D. McGivan and B. Nicholson describe some characteristics of glutamate transport regulation with regard to a specific experimental model of the bovine renal epithelial cell line NBL-1. Finally, T. C. Welbourne and J. C. Matthews introduce the “functional unit” concept of glutamate transport and how this relates to both glutamine metabolism and paracellular permeability.

Excitatory amino acid transporter; amino acid deprivation; hypertonic stress; acute pH change; liver; brain; astrocytes; neurons; tricarboxylic acid cycle; urea cycle

The brief reviews in this forum focus on the emerging role of glutamate transporter activity in cellular signaling, metabolism, and organ function. Because these roles depend upon glutamate availability, a brief overview of the physiological context in which this family of closely related proteins function is presented (Fig. 1). We know that the source of circulating L-glutamate is the liver (and not dietary intake), where a sinusoidal glutamate transporter operating in an efflux mode releases glutamate produced from glutamine in a reaction catalyzed by the phosphate-dependent glutaminase (PDG). Glutamate generated by these upstream periportal hepatocytes is in part captured by glutamate transporter activity (GLT1?) in the downstream perivenous hepatocytes coupled to glutamine synthesis and release (5), supporting an interorgan glutamine flux. Glutamate transport proteins present in muscle (EAAC1 and H+ dependent, Ref. 6) and lung (EAAC1, Ref. 8) take up glutamate coupled to glutamine synthesis, with released glutamine reinforcing the interorgan glutamine flux. A low-affinity, sodium-dependent glutamate transporter and high-affinity sodium-dependent glutamate transporter are present on opposite poles of renal tubules, and together they remove more than half of all L-glutamate delivered to the kidneys. However, this deficit is essentially nulled by intraluminal glutamine hydrolysis (and glutathione when available) catalyzed by the phosphate-independent but bicarbonate-dependent glutaminase activity (PIG) associated with the ectoenzyme γ-glutamyltranspeptidase. The site for this glutamate formation overlaps the distribution of the apical membrane EAAC1 particularly significantly in the S2 and S3 nephron segments. Similarly, the apical glutamate transporter (EAAC1?) of the epithelium lining the bile duct is driven by the bile acid-activated (1) PIG-dependent intraorgan glutamate flux (2). Indeed, organs lacking the intraorgan pathway, e.g., placenta, rely upon the interorgan glutamate flux to...
maintain their transporter activity (9). Brain, on the other hand, expresses an intraorgan glutamate flux at the blood-brain barrier where endothelial PIG, induced by glial cells (3), converts the microvasculature to an epithelial-like structure. Within the protected confines of this barrier, presynaptic glutamate release, derived from glutamine via PDG, is collected postsynaptically by neurons (EAAC1 and EAATs) and glial cells (GLT1) coupled to glutamine synthesis and release, mirroring in miniature the above interorgan flux. The normal arterial glutamate concentration is 10–30 µM, approximating the $K_m$ of the high-affinity transporter, indicating that this activity is determined in part by these inter- and intraorgan fluxes, whereas pathophysiological conditions such as acquired immunodeficiency syndrome (AIDS) and malignancies exhibit arterial glutamate levels 5- to 10-fold higher (4).

How then do the glutamate transporter activities translate these fluxes into signals capable of modulating cellular and hence organ function? The reports that follow present the strategies and techniques deployed in elucidating these pathways and their elicited responses. Fairman and Amara focus on the EAAT4 expressed on postsynaptic neurons and its novel interactive role in modulating the glutamate receptor. At the renal tubule, Hediger relates the apical cell surface EAAC1 to cellular signals (7) regulating acid-base and osmolar homeostasis, whereas Nissim, deploying $^{15}$N-labeled glutamate, definitively maps glutamate metabolism in kidney, liver, and brain and identifies the pathways responding to transporter signaling. McGivan and Nicholson elucidate a unique role played by intracellular glutamate in regulating the functional expression of EAAC1 in a model epithelium as well as

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**Fig. 1.** Interorgan and intraorgan glutamate fluxes in relation to glutamate transporter activity. Organs expressing net glutamate (Glu) release or uptake are shown as open circles with + or −, respectively; organs with high unidirectional uptake but no net removal are shown as empty open circles (○). Liver and proximal renal tubule heterogeneity are presented by portal and perivenous hepatocytes (ph and pvh, respectively) and proximal convoluted and straight tubule segments (S1 and S3, respectively). Double-arrowed dotted lines represent bidirectional fluxes. Extracellular and intracellular glutamine (Gln) or glutathione (GSH) hydrolytic sites are represented as PIG and PDG gene expression, respectively (phosphate-independent and dependent, respectively). Glutamine and alanine synthesis sites are represented by glutamine synthetase (GS) and alanine aminotransaminase (ALT), respectively. Glutamate transporters expressed are low-affinity sodium or high-affinity glutamate transporters (LSGT and HSGT, respectively), and EAAC1, EAAT4, and GLT1 subtypes. BBB, blood-brain barrier.
its response to hypertonic stress. Lastly, Welbourne and Matthews show how extracellular glutamine conversion to glutamate and coupled transporter activity can regulate energy metabolism and paracellular permeability in the functioning kidney. Together these studies extend the perspective of glutamate and transporter function beyond the traditional role to that of cell signaling involved in regulating cellular and organ function.

The support of the American Physiological Society and the Renal, Epithelial, and Neuroscience Sections is gratefully acknowledged.

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