Glutamine Metabolism: Nutritional and Clinical Significance

Session I: Basic Aspects of Glutamine Metabolism—Discussion Summary

John T. Brosnan

Memorial University of Newfoundland, St. John’s, Newfoundland, Canada

Dr. Brosnan opened the discussion by referring to the most obvious difference between glutamine and glutamate, i.e., the presence of the amide group in glutamine. He pointed out that this amide serves as a very important nitrogen donor for a number of amidotransferases, e.g., in nucleotide biosynthesis, and that the amide group could be regarded as an “activated” form of ammonia, in the same way as the γ-phosphate of ATP is an “activated” form of phosphate and carboxybiotin is an “activated” form of CO₂. The fundamental activating reaction is the glutamine synthetase reaction, which incorporates ammonia into glutamine (at the expense of a high energy phosphate bond). Dr. Dan Atkinson has pointed out that these activated intermediates conserve the solvent capacity of the cell because only low concentrations of these intermediates are required. In principle, the amination reactions that use glutamine as a source of amino groups could occur with ammonia, rather than glutamine, but the thermodynamics would be highly unfavorable and enormous concentrations of ammonia would have to exist. Very high concentrations of cellular intermediates not only challenge the solvent capacity of cells but increase the probability of undesirable side-reactions.

Dr. Matthews made the point that one of the key features of glutamine, in addition to being an “activated” ammonia or a precursor for glutamate, is that it can be transported through the circulation without any deleterious effects. In contrast, both ammonia and glutamate are neurotoxic.

Dr. Medina Torres pointed out that, although glutaminase, glutamine synthetase and the glutamine transporters are of vital importance to animal metabolism, one should not lose sight of the role of glutamine in plants. From a global point of view, glutamate synthetase may be regarded as the most important enzyme of glutamine metabolism because it is on the main pathway by which plants introduce nitrogen into organic matter. Dr. Watson argued that the importance of glutamine goes back even farther than plants, i.e., to bacteria.

Dr. Häussinger raised the question of the very high concentrations of glutamine that occur in many cell types. He asked whether glutamine may act as a sort of “chaperone” and play a role in stabilizing protein structures, as is suggested for betaine and taurine. Dr. Brosnan pointed out that recent work by Dr. Roth and by Dr. Wischmeyer showed that glutamine can induce the production of heat-shock proteins in a number of cell lines. These have protective, chaperone effects. Dr. Brosnan pointed out that the amide group (—CO NH₂) has excellent hydrogen bonding capacity because both the oxygen and the hydrogens can be involved in these linkages. Dr. Young emphasized this point and referred to a number of neural degenerative diseases (e.g., Huntington’s disease) that involve a polyglutaminated protein. This occurs as a result of an expansion of the CAG repeats in mutant genes. The result is an aggregated protein that plays a role in the pathogenesis of these disorders.

Dr. Young addressed Dr. Jefferson’s paper. What is known of the molecular basis for the effects of amino acids on gene expression? Dr. Jefferson pointed out that there are multiple recognition sites for amino acid sufficiency. tRNA charging is a mechanism that has been discussed for some time and this appears to be the way severe amino acid insufficiency is recognized. The GCN2 protein kinase regulates translation, in amino acid-starved cells, by phosphorylating the elongation factor, eIF2. There are likely to be other mechanisms, as yet undetermined. He has carried out some studies with chemical analogs of leucine, and there is clearly a structural requirement, reminiscent of ligand binding. It is not known whether such ligand binding occurs through a molecule on the cell membrane or inside the cell. Yeast provides a fascinating model because these organisms express transport-type molecules on the cell surface that recognize the extracellular environment and then communicate through intracellular signaling pathways. However, there is as yet no evidence for such a mechanism in mammalian cells. It is quite possible that glutamine may signal intracellularly; Dr. Abcouwer commented that glutamine deficiency decreases the turnover of glutamine synthetase and heat-shock proteins may be induced by glutamine. These are two examples in which intracellular signaling could play a role.

A number of questions were addressed to Dr. Abcouwer concerning the regulation of the expression and turnover of glutaminase and of glutamine synthetase. With regard to the mechanism whereby glutamine regulates glutamine synthetase’s degradation, he pointed out that this enzyme is ubiquinated and glutamine may play a role at this level. With respect to possible glucocorticoid regulation of glutaminase expression, Dr. Abcouwer said that they have tried a number of different inducers in a number of different cell lines without success. Dr. Häussinger pointed out that some cell types have abundant mRNA for glutamine synthetase but do not express the protein. For example, the Kupffer cells of the liver have...
mRNA levels for glutamine synthetase 5- to 10-fold greater than perivenous hepatocytes yet they do not synthesize glutamine. Dr. Watford raised the possibility that glutamine feeding could suppress glutamine synthetase activity. In his laboratory, they raised the blood glutamine level in rats by ~20% for 10 d but could not find any change in muscle glutamine synthetase. Dr. Abcouwer said that he and others, in Dr. Souba's laboratory, put great effort into altering blood glutamine in rats (either by feeding or via a central line) with little success. Dr. Bode did a very elegant study in which he examined glutamine synthetase regulation in different tissues (e.g., lung and muscle) by diet, and by treating animals with methionine sulfoxamine to inhibit glutamine synthetase and, thus, glutamine synthesis. In these experiments glutamine synthetase levels could be increased, either by depriving the animals of dietary glutamine or by methionine sulfoxamine administration. He agreed that glutamine homeostasis is very tightly controlled, and one of the homeostatic mechanisms is likely to be the mechanism whereby glutamine controls glutamine synthetase turnover.