BIOCHEMICAL LETTERS

The possible role of glutamine substrate cycles in skeletal muscle

The paper by Wu *et al.* (1991) raises some interesting points regarding the metabolism of glutamine by skeletal muscle. They provide evidence that the rate of glutamine utilization by skeletal muscle may be high: the rate of oxidative decarboxylation of L-[1-¹⁴C]glutamine exceeds that of L-[1-¹⁴C]leucine and the activity of phosphate-activated glutaminase is present in a number of different muscles. In addition, Rennie *et al.* (1986) have shown that glutamine can be taken up by perfused skeletal muscle and that this process has a high $V_{\max}$. However, there is considerable evidence that glutamine is synthesized, stored and released by skeletal muscle: glutamine synthetase is present in muscle, the concentration of intracellular glutamine may be as high as 20 mM and muscle can release glutamine at a rate higher than that of any other amino acid (Felig, 1975; King *et al.*, 1983; Rennie *et al.*, 1986; Parry-Billings *et al.*, 1990). The question arises as to whether it is possible to reconcile these two different and apparently opposite interpretations of glutamine metabolism in muscle?

A substrate cycle between glutamine and glutamate in muscle and a translocation cycle of glutamine across the plasma membrane may provide an answer. There is evidence for a glutamine/glutamate substrate cycle in such diverse systems as liver (Häussinger, 1990) and *Neurospora crassa* (Mora, 1990). In the liver, high activities of glutaminase and glutamine synthetase are present in different cell populations: the cycle operates between periportal and perivenous hepatocytes and not within the same cell. Since the enzymes glutaminase and glutamine synthetase are both present in muscle, at least the enzymic basis for the cycle exists (Fig. 1). For future work, it will be important to show that these enzymes are present in the same muscle fibre and that they are simultaneously active. In addition, since glutamine may be both taken up and released by muscle and since calculations of ΔG values indicate that both these processes are non-equilibrium (Newsholme & Parry-Billings, 1990), they must be considered as separate processes. Consequently, if they are simultaneously active, a translocation cycle for glutamine should exist across the muscle membrane (Fig. 1). This would be similar in principle to the Na⁺ translocation cycle across the plasma membrane (Newsholme & Crabtree, 1976) or the Ca²⁺ translocation cycle across the mitochondrial membrane (Crompton *et al.*, 1976). There is, however, no direct evidence for the existence of either of these cycles involving glutamine in muscle. Furthermore, our present knowledge suggests that these cycles operate in all conditions in the direction of net glutamine synthesis and net glutamine release from muscle.

Substrate cycles may improve sensitivity in metabolic control (Newsholme & Crabtree, 1976) and given the important role that muscle appears to play in control of the plasma glutamine level (Newsholme & Parry-Billings, 1990), it is tempting to suggest that they are necessary in muscle. Thus, in a similar manner to

Fig. 1. The proposed substrate and translocation cycles in skeletal muscle involving glutamine

The substrate cycle between glutamine and glutamate involves the reactions catalysed by glutamine synthetase and glutaminase. The translocation cycle across the muscle membrane involves the transporter-mediated processes of glutamine uptake and release.

the triacylglycerol/fatty acid cycle, which provides a feedback control mechanism for mobilization of fatty acids according to changes in the plasma fatty acid level, the translocation cycle for glutamine could play a similar role for maintenance of a constant plasma glutamine level. A decrease in the plasma glutamine level would lower the rate of uptake and hence increase the net rate of release, which would thus help to maintain the plasma level, whereas an increase in the plasma glutamine level would increase the rate of uptake and consequently decrease the net rate of release. This mechanism requires that the rate of release of glutamine is independent of the intracellular concentration, for which there is some evidence (Parry-Billings *et al.*, 1990). This hypothesis does not, of course, rule out the existence of a number of external regulators of the enzymes and/or the transport proteins involved in these substrate cycles.

There may be considerable inter-species variation regarding glutamine metabolism. However, the current discussion may encourage further work to be undertaken in this field, which would be of importance in understanding the mechanisms that control the metabolism of glutamine by skeletal muscle, which appears to be of considerable biochemical, physiological and clinical importance.

Mark PARRY-BILLINGS and Eric A. NEWSHOLME

Cellular Nutrition Research Group, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, U.K.

Crompton, M., Capano, M. & Carafoli, E. (1976) *Eur. J. Biochem.* **69**, 453–462

Felig, P. (1975) *Annu. Rev. Biochem.* **44**, 933–955

Häussinger, D. (1990) *Biochem. J.* **267**, 281–290

King, P. A., Goldstein, L. & Newsholme, E. A. (1983) *Biochem. J.* **216**, 523–525

Mora, J. (1990) *Microbiol. Rev.* **54**, 293–304

- Newsholme, E. A. & Crabtree, B. (1976) *Biochem. Soc. Symp.* **41**, 61–110
- Newsholme, E. A. & Parry-Billings, M. (1990) *J. Parent. Ent. Nutr.* **14**, 63S–67S
- Parry-Billings, M., Dimitriadis, G. D., Leighton, B., Bond, J., Bevan, S. J., Opara, E. & Newsholme, E. A. (1990) *Biochem. J.* **252**, 319–322
- Rennie, M. J., Hundal, H., Babij, P., MacLennan, P., Taylor, P. M., Watt, P. W., Jepson, M. M. & Millward, D. J. (1986) *Lancet* **ii**, 1008–1012
- Wu, G., Thompson, J. R. & Baracos, V. E. (1991) *Biochem. J.* **274**, 769–774

Received 17 May 1991

Nomenclature errors

There are a dozen phosphoribosyltransferases (EC 2.4.2.7 to 2.4.2.22) which are named as acceptor phosphoribosyltransferases or donor pyrophosphorylases. With the exception of xanthine phosphoribosyltransferase (in which the classification is based on xanthine as acceptor; why?), all the enzymes are classified on the basis of pyrophosphate as acceptor. There is one more name which does not fit into this general pattern. The enzyme catalyses the committed step in purine nucleotide biosynthesis and is named as amidophosphoribosyltransferase (EC 2.4.2.14). The more objectional name for this enzyme is glutamine:phosphoribosylpyrophosphate (PRPP) amidotransferase or phosphoribosyldiphosphate 5-amidotransferase, which

appears in the column captioned 'other names' [1] and which was adopted by the Hartman group [2] for convenience. This name was probably coined to convey two changes brought about by the enzyme, i.e. phosphoribosyl transfer and amidation. This violates rule 14B for systematic nomenclature which states that in case of a reaction involving two changes, the name is based on one change and the other one is to be indicated in parentheses. Moreover, the name wrongly implies amide group transfer, as given in Stryer's book [3]. Actually, it is the amino portion of the amide group in glutamine which displaces the pyrophosphate group in PRPP. In analogy with other enzymes in this subgroup, the enzyme should be named as glutamine phosphoribosyltransferase (deamidating).

For fumarase and aconitase, the correct names fumarate hydratase and aconitate hydratase have been adopted. Similarly, enolase (EC 4.2.1.11) should be called enol hydratase (rule 25A) since the name enolase suggests that the enzyme catalyses hydrolysis of the substrate enol.

S. K. SINGLA

University of Horticulture and Forestry, Nauni, Solan 173230, India

1. Enzyme Nomenclature (1984) Recommendations of the Nomenclature Committee of the International Union of Biochemistry, Academic Press, London and New York
2. Buchanan, J. M. & Hartman, S. C. (1959) *Adv. Enzymol.* **21**, 242–247
3. Stryer, L. (1988) *Biochemistry*, pp. 603, Freeman

Received 10 July 1991