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Channelling and Evolution of Metabolism

This review on channelling by Ovádi (1991) covers practically all the general metabolic features related to this mechanism. This very complete overview prompts some reflections on the possible role of this mechanism in the evolution of living cells.

Channelling provides a mechanism through which the diffusion of intermediary metabolites can be avoided. This has an immediate effect on the coupling-stoichiometry among processes of material transfer coupled through a common intermediate. In the extreme case, if the diffusion is totally eliminated, the coupling degree (q) is equal to 1, and as a consequence, the stoichiometry is constant. Stoichiometry is the ratio between fluxes (J_1/J_2); linear thermodynamics provides the following relaionship between stoichiometry and the coupling degree:

$$\frac{J_1/J_2}{Z}=\frac{q+Z(x_1/x_2)}{1+q\,.\,Z\,.\,(x_1/x_2)},$$

where $Z=\sqrt{L_{11}/L_{12}}$, L_{11} and L_{12} being the direct phenomenological coefficients, and (x_1, x_2) the conjugate strengths (reaction affinities) of the fluxes J_1 and J_2 (reaction rates), respectively.

If $q=1$, $J_1/J_2=Z$ is constant and independent of the strength ratio. Since the efficiency (the yield) of the coupling is, in turn, a function of the coupling degree and of the strength ratio:

$$\mu=-\frac{q+Z(x_1/x_2)}{q+1/Z(x_1/x_2)},$$

and the greatest efficiency for a degree of coupling q, is

$$\mu_{max}=\frac{q^2}{(1+\sqrt{1-q^2})^2},$$

which implies that an increase of the coupling degree produces an increase in the greatest efficiency, i.e. the channelling increases the energetic yield in coupled chemical reactions.

Therefore, in the course of evolution channelling may have produced local potential basins which would have produced a strong selective pressure on this channelling mechanism once it was triggered. Thus, once the channelling was initiated on a given pathway out of several possible ones, that particular path might have been fixed, while the others were eliminated. This process is highly feasible.

In the present metabolic design of the cells, every chain of reactions (metabolic pathway) is strictly determined by the high specificity of the different enzymes for their substrates. This design is the result of an optimization process (an instance of which has been proved for the pentose-phosphate cycle, by means of the game of the pentose-phosphate cycle theory). Cells may have achieved their metabolic structure by testing different solutions until finding the best solution to every problem

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(the present structure of the pentose pathway is, in fact, the best strategy of the game). The previous conclusion leads us to consider that in the course of evolution some channelling might have been organized on a given solution (pathway) which was not the best solution to solve a particular problem, promoting the removal of the other possibilities. Thus, this might eliminate the possibilities of improving the metabolic design in a certain group of organisms, denying them adequate chemical support for some important functions. This can explain the poor success which some groups have had.

Regarding the whole set of metabolic pathways, one easily sees two facts: (a) all the pathways are well-interconnected through common intermediates, which allow relations among the different processes; (b) with only very few new enzymes, a new—and very different—physiological function can be achieved. The first fact is a consequence of the second; the new enzymes which promote a new pathway are arranged over a more general and ubiquitous chain of conversion. For example, the glyoxylate cycle, which accounts for the capacity to convert fatty acids into carbohydrates, has only two specific enzymes (isocitrate lyase and malate synthase), besides the normal ones of the Krebs cycle; gluconeogenesis also has few enzymes different from glycolysis; serine biosynthesis is a divergent branch from glycolysis with few specific new enzymes, and there are a large number of other examples. These facts suggest that the origin of certain pathways could have been based on pre-existing ones, i.e. their design may have been obtained by taking advantage of all possible pre-existing materials (enzymes and intermediates).

Many metabolic pathways could have been designed by different (and more complicated) ways, such as a particular chain of specific sequential reactions. This design procedure would have led to quite a different set of metabolic pathways, having many sequential (and unbranched) chains of reactions, and involving specific paths (and enzymes) for every end product. In this case, the new pathway would be created without taking advantage of pre-existing material. Thus, the resulting metabolism would have little or no versatility and would require about ten or 20 more enzymes than the present one. This means an expense of protein and genetic information that the cells cannot afford. Moreover, this would also promote the existence of a large amount of new intermediary metabolites, which would increase their total concentration beyond the permissible limits for which water can keep its solvent capacity (a fact which has been discussed by Ovádi in her review).

In most cases the design of metabolic pathways has not happened in this way. The existence of many common intermediates in all pathways demonstrates this. On the contrary, new problems have been solved and new pathways designed with the addition of very few new resources on the pre-existing material, or pathways.

Although a tendency towards channelling in the evolution of metabolism seems feasible (which is logical), it is clear that channelling is a mechanism which cannot be generalized absolutely. In principle, only certain highly specialized processes, such as the respiratory chain, can be structured as channelling. All the intermediates of glycolysis and the Krebs cycle, and most of the pentose-phosphate cycle are also intermediates of many other important processes. This means that these intermediates must be diffused in order to attain a concentration high enough for other

enzymes to work on them. This allows relative independence among different pathways, which requires a variable coupling degree, and this provides versatility in metabolism.

On the other hand, having such a number of different intermediates, the concentration of every one of them must necessarily be very low as Ovádi discusses well in her review. This causes enzymes to work at low saturation conditions, which in turn leads to a general high sensitivity of enzyme activity to the concentration of their substrates. Thus, enzyme activity can be well-modulated by the concentration of intermediates: the concentration of oxalacetate, e.g. can modulate the activity of the Krebs cycle and, in general, anaplerotic reactions can play a clear role in the control of metabolic cycles. It may be noted that these features of the metabolism, which allow its versatility, are based on the existence of common intermediate metabolites; their low concentration can be varied within a certain range changing the activity of the other branching enzymes.

Channelling is a mechanism that modifies this situation, increasing the local concentration of intermediates without practically influencing the whole cellular concentration of metabolites. This can largely enhance the catalytic efficiency of a given metabolic pathway, promoting a faster conversion process (which involves a greater flux and lesser transition time). However, it cannot be a general mechanism, as this would lead to the destruction of many other metabolic pathways, providing that channelling does not allow branching points for connecting with other metabolic processes. Therefore, with the metabolic design that we find in the cells, most of the cases of channelling will only be possible in very specific processes of very specialized cells.

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