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Action of uroporphyrinogen decarboxylase on uroporphyrinogen III

One of the outstanding questions concerning the enzymic decarboxylation of uroporphyrinogen III is whether the reaction is clockwise and orderly starting from the ring-D acetate group or is random. Evidence in support of a clockwise mechanism was provided by the fact that the intermediates isolated from the faeces of hexachlorobenzene-poisoned rats were 7d, 6da and 5dab, respectively (Jackson *et al.*, 1976). We have also confirmed this by h.p.l.c. analysis. On the other hand, all 14 intermediates were detected in normal human urine (Lim *et al.*, 1983) and incubation of uroporphyrinogen III with red cell haemolysates produced a mixture of isomers (Lash, 1979; Luo & Lim, 1990), indicating random decarboxylation.

Lash (1991) postulates that the uroporphyrinogen III used in the enzyme reaction may be presented randomly to the enzyme leading to random decarboxylation while with PBG as substrate the enzymically produced uroporphyrinogen III is 'handed on' to uroporphyrinogen decarboxylase in a specific orientation, resulting in specific decarboxylation of the ring-D acetate group. We accept this explanation is plausible and agree that it should be tested experimentally.

Whether the preferential accumulation of 7d in PCT and in hexachlorobenzene-poisoned rats is a result of damage to uro-

porphyrinogen decarboxylase, however, remains an open question.

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Inhibition of adenylate cyclase by Ca^{2+} — a counterpart to stimulation by Ca^{2+} /calmodulin

Stimulation of adenylate cyclase, mediated by Ca^{2+} acting via calmodulin, is the longest established example of potential positive 'crosstalk' between the Ca^{2+} and cyclic AMP-signalling systems [1]. Ca^{2+} , in concentrations that are achieved intracellularly, elicits a prominent stimulation of adenylate cyclase, which is variable in magnitude, depending on the tissue [2]. It is assumed that neurotransmitters that elevate $[\text{Ca}^{2+}]_i$ should also elevate cyclic AMP by this mechanism in intact neurons. Whether this actually occurs in cells has never been proven, although a considerable number of reports indicate that $[\text{Ca}^{2+}]_i$ -mobilizing neurotransmitters elevate cyclic AMP in brain slice preparations [3–5]. It has also been proposed that such Ca^{2+} /calmodulin-stimulated adenylate cyclase is the form that is susceptible to neurotransmitter inhibition [2,6,7] and that this inhibition is a significant component of presynaptic autoinhibitory mechanisms [8]. Ca^{2+} /calmodulin-stimulated adenylate cyclase was first described in brain [9,10] and partially purified from this source. Development of antibodies against such preparations suggested a rather limited tissue distribution [11,12]. Further purification, leading to the recent cloning and expression of a Ca^{2+} /calmodulin-stimulated adenylate cyclase [13] has confirmed the largely neuronal distribution of the mRNA encoding this species [14].

In contrast to the stimulatory effect of Ca^{2+} /calmodulin on brain adenylate cyclase, a growing number of reports indicate that low concentrations of Ca^{2+} inhibit adenylate cyclase in plasma membranes from other sources. Adenylate cyclase from pituitary tissue [15], purified somatotrophs [16], GH3 cells [17], platelets, NCB-20 cells [18] and cardiac sarcolemma [19] is inhibited by 35–50% by Ca^{2+} in the same concentration range that stimulates brain adenylate cyclase. The magnitude of inhibition is greater than that elicited by G_i -protein-coupled receptors and is additive with their effects [15–19]. (Inhibition by Ca^{2+} in the low micromolar range is not to be confused with inhibition by Ca^{2+} in the submillimolar range. This latter inhibition is displayed by all adenylate cyclases regardless of their source and of their response to Ca^{2+} in the submicromolar range, including, for instance, the enzymes from brain, liver and cardiac tissue, which are stimulated, unaffected and inhibited, respectively, by submicromolar $[\text{Ca}^{2+}]$. In a system in which inhibition by Ca^{2+} is encountered both in the submicro- and submillimolar range, the two inhibitory effects are generally separated by a