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Biological Function of Terpenoid Quinones

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The terpenoid quinones are widely distributed in Nature. In bacteria, plant and animal tissues the quinones are localized in the subcellular organelles involved in the biological processes of respiration and bioenergetics. Information concerning the role played by quinones in cellular metabolism has been obtained with bacterial systems after irradiation with light at 360nm. The sensitivity of the quinones to light at 360nm has made it possible to destroy the endogenous quinone without disruption of organelle structure or disassociation of the spatial arrangement of enzymes and coenzymes necessary for oxidative phosphorylation. Irradiation of extracts of *Mycobacterium phlei* was found to result in a loss of the endogenous quinone and in a loss of both oxidation and phosphorylation. The addition of the natural quinone, vitamin K₁, or closely related homologues was found to result in the restoration of oxidative phosphorylation. Although irradiation of the extracts was found to result in the loss of oxidative activity with succinate and NAD⁺-linked substrates, restoration of activity by the addition of quinone occurred only with NAD⁺-linked substrates. The succinate oxidase pathway appears to contain a light-sensitive water-soluble component that differs from the quinones.

The possibility arises that the restoration of activity by quinones is not directly related to a

role in respiration but may be due to removal of a possible inhibitor formed during quinone destruction by light, or to a non-specific physical effect. This possibility, however, seems unlikely since restoration of oxidative phosphorylation occurs only with certain specific quinones. Certain substituted quinones, with physical and chemical properties similar to the quinones capable of restoring activity, were found to restore only oxidation and usually by an electron-transport by-pass reaction. In addition, the possible presence of an inhibitor formed during destruction of the endogenous quinone appears improbable since the first and third phosphorylative sites are operative in the irradiated system. Further, competitive inhibitors of vitamin K were shown to inhibit respiration in the untreated and quinone-restored system. Other methods of quinone depletion are available. Lipid extraction of the cell-free system results in a loss of oxidative phosphorylation. As in the irradiated system, restoration of activity occurs only on the addition of certain specific quinones.

The site of participation of the quinones in the respiratory chain has been determined with respiratory inhibitors and analysis of the reduction of the cytochromes in the irradiated system. For example, after irradiation, both NAD⁺ and flavo-proteins are reduced on the addition of substrate; however, the cytochromes remain in the oxidized state. Addition of a suitable quinone results in a reduction of the cytochromes. Thus, the quinone participates between flavin or non-haem iron and cytochrome *b* in the respiratory chain. Further, the quinone may function as a lipid cofactor since the rate of reduction and oxidation was found to be greater than the overall rate of oxidation from substrate to oxygen.

The ability of naphthaquinones to restore oxidation and phosphorylation to the light-treated system appears to depend on specific quinone structures. The naphthaquinones that restore both activities require the presence of a methyl group in the C-2 position and at least a C₅ unsaturated side chain in the C-3 position of the naphthaquinone nucleus. Studies of the structural requirements of the side chain for restoration of oxidative phosphorylation have indicated that the β - γ bond of the first isoprene unit must be unsaturated and that the second isoprenoid unit from the ring must be saturated as in MK₉(II-H). In addition, restoration of oxidative phosphorylation was only found to occur with the *trans* geometric isomers of MK₉(II-H) or vitamin K₁. In contrast, the *cis* isomers were found to partially restore oxidation but failed to restore phosphorylation.

Restoration of oxidation by quinones has been shown to be less specific than the requirements for restoration of oxidative phosphorylation. Although

a large number of quinones are capable of restoring oxidation, they do not restore this activity by the same respiratory sequence as does the natural quinone. By the use of respiratory inhibitors or by following the reduction of the respiratory carriers spectrophotometrically, it has been possible to show that many of the quinones that restore only oxidation fail to utilize the major respiratory chain but instead by-pass completely or bridge a section of the respiratory chain. Since quinones may accept electrons from one segment of the respiratory chain, by-pass other respiratory carriers and re-enter the terminal position of the major chain, it is possible to determine sites of phosphorylation within the segments that have not been by-passed. In this manner it has been possible to demonstrate phosphorylative sites in the span between NAD^+ and quinone, between quinone and cytochrome *b* and between cytochrome *c* and oxygen.

Studies with the quinone-depleted system have indicated that the quinones may be directly involved in the phosphorylative events. Incubation of the quinone-depleted system with vitamin K_1 , inorganic phosphate containing ^{32}P , and an electron donor resulted in the formation of a lipid-extractable quinone that was distinct from vitamin K_1 and dihydrovitamin K after chromatography. Of interest was the finding that the enzymically formed compound co-migrated with the synthetic chromanyl phosphate derivative of vitamin K_1 . The enzymically formed compound appeared to be derived from vitamin K_1 , since it was found to contain ^{14}C in experiments in which the starting quinone was ^{14}C -labelled vitamin K_1 . The u.v. and i.r. spectra and chromatographic properties of the enzymically formed compound were found to be compatible with a phosphorylated derivative of reduced vitamin K . Although the enzymically formed compound is unstable, a stable addition complex can be formed with mercaptoethanol. This stable complex may permit chemical characterization of the quinol derivative.

It has been possible to obtain some information about the role of quinones in oxidative metabolism. However, it has been shown that bacteria contain a large number of different types of quinones. For example, *M. phlei* contains $\text{MK}_9(\text{II-H})$ and $\text{MK}_8(\text{II-H})$. Other micro-organisms may contain both benzo- and naphtha-quinones, a series of one type of quinone differing in side chain length ($\text{C}_4\text{--C}_{10}$), or differing in the number of saturated isoprenoid units in the side chain. Any analysis of the role of quinones in oxidative metabolism must take into account the possible function of the numerous quinones found in one system. These compounds may represent residual products of quinone biosynthesis or degradation or may play a more subtle metabolic role.

Terpenoids in Insects

By PETER KARLSON. (*Institut für Physiologische Chemie der Philipps-Universität, Marburg/Lahn, Germany*)

This review deals with the occurrence and function in insects of various compounds that are presumably derived from mevalonic acid. The biochemical pathways of their biogenesis are largely unknown.

Sterols and steroid hormones. It is well known that insects are unable to synthesize cholesterol or other sterols from mevalonate. Sterols are essential nutritional factors. However, insects are able to convert cholesterol into ecdysone and 20-hydroxyecdysone. The biochemistry of these 'moulting hormones' will be reviewed briefly. Recent work in my laboratory has led to the preliminary characterization of an enzyme system that converts ecdysone into two metabolites that are biologically inactive.

Juvenile hormones. Two naturally occurring juvenile hormones have been identified. They differ from methyl 10,11-epoxyfarnesoate in having one or two ethyl groups instead of the usual methyl groups. Several C_{15} terpenoids from plants, e.g. juvabione, have considerable juvenile-hormone activity. The same is true for derivatives of farnesol and for synthetic substances structurally related to juvabione.

Pheromones and defence substances. Pheromones are secretions that serve as 'chemical messengers' among individuals of the same species. Among these, we find some terpenoid alcohols and aldehydes (e.g. geraniol, citronellal). The biology of these compounds will be reviewed. Even larger is the spectrum of the defence substances. Remarkably, cortexone and other corticosteroids serve as defence substances for some aquatic beetles. Ants produce a wide variety of defence substances, which are mostly related to terpenoids, e.g. dendrolasin and iridomyrmecin, a lactone possessing antibiotic and insecticidal properties.

Biosynthesis of Terpenoid Alkaloids

By A. R. BATTERSBY. (*Department of Organic Chemistry, University of Liverpool*)

Both the fungi and the higher plants form natural products in which nitrogen has been built into a skeleton which, by its structure, is apparently terpenoid in origin or at least partly so. Examples are the alkaloids of ergot, the diterpene bases present in many *Aconitum* species, the simple pyridine and piperidine alkaloids from *Skytanthus* and so on. Undoubtedly the largest group of nitrogenous terpenes, however, is that containing