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Minireview

Protein-radical enzymes

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Protein-radical enzymes use a free radical located on an intrinsic amino acid residue as a cofactor. The amino acid involved can be a tyrosine (ribonucleotide reductase, photosystem II, prostaglandin H synthase), a modified tyrosine (amine oxidase, galactose oxidase), a tryptophan (cytochrome *c* peroxidase), a modified tryptophan (methylamine dehydrogenase) or a glycine (ribonucleotide reductase, pyruvate formate lyase). The mechanistic role of these radicals appears to be that of a one-electron gate, allowing the separation of single reducing equivalents in time and space.

Protein-radical enzyme; Pyrroloquinoline quinone; Trioxyphenylalanine; Tryptophan tryptophyl quinone; Free radical; ESR

1. INTRODUCTION

The term 'protein-radical enzymes' is loosely applied to enzymes operating through a free radical mechanism, with the radical located directly on a protein amino acid residue and not at an extrinsic cofactor or substrate. Development in this field was greatly stimulated by the suggestion that pyrroloquinoline quinone (PQQ), found in bacterial dehydrogenases, was a common redox active cofactor in various enzymes with poorly characterized reaction mechanisms. Three of these enzymes have now been shown to act through hitherto unknown amino acid-derived prosthetic groups [1–3]. It is somehow ironical that not only have these findings excluded a role for PQQ in eukaryotic enzymes and in prokaryotic methylamine dehydrogenases, but the true PQQ-enzymes apparently do not act through a free radical mechanism [4].

The following is a presentation of the protein-radical enzymes established so far (Tables I and II) and of the radical structures involved (Fig. 1). This review does not attempt to be comprehensive but merely to present an overview of this rapidly evolving field.

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Abbreviations: PQQ, pyrroloquinoline quinone; TOPA, trioxyphenylalanine (2,4,5-trihydroxyphenylalanine); TTQ, tryptophan tryptophyl quinone.

2. THE ENZYMES

2.1. *Amine oxidase*

It was recently discovered that copper amine oxidases have a unique amino acid, TOPA, in their amino acid sequence at the active site [1,5]. TOPA is a quinone compound and the reduced form corresponds to a dihydroxylated tyrosine; the presence of a Tyr codon in the DNA sequence suggests that TOPA arises from post-translational modification of a tyrosine residue [6,7]. In the resting enzyme TOPA is in the oxidized form, most likely a *para*-quinone since isolated *p*-TOPAquinone shows absorption spectra identical to the enzyme [8], whereas the *ortho* form absorbs at lower wavelengths and does not mimic the characteristic pink colour of copper amine oxidase [4].

During the catalytic cycle TOPA is reduced by an amino substrate, and a semiquinone is generated with concomitant reduction of the Cu(II) site [9]. However, it is not the TOPA semiquinone itself which is formed, but a radical intermediate with substrate nitrogen bound covalently to the aromatic ring system [8,10,11]. Neither the structure of the radical nor the nature of the transient states in the reaction are yet known. Under anaerobic conditions the radical species is stable for hours at room temperature, but it disappears immediately upon reaction with oxygen, with concomitant release of the products NH_3 and H_2O_2. Presumably the oxidation of the radical is the ultimate or penultimate step that restores the oxidized TOPA; the intramolecular rearrangements following initial reduction of the TOPAquinone by a primary amine are rate limiting [10,12]. Reaction of O_2 with the semiquinone does not

Table I

Reactions catalyzed by protein-radical enzymes.

Enzyme	Reaction catalyzed
Amine oxidase	$R\text{-}CH_2NH_2 + O_2 \rightarrow R\text{-}CHO + NH_3 + H_2O_2$
Methylamine dehydrogenase[a]	$CH_3NH_2 + H_2O \rightarrow HCHO + NH_3 + 2e^- + 2H^+$
Galactose oxidase	$R\text{-}CH_2OH + O_2 \rightarrow R\text{-}CHO + H_2O_2$
Ribonucleotide reductase[b]	$NDP + 2e^- + 2H^+ \rightarrow dNDP + H_2O$
Cytochrome *c* peroxidase	$CcP + H_2O_2 \rightarrow$ compound I + H_2O
	compound I + cyt c^{2+} + $2H^+ \rightarrow$ compound II + cyt c^{3+} + H_2O
	compound II + cyt $c^{2+} \rightarrow CcP$ + cyt c^{3+}
Photosystem II[c]	$2H_2O \rightarrow O_2 + 4e^- + 4H^+$
Prostaglandin H synthase[d]	arachidonic acid + $2O_2 \rightarrow$ prostaglandin G_2
	prostaglandin G_2 + $2e^-$ + $2H^+ \rightarrow$ prostaglandin H_2 + H_2O
Pyruvate formate lyase	pyruvate + PFL → formate + PFL-acetyl
	PFL-acetyl + CoA → PFL + acetyl-CoA

[a] Other primary amines can be substrates, the electron acceptor is a metalloprotein (amicyanin, azurin or cytochrome).
[b] NTPs are substrates as well, the normal electron donor is thioredoxin.
[c] The final electron acceptor is plastoquinone.
[d] The physiological reductant is not known.

lead to superoxide release, O_2^- may instead be reduced in an intramolecular concerted action with Cu(I) to form H_2O_2, as in superoxide dismutase [13].

2.2. *Methylamine dehydrogenase*

Once a presumed PQQ-protein, this enzyme has recently been shown to use a prosthetic group composed of two cross-linked tryptophan residues, forming a tryptophan tryptophyl quinone (TTQ) [3,14–16]. The reaction catalyzed resembles that of amine oxidase (Table I) but with two important differences: first, the enzyme contains no metal centre and in fact depends on small electron transport proteins (amicyanin, azurin or cytochromes) for its reoxidation; and second, O_2 is not consumed and no reactive oxygen species is generated.

TTQ-semiquinones are apparently not formed in the reduction of the dehydrogenase with methylamine at physiological pH, only a two-electron reduced quinole is found [17]. Semiquinones can be seen at high pH, and this has led to speculate that the enzyme mechanism involves comproportionation of reduced and oxidized cofactors [17]. Unfortunately most studies on this aspect have focused on the possible role of PQQ, and the semiquinones have normally been generated using one-electron reductants [16,18]. With the present knowledge of the amine oxidase reaction it seems more likely that

Table II

Cofactors and radical potentials in protein-radical enzymes.

Enzyme	External cofactors	Radical position	E'_m[a] (mV)	Ref.
Amine oxidase	Cu	TOPA	< −200	[b]
Methylamine dehydrogenase	None	TTQ	+ 100	[53]
Galactose oxidase	Cu	Tyr-272-S-Cys	+ 400–500	[21]
Ribonucleotide reductase[c]	2 Fe-O_2-Fe	Tyr-122	+ 940[d] ?	[54]
		Cys (?)	?	
Ribonucleotide reductase[e]	None (?)	Gly-681	< −200	[b]
Cytochrome *c* peroxidase	Heme-Fe^{3+}	Trp-191	+ 1050[d] ?	[54]
		Tyr-?	+ 940[d] ?	[54]
Photosystem II[f]	Mn_4, Fe^{2+}, P_{680}	Tyr-161	+ 760	[55]
	2 plastoquinones	Tyr-160	+ 1000	[55]
	pheophytin, cyt b_{559}	His (?)	+ 1000	[40]
Prostaglandin H synthase	Heme-Fe^{3+}	Tyr-385	+ 940[d] ?	[54]
Pyruvate formate lyase	None	Gly-734	< −200	[b]

[a] Radical potential vs. normal hydrogen electrode, room temperature pH 7.
[b] Estimated from reaction with oxygen.
[c] From aerobically grown *E. coli*.
[d] Potential for the free amino acid.
[e] From anaerobically grown *E coli*.
[f] Tyr-161 of the D1 polypeptide and Tyr-160 of the D2 polypeptide corresponds to Y_Z^+ and Y_D^+, respectively.

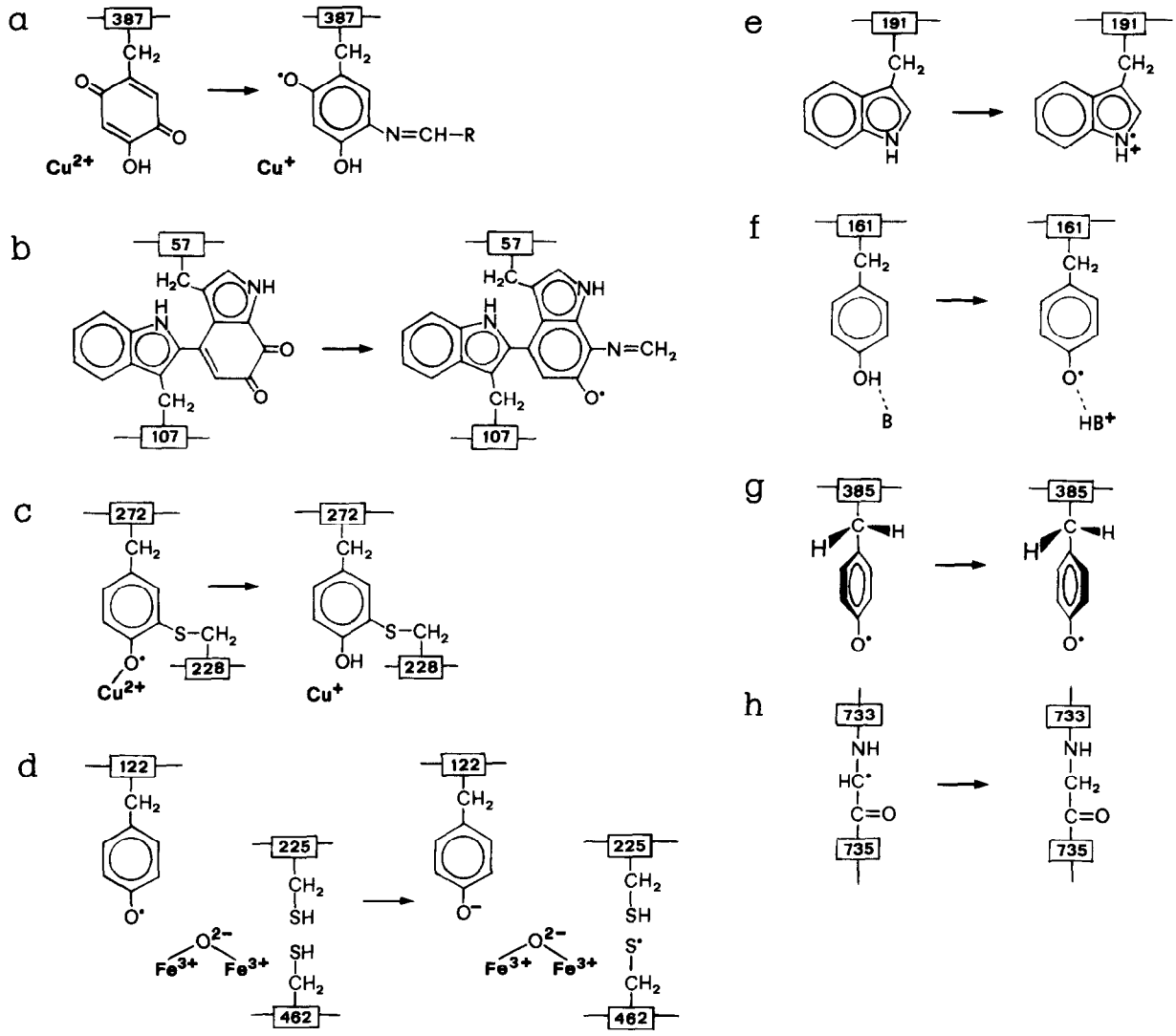

Fig. 1. Structures of the free radicals found in protein-radical enzymes. The rectangles indicate the amino acid positions in the sequences from commonly used enzymes. (a) One possible structure for the TOPA-substrate radical in amine oxidase; (b) formation of a hypothetical TTQ radical in methylamine dehydrogenase after two-electron reduction with methylamine and one-electron oxidation with amicyanin; (c) two-electron reduction of Tyr-S-Cys in galactose oxidase, it is not known whether the tyrosine is still a ligand to Cu^+; (d) a model for the transient reduction of the stable tyrosyl in ribonucleotide reductase; (e) generation of the tryptophyl species in cytochrome *c* peroxidase; (f) formation of Y_Z^+ in photosystem II, in spite of the name the phenoxyl is not protonated; (g) a possible conformation change of the tyrosyl radical in prostaglandin H synthase; (h) a hypothetical transient reduction of the glycyl radical in pyruvate formate lyase.

a semiquinone will be formed during re-oxidation, considering that the oxidizing protein is a one-electron carrier. In analogy with amine oxidase the semiquinone may still have a substrate nitrogen bound to the indole ring system (Fig. 1), an imine intermediate has been suggested [19].

2.3. *Galactose oxidase*

Like amine oxidase, this mononuclear copper enzyme carries out two-electron oxidation of a substrate (primary alcohol) with formation of an aldehyde and H_2O_2. But in contrast to amine oxidase, the oxidized enzyme harbours a stable free radical, which is reduced transiently to a diamagnetic intermediate during the catalytic cycle [20–22]. This radical species is a modified tyrosyl (Tyr-272), with the aromatic ring covalently linked through a thioether bond to a nearby cysteine [2]. The radical is exchange coupled to Cu(II) with the result that both metal and radical are ESR silent in the native enzyme. The apoenzyme radical is delocalized over the phenoxyl ring, with spin distribution similar to other tyrosine radicals, thioether notwithstanding [22]. The redox potential of +450 mV is 0.5 V lower than expected, but this may not be due to the thioether alone as the Tyr-272 ring oxygen is also a ligand to the Cu(II), at a distance of only 1.9 Å [2,22]. Although the active site is now well described, virtually nothing is known about the catalytic intermediates with bound substrates.

2.4. *Ribonucleotide reductase*

This was the first enzyme shown to have an amino acid radical cofactor, and for a long time the only such enzyme known. The radical is an extremely stable tyrosyl (Tyr-122), and exists in the phenoxyl form and not as the protonated cation [23]. It is buried in the enzyme interior, some 10 Å from the surface, but situated only 5 Å from one of the two bimolecular Fe(III) clusters of the enzyme [24]. The iron center is probably important for the formation of the radical, although there is no evidence for redox changes of the irons during catalysis [23]. It has only recently been demonstrated that the tyrosine is actively involved in the catalytic process; the radical is reduced with simultaneous cleavage of a substrate C–H bond [25]. The reaction model predicts transient formation of thiyl radicals; a new iron-coupled radical intermediate was indeed detected during assembly of the iron center, but the identity and significance of this species are unknown [26].

The enzyme is inhibited by hydroxyurea, which is small enough to enter the active site and reduce the radical by one-electron transfer [27]. Recently nitric oxide was found to suppress the tyrosyl radical of ribonucleotide reductase in living cells; this may be the mechanism underlying inhibition of DNA replication by NO [28].

The enzyme from *Lactobacillus leichmannii* does not form a tyrosyl radical but catalyzes the same reaction using a different cofactor, adenosyl cobalamin. However, the radical (5′-deoxyadenosyl) formed by this cofactor is not directly responsible for the initial hydrogen abstraction reaction, and apparently a protein-radical participates also in this case, perhaps in the form of a cysteinyl species [23]. In anaerobically grown *Escherichia coli* a third type of the enzyme has recently been isolated; this form apparently uses a glycyl radical analogous to the one found in pyruvate formate lyase [29].

2.5. *Cytochrome c peroxidase*

A ferric heme protein found in yeast only, it catalyzes the reduction of H_2O_2 by cytochrome *c* in a three step sequence (Table I). In the first step it gains two oxidizing equivalents, one of which is accounted for by the formation of a ferryl state: Fe(III) → Fe(IV)=O. The other is found as an amino acid radical, mainly localized on a tryptophan (Trp-191) close to the heme. The radical is aromatic, probably delocalized over the indole ring system, and cationic [30–32]; a transient porphyrin radical is likely to be involved in the formation of the tryptophyl species [31]. It is interesting that the structurally similar enzyme lignin peroxidase only forms a porphyrin radical and not an amino acid radical; this enzyme has phenylalanines instead of tryptophans next to the heme [33].

It is known that the two reductive steps in the catalytic cycle involve reaction with cytochrome *c* at a surface site far from the heme iron. Recent studies on a peroxidase-cytochrome*c* crystal complex has directly indicated a role for Trp-191 in the electron-tunneling pathway between the cytochrome heme and the peroxidase heme [34]. Thus this radical appears to be the most stable 'sink' for oxidizing equivalents along the pathway in the absence of reduced cytochrome c. However, the tryptophyl species is not the only amino acid radical in this enzyme. A minor component, accounting for approximately 10% of the total spin intensity, is seen in the ESR spectra and has been attributed to a tyrosyl radical [32]. Whereas the tryptophan radical positioned 5 Å from the heme is strongly coupled to Fe(IV) = O, the tyrosyl is not, indicating a more distant location of the latter. A tyrosyl radical might be generated at various tyrosine residues adjacent to the electron-tunneling pathway [32]. The exact interplay between tryptophan, tyrosine and porphyrin radicals is not understood at present, but they probably all participate in the electron transfer mechanism.

2.6. *Photosystem II*

The membrane enzyme complex photosystem II contains many different cofactors, including two tyrosine radicals, named Y_D^+ and Y_Z^+. They can actually be considered structurally equivalent; for obscure reasons part of the electron pathway in photosystem II exists as almost identical duplicate polypeptide structures, of which only one is active in electron transport [35,36]. Thus Y_Z^+ is reduced in microseconds by the oxygen evolving Mn_4 cluster and oxidized in nanoseconds by the reaction center P_{680}^+; in contrast Y_D^+ is a stable radical, not essential for photosystem II activity, but somehow fundamental for the correct functioning of Y_Z^+ [37]. The radicals are spectroscopically almost identical [38], but Y_Z^+ has an increased relaxation rate, probably due to the proximity to the manganese site [35,36]. The tyrosines are buried in the middle of the membrane-spanning enzyme, and the phenol proton is not readily exchangeable. Upon radical formation it is transferred to an adjacent base, stabilizing the phenoxyl radical through a hydrogen bond [35,39].

A radical generated during the operation of the manganese cluster has been indicated as a histidyl [40,41], but the exact assignment of this species is not certain.

2.7. *Prostaglandin H synthase*

A single heme supports the two reactions catalyzed by the enzyme: cyclooxygenase activity and peroxidase activity (Table I). During the catalytic cycle the ferric heme is oxidized, most likely to Fe(IV) = O, and tyrosine radicals are formed transiently [42]. Two radical species have been identified from their ESR spectra; one is formed immediately at the onset of the reaction and decays rapidly, with the simultaneous appearance of a second, more stable radical [43,44]. Both radicals are tyrosyls, but spectral simulations indicate different bond angles for the methylene hydrogens with respect

to the phenoxyl plane, suggesting different polypeptide environments [45]. The radicals may arise from two different tyrosines or from a single tyrosine undergoing a conformational change. A presumed third radical species has later been shown to arise through a spectral combination of the other two [45].

Much evidence now indicates that the tyrosyls are not involved directly in the cyclooxygenase reaction, but instead play a role in the suicide process that accompanies catalysis [42–44], although this point is still controversial [46].

2.8. *Pyruvate formate lyase*

This strictly anaerobic enzyme from *E. coli* was the first reported to utilize a glycine radical mechanism [47]. The radical is involved in homolytic C–C bond cleavage, probably in a redox reaction since the glycine hydrogen exchanges rapidly with solvent protons. The enzyme is activated to its radical-state by an activase using *S*-adenosylmethionine for hydrogen abstraction, and subsequently converted to the inactive native form by a deactivating protein [48]. The glycyl radical is extremely stable in the absence of oxygen; it is likely to be stabilized by the neighbouring carboxamide groups, but so far very little else is known about this radical type [47].

3. A HETEROGENEOUS FAMILY OR AN INFORMAL GATHERING?

Considering the structural and mechanistic differences among these enzymes, it seems obvious to ask if they have anything else in common apart from a free radical intermediate. The name quinoprotein was connected with the idea of ubiqitous PQQ but it is applicable only to TOPA and TTQ. Photosystem II would qualify as well but only because of its bound radical-forming plastoquinone, Q_A. Clearly the nature of TOPA and TTQ prosthetic groups is different from that of an extrinsic quinone cofactor. The denomination protein-radical enzyme seems more appropriate.

Several of these enzymes use tyrosyl radicals with approximately the same spin density pattern [21,38,45,49], but their reactivity differs widely, depending on the protein environment [50]. The tryptophyl radical is clearly analogous, and TTQ and TOPA are modifications of the two amino acids; subdivision of these enzyme types is not reasonable. Tyrosyl radicals have also been suggested to be implicated in the highly reactive intermediates formed by oxidation of methemoproteins with H_2O_2, but their identity and physiological importance are uncertain [51–52].

Neither the interaction with other cofactors nor the radical redox potentials provide a clue to a common mechanistic function of amino acid radicals (Table II). However, their basic role is to provide a one-electron gating mechanism, in which a single redox equivalent is processed at a time. This may be as an intermediate in long-range intramolecular electron transfer (e.g. cytochrome *c* peroxidase and photosystem II), or as a single-electron storage (e.g. galactose oxidase and pyruvate formate lyase). However, these functions might also be accomplished by external cofactors (like flavins and quinones). That three completely different radical reaction mechanisms have developed for ribonucleotide reductase may suggest that intrinsic radicals represent an evolutionary ad hoc solution; if so, the occurrence of protein-radical enzymes will be rather unforeseeable. It is consistent with this idea that the modified amino acids TOPA, TQQ and Tyr-S-Cys have not been found in other enzymes so far. The formation of TQQ and Tyr-S-Cys depends on the correct positioning of adjacent polypeptide chains, making it possible that a similar combination will not be found in any other enzyme.

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