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COMMENTARY

Some Aspects of Tyrosine Secondary Metabolism

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ABSTRACT. The origin and fate of some tyrosine secondary metabolites within specialized eukaryotic cells are discussed in the light of our knowledge of the plasma environment to which they are exposed throughout their lifetime. Attention is focused on *ar*-dihydroxy and -trihydroxy derivatives and the corresponding quinoidal counterparts, as well as on the enzymic activities involved in the formation and degradation of these potentially toxic molecules. Some physiopathological and pharmacological implications of the above-mentioned topics are considered, taking into account the well known toxicity of reactive intermediates in molecular oxygen reduction, as well as the reactivity of both semiquinonic and quinonic products of catecholamine oxidation. BIOCHEM PHARMACOL **56**;9:1089–1096, 1998. © 1998 Elsevier Science Inc.

KEY WORDS. dopa; dopamine; topa; topamine; metabolism; neurotoxicity

Several studies have been carried out on catecholamine neurotoxicity [1–8]; their quinoid derivatives [9] as well as oxygen free radicals [3, 10] have been suggested as the true toxic species. It was observed that under certain conditions the loss of dopaminergic fibers could be blocked by glutamatergic antagonists [5]. Besides uncontrolled activation of certain glutamatergic receptors [11–14] that could lead to neuronal damage, this observation confirmed the hypothesis that catecholamine derivatives could activate glutamate receptors [15]. It was also conclusively shown that 2,4,5-trihydroxyphenylalanine (topa) is easily oxidized in aqueous solution to form a hydroxyquinone derivative, topa quinone, which is a non-*N*-methyl-D-aspartate agonist and a neurotoxin [6, 16]. Also important is the fact that human tyrosinase can perform such an oxidation [17]. The ability of some catecholamine derivatives to act as excitotoxins [7] elicited further interest in the chemistry, biochemistry, and toxicology of topa and its derivatives; many biochemists have become familiar with topa quinone since it has been shown to be the catalytically active molecule covalently bound at the active site of copper amine oxidases [18]. Dopamine depletion and some effects of administered catecholamine precursors and/or derivatives are now strictly linked and are in a focal position for a biochemical interpretation of Parkinson's and other degenerative neural diseases [7].

ORIGIN, CHEMISTRY, AND BIOCHEMISTRY OF SOME TYROSINE SECONDARY METABOLITES

The chemistry of naturally occurring quinones is a very attractive topic, with respect to its biochemical and physiological implications. Among the quinoidal compounds found in higher animals, those quinones and related products arising from tyrosine metabolism are of particular importance, being involved in both melanogenesis and neurotoxicity [6, 7, 19]. An impressive number of articles and reviews dealing with the biochemistry, physiology, and toxicology of catecholamines have appeared in the past years. However, the topic is far from being explored completely, due to the high complexity of catecholamine chemistry and biochemistry; a few opposite theories exist, each supported by apparently univocal experimental results.

The main tyrosine (and, of course, phenylalanine) degradative pathway in higher animals goes through 4-hydroxyphenylpyruvic acid, whose further fate leads to oxidation and aromatic ring fission. A relatively smaller number of tyrosine molecules, however, are hydroxylated further to 3,4-dihydroxyphenylalanine (dopa).

A nomenclature observation is necessary at this point, as much confusion arises from a careless ring numeration of dopa ring-substituted derivatives. So, by following the international rules, terms such as 6-hydroxydopa and 6-hydroxydopamine, although popular and intuitive in underlining the biogenesis of the compounds, should be replaced by the more appropriate acronyms topa and topamine, respectively, taking also into account that the correct numeration is 2,4,5-trihydroxyphenyl . . . and not 3,4,6-trihydroxyphenyl. . . .

Dopa, in turn, can undergo various fates. In more detail, it can be decarboxylated to dopamine, whose main metabolism is to norepinephrine and epinephrine. Dopa and dopamine, owing to their *o*-diphenolic structure, can readily autoxidize to dopa quinone and dopamine quinone, respectively [20, 21]. Quinonization can also be accomplished with the intervention of tyrosinase [17, 22]. Both of

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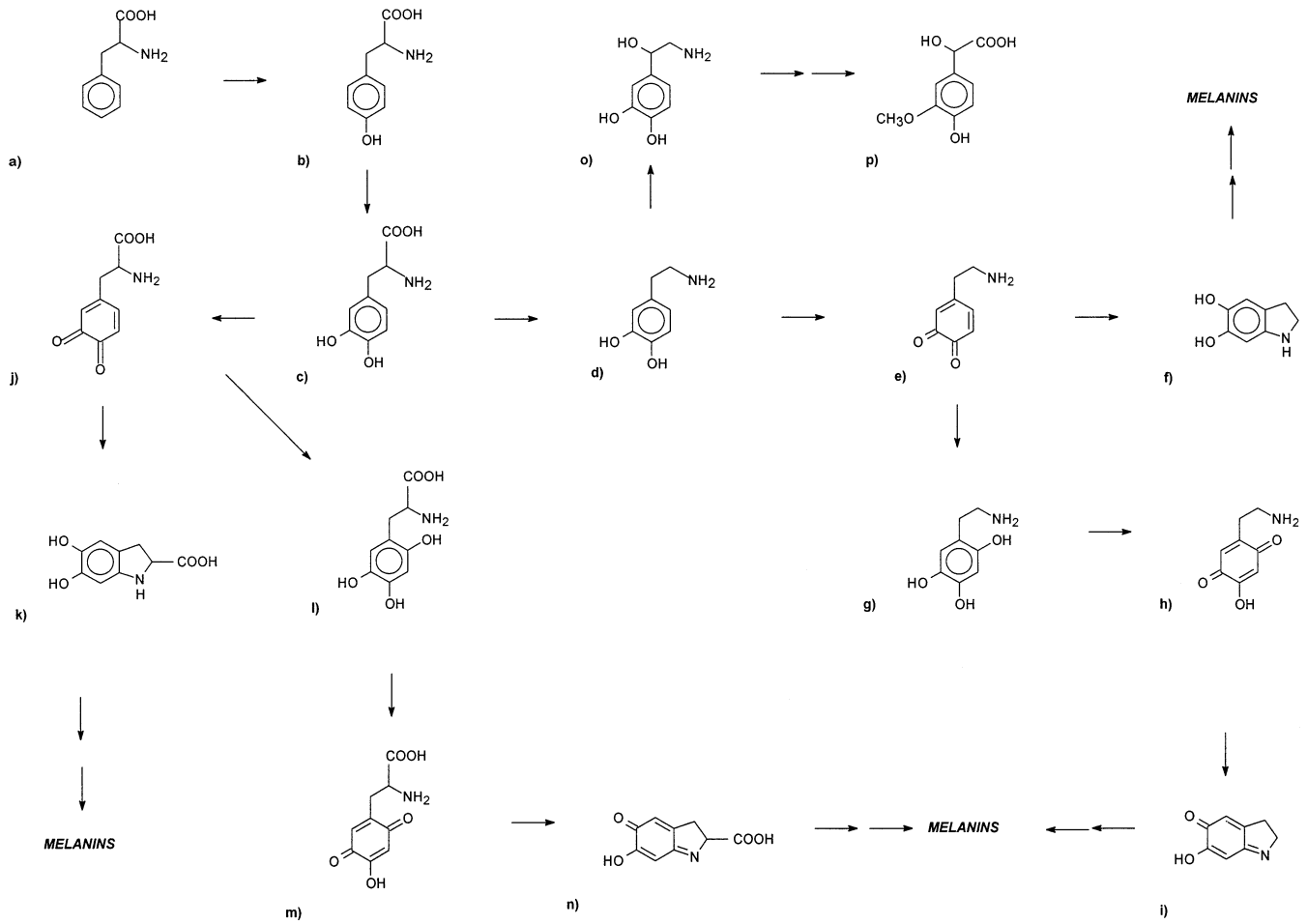

SCHEME 1. (a) Phenylalanine. (b) Tyrosine. (c) Dopa. (d) Dopamine. (e) Dopamine quinone. (f) Leukodopaminechrome. (g) Topamine. (h) Topamine quinone. (i) Dopaminechrome. (j) Dopa quinone. (k) Leukodopachrome. (l) Topa. (m) Topa quinone. (n) Dopachrome. (o) Norepinephrine. (p) Vanylmandelic acid.

these *o*-quinones are very reactive compounds, prone to attack by a wide range of nucleophiles [23]. In particular, they can readily cyclize, leading to melanins [9]. Other nucleophiles, different from the amino group present in the quinone molecules, can covalently attack the quinoid structure, leading to ring-substituted catechols [23]. In particular, it was shown recently by working on model quinones that the hydroxide ion can perform such an attack [24], which could be regarded as a hydration of the quinone ring leading to a 2,4,5-trihydroxyphenyl derivative. As hydroxyquinol derivatives, topa and topamine are extremely prone to both autoxidation and enzyme-catalyzed oxidation, leading to the corresponding hydroxyquinones, whose more stable tautomers show a *p*-quinoid structure. The latter are not very stable and easily undergo a further nucleophilic attack, as well as cyclization and melanin formation. The interrelations between these compounds and their precursors, phenylalanine and tyrosine, are shown in Scheme 1.

Despite the huge number of studies devoted to melanogenesis [25], some aspects of melanin biosynthesis still remain unclear. The most accepted pathway involves the above-mentioned dopa quinone cyclization to leukodopachrome, a putative intermediate [19], and the further, very rapid oxidation of the latter to the *o*-quinoid 2,3-dihydroindole derivative dopachrome. It was found that cyclization of dopa quinone and dopamine quinone prevails at pH 6 or higher, whereas at lower pH they undergo hydroxylation [20, 26–33]. However, by working on non-cyclizable catechols, it was found that hydroxylation (hydration) also is favored by higher pH values [34].

The possible role of topa and topa quinone in melanogenesis was investigated by different research groups, and contradictory results have been reported [19, 35, 36]. This is due mainly to the competitive nature of the two reactions, i.e. cyclization involving the amino group, and hydration as a result of the hydroxide attack on the quinone ring. Both reactions are pH dependent in the same way, and slight differences in experimental conditions could lead to quite different results. Moreover, not only dopa quinone, but also topa quinone could, in turn, cyclize intramolecularly, by means of their amino group, leading to a very reactive *o*-quinoid indolic derivative. The possibility that topa and topa quinone in physiological solutions may

simply arise also non-enzymically from dopa is now well ascertained [20].

A further, important consideration concerns a possible third competitive group of reactions, i.e. the attack from nucleophiles *other* than the hydroxide ion or the amino group on the side chain of the same quinone molecule. Such reactions are well known in the case of *o*- and *p*-benzoquinones [23], whereas their occurrence in the case of hydroxybenzoquinones is less certain as the hydroxy substituent weakens the electrophilic character of the quinone ring. This is true especially around physiological pH values, hydroxyquinones being definitely acidic compounds (as carboxylic acid vinyl analogs) and, therefore, existing mainly as the corresponding anionic forms near neutrality [34]. However, the presence of a hydroxy substituent does not suppress the electrophilic character of the *p*-quinonic ring, and so covalent interactions with proteins and/or other cellular nucleophiles are most probable [9, 37, 38]. Recently, the determination of catechol–protein conjugates in rat brain neostriatum slices after incubation in the presence of [^{3}H]dopamine [39] has given definite support to the hypothesis. It was found that cysteinyl residues are the main agent responsible for the covalent conjugation; the extent of the reaction is at least partially determined by the redox potential of the environment. Both dopamine and its catabolic derivative, 3,4-dihydroxyphenylacetic acid, have been found to be covalently linked to cysteinyl residues of proteins, thus showing that this mode of reaction is not restricted to dopamine quinone (or dopa quinone) but is shared with other 4-substituted *o*-benzoquinones.

AUTOXIDATION OF TYROSINE-DERIVED 1,2-DIPHENOLS AND 1,2,4-TRIPHENOLS

Two main reactions with molecular oxygen (autoxidation) can be written for these compounds, regardless of their intimate mechanism:

$$QH_2 + O_2 \rightarrow Q + H_2O_2 \quad (1)$$

$$QH_2 + H_2O_2 \rightarrow Q + 2H_2O \quad (2)$$

where QH_2 represents a catechol (or a 1,2,4-triphenol) and Q the corresponding quinone.

Reaction (2) may be considered as a competitive oxidation reaction of QH_2, therefore H_2O_2 consuming. The problem of the relative importance of reactions (1) and (2) when QH_2 is topamine was studied by Liang *et al.* [40] by polarographic methods; they concluded that reaction (2) is very important *in vivo*, as the intracellular oxygen concentration is as low as approximately 0.03 mM. Moreover, the H_2O_2 concentration was always far less than expected from reaction (1), indicating an efficient consumption of hydrogen peroxide by topamine. Addition of ascorbic acid, taking into account an estimated concentration of 2–3 mM in mammalian brain, enhanced O_2 consumption, but not H_2O_2 production. Ascorbic acid is an effective reductant for many quinones and also for topamine quinone; therefore, it can recycle Q into QH_2, which is oxidized again by both molecular oxygen and hydrogen peroxide. The consumption of oxygen by means of reaction (1) obviously favors reaction (2). Ascorbic acid can act as a prooxidant (as it reduces and recycles quinones) or as an antioxidant (as it scavenges both superoxide and peroxide) [21].

The whole oxidative process is actually much more complex [41–43] than shown in reactions (1) and (2), being strongly affected by a number of factors such as pH and the presence of transition metal ions, capable of redox cycling. It is common knowledge that phenolics become more easily oxidizable at higher pH values, where they exist as the corresponding electron-rich anions.

The possible formation of redox intermediates in both oxygen reduction (i.e. superoxide $HO_2^{\cdot}$ or $O_2^{-\cdot}$ depending on pH) or catechol oxidation (i.e. the semiquinone $QH^{\cdot}$ or $Q^{-\cdot}$ depending on pH) is of the highest importance [26]. Unfortunately, since it is difficult to reproduce the actual living cell situation exactly, even most carefully planned and carried out *in vitro* experiments could lead to inconsistent results. Not only superoxide, but also $^{\cdot}OH$ hydroxyl radicals must be considered as intermediates of oxygen reduction, especially in the presence of the above-mentioned metal ions. Production of hydroxyl radical during polyhydric phenol oxidation could be responsible, in part, for triphenol and/or hydroxyquinone formation, when catechols or quinols are oxidized by molecular oxygen. It was also found that $^{\cdot}OH$ radicals, generated by the Fenton reaction, rapidly attack and oxidize dopa, dopamine, topa, and topamine [32, 33].

The role of transition metal ions is crucial for the autoxidation mechanism and rate; in some cases different metal chelators can abolish their catalytic activity and in others enhance it [26, 34, 44]. Also, compulsory hydroxyl radical production by Fenton-like reactions in the presence of low-valence transition metal ions and hydrogen peroxide has often been shown to be a mistaken assumption [45, 46].

Superoxide can be an intermediate in topamine autoxidation, according to the following reactions, in which a fully protonated state of the reactants is assumed for clarity:

$$QH_2 + O_2 \rightarrow QH^{\cdot} + HO_2^{\cdot} \quad (3)$$

$$QH^{\cdot} + O_2 \rightarrow Q + HO_2^{\cdot} \quad (4)$$

$$QH_2 + HO_2^{\cdot} \rightarrow QH^{\cdot} + H_2O_2 \quad (5)$$

$$QH^{\cdot} + HO_2^{\cdot} \rightarrow Q + H_2O_2 \quad (6)$$

As an intermediate, superoxide is produced in reactions (3) and (4), and consumed in reactions (5) and (6) [47, 48]. Therefore, any increase in QH_2 concentration (caused, for example, by an enzymatic or non-enzymatic reduction of Q) should be void of any substantial effect on superoxide concentration, as already seen for hydrogen peroxide. In

fact, QH_2 figures in both reactions (3) and (5), the former producing and the latter consuming superoxide. Moreover, reaction (3) is only of secondary importance in topamine autoxidation because of electron spin restrictions [27]. Topamine is also a substrate whose autoxidation is strongly inhibited by superoxide dismutase [48]. This inhibition is proof that superoxide is not only generated, but also compulsorily *consumed* during topamine autoxidation. This must also be true in the case where the participation of transition metal ions in the autoxidation process enhances superoxide production. Topamine and, presumably, related polyphenolics could be regarded as *superoxide scavengers*. Recently, Padiglia *et al.* [49] claimed a paradoxical effect of reductants, which would increase the cytotoxicity of topamine, by increasing superoxide, peroxide, and hydroxyl production as a result of redox cycling. In the light of the above considerations, this hypothesis is quite inconsistent.

The autoxidation of 1,2,4-benzenetriol, a benzene toxic metabolite in liver, as a simple model for mechanistic studies on the general autoxidation mechanism(s) of polyhydric phenolics was examined carefully by Zhang *et al.* [50], who found that: (1) Fe^{3+} has a low, and Cu^{2+} a very high, enhancing effect on benzenetriol autoxidation; (2) in the absence of added metals or in the presence of Fe^{3+}, superoxide dismutase has a negative effect, whereas in the presence of Cu^{2+}, the enzyme is indifferent. It was concluded that: (1) under certain conditions, superoxide is an intermediate in the autoxidation radical chain; (2) the catalytic action of ferric and cupric ions must be different, and no superoxide intermediacy is required for autoxidation in the presence of Cu^{2+}. In conclusion, in the presence of ferric ions, or in the absence of added metal ions, superoxide is produced, but also consumed, during the autoxidation process.

ENZYME-ASSISTED OXIDATION OF TYROSINE-DERIVED 1,2-DIPHENOLS AND 1,2,4-TRIPHENOLS

Various enzymes could actually or potentially be involved in the complex pathway leading from dopa to dopamine, topa, topamine and their quinoidal counterparts. Among these, tyrosinase (EC 1.14.18.1) is the obvious candidate as regards quinonization steps, although it is also worth noting that neither superoxide nor peroxide is produced by oxygen reduction when the enzyme oxidizes catechols. Therefore, in the presence of tyrosinase, oxidation of dopa, dopamine, topa, and topamine by molecular oxygen should proceed quickly to the corresponding quinones and water without any intermediacy of reactive oxygen species. However, recent EPR studies confirmed the transient existence of *o*-semiquinone intermediates, when tyrosinase oxidized catechols such as dopa and dopamine [51]. These *o*-semiquinone derivatives arise from a comproportion reaction between *o*-quinone and the yet unoxidized catechol. These semiquinones could interact with molecular oxygen, giving rise to superoxide according to reaction (4). The presence of tyrosinase in the brain has been the object of much controversy [52–54]; its presence has been shown unequivocally in the substantia nigra of the human brain [55]. Ceruloplasmin, a blue copper protein, whose biological function(s) has not been fully elucidated, has been shown to have a very low oxidase activity towards several polyphenolic substrates [56]. More recently, Medda *et al.* [57] claimed a catalytic action of the protein on topamine oxidation. Unfortunately, this "activity," which is very feeble around pH 4, is not detectable at physiological pH values, so that a role for ceruloplasmin in dopa metabolism is to be ruled out completely.

Different is the case of peroxidase (EC 1.11.1.7), a hemoprotein that resembles catalase (EC 1.11.1.6) in many features and uses hydrogen peroxide to carry out the quinonization of several polyphenols. Peroxidase from horseradish can facilitate the spontaneous oxidation of topamine (and presumably of dopamine, dopa, and topa) [58] to the corresponding quinone(s). However, the data obtained are not sufficient to conclude in favor of quinonization of the substrate(s) by a neuronal peroxidase. No data are available on how many hydrogen peroxide molecules—if any—escape from catalase action within the living brain tissue. So, the effective role of peroxidase in modulating the oxidation of dopa, dopamine, topa, and topamine to the corresponding quinones remains at least debatable.

Another peroxidase, glutathione peroxidase (EC 1.11.1.9), which consumes hydrogen peroxide at the expense of reduced glutathione, on the contrary could be deeply involved in hydrogen peroxide scavenging. A small but significant reduction of enzyme levels has been found [59] in the substantia nigra of Parkinson's disease patients. This could suggest that a defect in the systems devoted to hydrogen peroxide elimination could at least be a contributing cause of the degenerative lesions in Parkinson's disease. However, a marked decrease in reduced glutathione levels has also been described in Parkinson's disease [60], so the dilemma between a defective peroxide and a quinone scavenging system [61] remains unresolved.

On the oxygen side, at least two enzymes could play an important role: superoxide dismutase (EC 1.15.1.1) and catalase. According to its name, superoxide dismutase catalyzes superoxide dismutation into molecular oxygen and hydrogen peroxide; catalase catalyzes hydrogen peroxide dismutation to molecular oxygen and water. Therefore, the combined action of the two enzymes, which are almost ubiquitous in higher animal tissues [48, 62], prevents the accumulation of reactive intermediates of oxygen reduction, water becoming its sole product. Moreover, a significant decrease in the autoxidation rate of catecholamines and related compounds is seen in the presence of the enzymes. It is worth noting that tyrosinase action is completely independent of the presence or absence of superoxide dismutase and/or catalase.

QUINONE DETOXIFICATION MECHANISMS

Whatever the oxidation mechanism for catecholamines and related compounds, the corresponding quinones are the end products of the process. "End products" is perhaps a restrictive term, as quinones are quite reactive species [23]; however, they are stable enough to be characterized (differently from semiquinones). In principle, various mechanisms could operate to detoxify these reactive molecules. They include: (1) the reversal of their formation, in other words their reduction to the corresponding diphenols; (2) covalent modifications through a nucleophilic attack on the quinone ring leading to substituted diphenols; (3) under certain conditions some quinones, and in particular *o*-quinones, can act as effective superoxide scavengers, being deeply oxidized and rearranged to furanones [63]. This reaction between *o*-quinones and superoxide is particularly important in that both toxic reactants are destroyed at the same time.

With reference to quinone reduction, the corresponding diphenols could also undergo a glucuronic conjugation, a sulfuric esterification, and so on. In all these cases, sharply hydrophilic compounds arise, relatively resistant against both enzymic oxidation and autoxidation, and very prone to leave the cell quickly. Quinone reduction to the diphenolic counterpart is, therefore, a device to protect the living cell against the toxic potential of quinones. A number of reducing agents are capable of performing such a reduction *in vitro* [23], but only a few are presumably involved in the same reaction *in vivo*. Among these, ascorbic acid has been found to be very effective [23]; this versatile biological reductant is also able to scavenge both superoxide and peroxide [21]. Also, reduced glutathione is an effective reducing agent for quinones [23]; however, its mode of action could also be a nucleophilic attack on the quinone ring, leading to a glutathione-diphenol adduct [23], as was found for other thiol-containing molecules. That this mode of thiol action can actually take place in living systems was shown by Hastings and Zigmond [39], who found cysteinyl residues of the acid-insoluble fraction of rat brain neostriatal proteins in covalent linkages with catecholamine-derived moieties after incubation with dopamine. As expected, the extent of the covalent coupling was attenuated by both ascorbic acid and glutathione acting as reducing agents towards the quinones and/or, in the case of glutathione, also forming glutathione–quinone covalent adducts [61]. The efficiency of reduced glutathione-based neuron protection could be impaired substantially as a consequence of oxidative stresses [64]. It was found very recently that tyrosine hydroxylase, the tetrahydrobiopterin-dependent enzyme of human substantia nigra, also has a noticeable dopa oxidase activity [65]. In the presence of an excess of cysteine or reduced glutathione, the reaction product was identified tentatively as a thioether dopa derivative.

Both NADH and NADPH can reduce several quinones non-enzymically [23]. However, various enzymes exist that can utilize reduced pyridine nucleotides to reduce quinones. The generic name "diaphorase" was attributed to the enzymes when an NAD(P)H-dependent reductase activity was found in the nervous system with histochemical methods [66]. Subsequently, it was shown that various distinct diaphorases exist; among them, NADPH-diaphorase (EC 1.6.99.1) [67, 68] and DT diaphorase (EC 1.6.99.2) [69] are certainly involved in brain tissue metabolism [70]. Both of these diaphorases are FAD-containing flavoproteins; NADPH-diaphorase utilizes NADPH only as the reducing substrate, whereas DT diaphorase uses both NADH and NADPH (formerly DPNH and TPNH) at equal rates. The two enzymes usually coexist in the same organism, but they are distributed differently among the various tissues [71], and most probably have different physiological functions. In particular, arginine seems to be the true physiological substrate of NADPH-diaphorase, whose identity with nitric oxide synthase has been proven [72]. Therefore, a significant involvement of the enzyme in reducing brain quinones is uncertain.

Among flavoenzymes, DT diaphorase (better named NAD(P)H:quinone oxidoreductase) has the almost unique feature of compulsorily catalyzing a two-electron redox reaction between NAD(P)H and the quinonic substrate, thus preventing semiquinone formation [73]. Its expression, amino acid composition, substrate specificity, activation, and inhibition have been investigated extensively [68–71]. However, a shared point of view on the physiological function(s) of DT-diaphorase does not exist, since there are well known examples of a quinone being rendered more toxic following enzymic reduction, whereas other quinones are efficiently detoxified by the same reductive reaction [68, 73, 74]. Other studies have demonstrated an active role of DT diaphorase in preventing glutamate toxicity produced by oxidative stress, suggesting that not only reduced glutathione, but also DT diaphorase is very important in protecting neurons against catecholamine-mediated damage [75]. In particular, it has been shown that in the N18-RE-105 neuronal cell line, glutamate toxicity, including the depletion of reduced glutathione and the accumulation of oxidants, is effectively countered by DT diaphorase activity. The protection is abolished by the specific DT diaphorase inhibitor dicoumarol, and is not affected by variations in reduced glutathione concentrations, thus confirming a prominent and direct action of DT diaphorase against catechol autoxidation and related "oxidative stress" [76]. Immunohistochemistry demonstrated that in some neurons a colocalization of diaphorase and tyrosine hydroxylase-like activity exists [71]. This could support the hypothesis that DT-diaphorase plays an important role in reducing the quinones arising from tyrosine oxidative catabolism. Another study showed the effectiveness of DT diaphorase in preventing topamine oxidation to the corresponding quinone [77].

As noted above, quinones undergo a one-step, two-electron reduction to diphenols in the presence of DT-diaphorase; however, this does not prevent semiquinone formation when the diphenol is (auto)oxidized again by

molecular oxygen and/or other reactive oxygen species [42]. This redox cycling, which could seem a gratuitous waste of NAD(P)H, is effectively broken by non-oxidative reactions that consume diphenols, such as glucuronic conjugations and/or the formation of covalent adducts with reduced glutathione. DT diaphorase keeps the polyphenol/quinone ratio very high, thus favoring reactions taking place at the expense of the reduced forms. This is particularly true in the case of the enzyme catechol-*O*-methyltransferase (EC 2.1.1.6), a key molecule in catecholamine detoxification and melanogenesis modulation [78]. The guaiacol-like compounds arising from the enzyme action are comparatively inert towards autoxidation and quinonization; moreover, they are not substrates for tyrosinase and could be expelled unchanged from the organism.

CONCLUSIONS

Catecholamines and related compounds show many pharmacological actions within the CNS, and their biotransformations in such an environment are well worth studying in detail. Neurotoxic properties, weak for dopa and dopamine but strong for topa and topamine (and, of course, for related quinones), have been well ascertained, but their mode of action remains largely unexplained. Despite some articles that deal with autoxidation and the consequent superoxide, peroxide, and hydroxyl production, the role of these reactive intermediates in oxygen reduction has been largely overestimated, since due account has not been taken of the fact that superoxide, peroxide, and hydroxyl are intermediates rather than products of the catecholamine autoxidation process. Therefore, the proposed significant accumulation of these reactive intermediates of molecular oxygen reduction should not take place, if one considers the existence of efficient devices for the elimination of both superoxide and peroxide, i.e. superoxide dismutase and catalase.

Other studies focus on the formation of reactive quinone and semiquinone, and their further reaction with cellular components such as cysteine-containing proteins and enzymes. It has also been found that at least under certain conditions it is topaquinone rather than topa that is a neurotoxin.

In the healthy cell, detoxifying mechanisms are most probably capable of scavenging both reactive oxygen species and quinones, while there are pathological conditions, where such mechanisms partly fail, and neurons could be more or less deeply damaged. Of particular importance seems the depletion of reduced glutathione, that has been observed in some cases, since the reduced glutathione is involved in both hydrogen peroxide and quinone scavenging. No conclusive data exist as regards superoxide dismutase, catalase, and glutathione peroxidase variations between the healthy and the Parkinsonian brain. A special role in neuron protection against excitotoxic quinones is certainly due to DT diaphorase, considering the sharp quinone reduction that is obtained without the intermediacy of semiquinonic species, thus maintaining quinone concentrations at a very low level. In conclusion, even if some evidence exists in favor of a defect in the reductive mechanisms of quinones in Parkinson's and other degenerative nervous diseases, the question of the neurotoxicity of catecholamines and related substances is still open.

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