Elaborare documentaţie pentru fizicieni medicali

Radiosensibilizatori

În acest document raportăm o serie de articole ştiinţifice noi, publicate în literatura de specialitate, referitoare la radicalii liberi generaţi prin folosirea radiaţiilor în tehnicile de radioterapie, la substanţe protectoare împotriva radicalilor liberi, mecanismul molecular de acţiune a radicalilor liberi. Aceste articole vor fi puse la dispoziţia studenţilor pe canalele de comunicare on-line (platform Teams, site-ul proiectului).

Documentul este organizat în felul următor:

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Lista articolelor propuse

Articol 1

Clifford W.Fong

Platinum based radio chemotherapies: Free radica lmechanisms and Radiotherapy sensitizers

FreeRadicalBiologyandMedicine99(2016)99–109

http://dx.doi.org/10.1016/j.freeradbiomed.2016.07.006

Abstract

The radiosensitizingability of Pt drugs can in the first instance be predicted based on the

ease that they undergo activation by electron attachment accompanied by structural modification prior to forming Pt- DNAadducts.Unlike cisplatin,carboplatin and nedaplatin,oxaliplatin does not undergo a facile dis- sociative electron transferre action when an electron is attached.However,oxaliplatin undergoes a facile nucleophilic assisted proton coupled electron transfer (NAPCET),which may be key element of the success of FOLFOX radiochemotherapy against certain cancers.Under acidic conditions,oxaliplatin is a superior radiosensitizer to cisplatin or carboplatin,in the presence of nucleophiles such as water, chloride ionsorthiols.Oxaliplatin may also be activated as a platinating agent and radiosensitizer by a minor hydrogen radical free radical mechanism as well as the more dominant NAPCET mechanism.The radiosensitizing synergism that is shown when oxaliplatin is combined with 5-fluorouracil can be due to the formation of a π complex between the two drugs ,which is more potent under acidic conditions. These factors have a bearing on Pt based chemotherapy clinical regimes as well as clinical radio-chemotherapy regimes,and could be a basis for optimizing how such drugs chedules are administered.

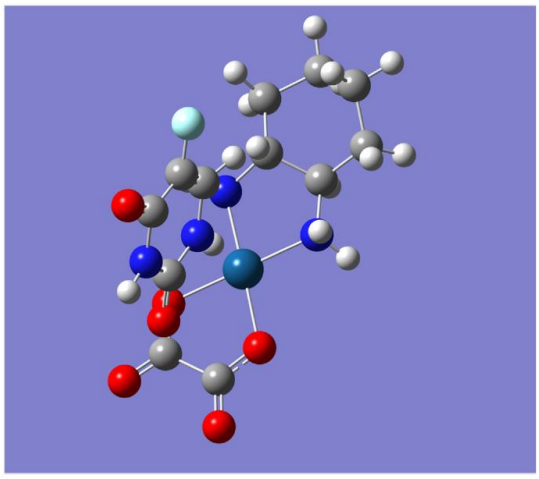


Fig. 4. {5Fluorouracil-Oxaliplatin} π complex showing plane of 5FU at right angle to plane of Oxaliplatin.

Concluzii

Conclusions: It has been shown that oxaliplatin undergoes a basically different activation mechanism to cisplatin,carboplatinandneda- platin when subject to free radical attack prior to platinating re-actions with DNA and other targets during anti-

cancer treatments. These activation mechanisms,in water within the DNA environment where a nucleo base such as guanine(G) is nearby,are:

(NH3)2PtCl2þe_-{(NH3)2Pt(——Cl)Cl}·_ (with elongatedPt——Cl bond) cisplatin (1)

{(NH3)2Pt(—Cl)Cl}·_þG - {(NH3)2Pt(G)Cl}þCl_ etc where G is guanine base (2)

(NH3)2Pt(CBC)þe_ - (NH3)2Pt(——O-CBC)·_ (with elongated Pt——O bond in bidentate PtCBCmoiety whereCBC is1,1-cyclo- butan edicarboxylato ligand of carboplatin) (3)

(NH3)2Pt(——O-CBC)·_þG-(NH3)2Pt(G)(-O*CBC) where G is gua- nine and(-O*CBC)is the monodentate CBCligand (4)

(DACH) Pt (Oxalato) or (DACH) P t(Oxalato(Hþ))þe_-no reaction with oxaliplatin where Oxalato is the bidentate oxalate ligand or Oxalto(Hþ) is the protonated bidentated oxalate ligand witha Pt- O(Hþ) bond,and DACH is the bidentate1,2-diaminocyclohexane ligand (5) (DACH)Pt(Oxalato) þHþ-(DACH)Pt(Oxalato(Hþ)) with a Pt-O (Hþ) bond

(6) (DACH)Pt(Oxalato(Hþ))þXþe_-{DACH)(X)Pt(——Oxalato (Hþ)}·_ where X is a nucleophilic ligand such as H2O, Cl_, RSH, guanine) and (——Oxalato(Hþ) is the protonated bidentate oxalate ligand with an elongated Pt——O(Hþ) bond

(7)

{DACH) (X) Pt(——Oxalato(Hþ)}·_þG - {DACH)Pt(G)(-O*Oxalato (Hþ)}þX or {DACH)(X)Pt(G)} where (-O*Oxalato(Hþ)) is the monodentate protonated oxalate ligand

(8) (DACH)Pt(Oxalato)þH·þH2O-(DACH)Pt(——Oxalato(H)·) withan elongated Pt——O(H) bond where H· is the hydrogen radical (9)

(DACH)Pt(——Oxalato(H)·)þG-{DACH)Pt(G)(-O*Oxalato(H)} where (-O*Oxalato(H))is the monodentate oxalate ligand

(10)

Eqs. (1)–(4) represent the attachment of a hydrated electron to cisplatin and carboplatin (nedaplatin shows the same behaviour as carboplatin) to form a radical anion via a dissociative electron transfer (DET) reaction characterized by an elongatedPt–Cl orPt–O bond in the radical anion and transition state. Conversely oxaliplatin does not undergo a DET mechanism (Eq. (5)) anywhere near the ease of cisplatin,carboplatin or nedaplatin. Oxaliplatin first requires the protonation of one of the Pt–O bonds, Pt–O(Hþ), (Eq. (6)) followed by a nucleophilic assisted electron attachment to labilize the Pt–O(Hþ) bond in

the radical species, forming an elongated Pt——O(Hþ) bond,as shown in Eq. (7). Eq. (8) shows this radical species reacting with a Gnucleo base to form a Pt-Glinkage, possible either by the formation of a protonated monodentate oxalate ligand attached to Pt,or the loss of this li- gand by forming a Pt-X linkage. X can be 5-fluorocil (5FU)and the source of protons can be folinic acidinEqs. (6) and (7). These agents constitute the FOLFOX regime. Eqs. (6)–(8) have been labelled as a nucleophilic assisted proton coupled electron transfer (NAPCET) mechanism. Eq. (9) is a hydrogen radical reaction (SH2) with oxaliplatin,and Eq. (10) is the reaction of the radical oxaliplatin species with a nucleobase such as guanineG. As these platinating agents are known to act as radiosensitizers when used in radiochemotherapy, these mechanisms are likely to be the basis of their radiosensitizingability.These electron attachment and consequent induced changes to their molecular structure processes are extremely facile compared to alternative non-radical (eghydrolysisnucleophilic) mechanism spreviously used to explain how these platinating agents are activated to formthe DNA adducts required for primary anti-cancer efficacy.

Elucidation of the mechanism of radiosensitizers have a bearing on the clinical conditions underwhich Pt based chemotherapy is coupled with radiationtherapy,particularly when

adjuvant and neoadjuvant regimes are coupled with combined chemotherapy combinations, such as FOLFOX and related regimes.

Synergistic interactions with the platinating agent and other adjuvant drugs such as 5FU could be tailored and optimized. Maintenance of a slightly acidic environment is needed to optimize efficacy in FOLFOX chemotherapy and radiochemotherapy. By contrast cisplatin plus 5FU radiochemotherapy regimes should not require acidic conditions to obtain some radiosensitizing synergism which might be a useful differentiator compared to OLFOX regimes for treating certain types of cancers.

Articol 2

1. Christian Bailly

Potential use of edaravone to reduce specific side effects of chemo-, radio and

immuno-therapy of cancers
International Immunopharmacology 77 (2019) 105967
https://doi.org/10.1016/j.intimp.2019.105967

Abstract

The drug edaravone (EDA) is prescribed for the treatment of patients with amyotrophic lateral sclerosis or after an acute cerebral infarction. This synthetic pyrazolone derivative is a potent scavenger of oxygen free radicals and also functions as a modulator of transcription factors, repressing NFκB and activating Nrf2, to regulate oxidative stress. EDA displays complementary anti-oxidative and anti-inflammatory effects. The injectable small molecule is currently investigated for the treatment of several non-neurological diseases. The potential interest of EDA in oncology is reviewed here. EDA is a mild antiproliferative agent but has been found to enhance significantly the anticancer and antimetastatic activities of irinotecan in a colon cancer model. Anticancer derivatives of EDA have been designed but they generally display a limited antiproliferative activity. The antioxidant and anti-inflammatory activity of EDA can be best exploited to protect non-tumor cells from damages induced by chemotherapeutic drugs and radiations. Notably EDA can reduce the renal dysfunction induced by cisplatin, the neurotoxicity of cyclophosphamide and the cardiotoxicity of doxorubicin. Upon treatment with EDA, a significant improvement in neurologic symptoms has been observed in patients with nasopharyngeal carcinoma after radiotherapy. The drug could be used to limit radiation-induced brain injury or oral mucositis.

EDA was found to ameliorate autoimmune thyroiditis (Hashimoto thyroiditis), which is a frequent side effect observed after treatment of cancer patients with monoclonal antibodies targeting the immune checkpoint PD-1.

Therefore, EDA could also be useful to reduce specific side effects of immuno-therapy. Collectively, the information suggests that the medical use of EDA, a drug with a proven safety after 18 years of use in brain-related Human diseases, could be extended to cancer-re Keywords: Edaravone, Cancer, Chemotherapy, Radiotherapy, Immunotherapy, Inflammation, ALS, Oxygen radicalslated conditions.

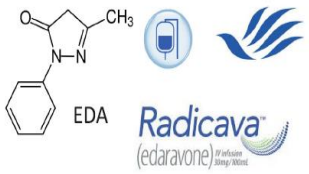
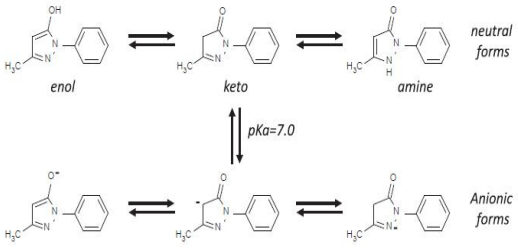


Fig. 1. Structure of Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, formerly MC-186). The drug is sold under different brand names including Radicut® and Radicava® (Mitsubishi Tanabe Pharma Corporation, Japan), Nuravon™ (Abbott), Univone and Arone and others. The keto-enol tautomerism and resonance of EDA as well as the equilibrium between the neutral and anionic forms of EDA are represented.
Adapted from [4].



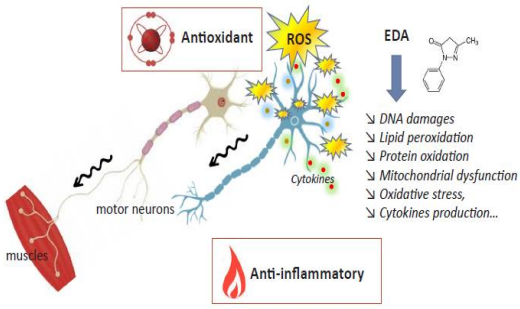


Fig. 2. Illustration of the mechanism of action of EDA which provides a cerebral neuroprotection by reducing oxidative stress and inflammation. The scavenging of reactive oxygen species (ROS) by EDA reduces the extent of DNA damages, oxidation of lipids and proteins, thus diminishing the cellular oxidative stress. The drug induces a reduction of the production of cytokines (such as IL-6, IL-10, IL-18, TNF-α, IL-1β) leading to the anti-inflammatory response. These effects limit the neuronal dysfunctions.

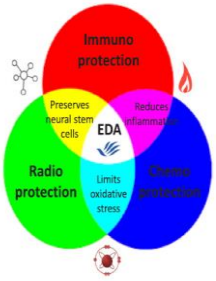


Fig. 5. EDA and cancer therapy. The drug can protect non-tumor cells from the oxidative damages and inflammation induced by chemo and radiotherapy of cancer. It could also help to alleviate the unwanted effects of immuno-therapy, such as autoimmune thyroiditis induced by anti-PD-1 antibodies, via its anti-inflammatory action.

Concluzii

EDA was developed first for the treatment of acute brain infarction and, a few years later, for the treatment of ALS. Today, the drug is currently investigated in a number of neurologic and non-neurologic pathologies. As discussed here, EDA may be useful to

improve specific cancer treatments. There are common genetic and metabolic characteristics between ALS and cancer (oxidative unbalance, inflammation processes). Epidemiological studies have suggested that ALS relates to cancer.

Another major advantage of EDA is its capacity to cross the blood–brain barrier, to diffuse into the central nervous system and to act on the cerebral vasculature and neuronal networks, offering a potent neuroprotection. Therefore, the drug is well adapted to combat the neurotoxicity of cisplatin and cyclophosphamide, as described above but possibly also the neurotoxic effects of other established anticancer drugs like the taxanes (e.g. paclitaxel) and vinca-alkaloids (e.g. vincristine). EDA is a remarkable anti-oxidative and anti-inflammatory drug. It functions as a NFκB inhibitor and Nrf2 activator, like for examples the cytoprotective and anticancer phytochemicals resveratrol, curcumin, epigallocathechin-3-gallate and sulforaphane. The polyphenol honokiol, the main active ingredient from the bark of Magnolia officinalis, also exhibits anticancer and neuroprotective activities. It functions as a potent ROS scavenger and promotes nuclear translocation and activation of Nrf2 and displays potent neuroprotection against oxidative stress-mediated cell damage. Its

mode of action resembles that of EDA.The potential interest of EDA to mitigate autoimmune thyroiditis is very interesting in the context of cancer therapy with immune checkpoint

inhibitors. Therapeutic antibodies targeting the PD-1/PD-L1 pathway have revolutionized the treatment of specific cancers, notably non-small cell lung cancer and melanoma, but they also induce lifethreatening toxicities. Autoimmune thyroiditis induced by antibodies that block the interaction between PD-1 and PD-L1 is frequently observed in cancer patients. It can lead sometimes to irreversible thyroid dysfunctions. Interleukin (IL)-17 (a hallmark cytokine of Thelper 17 cells) plays a significant role in the pathogenesis of autoimmune thyroid diseases, in particular Hashimoto's thyroiditis and EDA has the capacity to inhibit expression of IL-17 implicated in the destruction of thyrocytes [48]. The use of EDA in the therapy of autoimmune

thyroiditis induced by anti-PD-1/PD-L1 antibodies could be important. It is interesting to note that the anti-inflammatory and antimalarial natural product dihydroartemisinin

(DHA) has also been found to attenuates autoimmune thyroiditis. For both EDA and DHA, the STAT3/PI3K/Akt pathway was found to be implicated in the process. The use of EDA to prevent from or to alleviate cancer immunotherapyinduced autoimmune thyroiditis no doubt merits further studies. The therapeutic impact can be very significant. Collectively, the information reviewed here clearly suggest that EDA can play a role to support cancer treatments. One of the limitations of EDA is its very low aqueous solubility (and solubilization in vehicle and intestinal fluids) which is the primary determining factor for its intestinal

absorption. This limitation imposes a parenteral administration of the drug, whereas oral administration would be preferable for the use in chronic diseases and cancer. Novel oral and sublingual tablet formulations of EDA are investigated currently to improve its oral bioavailability. The results look promising. Formulations to facilitate the brain delivery are also investigated.They could be useful for the treatment of brain tumors or metastases. A future for EDA in cancer can be envisaged.

Articol 3

2. Patrick Trouillas, Jacqueline Bergere, Chantal Houee-LeVin

Toward Understanding the Protein Oxidation Processes: OH Addition on Tyrosine, Phenylalanine, or Methionine ?

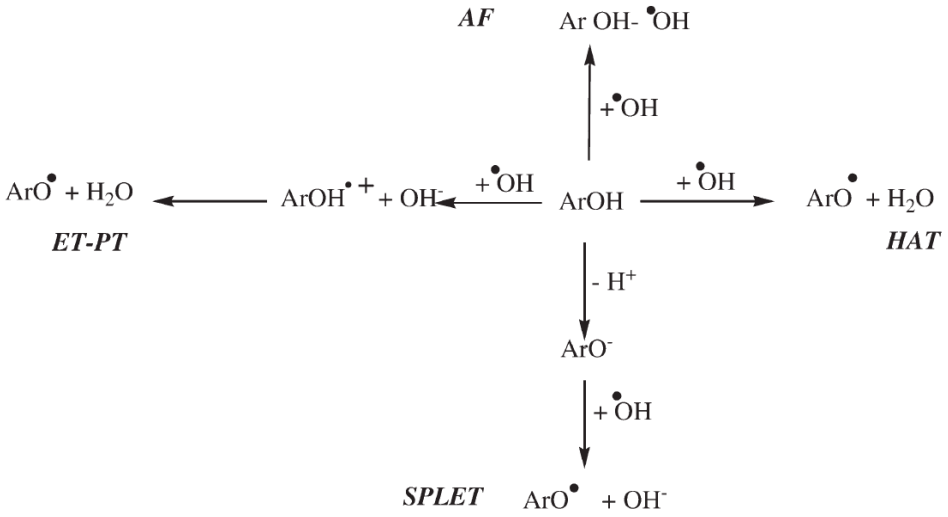
International Journal of Quantum Chemistry, Vol 111, 1143–1151 (2011)

Doi: 10.1002/qua.22556

Abstract

Abstract: Oxidation of peptides and proteins by OH radicals produced in oxidative stress or in radiotherapy, accidental irradiations, etc., is well known to form oxidative metabolites that are responsible for numerous diseases including neurodegenerative pathologies. Tyrosine (Tyr), Phenylalanine (Phe), and Methionine (Met) residues are known to be the major targets of OH radicals. This study aims at better understanding the OH addition process on these three amino acids. On the basis of different amino acid prototypes, the Gibbs energy (DG) (B3P86/6-31þG(d,p)) and rate constants (kTST)

(MPWB1K/6-31þG(d,p)) of OH addition were calculated. The OH addition capacity was studied (i) on the different positions of the aromatic rings of Tyr and Phe and (ii) on the S-atom of Met. The addition was favored on the aromatic rings of Tyr and Phe with almost the same DGaddition values for both amino acids. No preferential position was found. The only parameter that may influence the OH-adduct formation is the presence or absence of intra-H bondings. In agreement with the experimental data available from the literature, the OH-adduct on Met appeared to be less favored.
Key words: OH addition on amino acids; tyrosine; phenylalanine; methionine; OH radicals; DFT Correspondence



SCHEME 1. Different possible reaction mechanisms.

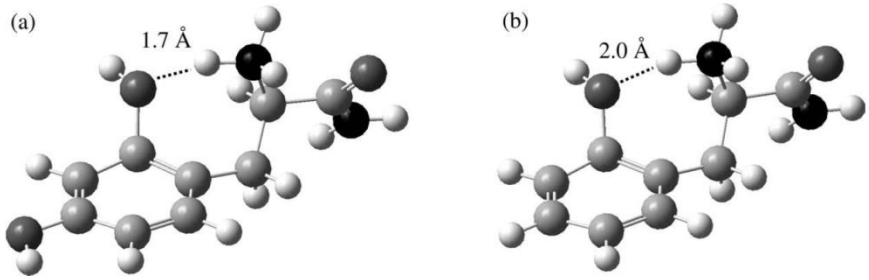


FIGURE 3. 3D conformations of (a) (S)-2OH-(R_3-ArOH) and (b) (R)-2OH-(R_3-Ar), exhibiting the intra H bonding between the added OH group and the NH_3 group.

Concluzii

The present study shed light on the _OH addition on amino acids. The _OH addition was proved to be thermodynamically favored on the aromatic rings of Tyr and Phe. Addition may
occur with almost equivalent probabilities on both residues (similar DG and kTST). It was slightly lessfavored on Met, which was confirmed by pulse radiolysis experiments (i.e., very low (microsecond)and long (millisecond) lifetimes respectively. Concerning Tyr the

_OH addition process is incompetition with the HAT, ET-PT, and SPLET mechanisms. These three mechanismsare usually invoked in order to explain the free radical scavenging capacity of antioxidants, e.g.,polyphenols, which usually exhibit a high H transfer capacity. To be active as an H atom donor, an OH group must possess a low O-H BDE (lower than 80 kcal/mol), whereas it is relatively high (around 87 kcal/mol in solution) for Tyr. As a consequence the OH group of Tyr was not a good candidate for HAT (and indirectly for the other two mechanisms). As explained in the introduction section HAT and SPLET are not favored for Phe. The ET mechanism would be feasible but the subsequent radical cation is highly unstable and must be stabilized by the PT step, which is not favored in this case. Indeed the whole ET-PT process would lead to the unstable [Phe-H] _ intermediate. Our conclusions drawn from thermodynamic results are in very good agreement with the experimental results for simple amino acids. These results could be extended to larger models modeling peptides. The presence or absence of stabilizing H bonds has to be carefully checked in polypeptides, since such bonds may modulate the OH-adduct stability. Different hydrogen bonding networks with other neighboring groups should be taken into account due to folding. In addition other factors like accessibility might modulate the addition reaction.

Articol 4

Clifford W.Fong, Platinum based radio chemotherapies: Free radica lmechanisms and Radiotherapy sensitizers, FreeRadicalBiologyandMedicine99(2016)99–109
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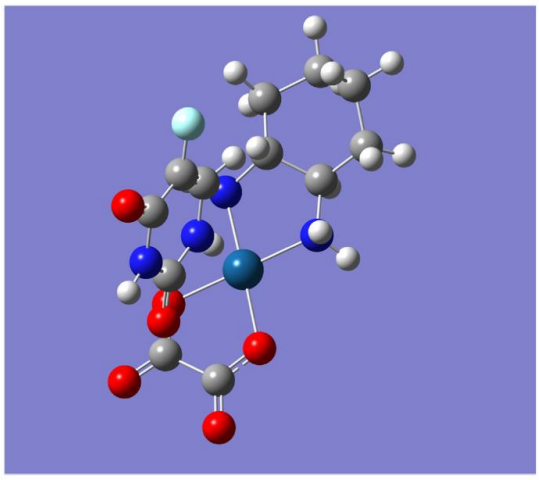

Fig. 4. {5Fluorouracil-Oxaliplatin} π complex showing plane of 5FU at right angle to plane of Oxaliplatin.

Concluzii

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Articol 5

Christian Bailly, Potential use of edaravone to reduce specific side effects of chemo-, radio and immuno-therapy of cancers, International Immunopharmacology 77 (2019) 105967; https://doi.org/10.1016/j.intimp.2019.105967

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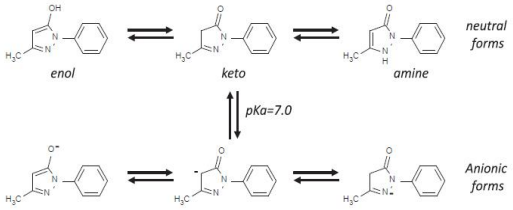
Adapted from [4].



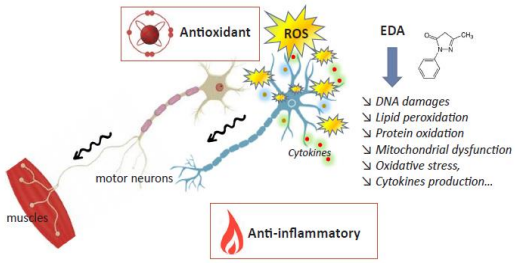


Fig. 2. Illustration of the mechanism of action of EDA which provides a cerebral neuroprotection by reducing oxidative stress and inflammation. The scavenging of reactive oxygen species (ROS) by EDA reduces the extent of DNA damages, oxidation of lipids and proteins, thus diminishing the cellular oxidative stress. The drug induces a reduction of the production of cytokines (such as IL-6, IL-10, IL-18, TNF-α, IL-1β) leading to the anti-inflammatory response. These effects limit the neuronal dysfunctions.

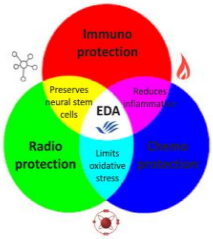


Fig. 5. EDA and cancer therapy. The drug can protect non-tumor cells from the oxidative damages and inflammation induced by chemo and radiotherapy of cancer. It could also help to alleviate the unwanted effects of immuno-therapy, such as autoimmune thyroiditis induced by anti-PD-1 antibodies, via its anti-inflammatory action.

Concluzii

EDA was developed first for the treatment of acute brain infarction and, a few years later, for the treatment of ALS. Today, the drug is currently investigated in a number of neurologic and non-neurologic pathologies. As discussed here, EDA may be useful to improve specific cancer treatments. There are common genetic and metabolic characteristics between ALS and cancer (oxidative unbalance, inflammation processes). Epidemiological studies have suggested that ALS relates to cancer.

Another major advantage of EDA is its capacity to cross the blood–brain barrier, to diffuse into the central nervous system and to act on the cerebral vasculature and neuronal networks, offering a potent neuroprotection. Therefore, the drug is well adapted to combat the neurotoxicity of cisplatin and cyclophosphamide, as described above but possibly also the neurotoxic effects of other established anticancer drugs like the taxanes (e.g. paclitaxel) and vinca-alkaloids (e.g. vincristine). EDA is a remarkable anti-oxidative and anti-inflammatory drug. It functions as a NFκB inhibitor and Nrf2 activator, like for examples the cytoprotective and anticancer phytochemicals resveratrol, curcumin, epigallocathechin-3-gallate and sulforaphane. The polyphenol honokiol, the main active ingredient from the bark of Magnolia officinalis, also exhibits anticancer and neuroprotective activities. It functions as a potent ROS scavenger and promotes nuclear translocation and activation of Nrf2 and displays potent neuroprotection against oxidative stress-mediated cell damage. Its
mode of action resembles that of EDA.The potential interest of EDA to mitigate autoimmune thyroiditis is very interesting in the context of cancer therapy with immune checkpoint
inhibitors. Therapeutic antibodies targeting the PD-1/PD-L1 pathway have revolutionized the treatment of specific cancers, notably non-small cell lung cancer and melanoma, but they also induce lifethreatening toxicities. Autoimmune thyroiditis induced by antibodies that block the interaction between PD-1 and PD-L1 is frequently observed in cancer patients. It can lead sometimes to irreversible thyroid dysfunctions. Interleukin (IL)-17 (a hallmark cytokine of Thelper 17 cells) plays a significant role in the pathogenesis of autoimmune thyroid diseases, in particular Hashimoto's thyroiditis and EDA has the capacity to inhibit expression of IL-17 implicated in the destruction of thyrocytes [48]. The use of EDA in the therapy of autoimmune
thyroiditis induced by anti-PD-1/PD-L1 antibodies could be important. It is interesting to note that the anti-inflammatory and antimalarial natural product dihydroartemisinin (DHA) has also been found to attenuates autoimmune thyroiditis. For both EDA and DHA, the STAT3/PI3K/Akt pathway was found to be implicated in the process. The use of EDA to prevent from or to alleviate cancer immunotherapyinduced autoimmune thyroiditis no

doubt merits further studies. The therapeutic impact can be very significant. Collectively, the information reviewed here clearly suggest that EDA can play a role to support cancer treatments. One of the limitations of EDA is its very low aqueous solubility (and solubilization in vehicle and intestinal fluids) which is the primary determining factor for its intestinal
absorption. This limitation imposes a parenteral administration of the drug, whereas oral administration would be preferable for the use in chronic diseases and cancer. Novel oral and sublingual tablet formulations of EDA are investigated currently to improve its oral bioavailability. The results look promising. Formulations to facilitate the brain delivery are also investigated.They could be useful for the treatment of brain tumors or metastases. A future for EDA in cancer can be envisaged.

Articol 6

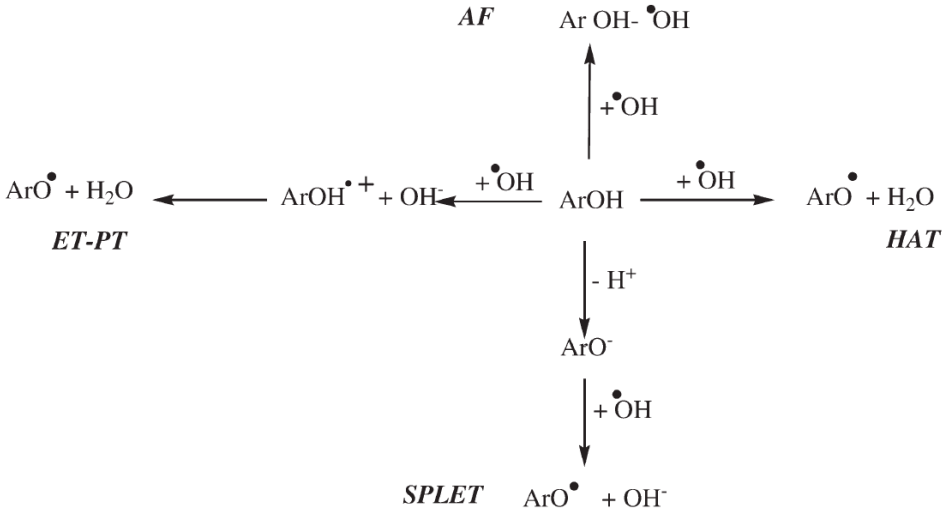
Patrick Trouillas, Jacqueline Bergere, Chantal Houee-LeVin, Toward Understanding the Protein Oxidation Processes: OH Addition on Tyrosine, Phenylalanine, or Methionine ?
International Journal of Quantum Chemistry, Vol 111, 1143–1151 (2011)
DOI: 10.1002/qua.22556

Abstract

Oxidation of peptides and proteins by OH radicals produced in oxidative stress or in radiotherapy, accidental irradiations, etc., is well known to form oxidative metabolites that are responsible for numerous diseases including neurodegenerative pathologies. Tyrosine (Tyr), Phenylalanine (Phe), and Methionine (Met) residues are known to be the major targets of OH radicals. This study aims at better understanding the OH addition process on these three amino acids. On the basis of different amino acid prototypes, the Gibbs energy (DG) (B3P86/6-31þG(d,p)) and rate constants (kTST) (MPWB1K/6-31þG(d,p)) of OH addition were calculated. The OH addition capacity was studied (i) on the different positions of the aromatic rings of Tyr and Phe and (ii) on the S-atom of Met. The addition was favored on the aromatic rings of Tyr and Phe with almost the same DGaddition values for both amino acids. No preferential position was found. The only

parameter that may influence the OH-adduct formation is the presence or absence of intra-H bondings. In agreement with the experimental data available from the literature, the OH-adduct on Met appeared to be less favored.

Key words: OH addition on amino acids; tyrosine; phenylalanine; methionine; OH radicals; DFT Correspondence



SCHEME 1. Different possible reaction mechanisms.

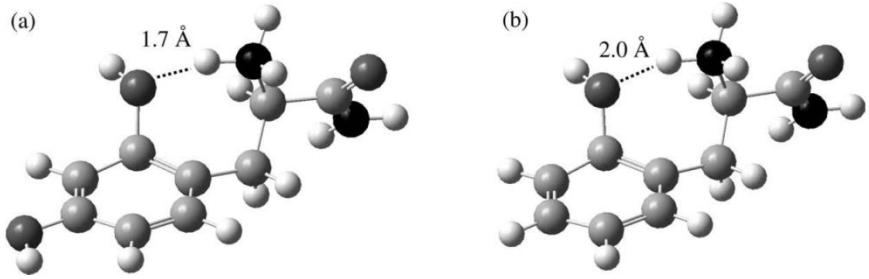


FIGURE 3. 3D conformations of (a) (S)-2OH-(R_3-ArOH) and (b) (R)-2OH-(R_3-Ar), exhibiting the intra H bonding between the added OH group and the NH_3 group.

Concluzii

The present study shed light on the _OH addition on amino acids. The _OH addition was

proved to be thermodynamically favored on the aromatic rings of Tyr and Phe. Addition may
occur with almost equivalent probabilities on both residues (similar DG and kTST). It was slightly lessfavored on Met, which was confirmed by pulse radiolysis experiments (i.e., very low (microsecond)and long (millisecond) lifetimes respectively. Concerning Tyr the _OH addition process is incompetition with the HAT, ET-PT, and SPLET mechanisms. These three mechanismsare usually invoked in order to explain the free radical scavenging capacity of antioxidants, e.g.,polyphenols, which usually exhibit a high H transfer capacity. To be active as an H atom donor, an OH group must possess a low O-H BDE (lower than 80 kcal/mol), whereas it is relatively high (around 87 kcal/mol in solution) for Tyr. As a consequence the OH group of Tyr was not a good candidate for HAT (and indirectly for the other two mechanisms). As explained in the introduction section HAT and SPLET are not favored for Phe. The ET mechanism would be feasible but the subsequent radical cation is highly unstable and must be stabilized by the PT step, which is not favored in this case. Indeed the whole ET-PT process would lead to the unstable [Phe-H] _ intermediate. Our conclusions drawn from thermodynamic results are in very good agreement with the experimental results for simple amino acids. These results could be extended to larger models modeling peptides. The presence or absence of stabilizing H bonds has to be carefully checked in polypeptides, since such bonds may modulate the OH-adduct stability. Different hydrogen bonding networks with other neighboring groups should be taken into account due to folding. In addition other factors like accessibility might modulate the addition reaction.