GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(SHORT COMMUNICATION)

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Potential molecular mechanism of radiation-induced cytotoxicity of Cetrimonium bromide to head and neck cancer cells

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GSC Biological and Pharmaceutical Sciences, 2021, 16(03), 241–244

Publication history: Received on 25 August 2021; revised on 28 September 2021; accepted on 30 September 2021

Article DOI: https://doi.org/10.30574/gscbps.2021.16.3.0291

Abstract

A previous study has shown that Cetrimonium bromide has a slight cytotoxicity to head and neck cancer cells due to the presence of the cationic quaternary amine group in this molecule that affects the function of mitochondria.The same study also found that the cytotoxicity of Cetrimonium bromide increased when combined with gamma radiation and this could be used to treat head and neck cancer in a mice in vivo tumor model.In the current study, an in vitro photochemical reaction between Cetrimonium chloride and tyrosine was investigated in order to understand the molecular mechanism of the in vivo observations and data. I found that Cetrimonium chloride could react with tyrosine upon simulated solar irradiation to produce an imine Schiff base which turned into cyano-tyrosine and a melanin polymer.It is possible that in the in vivo study mentioned earlier, the gamma radiation and Cetrimonium bromide together destroyed the tyrosine residues in some cellular proteins chemically, and as a result, tyrosine phosphorylation was inhibited in the cancer cells which slowed the growth of the tumor.

Keywords: Cetrimonium bromide; Radiation; Tyrosine; Photochemical reaction; Slow tumor growth

1. Introduction

In 2015, the total number of new cases of cancer was 4.292 million, equivalent to an average of 12,000 new cases per day.There are 2.814 million cancer deaths, an average of 7,500 cancer deaths per day.Among them, 60,600 new cases are nasopharyngeal cancer (a form of head and neck cancer) and 34,100 deaths were reported annually.The latest medical research confirms that the number of people suffering from nasopharyngeal canceris is increasing, with the age trending younger.Most of the nasopharyngeal cancer cases occur in southern China and Southeast Asia.

There are multiple causes of nasopharyngeal cancer: 1) Family genetic factors: many nasopharyngeal carcinoma patients have a family history of cancer. Nasopharyngeal carcinoma has a vertical and horizontal family tendency; 2) Eating habits: salted food and Guangdong preserved ham are related to the incidence of nasopharyngeal carcinoma. These foods contain the nitrosamine precursor nitrite generated by the pickling process. In addition, in recent years people prefer appetizing snacks which also contains nitrite or nitrate, and these substances have a strong carcinogenic effect; 3) Climate factors: the warmer weather in the south is more suitable for the growth of bacteria and viruses; 4) Environmental factors: smoking, cooking emissions, and increasingly serious air pollution have a great impact on the human respiratory system.

At present, there are two ways to treat nasopharyngeal carcinoma: drug chemotherapy and radiotherapy (gamma ray).Most of the patients with nasopharyngeal carcinoma are treated with radiotherapy in the early stage [1], while those in the advanced stage are treated with radiotherapy combined with drug chemotherapy.Currently, the main drugs used in chemotherapy are fluorouracil (5 -FU) and cisplatin [2, 3]. Because the toxicity of chemotherapy is strong, it

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cannot be overused, nor can it kill cancer cells completely. Hence, radiotherapy is the main method to cure nasopharyngeal carcinoma presently. However, radiation can also be very damaging to normal cells and therefore this method also needs improvement.

Recently, there was an interesting paper published regarding a study on the utilization of Cetrimonium bromide (Cetyltrimethylammonium bromide) as an anticancer agent for head and neck cancer [4].The paper showed that in vitro, Cetrimonium bromidewhen combined with gamma radiation had anti-cancer effects on several head and neck cancer cells. Cetrimonium bromide was also shown to ablate FaDu cells (a head and neck cancer cell line) tumorigenesis and delay tumor growth in mice in vivo study; Furthermore, Cetrimonium bromide interacted additively with radiation, i.e. the efficacy of combined therapy is higher than the two individual therapies alone. When the paper was published, the exact molecular mechanism of these observed phenomena was not immediately clear although the authors believed that it could be attributed to the positively charged quaternary amine group of Cetrimonium bromide which changed the plasma and mitochondrial membrane potential and perturbed the mitochondrial function. A little before the publication of this paper, I did some work in collaboration with the University of Connecticut and Bayer Pharmaceutical Corporation which aimed at studying a different field of research – pharmaceutical formulation compatibility. We found that Cetrimonium chloride (cetyltrimethylammonium chloride) could react with an amino acid (tyrosine) under the radiation of simulated sunlight [5, 6]. Tyrosine is a crucial messenger in many biochemical processes including cancer proliferation via a bio-reaction called tyrosine phosphorylation [7]. It is possible that in the cancer research study mentioned earlier, the gamma radiation and Cetrimonium bromide together destroyed the tyrosine residues in some cellular proteins chemically, and that's why the tumor growth stopped. The purpose of the current paper is to discuss the photochemical reaction between tyrosine and Cetrimonium chloride in order to demonstrate this possibility.

2. Material and methods

Tyrosine and five tyrosyl compounds (N-Acetyl tyrosine, Gly-Tyr, Glu-Tyr, Tyr-Arg and Lys-Tyr-Ly) were used in this study and their molecular formula can be found in Reference [5] and the websites of Sigma Chemical Co. and Bachem Bioscience Inc. where they were purchased.These compounds were chosen in such a way that tyrosine was adjacent to the positively charged Arg and Lys residues or negatively charged Glu residue or had the N-terminus blocked by a Gly residue or an Acetyl group.The compounds were reacted with three different surfactants, cetyltrimethylammonium chloride, sodium lauryl sulfate and polysorbate 80 by a photo-oxidation method previously described in Reference [5].The reaction rate constants were calculated from the concentration versus time profiles of the tyrosyl compounds.

3. Results and discussion

Figure 1 shows that the rate of photo-degradation of the tyrosine, Gly-Tyr, Glu-Tyr and N-Ac-Tyr was significantly increased by cetyltrimethylammonium chloride compared to sodium lauryl sulfate and Polysorbate 80. This suggests that a chemical interaction took place between cetyltrimethylammonium chloride and tyrosine. The formula of these reactions is illustrated in Figure 2. The quaternary amine group of cetyltrimethylammonium chloride reacted with the phenolic group of tyrosine upon simulated solar irradiation to produce an imine Schiff base which turned into cyano-tyrosine and a melanin polymer.The structure of melanin is not very well defined and its molecular weight ranges from 500 to 30,000 Da. The reaction rate of Tyr-Arg and Lys-Tyr-Lys was almost the same in the presence and absence of cetyltrimethylammonium chloride due to an intramolecular reaction between the guanidine group of Arg and the amino group of Lys with the phenolic group of tyrosine. The photo-oxidation of Lys-Tyr-Lys was enhanced by Polysorbate 80, which may be attributed to the interaction of the amino group of the Lys residues with the oxygen atoms on Polysorbate 80. The N-terminus of tyrosine was somewhat reactive to sodium lauryl sulfate and Polysorbate 80 as well as its own phenolic side chain; blocking this group decreased its reactivity. There are two other amino acids (serine and threonine) in proteins that can also react with cetyltrimethylammonium chloride potentially upon irradiation to produce a Schiff base because they contain a hydroxyl group on their side chains.

If this photochemical reaction is indeed the reason why Cetrimonium bromide can slow the growth of the head and neck cancer cells as shown in Reference [4], it may also inhibit the growth of other cancer cells, which would offer this compound broader uses as a radiochemotherapy agent to shorten the course of treatment and reduce the toxicity of radiation to the patients. In addition, Cetrimonium bromide (or chloride) is a commonly used antimicrobial agent and surfactant, its production method is relatively easy and inexpensive and the product can be manufactured in large quantities. This is another advantage of using it as an anticancer drug.

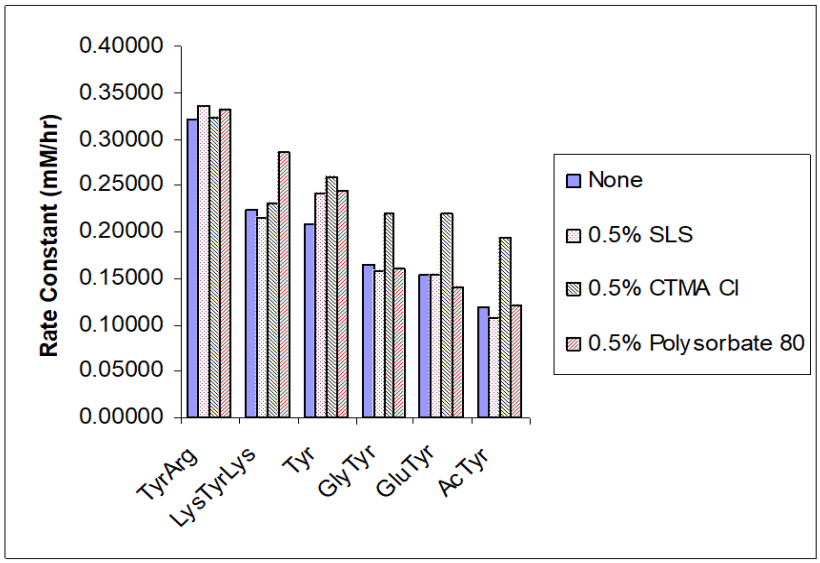

Figure 1 Effect of different surfactants on the rate of photo-degradation of model tyrosyl compounds (2mM) at pH 10 (simulated solar irradiance = 760 W/m^2)

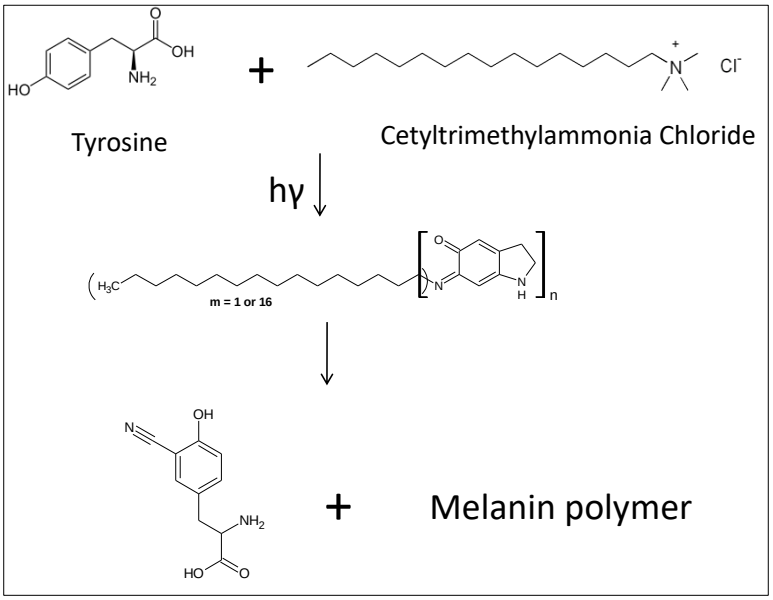

Figure 2 Formula of photochemical reaction between tyrosine and Cetrimonium chloride

4. Conclusion

Cetrimoniumbromide (or chloride) can be reacted with tyrosine upon irradiation to produce an imine Schiff base which turned into cyano-tyrosine and a melanin polymer. This photochemical reaction may explain the molecular mechanism of the increased cytotoxicity of this compound toward head and neck cancer cells when combined with radiation.

Compliance with ethical standards

Acknowledgments

The author would like to thank University of Connecticut School of Pharmacy and Bayer Pharmaceutical Corporation for providing technical and financial support for this study.

Disclosure of conflict of interest

The author declares that there is no conflict of interest associated with this work.

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