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Physico-chemical research of the interaction between gaseous plasma and living organism
プラズマ生体相互作用の物理化学研究

Katsuhisa Kitano [1], Satoshi Ikawa [2], Yoichi Nakashima [2], Atsushi Tani [3]
北野勝久 [1],井川聡 [2],中島陽一 [2],谷篤史 [3]

[1] *Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan.*
[2] *Technology Research Institute of Osaka Prefecture 2-7-1 Ayumino, Izumi, Osaka 594-1157, Japan*
[3] *Department of Earth and Space Science, Graduate School of Science, Osaka University 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan*
[1] 大阪大学工学研究科　アトミックデザイン研究センター　〒565-0871　大阪府吹田市山田丘2-1、
[2] 大阪府立産業技術総合研究所、[3] 大阪大学理学研究科

Many types of applications to plasma medicine have been tried. The combination with plasma science and medical science belongs to interdisciplinary science, and more attentions should be done to cross-disciplinary study between them. Plasma generates active species in gas and liquid phases, and they react with biomacromolecules of living organism, and some desirable effect would be finally obtained. Plasma is not an instrument of magic. For beneficial use of plasma, it is important to find applications which cannot be achieved by other methods (commercially available chemicals, UV lamp, etc.). In this paper, expected elementary reactions are discussed step by step.

1. Plasma induced chemical reactions for plasma medicine

Based on unique characteristics of atmospheric pressure plasmas, novel plasma applications to human body 'Plasma Medicine' have attracted attention. Considering wet conditions of body systems, the concept of plasma process in a liquid phase is essential. Various types of active species (ions, electrons, neutrals, radicals, UV, and so on) generated in plasma (gas phase) can be used for some chemical reactions in a liquid phase. For that purpose, atmospheric pressure plasmas with room temperature are suitable (Fig. 1) to avoid thermal damages to human body. Of course, instead of plasma itself some chemical species can penetrate into the liquid to induce some chemical reactions. In other words, plasma is a sort of tool for producing reactive species. Although many applications in plasma medicine have been proposed, such a plasma-induced reactive species is known to be toxic to living organism in general. Our research target is the disinfection of human body, achieving beneficial use of these active species. We have developed the reduced pH method, where strong bactericidal activity can be achieved if the solution is sufficiently acidic [1]. This method has been confirmed to be effective to sterilize human extracted tooth as caries infected model [2]. In this paper, the interactions between gaseous plasma and living organism are discussed in turn based on physico-chemical approach, by taking the theme of the reduced pH method.

Fig. 1 Plasma jet exhausted to a finger without burning.

2. Effective sterilization by the reduced pH method

For the plasma disinfection in the body fluid, we have successfully developed the reduced pH method that strong bactericidal activity can be achieved when the solution is sufficiently acidic. It is considered that strong bactericidal activity is brought by hydroperoxy radical (HOO•) generated from the association of hydrogen ion (H^+) and superoxide anion radical (O_2^-•). The critical pH value is associated with p*K*a of the dissociation equilibrium between these radicals, which is known to be approximately 4.8. This means that O_2^-• can be changed into HOO•, which have much stronger bactericidal activity, in lower pH [3].

3. Active species in gas and liquid phases

Atmospheric plasmas generate ROS (reactive oxygen species) and RNS (reactive nitrogen species) by contacting and/or mixing source gas (e.g. air, oxygen, and nitrogen). These active species exist not only inside plasma plume but outside. Some ions with hydrated cluster can exist apart from plasma source, which sometimes called as air ions. Spatial distributions of each species are dependent on chemical reaction, charge transfer and so on. Many types of negative and positive ions were analyzed by atmospheric MS (mass spectrometer) with 3-stage differential pumping.

Species in a gas phase can be transferred into a liquid phase beyond the gas-liquid interface. Chemical reactions occur in the liquid and penetration depth depends on primary reactions. Numerical simulation of assumed chemical reactions in the liquid was done using our experimental results. In short, species with short half-life hardly diffuse into the liquid. ESR (electron spin resonance) measurements was used to measure O_2^{-}•, OH•, $^1O_2$, and H• [4]. IC (ion chromatography) was to nitrate (NO_3^-) and nitrite ions (NO_2^-). Ozone (O_3) and hydrogen peroxide (H_2O_2) was done by another method. For scientific discussion on complex and extreme reaction fields induced by plasmas, positive and negative control experiments were done.

4. Biochemical reactions of biomacromolecule

Active species in the liquid react with biomacromolecule (protein, polysaccharide, lipid, nucleic acid) of living organism as elementary reaction, and macro effect (propagation, aging, apoptosis, necrosis, sterilization and so on) would be brought in consequence. To understand this chemical reaction process, the solutions of biomacromolecules were treated by plasma and analyzed by MALDI-TOFMS, CD (circular dichroism) spectroscopy, quantitative PCR, enzyme assay and so on [5-7]. Key point is that chemically modified biomacromolecules should be analyzed from the view point of 'function'. For instance, FT-IR and XPS measurements of chemical binding have little information against such macromolecules. This is a fundamental step for elucidating chemical reactions by plasma for biomedical applications.

5. Molecular biological approach

Although many types of molecular reactions are brought to living organism at the same time, key reaction (factor) to contribute should be identified using molecular biological method. Usually, one affect is brought by one reaction with other irrelative reactions. By the reduced pH method, bacteria are not simply killed but proliferation activity is inactivated with some physiological activity. This resembles UV sterilization, but no effective damage of DNA is observed.

6. How to supply active species

For the purpose of supplying chemical species, indirect plasma exposure can be used besides direct plasma exposure. It is not necessary that plasma and liquid (human body) are in contact. Remote (afterglow) plasma can be used for some application like ozone therapy. The plasma treated water (PTW) with strong bactericidal activity can be used by cryopreservation. Key concept is selective supply of active species with many types of supplying methods. To minimize undesirable side effects, non-related species should not be supplied. To maximize the desired effect, related species should be supplied selectively with adequate quantity.

7. Plasma medical applications as science

Although many types of applications to medicine have been proposed and tried, experimental researches have been done with theoretical research postponed. For scientific research, reactions should be understood step by step.

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