INTERNATIONAL JOURNAL OF ADVANCE RESEARCH, IDEAS AND INNOVATIONS IN TECHNOLOGY

ISSN: 2454-132X
Impact Factor: 6.078
(Volume 7, Issue 6 - V7I6-1349)
Available online at: https://www.ijariit.com

Medication beyond the 3 states of matter in healthcare

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ABSTRACT

Plasma, the fourth state of matter, is slowly making its way into the pharmaceutical business and medicine. It's already being used in a variety of applications, including causing apoptosis, necrosis, and cell detachment, as well as in the form of CAP (cold atmospheric plasma) and jett plasma (used for skin care). It is unquestionably regarded as a major and potentially useful tool in the future of medicine. Plasma is essentially an ionised gas, and the plasma sources employed in plasma medicine are mainly 'low temperature' plasma sources that operate at atmospheric pressure. It eliminates reactive species and can be used on cells and tissues without causing heat damage. It eliminates reactive species and can be used on cells and tissues without causing heat damage. Low temperature is defined here as room temperature, with a tight upper limit of 50 degrees Celsius. The overall goal of this article is to provide an understanding of how much plasma that has been ionised gas can be used to cure a variety of diseases and pathological situations with minimal adverse effects. Also, to provide information about its development history, current use, and prospective future. To raise awareness that this is being thoroughly examined by research groups all over the world as part of the extremely interdisciplinary subject of 'plasma medicine.

Keywords: *Plasma, Cold atmospheric plasma, Ionized gas, Anti- tumour and glucose uptake*

1. INTRODUCTION

CAP, which stands for cold atmospheric plasma, releases a variety of reactive species. These reactive species play an important role in redox regulation(Bekeschus et al., 2017). It's amazing how many seemingly harmful ions and molecules can function as vital messages. This is due to the very mechanism that carefully controls their intracellular amounts of calcium and reactive species like as ROS (reactive oxygen species)(Fedoroff, 2006). Because these cold plasmas are not actually cold, but rather work at body temperature, they can be safely applied to cells and tissues(Bekeschus et al., 2017). Take the plasma needle, which generates non-thermal plasma at atmospheric pressure, as an example of how effective plasma-related technologies are. The needle is not surrounded in a reactor on this device, which is a unique feature that makes it suited for biomedical applications. In addition, the temperature of the gas in the plasma remains below that of the body. When exposed to plasma, this characteristic prevents thermal injury to the tissues. Apoptosis, which is triggered by ROS, is likewise induced by plasma treatment(Kieft et al., 2006). Three German medical institutions have been accredited after demonstrating the safe use of plasma devices in pre-clinical and clinical studies. The first is an argon plasma jet in the atmosphere, while the other two are dielectric barrier discharges that work on a different principle than the plasma jet(Bekeschus et al., 2017). In some circumstances, however, it is critical, such as in cancer, when controlled DNA damage is desired(O'Connell et al., 2011). Identifying and quantifying active chemicals in specific plasma is one of the major experimental difficulties in plasma medicine. This will provide a thorough understanding of the mechanisms underlying the biological impacts of plasma in living systems. Cellular redox signalling is influenced by low-intensity plasma. This leads to an increase in anti-oxidative capacity as well as the start of the necessary repair process(H.-R. Metelmann et al., 2016)

2. PLASMA

2.1 What is it?

Plasma is a separate fourth state of matter since it is essentially ionized gas. Irving Langmuir invented the term "plasma." When at least one electron is not attached to an atom or a molecule, the atoms or molecules become positively charged ions. When the temperature rises, molecules gain energy and undergo transformations that include solid, liquid, gas, and plasma(Fridman, 2008). Take, for example, a very solid explanation provided in the book 'The fourth state of matter- an introduction to plasma science written by S. Eliezer and Y. Eliezer'. Assume we are spectators at a dance competition. The dancers are holding their hands and standing in a symmetrical fashion with scarcely any motions at the start of the competition, which has yet to begin, and the mood is frigid. This is the solid phase. After that, soft and mellow music is played, and the dancers are divided into pairs and begin to dance.

They are limited in their ability to move and express their energies in this situation. This is the liquid phase. The tempo of the music is now increasing, the dancers are dancing energetically, and the atmosphere is heating up. This is the gaseous state. At the end, the tempo picks up even more, and the dancers abandon their partners, free to perform their routines with all their might. This is the condition of plasma(Eliezer & Eliezer, 2001). Stars, lightning, and the sun are examples of naturally occurring plasmas. Fluorescent lamps, neon signs, plasma displays, and monitors are all instances of artificial plasma.

2.2 Generating Plasma

The use of a sufficient electric field in various gas combinations enclosed in a low pressure cylinder is one approach to make plasma. These low-pressure plasmas can be used to adjust the surface properties of various materials for film deposition and non-living matter sterilization. These low-pressure plasmas should not be used on living tissues. Only living tissues should be treated using devices that operate at atmospheric pressure. The limiting of the current flowing through the living object is crucial for the gentle handling of live objects at atmospheric circumstances. This can be accomplished by keeping the object slightly away from the active plasma or by using an insulator, also known as DBD (Dielectric Barrier Discharge)(Bibinov et al., 2011).

2.3 Dielectric barrier discharge (DBD)

DBDs are plasmas that are formed in configurations with an insulating substance between the electrodes and are responsible for self-pulsing processes. These are typical examples of normal gas discharges or non-thermal atmospheric pressures. As a result, DBDs are both a useful instrument in modern plasma technology and a subject of basic research(Brandenburg, 2018). The planar electrode plasma model is the first DBD model. Two 3mm thick copper plates measuring 45mm*55mm are paralleled and separated by air and 2mm thick acrylic. Acrylic plates having a surface area of 70*70 mm2 and a thickness of 3mm encased both copper plates. On the lower acrylic plate, three holes for gas and gas outlet were drilled. Plasma jet is another model. A copper anode rod with a diameter of 1mm and a length of 150mm was put into the center of a gas tube with a diameter of 6mm and a length of 200mm. A copper ring-shaped cathode with a diameter of 1mm was worn on the exterior of the glass tube. The model was supplied Argon gas from an Argon gas cylinder through a plastic tube and hooked by a plastic stopper at the glass tube's tip(Matra & Wongkuan, 2016).

3. CAP BENEFITING HUMAN BODY

3.1 Potentiating anti-tumor immunity with physical plasma

The age of checkpoint blockage emphasizes the importance of adaptive antitumor immune responses. This arm of immune defense is key in recognizing molecules via specific receptors to distinguish between self and foreign or mutated structures. Antigen-specific T-cells identify non-self epitopes, tumour-associated antigens, or neoepitopes on tumours to carry out attacks on malignant cells. Although tumor cells are immunogenic by nature, they have developed strategies to evade an immune response that would otherwise facilitate their clearance. Several steps in antitumor immunity utilize the toxic and signalling properties of reactive oxygen and nitrogen species (ROS/RNS). Cold physical plasmas are potent generators of such ROS/RNS and are demonstrated to have pro found antitumor activity in vitro and in vivo. Here we discuss recent evidence and concepts on how plasmas may boost immunity against pathological cells. Specifically, plasma treatment may enhance the immunogenicity of tumor cells by induction of the immunogenic cancer cell death (ICD) and redox regulation of the antigen presenting machinery. These aspects provide a rationale for localized plasma-based onco-therapies enhancing systemic antitumor immunity, which eventually may target distant tumor metastasis in cancer patients in a T cell dependent fashion.

3.2 Selectivity of CAP towards Malignant Cells

A new treatment for cancer has been the potential selectivity of CAP for cancerous cells in their non-malignant counterparts. Yan et al. observed that 26 of the 33 cell lines investigated were strong, 5 in 33 were moderate and just 2 out of 33 had negative selectivity, compared with identical normal cells, in a literature review. (Yan et al., 2015). In this context, however, it should be noted that "homology" means that cancer cells as well as normal cells come from the same sort of tissue. That is to say, in this study the cells compared did not always come from or were of the same cell type. In various settings, cancer cells were often grown in medium different from normal cells. However, normal and malignant cells originate from similar tissue are currently routine practise to be compared in a selectiveness survey. Moreover, cells of the same type should be grown under similar conditions. In reality, a recent study indicated that CAP therapy has a considerable impact on cell type, malignancy type, and culture and should be tackled when determining CAP selectivity(Biscop et al., 2019). Differences, on the other hand, could explain the probable selective impact in malignant and non-malignant cells. Neoplastic cells appear to be more reactive than normal cells to oxidative damage. (Yan et al., 2015). The amount of aquaporins in the cell membrane is one difference between cancer cells and normal cells. Aquaporins are usually more prevalent in cancer cells. Aquaporins were originally thought to be water channels. (Semmler et al., 2020).

3.3 Molecular Mechanism

Any anti-cancer therapy strategy must be able to target tumour cells while ignoring surrounding normal cells. The growing body of research implies that the CAP treatment can kill tumour cells while leaving non-malignant tissues unharmed(Semmler et al., 2020). Several in vitro investigations, including murine melanoma cells,(Bignon et al., 2018)colon carcinoma cells, skin cancer, neuroblastoma cells and ovarian cancer cells support the hypothesis of CAP selectivity in neoplastic cells. The creation of RNS and ROS in target cells that comes from the CAP jet and is produced by Cold Atmospheric Plasma is regarded to be a major actor in the anti-cancer capabilities of CAP treatment(Bignon et al., 2018). After CAP treatment, intracellular ROS levels were shown to rise, causing DNA death and damage in the target cells. The cancer healing therapeutic effect of ROS has been investigated to find the ‘‘threshold" between levels of ROS in cancer cells and normal cells, which allows to maintain the ‘‘CAP selectivity" toward neoplastic cells. This is due to the levels of ROS in neoplastic cells are similar to the limit at which cell death occurs and are much higher than in non-cancer cells(Semmler et al., 2020).

3.4 CAP Clinical Application in Treating Cancer

Whilst in vitro studies with in-vivo studies and cell cultures with mice modelling suggest that CAP has a great deal of cancer therapeutic potential, it still needs to be more tested for reliability for human patients for a possible clinical scenario. Six patients with locally advanced head and neck malignancies were treated for the first time(H. R. Metelmann et al., 2018). These patients were treated with a plasma jet (KINpen MED) in three cycles of single applications in less than a week. This treatment enhanced quality of life by reducing odour and the need for pain medication. Two patients experienced a nine-month partial remission, with biopsies from remission tissues revealing a moderate proportion of apoptotic tumour cells. In a second research with 12 individuals, similar outcomes were observed(H. R. Metelmann et al., 2015). When the resected CAP tumour tissue was compared into untreated tissue, there was an increase in apoptotic cells (Schuster et al., 2016). Another case study examined how CAP affects actinic keratosis (squamous cell cancer precursor lesions). This research treated a total of 17 lesions. Nine lesions demonstrated overall remission, three partial remission, and only 5 lesions exhibited minor or no improvement one month after CAP treatment. (Semmler et al., 2020).

3.5 Possible Mechanism of Glucose Uptake Enhanced by Cold Atmospheric Plasma

Cold atmospheric plasma (CAP) has shown its potential in biomedical applications, such as wound healing, cancer treatment and bacterial disinfection. Recent experiments have provided evidence that CAP can also enhance the intracellular uptake of glucose molecules which is important in diabetes therapy. In this respect, it is essential to understand the underlying mechanisms of intracellular glucose uptake induced by CAP, which is still unclear. Hence, in this study we try to elucidate the possible mechanism of glucose uptake by cells by performing computer simulations. Specifically, we study the transport of glucose molecules through native and oxidized membranes. Our simulation results show that the free energy barrier for the permeation of glucose molecules across the membrane decreases upon increasing the degree of oxidized lipids in the membrane. This indicates that the glucose permeation rate into cells increases when the CAP oxidation level in the cell membrane is increased(Razzokov et al., 2018).

4. CONCLUSION

CAP has convincingly showed potential in causing death of malignant cells. A new perspective of CAP treatment for cancer can be seen. One way is to enable cancer cells to become sensitive to ROS and RNS, including H2O2 and NO2. However, the activation of these cells will not lead to an apparent growth inhibition or cell death, unless reactive species are available in an external environment. The activated cells will gradually de-sensitize within the first 5 hours after CAP treatment. CAP-treated cancer cell activation has two fundamental characteristics: rapid sensitization and progressive de-sensitization. Another key role of CAP therapy on cancer cells is the build-up of reactive species in the extracellular environment(Yan et al., 2018)

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