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Review Paper

Investigating the Role of Sulfur Mustard in Triggering Molecular Inflammatory Mechanisms

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ABSTRACT

Sulfur mustard, a chemical warfare agent, that has been used in the Iraq-Iran conflict, exerts its devastating effects through multifaceted biochemical pathways. Its primary mode of action involves the alkylation of cellular macromolecules, particularly DNA and proteins, leading to cellular dysfunction and damage. DNA alkylation by sulfur mustard results in the formation of adducts, causing genetic mutations, chromosomal aberrations and ultimately cell death or malignant transformation. Similarly, protein alkylation disrupts cellular signaling pathways and homeostasis, contributing to tissue damage and dysfunction. Additionally, sulfur mustard exposure induces the generation of reactive oxygen species, exacerbating cellular damage, inflammation, and oxidative stress. This triggers the activation of inflammatory pathways, including NF-κB, MAPK, JAK/STAT and inflammasome activation, leading to the production of cytokines, adhesion molecules, chemokines, activator protein-1 (AP-1), and other inflammatory mediators. The inflammatory cascade initiated by sulfur mustard exposure perpetuates tissue damage, immune cell recruitment and systemic effects, enhancing acute symptoms and potential long-term health complications.

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Introduction

Sulfur mustard is a chemical warfare agent with a notorious history of use in warfare due to its devastating effects on the human body. Sulfur mustard has its origins in the late 19th and early 20th centuries, coinciding with the rapid progress of organic chemistry and the emergence of chemical warfare [1]. It was synthesized inadvertently by German chemist Frederick Guthrie in 1860 during experiments with thiodiglycol. Sulfur mustard's potential as a chemical weapon was not fully realized until later. With the beginning of World War I, military strategists recognized the potential of chemical agents to break the trench warfare stalemate. With its ease of synthesis, stability and devastating effects on the human body, sulfur mustard emerged as a prime candidate for weaponization. The onset of World War II saw the resurgence of sulfur mustard, utilized by both Axis and Allied powers, although its actual use remained limited during the conflict [1]. Subsequent conflicts, including the Iraq-Iran War in the 1980s, saw the continued use of sulfur mustard by the Iraqi military, resulting in significant casualties in Iranian soldiers and civilians and long-term health consequences for affected populations [2].

This chemical exerts its toxic effects through several mechanisms, primarily targeting cells with high metabolic activity. Upon contact with biological tissue, sulfur mustard rapidly penetrates cell membranes and enters the intracellular environment, where it initiates its destructive actions. One of the primary mechanisms of sulfur mustard toxicity is its alkylating properties [3]. Sulfur mustard contains electrophilic sulfur atoms that react with nucleophilic groups on cellular components such as proteins and DNA. These reactions result in the formation of covalent bonds, disrupting the structure and function of these biomolecules and leading to cellular dysfunction and tissue damage [4].

Sulfur mustard induces oxidative stress within cells by generating reactive oxygen species (ROS). These ROS can cause oxidative damage to cellular macromolecules, such as DNA, proteins and lipids, which exacerbate cellular dysfunction and contribute to tissue injury [5, 6]. Additionally, sulfur mustard interferes with cellular signaling pathways involved in inflammation and immune response. It activates pro-inflammatory transcription factors, leading to the upregulation of inflammatory mediators and cytokines. This dysregulated inflammatory response amplifies tissue damage and contributes to the pathogenesis of sulfur mustard toxicity [6].

Sulfur mustard exposure can have profound and widespread effects on various organ systems, resulting in acute and chronic health consequences. The skin, eyes, respiratory system and immune system are particularly vulnerable to the toxic effects of sulfur mustard [7].

In the immune system, sulfur mustard disrupts the function of immune cells, such as lymphocytes, macrophages, and neutrophils, impairing host defense mechanisms and predisposing individuals to opportunistic infections [8]. It plays a significant role in triggering inflammation through its actions on cellular signaling pathways and immune responses. The alkylating properties of sulfur mustard and its ability to induce oxidative stress lead to the activation of pro-inflammatory transcription factors, pro-inflammatory cytokines, chemokines, adhesion molecules and the upregulation of inflammatory mediators [9].

However, sulfur mustard is a potent chemical warfare agent that causes severe damage to the human body through its alkylating properties, induction of oxidative stress and dysregulation of inflammatory pathways. Determination of its mechanisms and its role in triggering inflammation would be useful to better realize the pathogenesis of sulfur mustard toxicity. This study reviews sulfur mustard's mechanisms, its effects on the body and its role in triggering inflammation.

Toxicity of sulfur mustard

Sulfur mustard possesses a biochemical arsenal that underlies its infamous reputation as a potent chemical warfare agent. This arsenal comprises a range of molecular mechanisms through which sulfur mustard inflicts damage at the cellular and molecular levels, leading to devastating effects on exposed individuals. These biochemical processes are crucial for comprehending the full extent of sulfur mustard's toxicity and for developing effective strategies to counteract its harmful effects [10].

One of sulfur mustard's primary actions involves the alkylation of cellular macromolecules, including DNA, and proteins. This leads to alterations in their structure and function, disrupting cellular processes and triggering downstream effects [11].

DNA alkylation, because of sulfur mustard, represents a critical aspect of its toxic mechanism, contributing to the genetic damage and cellular dysfunction observed following exposure to this chemical agent. Sulfur mustard's ability to alkylate DNA arises from its electrophilic nature, which allows it to form covalent bonds with nucleophilic sites on the DNA molecule [12].

Upon contact with biological tissues, sulfur mustard undergoes hydrolysis, leading to the formation of highly reactive intermediates, such as episulfonium ions and cyclic sulfonium ions. These reactive species readily react with nucleophilic sites on DNA bases, including adenine, guanine, cytosine, and thymine, resulting in the formation of DNA adducts [13].

The alkylation of DNA by sulfur mustard can occur through various mechanisms, including the following items.

Monoadduct formation

Sulfur mustard can form monoadducts by alkylating a single nucleotide base within the DNA molecule. This may involve the transfer of an alkyl group from sulfur mustard to the N7 position of guanine, the N3 position of adenine, or the O6 position of guanine, resulting in the formation of alkylated DNA bases [14].

Cross-link formation

Sulfur mustard can also induce the formation of interstrand and intrastrand DNA cross-links, where covalent bonds are established between adjacent or distant nucleotide bases. Interstrand cross-links occur when sulfur mustard alkylates bases on opposing DNA strands, while intrastrand cross-links involve the alkylation of adjacent bases within the same DNA strand [15].

DNA-protein cross-linking

In addition to DNA-DNA cross-links, sulfur mustard can also induce cross-links between DNA and proteins, particularly histones. This can interfere with chromatin structure and DNA packaging, disrupting gene expression and DNA repair processes [16].

The formation of DNA adducts by sulfur mustard can have profound consequences for cellular function and genomic stability. DNA adducts can distort the structure of the DNA molecule, interfere with DNA replication and transcription, and impede the activity of DNA repair enzymes. As a result, cells may accumulate genetic mutations, chromosomal aberrations and DNA strand breaks, leading to cell death, apoptosis, or malignant transformation [17, 18]. The genotoxic effects of sulfur mustard-induced DNA alkylation extend beyond the immediate site of exposure, affecting both dividing and non-dividing cells throughout the body. This can lead to a wide range of acute and long-term health effects, including carcinogenesis, mutagenesis, and heritable genetic damage [18, 19].

Protein alkylation, because of sulfur mustard exposure, represents a critical aspect of its toxic mechanism, contributing to cellular dysfunction, disruption of signaling pathways, and ultimately, tissue damage. Sulfur mustard reacts with nucleophilic sites on proteins and alters protein structure and function, with profound implications for cellular homeostasis and function [20, 21].

Protein alkylation by sulfur mustard can occur through various mechanisms as follows. Firstly, the modification of nucleophilic amino acid residues, in which sulfur mustard primarily targets nucleophilic amino acid residues within proteins, such as cysteine, histidine and lysine. The reactive sulfur atoms in sulfur mustard can form covalent bonds with the thiol group (-SH) of cysteine residues, resulting in the formation of S-alkylated cysteine adducts. Similarly, sulfur mustard can react with the imidazole group of histidine residues and the amino group of lysine residues, leading to the formation of alkylated histidine and lysine adducts, respectively [21, 22]. Secondly, through the disruption of protein structure and function, the alkylation of critical amino acid residues within proteins can lead to structural alterations that disrupt protein folding, stability and function. This may interfere with enzymatic activities, protein-protein interactions, and cellular signaling pathways, leading to dysregulation of essential cellular processes. For example, the alkylation of cysteine residues within enzymes can impair their catalytic activity, while the alkylation of histidine residues within receptors or ion channels can disrupt their function [21]. Thirdly, via the formation of cross-links and aggregates, in addition to single-site alkylation, sulfur mustard can induce the formation of protein-protein cross-links and aggregates through the alkylation of multiple amino acid residues within or between protein molecules. These cross-links and aggregates can alter the physical properties of proteins, leading to the formation of insoluble aggregates or fibrils that are resistant to degradation. This can impair cellular protein turnover and clearance mechanisms, contributing to cellular dysfunction and toxicity [23]. Fourthly, by activation of stress response pathways, protein alkylation by sulfur mustard can trigger cellular stress response pathways, such as the unfolded protein response and the heat shock response. These pathways are activated in response to protein misfolding, aggregation, or damage, and serve to restore protein homeostasis and promote cell survival. However, chronic activation of stress response pathways can overwhelm cellular defenses and contribute to cell death or apoptosis [24].

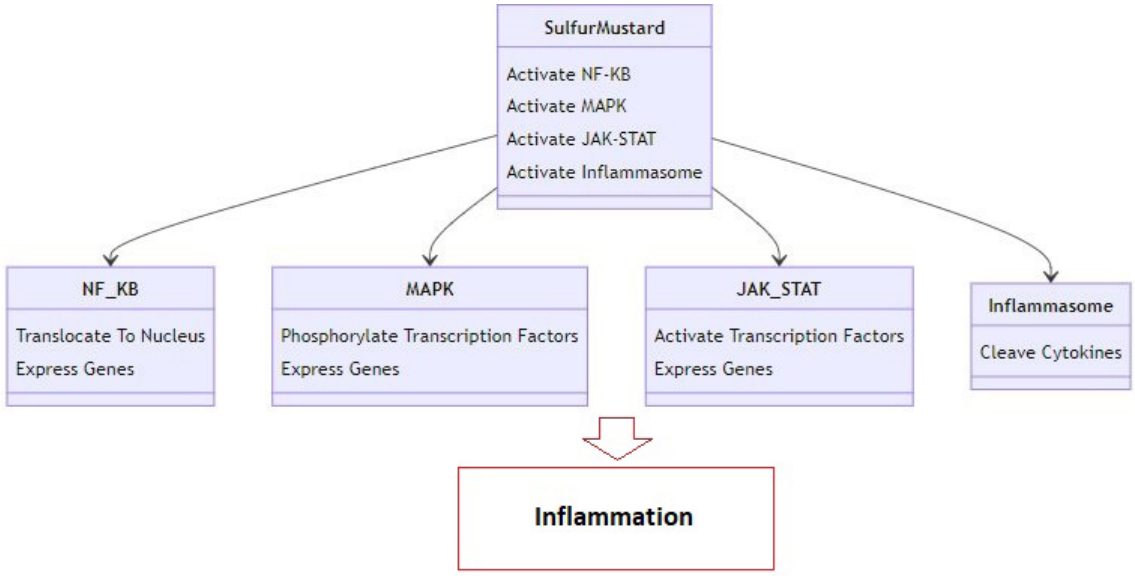

Figure 1. Molecular mechanisms of inflammation induced by sulfur mustard

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The consequences of protein alkylation by sulfur mustard extend beyond the immediate site of exposure, affecting cellular function and viability throughout the body. Dysregulation of essential proteins and signaling pathways can lead to a wide range of acute and long-term complications, including inflammation, cytotoxicity, and tissue damage. Moreover, protein alkylation may contribute to the development of chronic inflammatory diseases and carcinogenesis through sustained activation of inflammatory and proliferative signaling pathways [21, 22, 24].

Generation of ROS by sulfur mustard

The generation of ROS due to sulfur mustard exposure represents a significant aspect of its toxic mechanism, contributing to oxidative stress, cellular damage, and inflammation. ROS is a highly reactive molecule containing oxygen atoms with unpaired electrons, such as superoxide anion (O2•−), hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2) [25]. Sulfur mustard can induce the production of ROS through several mechanisms.

Direct oxidative reactions

Sulfur mustard contains electrophilic sulfur atoms that can directly react with cellular molecules, including proteins, lipids, and DNA, leading to the generation of ROS as byproducts. For example, sulfur mustard can undergo redox reactions with thiol (-SH) groups in proteins, resulting in the formation of sulfenic acid intermediates and subsequent release of superoxide radicals [26, 27].

Induction of enzymatic pathways

Sulfur mustard exposure can activate cellular enzymes, such as nicotinamide adenine dinucleotide phosphate oxidases and xanthine oxidase, which are responsible for the production of ROS under physiological conditions. Increased enzymatic activity in response to sulfur mustard exposure can lead to elevated ROS levels, contributing to oxidative stress and cellular damage [26].

Mitochondrial dysfunction

Sulfur mustard-induced cellular stress can impair mitochondrial function, leading to the leakage of electrons from the electron transport chain and the production of ROS. Mitochondria are a major source of ROS in cells, and disruption of mitochondrial integrity by sulfur mustard can exacerbate oxidative stress and cellular injury [28, 29].

Inflammatory responses

Inflammation triggered by sulfur mustard exposure can further contribute to ROS generation through the activation of immune cells, such as neutrophils and macrophages. These cells produce ROS as part of their antimicrobial defense mechanisms, but excessive ROS production can lead to collateral damage to surrounding tissues and exacerbate oxidative stress [29, 30].

The consequences of ROS generation due to sulfur mustard exposure are manifold and can impact various cellular components and signaling pathways. Firstly, by oxidative damage to biomolecules, ROS generated by

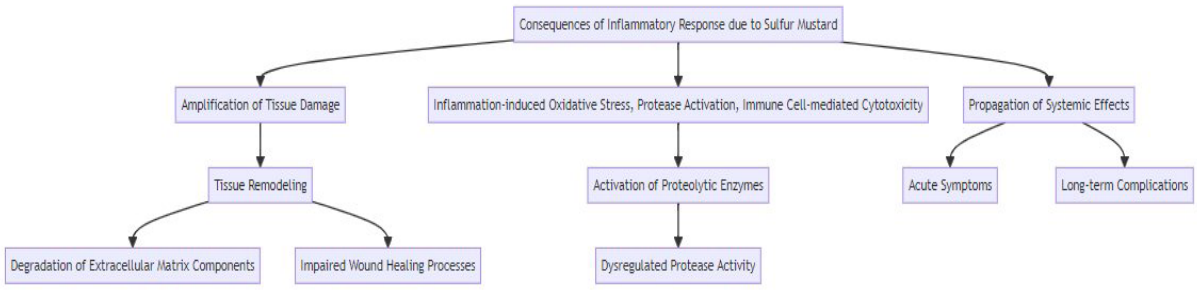

Figure 2. Consequences of inflammatory response induced by sulfur mustard

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sulfur mustard can react with cellular macromolecules, including lipids, proteins and DNA, leading to oxidative modifications and damage. Lipid peroxidation, protein oxidation, and DNA strand breaks can occur, compromising cellular integrity and function [7, 31, 32]. Secondly, by the activation of inflammatory responses, ROS can act as signaling molecules that modulate inflammatory pathways and cytokine production in response to sulfur mustard exposure. Elevated ROS levels can trigger the activation of transcription factors, such as nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1), leading to the expression of pro-inflammatory genes and amplification of the inflammatory response [18, 33-35]. Thirdly, through cellular dysfunction and apoptosis, Excessive ROS production can disrupt cellular homeostasis and induce programmed cell death pathways, such as apoptosis. ROS-mediated damage to mitochondria, DNA, and other cellular components can trigger apoptotic signaling cascades, leading to cell death and tissue injury [36, 37]. lastly, by the amplification of oxidative stress, ROS can propagate oxidative damage through a process known as oxidative stress, wherein the imbalance between ROS production and antioxidant defenses leads to sustained cellular damage and dysfunction. This can perpetuate a cycle of inflammation, oxidative stress, and tissue injury in sulfur mustard-exposed tissues [38, 39].

Activation of inflammatory pathways by sulfur mustard

The activation of inflammatory pathways by sulfur mustard is a pivotal aspect of its toxic mechanism, contributing to tissue damage, immune cell recruitment, and the amplification of the inflammatory response. Sulfur mustard exposure triggers a cascade of molecular events that culminate in the activation of pro-inflammatory signaling pathways, leading to the production of cytokines, chemokines, and other inflammatory mediators [40-42]. Several key pathways are involved in this process. First, the NF-κB pathway is involved as NF-κB is a transcription factor that plays a central role in regulating the expression of genes involved in inflammation, immune response, and cell survival. Sulfur mustard exposure activates NF-κB signaling through various mechanisms, including the direct oxidation of inhibitory proteins and the activation of upstream kinases such as IκB kinase. NF-κB can translocate to the nucleus and induce the expression of pro-inflammatory genes, including cytokines (e.g. interleukin-1, tumor necrosis factor-alpha), chemokines, adhesion molecules and inflammatory enzymes (e.g. cyclooxygenase-2, inducible nitric oxide synthase). This leads to the recruitment of immune cells, vasodilation, and tissue inflammation [43, 44]. Secondly, through the mitogen-activated protein kinase (MAPK) pathway as MAPKs are a family of serine/threonine protein kinases involved in cellular signaling pathways regulating inflammation, cell proliferation and apoptosis. Sulfur mustard exposure can activate MAPK signaling pathways, including extracellular signal-regulated kinase, c-Jun N-terminal kinase and p38 MAPK. The activation of these pathways leads to the phosphorylation and activation of transcription factors, such as AP-1, which promotes the expression of pro-inflammatory genes and amplifies the inflammatory response [43, 45]. Thirdly, through Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, as the JAK/STAT pathway is another key signaling pathway involved in inflammation and immune responses. Sulfur mustard exposure can activate the JAK/STAT pathway through the release of cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8), which bind to their respective receptors and activate JAK kinases. Activated JAK kinases phosphorylate and activate STAT transcription factors, which translocate to the nucleus and regulate the expression of genes involved in inflammation, cell proliferation, and immune regulation [46]. Fourthly, through inflammasome activation as the inflammasome is a mul-

tiprotein complex involved in the activation of inflammatory responses and the processing of pro-inflammatory cytokines, such as interleukin-1β and interleukin-18. Sulfur mustard exposure can trigger inflammasome activation through various mechanisms, including the release of danger-associated molecular patterns from damaged cells, such as adenosine triphosphate and ROS. Activated inflammasomes cleave pro-interleukin-1β and pro-interleukin-18 into their active forms, leading to the release of mature cytokines and the amplification of inflammation [47, 48].

The activation of inflammatory pathways by sulfur mustard contributes to the recruitment of immune cells, such as neutrophils, macrophages, and lymphocytes, to the site of injury. These immune cells release additional pro-inflammatory mediators and ROS, further exacerbating tissue damage and inflammation. Chronic activation of inflammatory pathways by sulfur mustard can lead to the development of chronic inflammatory diseases, tissue fibrosis, and long-term health complications in exposed individuals [49]. Figure 1 shows a brief review of the molecular mechanisms of inflammation induced by sulfur mustard.

Inflammatory cascade induced by sulfur mustard

The cascade of inflammatory responses elicited by sulfur mustard exposure, ignite a destructive cycle of tissue damage and immune activation. Upon contact with biological tissue, sulfur mustard triggers a rapid and robust inflammatory reaction characterized by the release of pro-inflammatory mediators and the recruitment of immune cells to the site of exposure. This inflammatory cascade is orchestrated by a complex network of signaling pathways and molecular interactions, leading to the amplification of tissue damage and the propagation of systemic effects [50].

Sulfur mustard exposure stimulates the release of various pro-inflammatory mediators, including cytokines, chemokines, and lipid mediators, from injured tissues, immune cells, and resident cells at the site of exposure. These mediators play diverse roles in modulating the inflammatory response, promoting vasodilation, increasing vascular permeability, and activating immune cells.

Pro-inflammatory cytokines, such as interleukin-1, tumor necrosis factor-alpha, and interleukin-6, are among the earliest mediators released in response to sulfur mustard exposure. These cytokines stimulate immune cell activation, promote inflammation, and contribute to tissue injury and repair processes [51, 52].

Chemokines are chemotactic cytokines that guide the migration of immune cells to sites of inflammation. Sulfur mustard exposure induces the production of chemokines, such as interleukin-8 and monocyte chemoattractant protein-1, which recruit neutrophils, macrophages, and other immune cells to the affected tissues [53].

Mediators, such as prostaglandins, leukotrienes, and platelet-activating factors, contribute to the inflammatory response by modulating vascular permeability, smooth muscle contraction, and immune cell activation. Sulfur mustard exposure can enhance the production of these mediators, exacerbating inflammation and tissue injury [50, 54].

Sulfur mustard exposure triggers the recruitment and activation of immune cells, including neutrophils, macrophages, and lymphocytes, to the site of injury. These immune cells play crucial roles in orchestrating the inflammatory response, phagocytosing damaged cells and debris, and initiating tissue repair processes. Neutrophils are among the first immune cells to respond to sulfur mustard exposure, migrating to the site of injury and releasing inflammatory mediators and cytotoxic substances. While neutrophils play a critical role in host defense, excessive neutrophil activation can contribute to tissue damage and inflammation [8]. Macrophages are phagocytic immune cells that engulf and digest cellular debris, pathogens and foreign substances. Sulfur mustard exposure activates macrophages, promoting the release of pro-inflammatory cytokines, chemokines and ROS, which amplify the inflammatory response and contribute to tissue damage [50]. Lymphocytes, including T cells, B cells and natural killer cells, are involved in regulating the inflammatory response and coordinating adaptive immune responses. Sulfur mustard exposure can modulate lymphocyte function and promote immune dysregulation, leading to prolonged inflammation and impaired tissue repair [55].

The inflammatory response triggered by sulfur mustard exposure causes oxidative stress, protease activation, and immune cell-mediated cytotoxicity leading to the development of acute symptoms and long-term complications [56].

Inflammatory mediators released during sulfur mustard exposure can activate proteolytic enzymes, such as matrix metalloproteinases and elastases, which degrade extracellular matrix components and promote tissue remodeling. Dysregulated protease activity can exacerbate tissue damage and impair wound-healing processes [39, 57, 58]. Figure 2 indicates the consequences of the inflammatory response induced by sulfur mustard.

Inflammatory processes and oxidative stress due to sulfur mustard exposure could progress senescence and cell aging which have been confirmed by telomere attrition, increased expression of aging-related genes and exacerbating of biological health [59-61].

Conclusion

The toxicity of sulfur mustard stems from its multifaceted biochemical mechanisms, which inflict damage at the cellular and molecular levels. Through the alkylation of cellular macromolecules such as DNA and proteins, sulfur mustard disrupts essential cellular processes, leading to genetic damage, cellular dysfunction, and tissue injury. The formation of DNA adducts and protein modifications impairs cellular function and contributes to long-term health effects, including carcinogenesis and chronic inflammatory diseases. Additionally, sulfur mustard induces the generation of ROS and activates inflammatory pathways, further exacerbating tissue damage and immune activation.

The cascade of inflammatory responses triggered by sulfur mustard exposure perpetuates a cycle of tissue injury and inflammation, leading to acute symptoms and potentially long-term health complications. Determination of these intricate mechanisms would be useful in finding effective strategies to mitigate the harmful effects of sulfur mustard exposure and alleviate the burden on chemical veterans.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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