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REVIEW ARTICLE

Hydrogen Sulfide Suppress the Pathological Alterations of Endocrine Glands Induced by Gamma Irradiation and Cyclophosphamide

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ABSTRACT

Background: Hydrogen sulfide (H_2S) is a gaseous mediator and is usually recommended to have antioxidant, anti-inflammatory, anticancer, and antiapoptotic consequences. In the endocrine system, H_2S can act at the thyroid, adrenal gland, and gonad through the hypothalamus–pituitary axis, in addition to at the pancreas, thereby collaborating within side the law of many hormones of the body, and the hypothalamus–pituitary axis can, in turn, adjust the manufacturing of H_2S. Chemotherapy Cyclophosphamide can cause damage of thyroid, pituitary, pancreatic, and adrenal glands. Radiation-induced thyroid, hypothalamus, and anterior pituitary gland disorders. Radiation-induced injury of the endocrine pancreas is known to increase the risk of diabetes mellitus (DM). Testis tissue, radiosensitive organ, has a variety of cells that differ in their degree of sensitivity. In this manner, cancer patient needs for protective agent against different side effects of anticancer therapy, especially in case of combination between chemo and radio therapies. **Presentation of the Hypothesis:** H_2S can guard endocrine organs and adjust hormone secretion through antioxidative effect and ion channel regulation. H_2S performs a function withinside the endocrine system to guard pancreatic cells, adjust insulin secretion, hold the characteristic of the adrenal cortex, sell the discharge of catecholamine, and adjust the secretion of pituitary hormones. **Implications of the Hypothesis:** Administrations of H_2S has protecting and therapeutic results on endocrine glands in opposition to numerous results of chemo- and radiotherapies. H_2S is a promising molecule for the development of new medications.

Keywords: Cyclophosphamide, Endocrine glands, Gamma irradiation, Hydrogen sulfide, Pathophysiology

INTRODUCTION

Over the closing several decades, hydrogen sulfide (H_2S) has obtained hobby as a manufacturer new signaling molecule, with physiological and pathophysiological roles in human issues affecting vascular biology, immune capabilities, cellular survival, metabolism, longevity, development, and strain resistance. Apart from its considered competencies in oxidative stress and inflammation, new proof has emerged revealing that H_2S consists of out physiological competencies thru focused on proteins, enzymes, and transcription factors through a post-translational modification known as per-sulfidation.[1]

In this study, results of H_2S donor sodium hydrosulfide (NaHS) on cyclophosphamide (CYP) and gamma irradiation which associated to pathological changes of endocrine glands.[2] H_2S has been verified to be generated withinside the endocrine and reproductive organs and elicits numerous actions. H_2S modulates insulin secretion

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in pancreatic islets. Adipose tissues have the ability to grant H_2S, which regulates the close by insulin sensitivity and vascular responsiveness. Moreover, it acts at the hypothalamic–pituitary–adrenal axis and is concerned in stress responses.[3]

CYP induces derangement in spermatogenesis and motives atrophy of seminiferous tubules and testosterone level depletion.[4] Thyroid gland damage[5] and vacuolation of interstitial spaces in the pituitary gland.[6] Pancreatic acini revealed focal slight hydropic degeneration, in addition to moderate edema and congestion. Besides, the Langerhans islets had been markedly strange and lowered in size, with atrophic and shrunken cells.[7] Adrenal glands, that are concerned withinside the frame's response to stress phenomena, demonstrated hypertrophy after high dose of CYP, with body weight relative developing and glucocorticoids hormones immoderate secretion.[8]

Endocrine late effects of irradiation may additionally be direct, ensuing in hypofunction of endocrine glands or indirect ensuing in metaplasia and most cancers.[9] Radiotherapy (RT) and chemotherapy are the handiest and systematic strategies for most cancers treatment which observed with unsafe consequences will commonly reduce the high-satisfactory of existence for victims with most cancers and may additionally purpose discontinuation of therapy.[10]

H_2S CHEMISTRY

H_2S is normally used referring to the complete sulfide species. Although H_2S has appropriate solubility in water, it is nevertheless very unstable in solution. It is easy oxidized in the presence of oxygen, forming oxidized sulfide species such as sulfite (SO_3^{2-}), sulfate (SO_4^{2-}), thiosulfate ($S_2O_3^{2-}$), polythionates ($S_nO_{n+2}^{-}$), and polysulfides (S_x^{2-}), as well as other oxidized polysulfide species.[11] H_2S, an everyday lethal, poisonous fuel with the odor of rotten eggs, is diagnosed as one of the three gasotransmitters in mammals, which, additionally, consist of nitric oxide (NO) and carbon monoxide (CO).[12,13] H_2S performs relies on the precise circumstance, its concentration, and the interplays with different signaling molecules, particularly NO and CO.[14] H_2S does not form hydrogen bonds and is lipophilic, allowing it to pass through biological membranes, and act as a paracrine signaling molecule.[15]

SYNTHESIS AND METABOLISM OF H_2S INTHE ENDOCRINE SYSTEM

At present, three primary recognized enzymes produce H_2S in organisms: Cystathionine b-synthase (CBS), cystathionine gamma-lyase (CSE), and 3-mercaptopyruvatesulfurtransferase (3-MST).[2] The substrate of (CBS) and (CSE) is L-cysteine,[4] while 3-MST can catalyze 3-mercaptopyruvate to produce H_2S.[5,6] Recently, it has been discovered that a form of human methanethiol oxidase-selenium binding protein 1 (SELENBP1) can convert methanethiol into H_2O_2, formaldehyde, and H_2S. In adipocytes, H_2S can be produced using SELENBP1 and is associated to the expression of CBS, CSE, and 3-MST.[7,9] However, the amount of the enzyme that produces H_2S varies in unique tissues and organs. In endocrine glands and endocrine organs, the RNA and protein expression levels of CBS are the easiest in the pancreas, specifically in acinar cells.[10] Moreover, the CBS is hardly ever dispensed in other endocrine glands such as thyroid, parathyroid, adrenal gland, and pituitary gland;[11] however, abnormally improved in thyroid carcinoma.[16] The expression of CSE is the amplest in the liver, however low in the thyroid, pancreas, testis, ovary, and other endocrine glands.[12,14] 3-MST is especially expressed in endocrine tissues (thyroid, parathyroid, and adrenal), pancreas, and gonad (testis and ovary).[17] H_2S can have an effect on the secretion of many hormones and participate in the prevalence and improvement of endocrine diseases,[18] however, the impact of H_2S on the physique may additionally be biphasic,[2] that is, the impact of too excessive or too low attention is the opposite, so to make certain the everyday physiological feature of the body, it is integral to preserve the attention of H_2S at an appropriate concentration. It is properly recognized that H_2S can be regulated in two ways: Synthesis and consumption. In phrases of synthesis, H_2S is synthesized broadly speaking thru enzymatic and non-enzymatic pathways (such as discount of

sulfur-containing compounds) and, in a few cases, launched by way of sure sulfur stored in cells.[19] The half-life of H_2S *in vivo* is very quick (a few seconds to a few minutes).[20,21] Nowadays, it, in the main, inhibits that the exercise of synthase or increases the donor *in vitro*, which brings awesome difficulties to the find out about of H_2S.

BIOLOGY OF H_2S

H_2S is regularly produced thru the anaerobic bacterial breakdown of natural substrates in the absence of oxygen, such as in swamps and sewers (anaerobic digestion). It additionally consequences from inorganic reactions in volcanic gases, herbal gas, and some properly waters. Digestion of algae, mushrooms, garlic, and onions is believed to launch H_2S through chemical transformation and enzymatic reactions.[17] Human physique produces small quantities of H_2S and makes use of it as a signaling molecule.[19]

In mammals, three enzymes are concerned in sulfur-containing amino acid metabolism and hence accountable for the *in vivo* manufacturing of H_2S. Two of them are pyridoxal-50-phosphate (PLP)-dependent enzymes: CBS and CSE. CBS is expressed predominantly in the central frightened device (CNS).[22]

H_2S DONORS

Inorganic sulfide salts, such as sodium sulfide (Na_2S) and hydrosulfide (NaHS),[20] diallyl disulfide,[21] Lawes son's reagent and its analogs,[23] and Thiol activated H_2S donors.[13] Structures of herbal meals releasing H_2S on digestion are proven in consuming mushrooms, garlic, and onions, which include chemical substances and enzymes accountable for the transformation of the sulfur compounds, which are accountable for H_2S production in the human intestine.[19]

Naturally occurring donors, presently handy H_2S-releasing compounds can be divided into two groups: Naturally taking place donors and artificial donors. Among the herbal source, allium household, and cruciferous greens are identified to be prosperous in organosulfur compounds.[24] Among Cruciferae, veggies such as broccoli, watercress, mustard, and garden cress are wealthy in isothiocyanates, such as sulforaphane (notably existing in broccoli), allyl isothiocyanate (pretty current in black mustard), benzyl isothiocyanate (relatively current in backyard cress), 4-hydroxybenzyl isothiocyanate (quite current in white mustard), and erucin (basically current in broccoli and rocket).[25]

H_2S -RELEASING THERAPEUTICS

The literature proof suggests that H_2S possesses the following activities: Anti-inflammatory,[26] anti-tumor,[27] ion channel regulation,[28,29] cardiovascular protection,[30] and antioxidation.[31] However, the actual function that H_2S performs relies on on the precise circumstance, its concentration, and the interplays with different signaling molecules, in particular NO and CO.[14] This is an important location of lookup in growing H_2S-based therapeutics.[32] There are additionally a range of therapeutics on world markets that can generate H_2S *in vivo* and the place there is at least some proof of H_2S contributing to their therapeutic benefits. Indeed, several beneficial effects of H2S for chemoprevention through reducing oxidative stress, and attenuating inflammation.[29,33] In rodent models, it has been proven to limit the formation of quite a number of cancers (colon, bladder, blood, liver, kidney, pancreas, lung, and mammary).[33] There is proof that the anticancer outcomes may additionally be mediated through activation of Nfr_2,[34] a signaling pathway recognized to be activated by means of H_2S.[35]

BIOLOGICAL EFFECTS OF H_2S IN THE ENDOCRINE DISORDERS INDUCED BY CHEMO AND RT

Pancreas

CYP toxicity influences many organs, inclusive of the pancreas, and is exotic through glutathione depletion, lipid peroxidation, altered DNA profile, proinflammatory response, and apoptosis.[36] In CYP intoxicated mice, the pancreatic acini confirmed focal average hydropic degeneration, as nicely

as average edema and congestion. Besides, the Langerhans islets have been markedly irregular and decreased in size, with atrophic and shrunken cells.[7]

Radiation-induced damage of the endocrine and exocrine pancreas. DM has been located in preceding retrospective studies.[16,37] DM has been pronounced in 1.03–8.3% of survivors. In youth and younger adults who have acquired complete physique irradiation traumatic brain injury or stomach irradiation, there is a threat of diabetes, which is associated to the whole dose of radiation administered to the tail of the pancreas the place the islets are concentrated.[16]

The essential roles of H_2S in the pancreas are defending pancreatic β-cells and regulating insulin secretion. H_2S may also guard pancreatic b-cells in the following three methods that consist of reduce the manufacturing of reactive oxygen species (ROS), which inhibit the expression of thioredoxin binding protein-2-a redox protein related with diabetes that promotes apoptosis and enlarge the content material of glutathione (GSH), all of which minimize the harm of oxidative stress.[38] On the contrary, an excessive awareness of H_2S induces apoptosis of pancreatic b cells.[39] Insulin secretion is affected by means of many factors. It is recognized that the attention and oscillation of Ca^{2+}, KATP channel is associated to H_2S.

H_2S can no longer solely inhibit the entry of Ca^{2+} from the plasma membrane into cells, to minimize insulin secretion, however additionally promote the launch of Ca^{2+} in mitochondria, and amplify insulin secretion.[40] It is properly known that an excessive awareness of glucose can promote insulin secretion.[41]

H_2S promotes thyroid dysfunction induced by chemo and RT

CYP can purpose thyroid injury and alternate thyroid function.[5] There are several pathophysiological mechanisms for thyroid dysfunction that has been defined as (1) version due to lively hypothalamic–pituitary axis involvement; (2) altered synthesis or clearance of thyroid hormone (TH) binding proteins detected in sure malignancies or brought about by means of most cancers cure that modifications complete however no longer free awareness of THs; and (3) alteration of THs metabolism, which can happen in chronically unwell most cancers patients.[42] A discount of THs may want to reason a proliferation arrest in G0–G1 in most cancers' cells, with viable influences on their sensitivity to chemotherapy agents.[43]

Gamma radiation-induced thyroid problems are customary problems after RT in sufferers with head and neck cancer. The thyroid gland is a predominant endocrine organ producing THs for keeping metabolism. Injury to the thyroid gland due to radiation can also result in momentary thyroiditis and hypothyroidism (HT). Moreover, post-RT-HT is related with the accumulative radiation dose to the thyroid gland.[44] RT-induced thyroid abnormalities continue to be under-estimated and beneath reported. These sequelae might also encompass principal or central HT, thyroiditis, Graves' disease, euthyroid Graves' ophthalmopathy, benign adenomas, multinodular goiter, and radiation – brought on thyroid carcinoma.[45] External-beam RT induces more than a few thyroid disorders, such as important HT (6–89%), Hashimoto's thyroiditis (0.7–48%), benign adenoma (0.6–3%), silent thyroiditis (0.6–3%), Graves' ailment (0.1–2%), Graves' ophthalmopathy (0.2–1.3%), and thyroid most cancers (0.35%).[45] The most frequent thyroid illnesses following publicity to ionizing radiation are hypofunction and thyroid nodules. However, the expanded incidence of thyroid cancers may additionally be worried in these diseases.[46]

The pathophysiological description of radiation-induced thyroid injury is associated to inhibition of follicular epithelial feature and subsequent innovative alteration of the endothelium, the impact will increase through time.[47]

Even although oxidative reactions take region in all tissues and organs, the thyroid gland constitutes such an organ in which oxidative approaches are vital for TH synthesis. It is estimated that massive quantity of ROS, specifically of H_2O_2, are shaped in the thyroid below the physiological situation. Yet, with extra oxidative mistreatment triggered with the aid of IR, multiplied injury to macromolecules occurs, probably main to one-of-a-kind thyroid diseases, most cancers included.[48]

Both anaplastic and papillary thyroid cancers are inhibited by means of H_2S, in anaplastic cancer, H_2S reasons the accumulation of ROS, which inhibits cell survival and will increase apoptosis. Besides that, it promotes phone DNA injury and reasons the cell cycle to end in the G2/M phase.[49] H_2S inhibited cell growth in papillary carcinoma.[50]

Uncertainty of the effect of H_2S on testicular damage

CYP reasons reproductive toxicity, consisting of azoospermia, oligospermia, histological adjustments in the epididymis and testis, diminished weight of reproductive organs, and impaired fertility and growth in people and experimental animals. Due to the excessive frequency of cell division in the cells of the seminiferous epithelium, the testis is extraordinarily touchy to chemotherapeutic drugs.[51] CYP handled male rats confirmed low serum attention of testosterone collectively with low serum follicle stimulating hormone and luteinizing hormone (LH). CYP motives extensive minimize in recreation of testicular steroidogenic enzymes which are the key enzymes for biosynthesis of testosterone.[52]

Decreased reproductive organ weights, oligo-, azoo- and teratozoospermia, low stages of testosterone and LH, atrophied seminiferous tubules, degenerated spermatogenic cells, and apoptosis are some of the damaging consequences caused through CYP.[53]

The expand in free radicals in cells can set off lipid peroxidation by means of oxidative breakdown of polyunsaturated fatty acids in the membranes of these cells. Obviously, peroxidation of sperm lipids destroys the shape of the lipid matrix in the plasma membranes, and it is related with fast loss of intracellular ATP, main to axonemal damage, lowered sperm viability and, in severe cases, even whole inhibition of spermatogenesis.[54] In addition to typical endocrinological imbalances such as ovarian failure, atypical sperm manufacturing decreased fertility and outcome, lowered implantation, and malformed or increase retarded fetuses.[55]

Testis tissue, radiosensitive organ, has a range of cells that range in their diploma of radiosensitivity. The spermatogonia are very radiosensitive and kill at doses much <3 Gy in differentiation period. The infertility following irradiation is induced due to apoptosis of spermatogonia alternatively of turning into differences.[18] The germinal epithelium is very touchy to radiation-induced injury with adjustments in spermatogonia following doses as low as 0.1 Gy and everlasting infertility after fractionated doses of two *Gy* and above.[56]

The deleterious consequences of irradiation in organ structures are on the whole mediated thru the era of ROS and cause lipid peroxidation in the cell membrane, thereby inducing DNA injury in immature germ cell's, DNA injury prompted by means of irradiation in premeiotic germ cells is detectable in essential spermatocytes and is nevertheless existing in mature spermatozoa.[57]

H_2S regulates testosterone secretion with the aid of influencing LH secretion, indicating that H_2S may also play an essential position in testosterone secretion.[58] It blanketed the testis from chemotherapeutic drug-induced oxidative stress and irritation and elevated the recreation of antioxidant enzymes.[59] The expression of CBS and CSE is located in rat testes; however, they are differentially expressed; CSE is ordinarily expressed in Sertoli cells and immature spermatogonia, while CBS is basically allotted in Leydig cells, Sertoli cells, and germ cells.[60]

Effect of H_2S on adrenal gland

Adrenal glands, which are concerned in the body's response to stress phenomena, exhibit organ hypertrophy after a quick length of CYP administration, with physique weight relative growing and glucocorticoids hormones extreme secretion.[8]

The impact of experimental irradiation of rats in the long-term duration is accompanied by accumulation of malondialdehyde (MDA) in spleen, adrenal glands, and lymph nodes of the small intestine.[61] The principal mechanism of the radiation-induced regular tissues injury is the response of radiation with water *in vivo* to generate immoderate ROS which is a most important inducer of apoptosis. Increasing proof suggests that ROS, MDA, superoxide

dismutase, and GSH peroxidase are oxidative-stress-related. Antioxidants or free radical scavengers can also provide safety toward radiation-induced harm to hepatic and different tissues.[44] H_2S can have an effect on the adrenal cortex and chromaffin cells in the adrenal gland. Inhibiting CBS/CSE can purpose mitochondrial oxidative stress and dysfunction in the adrenal cortex.[33]

The role of H_2S in hypothalamus and pituitary gland

Chemotherapy CYP has been linked to hypothalamic–pituitary dysfunction in childhood most cancers survivors, manifesting as deficiencies of man or woman hormones or, in some cases, a couple of hormone deficiencies.[62]

It has, additionally, been mentioned that this anticancer agent might also have a poor influence on talent.[63] vascular complications, seizures, and peripheral neuropathies synthesis by way of impairing neurogenesis and synaptic plasticity in hypothalamus. The majority of this neurotoxicity may want to be attributed to the improvement of oxidative stress.[64]

CYP prompted a hemorrhagic lesion and congestion of veins and capillaries, parenchymal cells manifested scanty and hypertrophied, and vacuolation of interstitial areas in the pituitary gland.[65]

Damage to the hypothalamic pituitary axis has been diagnosed as an aspect impact of radiation remedy to the base of skull. Effects brought about through non-lethal events at the cellular level are referred to as "stochastic effects." These have no dose threshold, and their incidence is associated to radiation dose; however, the severity of the impact is no longer dose related. In contrast, outcomes mediated by means of cell killing and ordinary tissue dysfunction are known as "deterministic" (or "non-stochastic") effects. These toxicities frequently have a dose threshold, and each the incidence and severity of the impact are dose associated.[66]

RT is a frequent reason of hypothalamic-pituitary dysfunction in most cancers' sufferers.[67] The hypothalamus and pituitary gland are localized shut collectively and engage using the hypothalamic–pituitary–adrenal and–gonadal axis. Several researches confirmed predominant characteristic loss of the hypothalamus. Growth hormone (GH) deficiency is the most familiar endocrine dysfunction after hypothalamus–pituitary gland irradiation, taking place at tremendously low doses.[68]

The hypothalamic–pituitary–target organ axis is a complicated organic structure, which performs an essential function in endocrine regulation. H_2S is disbursed in more than one sites in the hypothalamus, pituitary–target organ, making it an essential molecule in regulating hormone secretion, which is no longer solely twin, however additionally bi-directional, that is, H_2S now not solely promotes that the secretion of certain hormones, however, can additionally inhibit them. The complex effect of H_2S on the endocrine system may be caused by its action on different organs.[69]

H_2S is concerned in several physiological and pathological approaches in the body, together with dilating blood vessels (regulating blood pressure), defending tissue from ischemia-reperfusion injury, anti-inflammatory, carcinogenesis, or most cancers inhibition, and regulating hormonal metabolism through the hypothalamus and pancreas.[69]

The learn about determined that hormones produced by way of the hypothalamus–pituitary axis have an effect on H_2S synthesis. TH and GH alter H_2S manufacturing in the liver with the aid of the TH receptor b1 and the GH receptor, respectively. In mechanism, TH inhibits CSE expression, while GH inhibits H_2S manufacturing by substrate availability manipulate with the aid of autophagy.[70]

CONCLUSION

H_2S can protect endocrine organs against side effects of chemotherapy and RT in addition to regulate hormone secretion through antioxidative stress and ion channel regulation.

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