FOLIA MEDICA CRACOVIENSIA
Vol. LXVI, 1, 2026: 69–79
PL ISSN 0015-5616 eISSN 2957-0557
DOI: 10.24425/fmc.2026.158986

High-fat diet-induced obesity affects sulfurtransferases activity in mice hearts

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Abstract: Introduction: Obesity is a chronic disease with complex etiology, characterized by excessive accumulation of fat tissue, which poses a health hazard and increases, among others, risk of cardiovascular diseases. Hydrogen sulfide (H_2S), an endogenous gaseous transmitter, plays an important role in the cardiovascular system, affecting blood pressure and heart function.
Aim: The aim of this study was to determine the effect of high-fat diet-induced (HFD-induced) obesity to hydrogen sulfide metabolism in mice hearts.
Materials and Methods: The research material consisted of hearts collected from male wild-type C57BL/6 mice fed for 8 weeks with a normal diet (ND) or high-fat diet. *Ex vivo* analyses included testing the activity of selected sulfur enzymes (cystathionine gamma-lyase — CGL, 3-mercaptopyruvate sulfurtransferase — MPST, and thiosulfate sulfurtransferase — TST), determining the sulfane sulfur level, and examining the ability of tissues to produce hydrogen sulfide.
Results: Tissues collected from HFD-fed mice were characterized by a lack of CGL activity, increased TST activity, and higher levels of sulfane sulfur compared to group of ND mice. Additionally, the capacity to produce H_2S was higher in the hearts of HFD mice.
Conclusions: Our study shows that HFD-induced obesity affects hydrogen sulfide levels and sulfur enzyme activity in mice hearts. It can be speculated that the increased ability of HFD mice tissues to produce H_2S is a compensatory mechanism for obesity-induced changes. The conducted research indicates the key importance of sulfurtransferases, MPST and TST, in sulfur metabolism in the heart and indicates a new area for further analysis.

Keywords: hydrogen sulfide, thiosulfate sulfurtransferase, 3-mercaptopyruvate sulfurtransferase, high-fat diet, obesity, heart.

Submitted: 19-Dec-2025; **Accepted in the final form:** 30-Jan-2026; **Published:** 31-Mar-2026.

Introduction

Obesity is a disease characterized by the harmful effects of excess body fat on health. In clinical practice, the degree of obesity is usually assessed using the body mass index (BMI) — the ratio of body weight in kilograms to height in square meters (kg/m^2). [1] According to a report by the World Health Organization, in Europe alone, almost 60% of adults and nearly 8% of children are overweight or obese. [2] The accumulation of excess body fat leads to insulin resistance, glucose intolerance, type 2 diabetes, increased blood pressure, dyslipidemia, inflammation, and endothelial damage. All of these factors are considered cardiovascular risk mediators and may result in hypertension, coronary artery disease, heart failure, arrhythmia, atrial fibrillation, and premature sudden death. [3]

There are many causes of obesity, including unhealthy diet, lack of physical activity, genetic, hormonal, and psychological factors (such as stress or sleep disorders), socio-economic factors, and lack of education. [4] In the context of contemporary social changes, the issue of diet deserves special attention, including the increasingly widespread use of the so-called Western diet (WD). WD is high in calories and low in nutritional density. It includes nutrient-poor foods that are high in added sugar, salt, and saturated fat, such as fast food, sugary beverages, and highly processed food. [5] In animal research models, a high-fat diet (HFD) is considered a well-established model of the western diet. [6]

An inappropriate diet not only leads to obesity, but also to disturbances in the homeostasis of the organism and the development of oxidative/nitrosative stress, i.e. increased production of free radicals, such as reactive oxygen species and reactive nitrogen species. Physiological free radicals such as superoxide anion radical ($\bullet O_2^-$) and nitric oxide ($\bullet NO$), and their derivative — peroxynitrite ($ONOO^-$), are important modulators of many diseases, including cardiovascular disease. [7]

In the cardiovascular system, hydrogen sulfide (H_2S), an endogenously produced gaseous signaling molecule, has significant cardioprotective effects related to its vasodilatory properties. [8, 9] H_2S has been shown to protect against heart failure by stimulating angiogenesis, stimulating cardiac mitochondrial biogenesis, and activating endothelial nitric oxide synthase. [9] Therefore, hydrogen sulfide donors appear to be particularly useful therapeutic agents. The presence of sulfur atom/thiol group (-SH) in the structure of antihypertensive drugs from angiotensin-converting enzyme inhibitors (ACEI) group may intensify the cardioprotective effect of these medicine. [10]

In mammalian cells, H_2S is formed from L-cysteine in reactions catalyzed by three enzymes: cystathionine beta-synthase (CBS), cystathionine gamma-lyase (CGL), and 3-mercaptopyruvate sulfurtransferase (MPST). Additionally, hydrogen sulfide can be produced by the reduction of sulfane sulfur-containing compounds. [8] An important role in the metabolism of endogenous sulfur, is played by the enzyme thiosulfate sulfurtransferase (TST), which participates in the transsulfuration reaction. It catalyzes the transfer of sulfane sulfur from thiosulfate to thiol or cyanide, leading to the formation of persulfides or thiocyanates. [11] TST is a protein related evolutionarily to MPST and it is hypothesized that both may cooperate, including in eliminating the effects of oxidative stress. [12]

The aim of this study was to determine the effect of high-fat diet-induced obesity on the ability of mice heart tissue to produce hydrogen sulfide and on the activity of selected enzymes involved in sulfur metabolism. This work is a continuation of our previous experiments focusing on sulfur metabolism in tissues of animals with diet-induced obesity.

Materials and Methods

Animals and tissue collection

This examination was a continuation of our earlier study [13] evaluating the metabolism of sulfur-containing compounds in visceral adipose tissues collected from animals on normal (ND) or high-fat diet (approval no. 43/2017 of the 1st Local Ethics Committee for Animal Experiments in Cracow).

12-week-old wild-type C57BL/6 male mice from Jackson Laboratory (Bar Harbor, Maine, USA) were bred and kept under standardized conditions (light: dark cycle 12:12h, temperature 22°C, humidity 55%) with free access to food and water. The first group of animals (n = 7) were maintained on a standard/normal diet. To induce obesity, a second group of C57BL/6 mice (n = 7) were fed a high-fat diet D12492 from Research Diets, Inc. (New Brunswick, USA) *ad libitum* for 8 weeks. The energy sources in both diets and their caloric values are shown in Fig. 1. Mice body weight was monitored using a digital scale (Scout Pro Electronic Balance, Ohaus).

For tissue collection, the skin of mice anesthetized with a ketamine/xylazine cocktail (90 mg/kg body weight ketamine and 10 mg/kg body weight xylazine) was sterilized with 70% ethanol, and the thorax was incised to expose the heart. The entire heart was removed using sterile scissors and forceps. The tissue was placed in sterile tube, immediately frozen in liquid nitrogen, and stored at –80°C until further use.

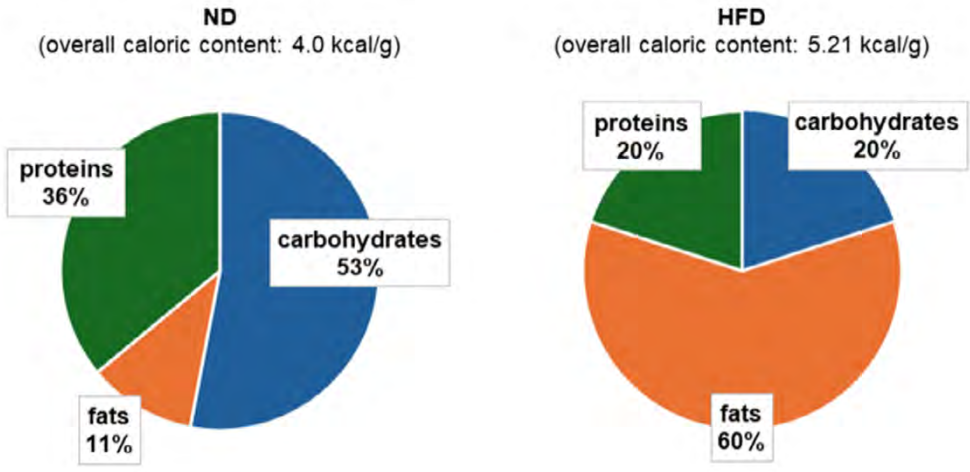

Fig. 1. Caloric composition of normal diet (ND) and high-fat diet (HFD) fed to animals.

Tissue homogenates

Sulfur enzyme activity, sulfane sulfur level, hydrogen sulfide production, and protein content were determined in mice heart homogenates prepared according to the procedures described in our previous work. [14] The obtained preparations were used immediately for further analyses.

Enzyme assay and determination of sulfane sulfur level

Cystathionine gamma-lyase activity was tested using the Matsuo and Greenberg method, [15] 3-mercaptopyruvate sulfurtransferase activity was determined according to the method of Valentine and Frankelfeld, [16] and thiosulfate sulfurtransferase activity was assayed by the Sörbo's method. [17] All these methods were modified by Wróbel *et al.* [18] The full composition of the reaction mixtures used and detailed procedures were described in our previous work. [19]

Sulfane sulfur was determined by Wood's cold cyanolysis method, [20] according to the procedure described previously. [19]

Protein content

Protein content in tissues was determined by the method of Lowry *et al.* [21] Crystalline bovine serum albumin was used as a standard.

H_2S production

The production of H_2S was examined by colorimetric method. [22, 23] The detailed composition of the reaction mixture and the experimental conditions were as described previously. [19]

Statistical analysis

All results are presented as arithmetic means ± standard error of the means. The Shapiro-Wilk test and Levene's test were used to assess the normal distribution of data and to analyze the homogeneity of variance. Statistical analysis was performed in StatSoft Statistica 13 software (Tibco, Palo Alto, California, USA) using the parametric Student's t test or the nonparametric Mann-Whitney test, as appropriate. Differences were considered statistically significant at the first level with a p value <0.05, at the second level when $p <0.01$, and at the third when $p <0.001$.

Results

Animal parameters

Fig. 2 shows the mean body weights of the animals at the zero point of the experiment (12-week-old animals) and after 8 weeks of feeding with a normal diet or a high-fat diet (20-week-old animals). In the ND group, a 31% weight gain was recorded during the experiment. In contrast, the HFD group of mice showed a 75% increase in mean body weight, confirming the occurrence of obesity in these animals.

There were no statistically significant differences in the weight of hearts collected from animals fed the normal diet (mean weight 0.164 ± 0.003 g) and the high-fat diet (mean weight 0.158 ± 0.013 g) (data not shown).

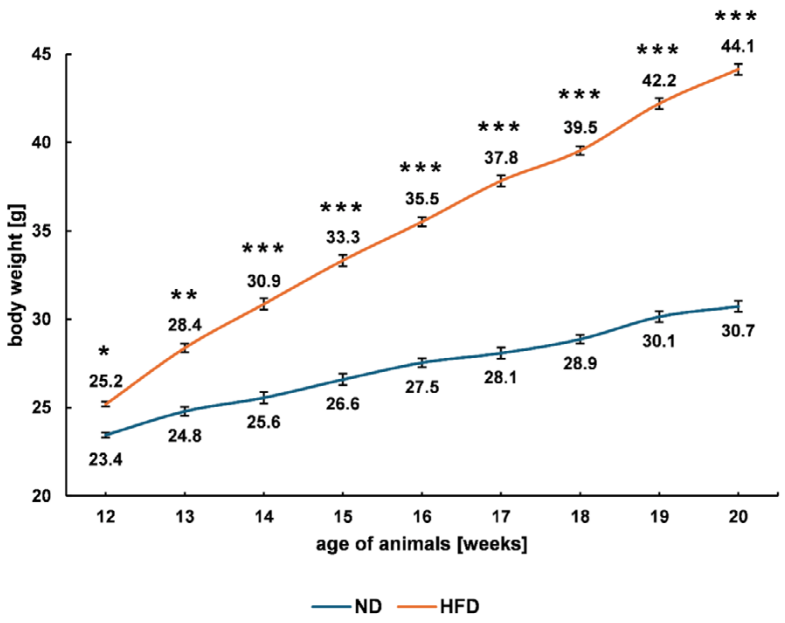

Fig. 2. Body weight changes of C57BL/6 mice fed a normal diet (ND) and a high-fat diet (HFD).
Values are represented as arithmetic mean ±SEM of 7 animals. *p<0.05, **p<0.01, ***p<0.001 high fat diet (HFD) vs. normal diet (ND) (Mann-Whitney test).

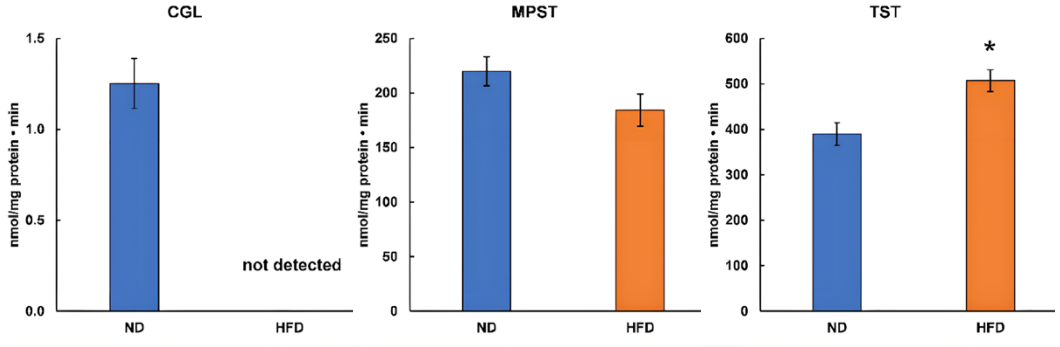

Fig. 3. The activity of cystathionine gamma-lyase (CGL), 3-mercaptopyruvate sulfurtransferase (MPST), and thiosulfate sulfurtransferase (TST) in mice hearts.
Values are presented as the arithmetic mean ±SEM of 3 animals. Each value is the mean of 10–15 repeats. *p<0.05 high fat diet (HFD) vs. normal diet (ND) (Mann-Whitney test).

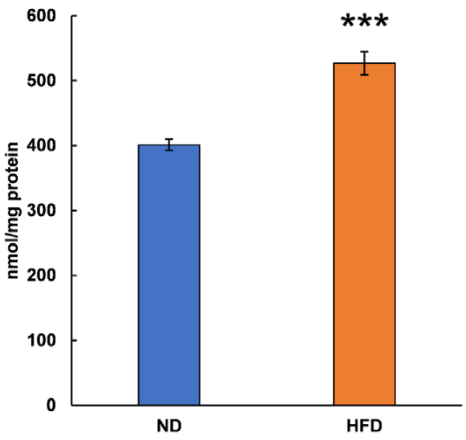

Fig. 4. The level of sulfane sulfur in mice hearts. Values are presented as the arithmetic mean ±SEM of 3 animals. Each value is the mean of 10–15 repeats. ***p<0.001 high fat diet (HFD) vs. normal diet (ND) (Mann-Whitney test).

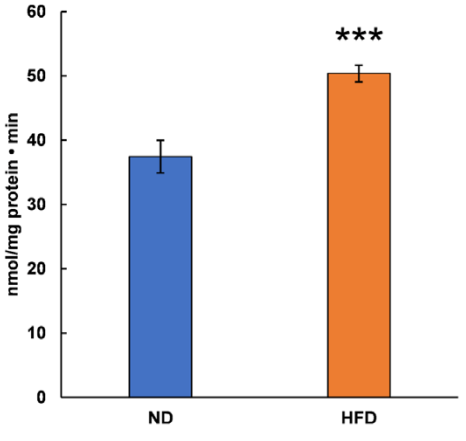

Fig. 5. Hydrogen sulfide (H_2S) production in mice hearts.
Values are presented as the arithmetic mean ±SEM of 4 animals. Each value is the mean of 10–12 repeats. ***p<0.001 high fat diet (HFD) vs. normal diet (ND) (Student's t test).

Enzymes activity and sulfane sulfur level

Enzymes activity in mice hearts are shown in Fig. 3. Low CGL activity was noticed in the tissues of animals fed a normal diet, while no CGL activity was detected in the HFD group. There were no statistically significant changes in MPST activity between the study groups. TST activity was significantly higher in the hearts of HFD mice compared to ND mice. Similarly, sulfane sulfur level increased significantly in the group of animals on the high-fat diet (Fig. 4).

H_2S production

The ability to generate hydrogen sulfide was confirmed in the tissues of animals from both study groups (Fig. 5). Hearts of HFD mice were characterized by significantly higher H_2S production.

Discussion

Obesity has been implicated as an indirect cause of heart disease for decades. Numerous studies in humans and animal models have shown that obesity leads to lipid accumulation in the heart, leading to cardiac steatosis. [24] Cardiac lipotoxicity, cardiomyocyte dysfunction and myocardial contractility dysfunction, is caused particularly by the deposition of saturated free fatty acids in heart cells. [25] The research by Alpert *et al.* [26] confirms the presence of left ventricular hypertrophy and impaired systolic and diastolic function in morbidly obese individuals, with the degree of impairment correlated with the duration of obesity. Left ventricular remodeling, along with increased heart rate and stroke volume, are characteristic of obesity and are thought to be

compensatory adaptations to increased adipose tissue mass. However, over time, they can lead to ischemic dilated cardiomyopathy. [27]

In this study, we focus on the changes in hydrogen sulfide metabolism induced in mice hearts by a high-fat diet. The results show that obesity determines the cardiac activity of sulfur enzymes. The new finding of this work is the important role of the TST enzyme in H_2S metabolism in the hearts of obese mice.

Cystathionine gamma-lyase has been the subject of interest of many research groups for many years as the main enzyme responsible for hydrogen sulfide production in the circulatory system. [28, 29, 30] CGL catalyzes the formation of H_2S from L-cysteine with the release of pyruvate. It can also induce the formation of thiosulfate from L-cystine and is responsible for the catabolism of cystathionine occurring on the pathway of L-cysteine formation from L-methionine. [31] Analysis of enzyme activity showed that the low CGL activity in the hearts of mice fed normal diet was reduced to undetectable level in HFD-fed animals. These results are consistent with immunohistochemical evaluation of CGL performed by Peh *et al*., [32] which showed a significant reduction or absence of CGL in aortic endothelial cells in C57BL/6 mice fed HFD for 16 weeks relative to mice on a standard diet. However, this change was not associated with a reduced ability of these tissues to produce hydrogen sulfide. These results indicate that other enzymes besides CGL are involved in maintaining the H_2S pool in heart cells.

Studies by various groups of scientists indicate the significant importance of 3-mercaptopyruvate sulfurtransferase in maintaining the proper functioning of the cardiovascular system. It has been shown that knockout of the MPST enzyme causes hypertension and cardiac hypertrophy in 18-month-old mice compared to younger animals. [33] Another study [34] showed that coronary rat homogenates produce larger amounts of hydrogen sulfide through the enzymatic pathway using MPST (desulfuration of 3-mercaptopyruvate leading to the formation of sulfane sulfur-rich compounds [35]) than through CGL. Our previous studies [14] in the rat model of hypertension also confirm that 3-mercaptopyruvate sulfurtransferase plays a major role in H_2S production in the heart. However, studies conducted on mice with HFD-induced metabolic syndrome did not show any changes in MPST expression at the protein level in the hearts of these animals compared to control mice. [36] Similarly, no changes were observed in the cardiac levels of free hydrogen sulfide and sulfane sulfur. The same study [36] and study by Katsouda *et al.* [37] showed that MPST knockout in mice resulted in increased pathological changes associated with metabolic syndrome (increased body weight, impaired glucose tolerance) and contributed to vascular inflammation. On the other hand, reports on MPST expression in other tissues of the body are contradictory — Li *et al.* [38] report that MPST expression in the liver at protein level increases in C57BL/6 mice fed a high-fat diet for 8 weeks, while Peh *et al.* [32] indicate a decrease in the hepatic MPST protein level in the same animal model after 8, 12, and 16 weeks of HFD application.

In this study, we did not observe significant changes in MPST activity in mice hearts under the influence of the high-fat diet. However, the obtained results suggest a tendency towards reduced activity of this enzyme in HFD-fed mice, which may be related to its antioxidant potential. Cysteine (Cys) located in the catalytic center of the enzyme and having reducing properties, plays a particularly important antioxidant role. The presence of Cys allows the reduction of oxidizing compounds such as reactive oxygen species, but also causes the inactivation of MPST. [39]

Another important enzyme involved in sulfur metabolism is mitochondrial thiosulfate sulfurtransferase. There are reports suggesting that persistent oxidative stress (especially in the

mitochondrial region) may lead to the induction of TST, which (in cooperation with MPST) regulates the level of sulfane sulfur, reduced glutathione or thioredoxin, causing an antioxidant effect. [12] In the current experiment, we observed a significant increase in cardiac TST activity under the influence of HFD, which may result from the activation of the mentioned antioxidant mechanism. Similarly, the level of sulfane sulfur was significantly higher in the HFD mice group. It is worth emphasizing that TST, although not classified as an H_2S-producing enzyme, catalyzes the reaction of thiosulfate with glutathione to produce hydrogen sulfide. [31] The presented results confirm that TST activity plays an important role in the metabolism of hydrogen sulfide in obese mice.

The increased bioavailability of sulfane sulfur (direct hydrogen sulfide precursor [40]) in HFD mice tissues explains the high capacity of these tissues to generate H_2S and may be due to its physicochemical properties. Elemental sulfur is characterized by high solubility in lipids. [41] Studies on obesity, both in humans and using animal models, [42, 43, 44] confirm that the heart is an important absorber of fatty acids from the plasma due to its high energy demand. At the same time, uptake of fatty acids from the circulation prevents their harmful effects on other tissues such as the pancreas. [43]

A limitation of our study is that we used only a male research model. Since there are reports of gender differences in cardiovascular risk, [45] further studies should be performed with a female research model. In addition, studies using an animal model have some inherent limitations, including the number of animals in each experimental group. The relatively small number of n in our research groups can be considered a limitation of this study.

Conclusions

In summary, high-fat diet-induced obesity affects hydrogen sulfide levels and sulfur enzyme activity in mice hearts. The increased capacity of heart tissue from mice fed a high-fat diet to produce H_2S could be interpreted as a compensatory mechanism aimed at counteracting obesity-induced changes, such as metabolic disorders or oxidative stress. Enzymatic analysis highlights the critical role of sulfurtransferases, MPST and TST, in cardiac sulfur metabolism, suggesting their key role in regulating hydrogen sulfide levels and maintaining redox balance in cardiac tissue. This demonstrates a potential role for these enzymes in cardiac adaptation to obesity and provides a new area for further investigation to understand the mechanisms behind obesity-related cardiovascular disease.

Declaration of competing interest

The authors declare no competing interests related to the present study.

Authorship contribution statement

D.S.: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing — original draft, writing — review and editing; A.M.-K.: data curation, formal analysis; M.M.-S.: data curation, funding acquisition, methodology; P.B.-A.: conceptualization, data curation, funding acquisition, project administration, supervision, writing — review and editing.

Funding

This work was supported by the Polish Ministry of Science and Higher Education (grants no. N41/DBS/000938 and K/ZDS/007123).

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