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Sodium Orthovanadate Changes Fatty Acid Composition and Increased Expression of Stearoyl-Coenzyme A Desaturase in THP-1 Macrophages

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Abstract

Vanadium compounds are promising antidiabetic agents. In addition to regulating glucose metabolism, they also alter lipid metabolism. Due to the clear association between diabetes and atherosclerosis, the purpose of the present study was to assess the effect of sodium orthovanadate on the amount of individual fatty acids and the expression of stearoyl-coenzyme A desaturase (SCD or Δ^9-desaturase), Δ^5-desaturase, and Δ^6-desaturase in macrophages. THP-1 macrophages differentiated with phorbol 12-myristate 13-acetate (PMA) were incubated in vitro for 48 h with 1 μM or 10 μM sodium orthovanadate (Na_3VO_4). The estimation of fatty acid composition was performed by gas chromatography. Expressions of the genes *SCD*, *fatty acid desaturase 1* (*FADS1*), and *fatty acid desaturase 2* (*FADS2*) were tested by qRT-PCR. Sodium orthovanadate in THP-1 macrophages increased the amount of saturated fatty acids (SFA) such as palmitic acid and stearic acid, as well as monounsaturated fatty acids (MUFA)—oleic acid and palmitoleic acid. Sodium orthovanadate caused an upregulation of *SCD* expression. Sodium orthovanadate at the given concentrations did not affect the amount of polyunsaturated fatty acids (PUFA) such as linoleic acid, arachidonic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). In conclusion, sodium orthovanadate changed SFA and MUFA composition in THP-1 macrophages and increased expression of *SCD*. Sodium orthovanadate did not affect the amount of any PUFA. This was associated with a lack of influence on the expression of *FADS1* and *FADS2*.

Keywords Sodium orthovanadate · Fatty acids · Macrophage · THP-1 · Desaturase

Introduction

Vanadium is a metal that forms numerous inorganic compounds and complexes with organic substances. They are the subject of growing interest among researchers thanks to their antitumor properties [1]. All vanadium compounds are competitive inhibitors of protein tyrosine phosphatases (PTP) [2, 3]. In experiments on cancer cells, vanadium compounds inhibited cell cycle at checkpoints G_0/G_1, G_1/S, and G_2/M [4–9]. This is partly related to the inactivation of PTP involved in the correct course of the cell cycle [10]. Vanadium compounds also act pro-apoptotically on tumor cells [4–7, 9]. In particular, they cause the opening of the mitochondrial permeability transition pore which initiates apoptosis [11]. They also increase the expression of Bax and decrease the expression of Bcl-2, i.e., proteins regulating apoptosis [9]. Vanadium compounds also inhibit the epithelial–mesenchymal transition, which inhibits the formation of tumor metastases [12]. Due to these properties, they are intensively tested for use as antineoplastic drugs [1, 13].

There are also advanced studies on the potential use of vanadium compounds in the treatment of diabetes [14, 15]. Vanadium compounds, due to the inhibition of PTP, increase the phosphorylation of proteins on tyrosine residues. This causes changes in various signaling pathways. In particular, vanadium compounds by inhibiting PTP-1B cause an increase in phosphorylation of the insulin receptor [16–19]. Thanks to

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this, they abolish insulin resistance and potentiate the effect of insulin. They also strengthen the signal transmission from the insulin receptor and inhibit phosphatase and tensin homolog (PTEN). PTEN is an enzyme that catalyzes a reverse reaction to that catalyzed by phosphatidylinositol 3-kinases (PI3K) [20]. Nevertheless, vanadium compounds not only increase the action of insulin but also exert other acts than insulin. They can inhibit the activity of protein kinase A (PKA) which inhibits gluconeogenesis and lipolysis [21]. Vanadium compounds, when compared with insulin, also have a more promitogenic effect inter alia, by affecting the activity of mitogen-activated protein kinases (MAPK) cascades [22].

Previous studies carried out in vivo [23–25] and in vitro [26] confirm the antidiabetic and insulin-enhancing properties of vanadium compounds, in particular vanadyl sulfate ($VOSO_4$), sodium orthovanadate (Na_3VO_4), and the organic derivatives: bis(ethylmaltolato)oxovanadium(IV) (BEOV) and bis(maltolato)oxovanadium(IV) (BMOV). These compounds reduce blood glucose levels in many ways. In the muscles, they increase the expression of GLUT4, which increases the absorption of glucose from the blood. In liver and muscle cells, vanadium compounds stimulate glycogen synthesis [27] and increase glucose processing via the glycolysis pathway [27, 28]. They also reduce the intensity of gluconeogenesis [29]. Vanadium compounds also reduce cholesterol and LDL levels, which were very elevated in streptozotocin-induced [30] or alloxan-induced [31] diabetic rats. Vanadium compounds also cause an increase in the number of beta-cells in the pancreas of streptozotocin-induced diabetic rats [24, 25]. Clinical trials involving $VOSO_4$ have shown that vanadium compounds can be used in therapy [32–34]. It was shown that at a blood concentration of approximately 4 μM (75 mg $VOSO_4$ daily, route of administration: oral 5 mg/day/kg body weight $VOSO_4$) was not toxic, even after 6-week therapy of patients with type 2 diabetes mellitus (T2DM) [33, 34] or supplementation with insulin through 2.5 years of therapy of patients with type 1 diabetes mellitus (T1DM) [32]. In a higher dose (300 mg orally), it caused mild diarrhea and malaise [32]. However, the therapeutic window for vanadium compounds is very narrow. Vanadium compounds in a dose above 30 mg/day/kg body weight are toxic, cause oxidative stress, and are harmful to the liver and kidneys. That has been proven in experiments on broilers [35] and on rats [36] and mice [36]. Vanadium compounds accumulate in the acidic environment of mitochondria in the form of decavanadate, which disturbs the functioning of these organelles [37, 38].

Diabetes has not only increased blood glucose levels, but also increased levels of plasma lipids, such as total cholesterol, low-density lipids (LDL), and triglyceride (TAG) as demonstrated in streptozotocin-induced [30] or alloxan-induced [31] diabetic rats as well as in patients with T2DM [39]. Increased blood glucose causes oxidative stress and inflammatory reactions in the blood vessels [40]. This process, combined with an increased amount of lipids in the plasma, causes the formation of oxysterols which are accumulated in macrophages [41]. This results in the formation of foam cells in the blood vessels and inflammation, resulting in atherosclerotic lesions. This increases the prevalence of atherosclerosis in patients with T2DM [42].

Macrophages play an important role in diseases associated with diabetes, such as nephropathy or diabetic retinopathy [43–45]. Infiltration and accumulation of these cells occur in the kidney and retina, especially in diabetes. In addition, elevated glucose levels result in macrophages producing and secreting various proinflammatory cytokines and reactive oxygen species (ROS) that contribute to the development of diabetic nephropathy and retinopathy.

An important role in the course of atherosclerosis is played by the macrophages and lipid metabolism in these cells. Therefore, the main objective of the study was to investigate the effect of selected vanadium compounds on the concentration of individual fatty acids and the expression of desaturases responsible for the formation of unsaturated bonds in fatty acids in macrophages. THP-1 macrophages grown with sodium orthovanadate at 1 μM and 10 μM were used for this purpose. These are the concentrations at which the vanadium compounds exhibit hypoglycemic properties and do not show toxic properties in humans and laboratory animals [32, 34, 46–49].

Materials and Methods

Cell Culture

THP-1 cells are a monocyte cell line commonly used in research on inflammatory reactions and atherosclerotic mechanisms [50–54]. Cultures of THP-1 cells (ATCC, Rockville, USA) were grown at 37 °C in 5% CO_2 on RPMI-1640 medium (BIOMED-LUBLIN, Poland) with the addition of 10% FBS (ALAB, Poland), along with penicillin (40 U/ml) and streptomycin (40 mg/l) (Sigma–Aldrich, Poland). Cells with a viability of over 97% were placed into 6-well plates, 3×10^6 wells altogether. The number of cells and their viability were determined using a Bright Line Hemacytometer (Sigma–Aldrich, Poznań, Poland) and trypan blue staining [55]. After inoculation, THP-1 monocytes were differentiated into macrophages by adding 100 nM phorbol 12-myristate 13-acetate (PMA) (carrier: DMSO) (Sigma–Aldrich, Poland) to the culture. After 24 h of incubation, the cells were washed with PBS (BIOMED-LUBLIN, Poland) and incubated in Na_3VO_4 (Sigma–Aldrich, Poland) (carrier: PBS). One micrometer and 10 μM Na_3VO_4 were used in the experiment. These concentrations were determined on the basis of in vitro studies on the antidiabetic properties [32, 34, 49, 56] and antineoplastic properties [4–7] of vanadium compounds. Cells were

incubated in a medium supplemented with FBS. After 48 h of incubation with Na_3VO_4, THP-1 macrophages were scraped from the plate. After centrifugation (4 °C, 800×*g*, 10 min), the supernatant was discarded and the obtained cell pellet was frozen at − 80 °C for further analysis.

Isolation and Analysis of Fatty Acid Concentration

The fatty acids from the collected cells were extracted using Folch mixture [57] (2:1, chloroform:methanol), and heneicosanoic acid (21:0) was added as an internal standard to the collected cells. The fatty acids were saponified and methylated with KOH and BF_3 in methanol. Extraction of the obtained fatty acid methyl esters was then carried out with hexane. They were then analyzed by gas chromatography, with the use of an Agilent Technologies 7890A GC System (SUPELCOWAX™ 10 Capillary GC Column (15 m × 0.1 mm × 0.1 μm)) (Supelco, Bellefonte, PA, USA). The following chromatographic conditions were applied: from an initial temperature of 60 °C increasing at a rate of 40 °C/min to 160 °C, then increasing at a rate of 30 °C/min to 190 °C, and then increasing at a rate of 30 °C/min to 230 °C for 2.6 min, where it was maintained for 4.9 min. The total analysis took approximately 8 min. The gas flow rate was 0.8 ml/min; the carrier gas was comprised of hydrogen. The identification of fatty acids was done by comparing their retention times with those of commercially available standards. The fatty acid concentrations were determined based on standard curves and were expressed in mg/ml.

Quantitative Real-time Polymerase Chain Reaction

Quantitative analyses of mRNA expression of stearoyl-coenzyme A desaturase (*SCD*), fatty acid desaturase 1 (*FADS1*), and fatty acid desaturase 2 (*FADS2*) were performed by two-step reverse transcription PCR. Total RNA was extracted from cells using an RNeasy Kit (Qiagen, USA). cDNA was prepared from 1 μg of total cellular RNA in 20 μl of reaction volume using a FirstStrand cDNA synthesis kit and oligo-dT primers (Fermentas, USA). The quantitative assessment of mRNA levels was performed by real-time RT-PCR using an ABI 7500Fast instrument with Power SYBR Green PCR Master Mix reagent. Real-time conditions were as follows: 95 °C (15 s), 40 cycles at 95 °C (15 s), and 60 °C (1 min). According to melting point analysis, only one PCR product was amplified under these conditions. Each sample was analyzed in two technical replicates, and the mean C_t values were used for further analysis. The relative quantity of the target, normalized to the endogenous control *GAPDH* gene and relative to a calibrator, is expressed as $2^{-\Delta\Delta Ct}$ (fold difference), where C_t is the threshold cycle, $\Delta C_t = (C_t$ of target genes$) - (C_t$ of endogenous control gene), and $\Delta\Delta C_t = (\Delta C_t$ of samples for target gene$) - (\Delta C_t$ of calibrator for the target gene). The following primer pairs were used: *FADS1* forward: CCAACTGCTTCCGC AAAGAC, *FADS1* reverse: GCTGGTGGTTGTAC GGCATA, *FADS2* forward: TGACCGCAAGGTTT ACAACAT, *FADS2* reverse: AGGCATCCGTTGCA TCTTCTC, *SCD* forward: TTCCTACCTGCAAG TTCTACACC, *SCD* reverse: CCGAGCTTTGTAAG AGCGGT.

Determination of Protein Content in the Sample

The results of the fatty acid content in the cells were converted to the protein content on the sample, which was determined using a Micro BCA Protein Assay Kit (Thermo Scientific, Pierce Biotechnology, USA) and spectrophotometer (UVM340, ASYS). The determination used biscynchonia acid (BCA), which allows detection of Cu^{1+} copper ions formed during Cu^{2+} reduction by proteins in alkaline environment. As a result of the chelation reaction of two molecules of BCA acid with one Cu^{1+} copper ion, the sample becomes violet. The method is based on the measurement of absorbance of the test substance at a wavelength of 562 nm. There is a linear relationship between the increase in protein concentration and intensity of the color.

Statistical Analysis

The obtained results were analyzed using the Statistica 10.0 software package. The arithmetical mean ± SD was calculated for each of the studied parameters. The distribution of results for individual variables was obtained with the Shapiro–Wilk *W* test. As most of the distributions deviated from the normal distribution, non-parametric tests were used for further analyses. To assess the differences between the groups studied, the non-parametric Kruskal–Wallis ANOVA followed by the Mann–Whitney *U* test was used. A probability at $p \leq 0.05$ was considered statistically significant.

Results

Sodium Orthovanadate Increased the Amount of Saturated Fatty Acids in THP-1 Macrophages

Sodium orthovanadate in THP-1 macrophages increased the amount of saturated fatty acids (SFA) (Fig. 1). At 10 μM, it statistically significantly increased the amount of palmitic acid by almost 50% ($p = 0.005$). The vanadium compound tested

increased statistically the amount of palmitic acid and stearic acid in comparison with the two tested concentrations ($p = 0.041$ and $p = 0.032$ appropriately).

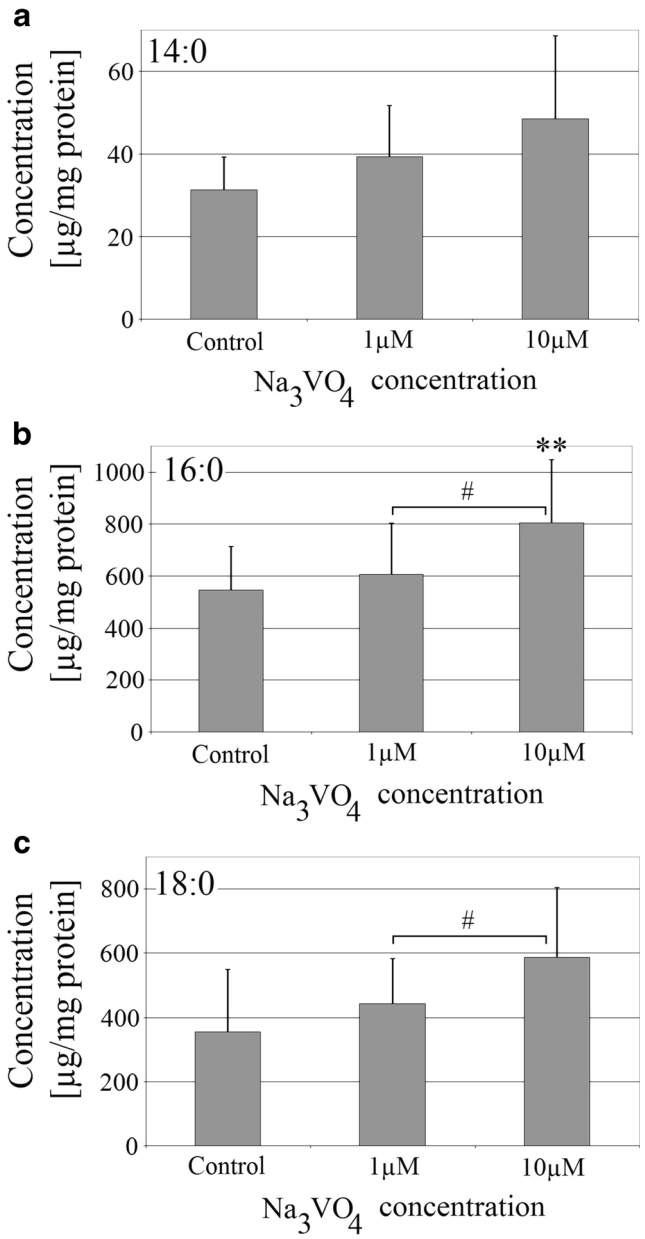

Fig. 1 Effect of sodium orthovanadate on SFA concentration in THP-1 macrophages. The effect of sodium orthovanadate on the amount of **a** myristic acid, **b** palmitic acid, and **c** stearic acid. PMA-activated macrophages of the THP-1 cell line were cultured at two concentrations of sodium orthovanadate. After 48 h of incubation, the cells were scraped and analyzed using a gas chromatograph. Data represent means ± SD for six independent experiments. Double asterisks indicate statistically significant difference in the amount of fatty acid in macrophages relative to control with PBS, $p \leq 0.01$. A number sign indicates a statistically significant difference in the amount of fatty acid in macrophages between two concentrations of sodium orthovanadate, $p \leq 0.05$

Sodium Orthovanadate Increased the Amount of Monounsaturated Fatty Acids in THP-1 Macrophages

Sodium orthovanadate increased the amount of monounsaturated fatty acids (MUFA) in THP-1 macrophages (Fig. 2). It statistically significantly increased the amount of oleic acid at both concentrations tested. At a concentration of 1 µM, the concentration of this fatty acid increased by 50% ($p = 0.032$), and with a concentration of 10 µM by 90% ($p = 0.012$). At the 1 µM concentration, the tested vanadium compound significantly increased the amount of palmitoleic acid by 70% ($p = 0.036$).

Sodium Orthovanadate Did Not Affect the Amount of Polyunsaturated Fatty Acids in THP-1 Macrophages

Sodium orthovanadate at the applied concentrations did not change the amount of polyunsaturated fatty acids (PUFA) in

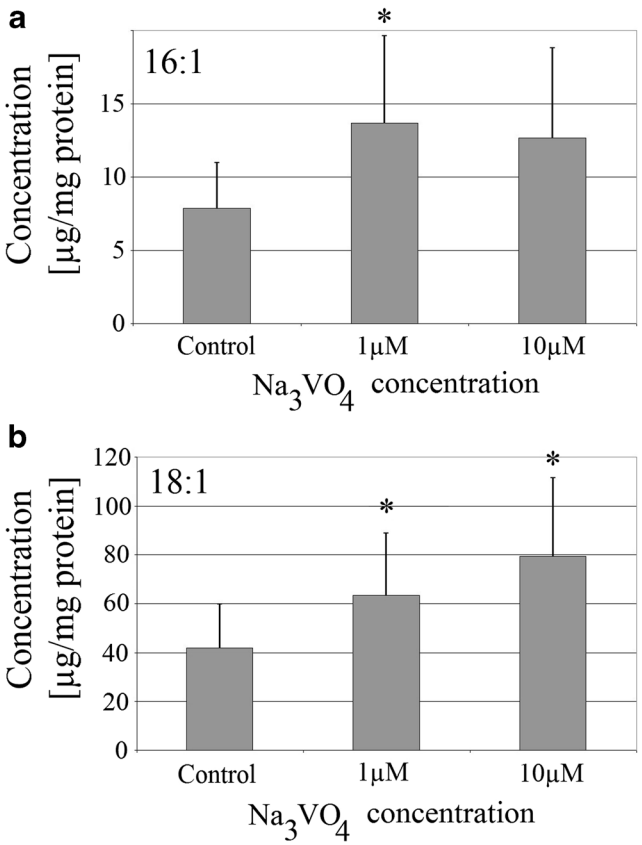

Fig. 2 Effect of sodium orthovanadate on the concentration of MUFA in THP-1 macrophages. The effect of sodium orthovanadate on the amount of **a** palmitoleic acid and **b** oleic acid. PMA-activated macrophages of the THP-1 cell line were cultured at two concentrations of sodium orthovanadate. After 48 h of incubation, the cells were scraped and analyzed using a gas chromatograph. Data represent means ± SD for six independent experiments. An asterisk indicates a statistically significant difference in the amount of fatty acid in macrophages relative to control with PBS, $p \leq 0.05$

THP-1 macrophages (Fig. 3). The concentration of linoleic acid, arachidonic acid, eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) did not significantly change relative to the control with PBS.

Sodium Orthovanadate Increased the Expression of Stearoyl-Coenzyme A Desaturase

Sodium orthovanadate at the concentrations used increased the *SCD* expression (Fig. 4). At 1 μM and 10 μM, it increased the expression of this gene four times ($p < 0.0001$) and above six times ($p < 0.0001$) relative to control, respectively. At 10 μM, it also significantly increased the *SCD* expression in comparison with 1 μM ($p = 0.0022$). At 1 μM, sodium orthovanadate increased the expression of *FADS1* two times. At all concentrations, it increased *FADS2* expression by two times relative to the control. Nevertheless, the effect on the expression of *FADS1* and *FADS2* was statistically insignificant ($p > 0.05$).

Discussion

Vanadium compounds are tested as promising drugs against T2DM [14, 15]. In addition to the effects on glucose metabolism, vanadium compounds such as sodium orthovanadate or vanadyl sulfate also reduce plasma cholesterol and LDL [30, 31]. These effects are the result of stimulating glycolysis, glycogen synthesis, and fatty acid synthesis in the liver, muscles, and adipose tissue [28, 31, 49, 58].

In this study, we found that sodium orthovanadate changed the fatty acid composition in THP-1 macrophages, increasing the amount of palmitic and stearic acids, as well as oleic and palmitoleic acids. This is associated with increased expression and activity of fatty acid synthase (FAS) and Δ^9-desaturase, enzymes responsible for SFA and MUFA biosynthesis. The results obtained in this work confirm numerous scientific reports. In a streptozotocin-induced diabetic rat model which caused deregulation of glucose and lipid metabolism enzymes as well as decreased expression and activity of FAS and acetyl-CoA carboxylase in the liver, an increased expression and activity of these enzymes after exposure to vanadium compounds was demonstrated [28, 31, 58]. This may result in increased plasma glucose uptake by various tissues and its incorporation into fatty acid metabolism, thereby normalizing blood glucose levels. In our study, sodium orthovanadate also increased the expression of *SCD* and hence the activity of Δ^9-desaturase. The expression of this enzyme is significantly altered by insulin and therefore decreases in diabetes [59]. Therefore, our results are consistent with the previously indicated insulin-enhancing property of vanadium compounds. This confirms the results by Arbo et al. where insulin increased the expression of *SCD* and thus the activity of Δ^9-desaturase [60].

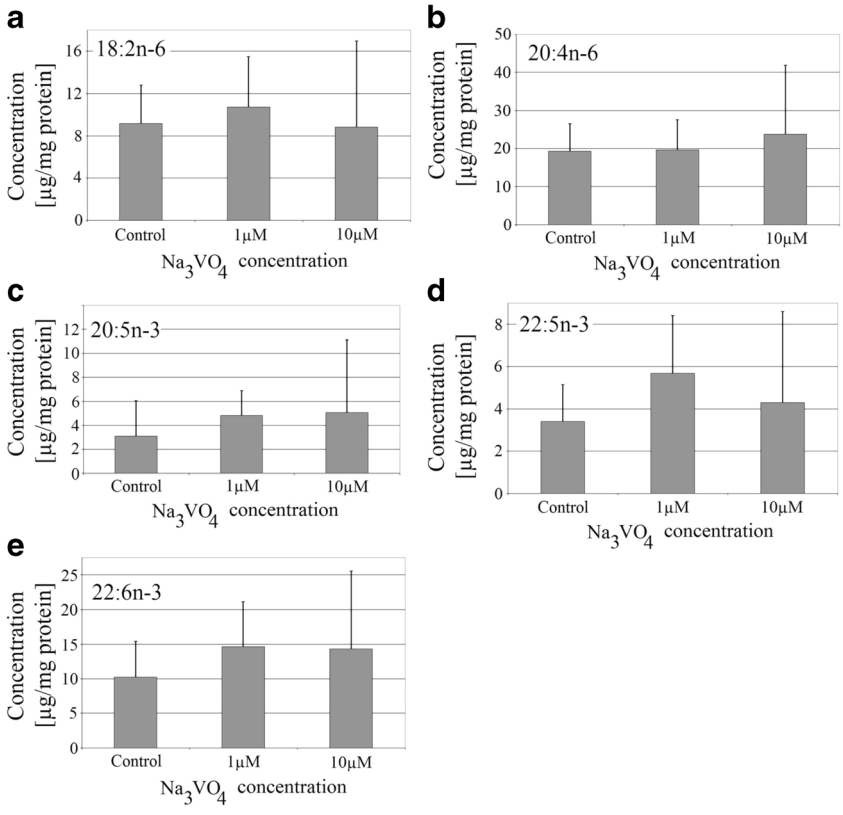

Fig. 3 Effect of sodium orthovanadate on PUFA concentration in THP-1 macrophages. The effect of sodium orthovanadate on the amount of **a** linoleic acid, **b** arachidonic acid, **c** eicosapentaenoic acid, **d** docosapentaenoic acid, and **e** docosahexaenoic acid. PMA-activated macrophages of the THP-1 cell line were cultured at two concentrations of sodium orthovanadate. After 48 h of incubation, the cells were scraped and analyzed using a gas chromatograph. Data represent means ± SD for six independent experiments

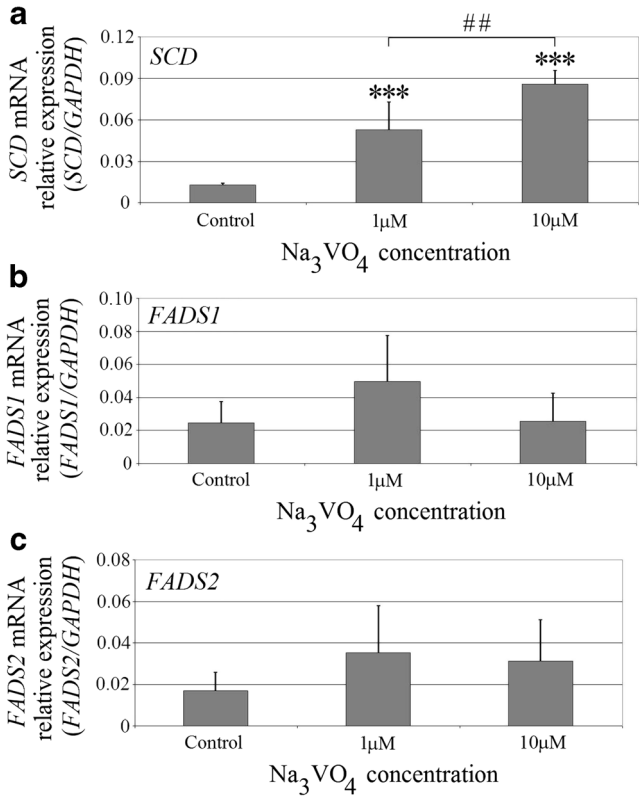

Fig. 4 The effect of sodium orthovanadate on the expression of desaturases involved in the conversion of fatty acids. The effect of sodium orthovanadate on the expression of **a** *SCD*, **b** *FADS1*, and **c** *FADS2*. PMA-activated macrophages of the THP-1 cell line were cultured at two concentrations of sodium orthovanadate. After 48 h of incubation, the cells were scraped and analyzed using qRT-PCR. Data represent means ± SD for six independent experiments. Triple asterisks indicate statistically significant difference in the expression of the given gene in macrophages relative to control with PBS, $p \leq 0.0001$. Double number signs indicate statistically significant difference in expression between two concentrations of sodium orthovanadate, $p \leq 0.01$

The present work is the first to show that in addition to the effects on the liver, muscle, and adipose tissue, macrophages under incubation conditions with vanadium compounds may participate in glucose uptake and incorporation into lipid metabolism pathways, thereby contributing to the normalization of blood glucose.

In this work, sodium orthovanadate did not affect the amount of any PUFA in THP-1 macrophages. This was associated with the lack of influence on the expression of *FADS1* and *FADS2*, genes encoding Δ^5-desaturase and Δ^6-desaturase, respectively, i.e., enzymes involved in the conversion of α-linolenic acid to EPA, DPA, and DHA and linoleic acid to γ-linolenic acid and arachidonic acid. We were the first to investigate the effect of sodium orthovanadate on the expression of *FADS1* and *FADS2*. The lack of effect on the expression of these enzymes to some extent contradicts the properties of vanadium compounds. In THP-1 macrophages, insulin increases the expression of *FADS1* and *FADS2* and hence the activity of enzymes they encode, i.e., Δ^5-desaturase and Δ^6-desaturase [60]. In streptozotocin-induced diabetic rats, disorders in the action of insulin resulted in the reduced expression of Δ^6-desaturase in the liver [61]. However, a study by Mašek et al. showed that the expression of *FADS2* does not change in diabetic rat liver [59]. The reason for these results may be the very properties of vanadium compounds. In particular, vanadium compounds affect metabolism via insulin-like growth factor 1 receptor (IGF-1R) [62]. Therefore, they have a more inductive effect on the proliferation of cells than insulin. Thanks to this action, vanadium compounds are more effective in increasing the expression of *SCD*, an enzyme involved in the proliferation of cells [63]. Vanadium compounds to a lesser extent affect the expression of *FADS1* and *FADS2* than insulin, which has a greater effect on metabolism. Another significant factor was the concentration of sodium orthovanadate, since the expression of *FADS1* and *FADS2* was affected at the higher concentration used (10 μM).

The results of our work show that sodium orthovanadate can affect the mechanisms involved in the development of atherosclerosis. Increased *SCD* expression and increased Δ^9-desaturase activity protect macrophages from the proinflammatory action of SFA [64–66]. Among other things, it reduces the activation of NLRP3 inflammasome and NF-κB and thus inflammatory reactions that are important in the development of atherosclerosis. Also, the increased expression and activity of this enzyme causes the efflux of cholesterol from macrophages [67]. These processes protect against the development of atherosclerosis.

On the other hand, in the same model of THP-1 macrophages, sodium orthovanadate increased the synthesis of prostaglandin E_2 (PGE_2) with arachidonic acid [68]. This may promote the development of atherosclerosis [69]. In addition, the sodium orthovanadate–induced increase in the amount of fatty acids in THP-1 macrophages demonstrated in our work may be not beneficial. Increased accumulation of SFA may cause inflammatory reactions and uptake of oxidized low-density lipoprotein (oxLDL) [66, 70]. Increased accumulation of SFA in macrophages may disturb cholesterol metabolism in them [71] and contribute to the formation of atherosclerosis, where macrophages are an important link. The accumulation of cholesterol esters derived from lipoproteins is followed by the de-esterification of cholesterol and removal of free cholesterol from these cells [72]. Low activity of FAS increases the process of removing free cholesterol from macrophages and thus slows down atherosclerosis [73].

Vanadium compounds generate ROS, which can consequently accelerate the development of atherosclerosis. As has been shown so far, vanadyl, a vanadium compound at the +4 oxidation state, is responsible for this process. It caused the oxidation of plasma lipids in in vitro and in vivo experiments [30, 74]. After entering the cytoplasm, vanadium compounds at the +5 oxidation state (vanadates, including sodium orthovanadate) are reduced by intracellular antioxidants to vanadium compounds at the +4 oxidation state to

give ROS [75, 76]. The inorganic vanadium compounds at the +4 oxidation state undergo Fenton reaction to form ROS and vanadate at +5 oxidation state [77, 78]. A cycle is formed in which ROS is constantly generated, compounds that destructively affect various molecules in the cell and cause formation of oxLDL [70, 74, 79].

The compounds with a large number of double bonds are particularly sensitive to oxidation by ROS. An example of such compounds is PUFA. These fatty acids contain many double bonds in one molecule, making them susceptible to oxidation by ROS. Therefore, increasing the amount of PUFA fatty acids in macrophage cells may exacerbate oxidative stress in them [80–82]. In our study, sodium orthovanadate did not increase the amount of PUFA fatty acids in the studied macrophages. Due to the generation of ROS by vanadium compounds, the lack of effect on the amount of PUFA in cells appears to be a positive property of the vanadium compound tested.

Increased expression of SCD by sodium orthovanadate may intensify cancer mechanisms. During its intensive division, a tumor cell synthesizes its components, including fatty acids, hence the increased expression of *SCD* in tumors, e.g., observed in human hepatocellular carcinoma [83], anaplastic thyroid carcinoma [84], breast cancers [85], prostate cancers [85], or lung adenocarcinoma [86]. The greater the *SCD* expression in a tumor, the worse the prognosis. Therefore, Δ^9-desaturase inhibitors are being investigated as potential anticancer drugs [87, 88]. If vanadium compounds increase the expression of *SCD*, they also increase tumor growth.

In conclusion, sodium orthovanadate changed SFA and MUFA composition in THP-1 macrophages and increased expression of *SCD*. Sodium orthovanadate did not affect the amount of any PUFA. This was associated with the lack of influence on the expression of *FADS1* and *FADS2*.

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References

1. Crans DC, Yang L, Haase A, Yang X (2018) Health benefits of vanadium and its potential as an anticancer agent. Met Ions Life Sci 18. https://doi.org/10.1515/9783110470734-015
2. Huyer G, Liu S, Kelly J, Moffat J, Payette P, Kennedy B, Tsaprailis G, Gresser MJ, Ramachandran C (1997) Mechanism of inhibition of protein-tyrosine phosphatases by vanadate and pervanadate. J Biol Chem 272:843–851
3. Irving E, Stoker AW (2017) Vanadium compounds as PTP inhibitors. Molecules 22. https://doi.org/10.3390/molecules22122269
4. Khalil AA, Jameson MJ (2017) Sodium orthovanadate inhibits proliferation and triggers apoptosis in oral squamous cell carcinoma in vitro. Biochemistry (Mosc) 82:149–155. https://doi.org/10.1134/S0006297917020067
5. Tian X, Fan J, Hou W, Bai S, Ao Q, Tong H (2016) Sodium orthovanadate induces the apoptosis of SH-SY5Y cells by inhibiting PIWIL2. Mol Med Rep 13:874–880. https://doi.org/10.3892/mmr.2015.4616
6. Wu Y, Ma Y, Xu Z, Wang D, Zhao B, Pan H, Wang J, Xu D, Zhao X, Pan S, Liu L, Dai W, Jiang H (2014) Sodium orthovanadate inhibits growth of human hepatocellular carcinoma cells in vitro and in an orthotopic model in vivo. Cancer Lett 351:108–116. https://doi.org/10.1016/j.canlet.2014.05.018
7. Rozzo C, Sanna D, Garribba E, Serra M, Cantara A, Palmieri G, Pisano M (2017) Antitumoral effect of vanadium compounds in malignant melanoma cell lines. J Inorg Biochem 174:14–24. https://doi.org/10.1016/j.jinorgbio.2017.05.010
8. Fu Y, Wang Q, Yang XG, Yang XD, Wang K (2008) Vanadyl bisacetylacetonate induced G1/S cell cycle arrest via high-intensity ERK phosphorylation in HepG2 cells. J Biol Inorg Chem 13:1001–1009. https://doi.org/10.1007/s00775-008-0387-2
9. Roy S, Banerjee S, Chakraborty T (2018) Vanadium quercetin complex attenuates mammary cancer by regulating the P53, Akt/mTOR pathway and downregulates cellular proliferation correlated with increased apoptotic events. Biometals 31:647–671. https://doi.org/10.1007/s10534-018-0117-3
10. Liu TT, Liu YJ, Wang Q, Yang XG, Wang K (2012) Reactive-oxygen-species-mediated Cdc25C degradation results in differential antiproliferative activities of vanadate, tungstate, and molybdate in the PC-3 human prostate cancer cell line. J Biol Inorg Chem 17:311–320. https://doi.org/10.1007/s00775-011-0852-1
11. Zhao Y, Ye L, Liu H, Xia Q, Zhang Y, Yang X, Wang K (2010) Vanadium compounds induced mitochondria permeability transition pore (PTP) opening related to oxidative stress. J Inorg Biochem 104:371–378. https://doi.org/10.1016/j.jinorgbio.2009.11.007
12. Petanidis S, Kioseoglou E, Domvri K, Zarogoulidis P, Carthy JM, Anestakis D, Moustakas A, Salifoglou A (2016) In vitro and ex vivo vanadium antitumor activity in (TGF-β)-induced EMT. Synergistic activity with carboplatin and correlation with tumor metastasis in cancer patients. Int J Biochem Cell Biol 74:121–134. https://doi.org/10.1016/j.biocel.2016.02.015
13. Bijelic A, Aureliano M, Rompel A (2018) Polyoxometalates as potential next-generation metallodrugs in the combat against cancer. Angew Chem Int Ed Engl 58:2980–2999. https://doi.org/10.1002/anie.201803868
14. Treviño S, Díaz A, Sánchez-Lara E, Sanchez-Gaytan BL, Perez-Aguilar JM, González-Vergara E (2019) Vanadium in biological action: chemical, pharmacological aspects, and metabolic implications in diabetes mellitus. Biol Trace Elem Res 188:68–98. https://doi.org/10.1007/s12011-018-1540-6
15. Crans DC (2015) Antidiabetic, chemical, and physical properties of organic vanadates as presumed transition-state inhibitors for phosphatases. J Org Chem 80:11899–11915. https://doi.org/10.1021/acs.joc.5b02229
16. Mohammad A, Wang J, McNeill JH (2002) Bis(maltolato)oxovanadium(IV) inhibits the activity of PTP1B in Zucker rat skeletal muscle in vivo. Mol Cell Biochem 229:125–128
17. Ou H, Yan L, Mustafi D, Makinen MW, Brady MJ (2005) The vanadyl (VO2+) chelate bis(acetylacetonato)oxovanadium(IV) potentiates tyrosine phosphorylation of the insulin receptor. J Biol Inorg Chem 10:874–886

18. Scior T, Mack HG, García JA, Koch W (2009) Antidiabetic Bis-Maltolato-OxoVanadium(IV): conversion of inactive trans- to bioactive cis-BMOV for possible binding to target PTP-1B. Drug Des Dev Ther 2:221–231
19. Zhao Z, Tan Z, Diltz CD, You M, Fischer EH (1996) Activation of mitogen-activated protein (MAP) kinase pathway by pervanadate, a potent inhibitor of tyrosine phosphatases. J Biol Chem 271:22251–22255
20. Schmid AC, Byrne RD, Vilar R, Woscholski R (2004) Bisperoxovanadium compounds are potent PTEN inhibitors. FEBS Lett 566:35–38
21. Jelveh KA, Zhande R, Brownsey RW (2006) Inhibition of cyclic AMP dependent protein kinase by vanadyl sulfate. J Biol Inorg Chem 11:379–388
22. Zhao Q, Chen D, Liu P, Wei T, Zhang F, Ding W (2015) Oxidovanadium(IV) sulfate-induced glucose uptake in HepG2 cells through IR/Akt pathway and hydroxyl radicals. J Inorg Biochem 149:39–44. https://doi.org/10.1016/j.jinorgbio.2015.05.005
23. Hussain Shah SZ, Naveed AK, Rashid A (2016) Effects of oral vanadium on glycaemic and lipid profile in rats. J Pak Med Assoc 66:1592–1596
24. Missaoui S, Ben Rhouma K, Yacoubi MT, Sakly M, Tebourbi O (2014) Vanadyl sulfate treatment stimulates proliferation and regeneration of beta cells in pancreatic islets. J Diabetes Res 2014:540242. https://doi.org/10.1155/2014/540242
25. Pirmoradi L, Noorafshan A, Safaee A, Dehghani GA (2016) Quantitative assessment of proliferative effects of oral vanadium on pancreatic islet volumes and beta cell numbers of diabetic rats. Iran Biomed J 20:18–25
26. Tsiani E, Bogdanovic E, Sorisky A, Nagy L, Fantus IG (1998) Tyrosine phosphatase inhibitors, vanadate and pervanadate, stimulate glucose transport and GLUT translocation in muscle cells by a mechanism independent of phosphatidylinositol 3-kinase and protein kinase C. Diabetes 47:1676–1686
27. Xie M, Chen D, Zhang F, Willsky GR, Crans DC, Ding W (2014) Effects of vanadium (III, IV, V)-chlorodipicolinate on glycolysis and antioxidant status in the liver of STZ-induced diabetic rats. J Inorg Biochem 136:47–56. https://doi.org/10.1016/j.jinorgbio.2014.03.011
28. Berg EA, Wu JY, Campbell L, Kagey M, Stapleton SR (1995) Insulin-like effects of vanadate and selenate on the expression of glucose-6-phosphate dehydrogenase and fatty acid synthase in diabetic rats. Biochimie 77:919–924
29. Kiersztan A, Modzelewska A, Jarzyna R, Jagielska E, Bryła J (2002) Inhibition of gluconeogenesis by vanadium and metformin in kidney-cortex tubules isolated from control and diabetic rabbits. Biochem Pharmacol 63:1371–1382
30. Tunali S, Yanardag R (2006) Effect of vanadyl sulfate on the status of lipid parameters and on stomach and spleen tissues of streptozotocin-induced diabetic rats. Pharmacol Res 53:271–277
31. Yadav UC, Moorthy K, Baquer NZ (2004) Effects of sodium-orthovanadate and Trigonella foenum-graecum seeds on hepatic and renal lipogenic enzymes and lipid profile during alloxan diabetes. J Biosci 29:81–91
32. Soveid M, Dehghani GA, Omrani GR (2013) Long- term efficacy and safety of vanadium in the treatment of type 1 diabetes. Arch Iran Med 16:408–411
33. Willsky GR, Halvorsen K, Godzala ME 3rd, Chi LH, Most MJ, Kaszynski P, Crans DC, Goldfine AB, Kostyniak PJ (2013) Coordination chemistry may explain pharmacokinetics and clinical response of vanadyl sulfate in type 2 diabetic patients. Metallomics 5:1491–1502. https://doi.org/10.1039/c3mt00162h
34. Goldfine AB, Patti ME, Zuberi L, Goldstein BJ, LeBlanc R, Landaker EJ, Jiang ZY, Willsky GR, Kahn CR (2000) Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies. Metabolism 49:400–410
35. Liu J, Cui H, Liu X, Peng X, Deng J, Zuo Z, Cui W, Deng Y, Wang K (2012) Dietary high vanadium causes oxidative damage-induced renal and hepatic toxicity in broilers. Biol Trace Elem Res 145:189–200. https://doi.org/10.1007/s12011-011-9185-8
36. Roberts GK, Stout MD, Sayers B, Fallacara DM, Hejtmancik MR, Waidyanatha S, Hooth MJ (2016) 14-day toxicity studies of tetravalent and pentavalent vanadium compounds in Harlan Sprague Dawley rats and B6C3F1/N mice via drinking water exposure. Toxicol Rep 3:531–538. https://doi.org/10.1016/j.toxrep.2016.05.001
37. Aureliano M, Ohlin CA (2014) Decavanadate in vitro and in vivo effects: facts and opinions. J Inorg Biochem 137:123–130. https://doi.org/10.1016/j.jinorgbio.2014.05.002
38. Aureliano M (2016) Decavanadate toxicology and pharmacological activities: V10 or V1, both or none? Oxidative Med Cell Longev 2016:6103457. https://doi.org/10.1155/2016/6103457
39. Katsiki N, Tentolouris N, Mikhailidis DP (2017) Dyslipidaemia in type 2 diabetes mellitus: bad for the heart. Curr Opin Cardiol 32:422–429. https://doi.org/10.1097/HCO.0000000000000407
40. Tangvarasittichai S (2015) Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes 6:456–480. https://doi.org/10.4239/wjd.v6.i3.456
41. Chistiakov DA, Bobryshev YV, Orekhov AN (2016) Macrophage-mediated cholesterol handling in atherosclerosis. J Cell Mol Med 20:17–28. https://doi.org/10.1111/jcmm.12689
42. Shah MS, Brownlee M (2016) Molecular and cellular mechanisms of cardiovascular disorders in diabetes. Circ Res 118:1808–1829. https://doi.org/10.1161/CIRCRESAHA.116.306923
43. Meshkani R, Vakili S (2016) Tissue resident macrophages: key players in the pathogenesis of type 2 diabetes and its complications. Clin Chim Acta 462:77–89. https://doi.org/10.1016/j.cca.2016.08.015
44. Klessens CQF, Zandbergen M, Wolterbeek R, Bruijn JA, Rabelink TJ, Bajema IM, IJpelaar DHT (2017) Macrophages in diabetic nephropathy in patients with type 2 diabetes. Nephrol Dial Transplant 32:1322–1329. https://doi.org/10.1093/ndt/gfw260
45. Xu H, Chen M (2017) Diabetic retinopathy and dysregulated innate immunity. Vis Res 139:39–46. https://doi.org/10.1016/j.visres.2017.04.013
46. Hamel FG, Duckworth WC (1995) The relationship between insulin and vanadium metabolism in insulin target tissues. Mol Cell Biochem 153:95–102
47. Boden G, Chen X, Ruiz J, van Rossum GD, Turco S (1996) Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism 45:1130–1135
48. Fawcett JP, Farquhar SJ, Thou T, Shand BI (1997) Oral vanadyl sulphate does not affect blood cells, viscosity or biochemistry in humans. Pharmacol Toxicol 80:202–206
49. Marita AR, Anilkumar KL (2001) Effect of vanadate on glycogen synthesis in dexamethasone-treated 3T3 adipocytes: evidence for a novel insulin sensitizing action. Diabetes Obes Metab 3:271–278
50. Wang YC, Hu YW, Sha YH, Gao JJ, Ma X, Li SF, Zhao JY, Qiu YR, Lu JB, Huang C, Zhao JJ, Zheng L, Wang Q (2015) Ox-LDL upregulates IL-6 expression by enhancing NF-κB in an IGF2-dependent manner in THP-1 macrophages. Inflammation 38:2116–2123. https://doi.org/10.1007/s10753-015-0194-1
51. Sha YH, Hu YW, Gao JJ, Wang YC, Ma X, Qiu YR, Li SF, Zhao JY, Huang C, Zhao JJ, Lu JB, Kang CM, Zheng L, Wang Q (2015) Lipoxin A4 promotes ABCA1 expression and cholesterol efflux through the LXRα signaling pathway in THP-1 macrophage-derived foam cells. Int J Clin Exp Pathol 8:6708–6715
52. Kawashima RL, Medh JD (2014) Down-regulation of lipoprotein lipase increases ABCA1-mediated cholesterol efflux in THP-1

macrophages. Biochem Biophys Res Commun 450:1416–1421. https://doi.org/10.1016/j.bbrc.2014.07.015
53. Horiuchi Y, Ohkawa R, Lai SJ, Yamazaki A, Ikoma H, Yano K, Kameda T, Tozuka M (2019) Characterization of the cholesterol efflux of apolipoprotein E-containing high-density lipoprotein in THP-1 cells. Biol Chem 400:209–218. https://doi.org/10.1515/hsz-2018-0284
54. Ackers I, Szymanski C, Duckett KJ, Consitt LA, Silver MJ, Malgor R (2018) Blocking Wnt5a signaling decreases CD36 expression and foam cell formation in atherosclerosis. Cardiovasc Pathol 34:1–8. https://doi.org/10.1016/j.carpath.2018.01.008
55. Crowley LC, Marfell BJ, Christensen ME, Waterhouse NJ (2016) Measuring cell death by trypan blue uptake and light microscopy. Cold Spring Harb Protoc 2016:pdb.prot087155. https://doi.org/10.1101/pdb.prot087155
56. Fantus IG, Deragon G, Lai R, Tang S (1995) Modulation of insulin action by vanadate: evidence of a role for phosphotyrosine phosphatase activity to alter cellular signaling. Mol Cell Biochem 153:103–112
57. Folch J, Lees M, Sloane-Stanley GH (1957) A simple method for the isolation and purification of total lipides from animal tissues. J Biol Chem 226:497–509
58. Brichard SM, Ongemba LN, Girard J, Henquin JC (1994) Tissue-specific correction of lipogenic enzyme gene expression in diabetic rats given vanadate. Diabetologia 37:1065–1072
59. Mašek T, Filipović N, Hamzić LF, Puljak L, Starčević K (2014) Long-term streptozotocin diabetes impairs arachidonic and docosahexaenoic acid metabolism and Δ5 desaturation indices in aged rats. Exp Gerontol 60:140–146. https://doi.org/10.1016/j.exger.2014.10.015
60. Arbo I, Halle C, Malik D, Brattbakk HR, Johansen B (2011) Insulin induces fatty acid desaturase expression in human monocytes. Scand J Clin Lab Invest 71:330–339. https://doi.org/10.3109/00365513.2011.566350
61. Rimoldi OJ, Finarelli GS, Brenner RR (2001) Effects of diabetes and insulin on hepatic delta6 desaturase gene expression. Biochem Biophys Res Commun 283:323–326
62. Mehdi MZ, Vardatsikos G, Pandey SK, Srivastava AK (2006) Involvement of insulin-like growth factor type 1 receptor and protein kinase Cdelta in bis(maltolato)oxovanadium(IV)-induced phosphorylation of protein kinase B in HepG2 cells. Biochemistry 45:11605–11615
63. Scaglia N, Igal RA (2005) Stearoyl-CoA desaturase is involved in the control of proliferation, anchorage-independent growth, and survival in human transformed cells. J Biol Chem 280:25339–25349
64. Brown JM, Chung S, Sawyer JK, Degirolamo C, Alger HM, Nguyen T, Zhu X, Duong MN, Wibley AL, Shah R, Davis MA, Kelley K, Wilson MD, Kent C, Parks JS, Rudel LL (2008) Inhibition of stearoyl-coenzyme A desaturase 1 dissociates insulin resistance and obesity from atherosclerosis. Circulation 118:1467–1475. https://doi.org/10.1161/CIRCULATIONAHA.108.793182
65. Peter A, Weigert C, Staiger H, Rittig K, Cegan A, Lutz P, Machicao F, Häring HU, Schleicher E (2008) Induction of stearoyl-CoA desaturase protects human arterial endothelial cells against lipotoxicity. Am J Physiol Endocrinol Metab 295:E339–E349. https://doi.org/10.1152/ajpendo.00022.2008
66. Riera-Borrull M, Cuevas VD, Alonso B, Vega MA, Joven J, Izquierdo E, Corbí ÁL (2017) Palmitate conditions macrophages for enhanced responses toward inflammatory stimuli via JNK activation. J Immunol 199:3858–3869. https://doi.org/10.4049/jimmunol.1700845
67. Nakaya K, Ayaori M, Uto-Kondo H, Sotherden GM, Nishida T, Katamoto H, Miura Y, Takiguchi S, Yakushiji E, Iizuka M, Ogura M, Sasaki M, Yogo M, Komatsu T, Adachi T, Maruyama C, Ikewaki K (2013) Overexpression of stearoyl-coenzyme A desaturase 1 in macrophages promotes reverse cholesterol transport. Biochim Biophys Acta 1831:1402–1411. https://doi.org/10.1016/j.bbalip.2013.05.009
68. Korbecki J, Baranowska-Bosiacka I, Gutowska I, Piotrowska K, Chlubek D (2015) Cyclooxygenase-1 as the main source of proinflammatory factors after sodium orthovanadate treatment. Biol Trace Elem Res 163:103–111. https://doi.org/10.1007/s12011-014-0176-4
69. Chen L, Yang G, Monslow J, Todd L, Cormode DP, Tang J, Grant GR, DeLong JH, Tang SY, Lawson JA, Pure E, Fitzgerald GA (2014) Myeloid cell microsomal prostaglandin E synthase-1 fosters atherogenesis in mice. Proc Natl Acad Sci U S A 111:6828–6833. https://doi.org/10.1073/pnas.1401797111
70. Afonso Mda S, Castilho G, Lavrador MS, Passarelli M, Nakandakare ER, Lottenberg SA, Lottenberg AM (2014) The impact of dietary fatty acids on macrophage cholesterol homeostasis. J Nutr Biochem 25:95–103. https://doi.org/10.1016/j.jnutbio.2013.10.001
71. Afonso MS, Lavrador MS, Koike MK, Cintra DE, Ferreira FD, Nunes VS, Castilho G, Gioielli LA, Paula Bombo R, Catanozi S, Caldini EG, Damaceno-Rodrigues NR, Passarelli M, Nakandakare ER, Lottenberg AM (2016) Dietary interesterified fat enriched with palmitic acid induces atherosclerosis by impairing macrophage cholesterol efflux and eliciting inflammation. J Nutr Biochem 32:91–100. https://doi.org/10.1016/j.jnutbio.2016.01.005
72. Holm C, Osterlund T, Laurell H, Contreras JA (2003) Molecular mechanisms regulating hormone-sensitive lipase and lipolysis. Annu Rev Nutr 20:365–393
73. Schneider JG, Yang Z, Chakravarthy MV, Lodhi IJ, Wei X, Turk J, Semenkovich CF (2010) Macrophage fatty-acid synthase deficiency decreases diet-induced atherosclerosis. J Biol Chem 285:23398–23409. https://doi.org/10.1074/jbc.M110.100321
74. Lapenna D, Ciofani G, Bruno C, Pierdomenico SD, Giuliani L, Giamberardino MA, Cuccurullo F (2002) Vanadyl as a catalyst of human lipoprotein oxidation. Biochem Pharmacol 63:375–380
75. Shi X, Dalal NS (1992) Hydroxyl radical generation in the NADH/microsomal reduction of vanadate. Free Radic Res Commun 17:369–376
76. Ding M, Gannett PM, Rojanasakul Y, Liu K, Shi X (1994) One-electron reduction of vanadate by ascorbate and related free radical generation at physiological pH. J Inorg Biochem 55:101–112
77. Shi X, Dalal NS (1993) Vanadate-mediated hydroxyl radical generation from superoxide radical in the presence of NADH: Haber-Weiss vs Fenton mechanism. Arch Biochem Biophys 307:336–341
78. Capella LS, Gefé MR, Silva EF, Affonso-Mitidieri O, Lopes AG, Rumjanek VM, Capella MA (2002) Mechanisms of vanadate-induced cellular toxicity: role of cellular glutathione and NADPH. Arch Biochem Biophys 406:65–72
79. Chen C, Khismatullin DB (2015) Oxidized low-density lipoprotein contributes to atherogenesis via co-activation of macrophages and mast cells. PLoS One 10:e0123088. https://doi.org/10.1371/journal.pone.0123088
80. Hsu YM, Yin MC (2016) EPA or DHA enhanced oxidative stress and aging protein expression in brain of d-galactose treated mice. Biomedicine (Taipei) 6:17. https://doi.org/10.7603/s40681-016-0017-1
81. Song EA, Kim H (2016) Docosahexaenoic acid induces oxidative DNA damage and apoptosis, and enhances the chemosensitivity of cancer cells. Int J Mol Sci 17. https://doi.org/10.3390/ijms17081257
82. Aguilar-Toral R, Fernández-Quintero M, Ortiz-Avila O, de la Paz LH, Calderón-Cortés E, Rodríguez-Orozco AR, Saavedra-Molina A, Calderón-Torres M, Cortés-Rojo C (2014) Characterization of the effects of a polyunsaturated fatty acid (PUFA) on mitochondrial bioenergetics of chronologically aged yeast. J Bioenerg Biomembr 46:205–220. https://doi.org/10.1007/s10863-014-9550-3

83. Bansal S, Berk M, Alkhouri N, Partrick DA, Fung JJ, Feldstein A (2014) Stearoyl-CoA desaturase plays an important role in proliferation and chemoresistance in human hepatocellular carcinoma. J Surg Res 186:29–38. https://doi.org/10.1016/j.jss.2013.07.001
84. von Roemeling CA, Marlow LA, Pinkerton AB, Crist A, Miller J, Tun HW, Smallridge RC, Copland JA (2015) Aberrant lipid metabolism in anaplastic thyroid carcinoma reveals stearoyl CoA desaturase 1 as a novel therapeutic target. J Clin Endocrinol Metab 100:E697–E709. https://doi.org/10.1210/jc.2014-2764
85. Peck B, Schug ZT, Zhang Q, Dankworth B, Jones DT, Smethurst E, Patel R, Mason S, Jiang M, Saunders R, Howell M, Mitter R, Spencer-Dene B, Stamp G, McGarry L, James D, Shanks E, Aboagye EO, Critchlow SE, Leung HY, Harris AL, Wakelam MJO, Gottlieb E, Schulze A (2016) Inhibition of fatty acid desaturation is detrimental to cancer cell survival in metabolically compromised environments. Cancer Metab 4:6. https://doi.org/10.1186/s40170-016-0146-8
86. Huang J, Fan XX, He J, Pan H, Li RZ, Huang L, Jiang Z, Yao XJ, Liu L, Leung EL, He JX (2016) SCD1 is associated with tumor promotion, late stage and poor survival in lung adenocarcinoma. Oncotarget 7:39970–39979. https://doi.org/10.18632/oncotarget.9461
87. Uto Y (2016) Recent progress in the discovery and development of stearoyl CoA desaturase inhibitors. Chem Phys Lipids 197:3–12. https://doi.org/10.1016/j.chemphyslip.2015.08.018
88. Imamura K, Tomita N, Kawakita Y, Ito Y, Ono K, Nii N, Miyazaki T, Yonemori K, Tawada M, Sumi H, Satoh Y, Yamamoto Y, Miyahisa I, Sasaki M, Satomi Y, Hirayama M, Nishigaki R, Maezaki H (2017) Discovery of novel and potent stearoyl coenzyme a desaturase 1 (SCD1) inhibitors as anticancer agents. Bioorg Med Chem 25:3768–3779. https://doi.org/10.1016/j.bmc.2017.05.016