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UDC: 502/504:57(477.81) 577.47: 504.054 doi: 10.25128/2078-2357.26.1.3

[2]V. KHOMA, [1]K. YUNKO, [1,3]V. MARTYNIUK, [2,4]L. GNATYSHYNA, [3]E. BEREZHENKO, [5]B. GYLYTE, [5]R. KARITONAS, [5]L. MANUSADŽIANAS, [1*]O. STOLIAR

[1]Ternopil Volodymyr Hnatiuk National Pedagogical University
M. Kryvonosa Str., 2, Ternopil, 46027
[2]Ternopil Scientific Research Forensic Center of the Ministry of Internal Affairs of Ukraine
Budny Str., 48, Ternopil, 46020
[3]Ternopil Ivan Puluj National Technical University
Ruska Str., 56, Ternopil, 46001
[4]I. Horbachevsky Ternopil National Medical University
Maidan Voli, 1, Ternopil, 46001
[5]State Scientific Research Institute Nature Research Centre
Akademijos Str., 2, Vilnius, 08412
E-mail: Oksana.Stolyar@tnpu.edu.ua

EFFECT OF CO-EXPOSURE TO GADOLINIUM, YTTRIUM AND CA-CHANNEL BLOCKER NIFEDIPINE ON BIVALVE MOLLUSCS. MODEL EXAMPLE OF MULTIPLE ENVIRONMENTAL CONTAMINANTS INTERACTION

Rare earth elements (REEs) became the micropollutants of particular concern due to their increasing rapidly application in modern technologies, including military and medical demands and, correspondingly, intensive mining and processing. These activities cause concern for environmental contamination, particularly input into surface waters. The combinations of micropollutants in the surface waters can cause unpredictable biological effects. Since the REEs are expected to impact the essential metals functionality, the goal of this study was to study the effects of co-exposure to the REEs gadolinium (Gd) and yttrium (Y) with popular pharmaceutical and Ca-channel blocker nifedipine (NFD) on the essential metals zinc- and calcium-dependent manifestations in bivalve mollusc *Unio tumidus*. The mussels were treated with the mixture of gadolinium (Gd, 30 nM), yttrium (Y, 30 nM) and Ca-channel blocker nifedipine (NFD, 10 µM) for 14 days. The distribution of zinc (Zn) in the tissue with the metallothioneins (MT) participation, as well as the redox state and signs of toxicity, was analysed in the digestive gland. The exposure elevated GSH, GSSG, MT, NADH, and NAD^+ levels, as well as the $NADH/NAD^+$ ratio, while decreasing lipid peroxidation (TBARS), indicating a reductive shift. The level of Zn in the tissue and in MT increased, indicating a Zn-related mode of action. The mixture induced approximately 2-fold increases in Cyp450-dependent EROD activity probably due to the biotransformation of NFD. The caspase-3, and GTPase activities were raised attesting the apoptotic and metabolic activation correspondingly.

Lysosomal integrity was not targeted, but cholinesterase inhibition was shown as the sign of neurotoxicity. Since the level of Gd in the tissue increased, unlike the level of Y, its input in the response would be of most importance. Summarizing, the applied model of multiple environmental contaminants interaction reflected the expected effect of the mixture on the functionality of essential metals resulting in the adaptive and specific responses of aquatic inhabitants.

Keywords: rare earth elements, nifedipine, multiple pollution, redox status, zinc, bivalve mollusc, thiol-containing compounds.

Rare earth elements (REEs) became the micropollutants of particular concern due to their increasing rapidly application in modern technologies, including military and medical demands and, correspondingly, intensive mining and processing. These activities cause concern for environmental contamination, particularly input into surface waters. Over the past decade, their use has increased nearly 20-fold [16]. Correspondingly, widespread interest in their supply has grown, and global production is projected to reach 247,7 tons by 2041, up from about 75,0 tons in the 1960s [8]. Among the REEs entering surface waters, particular attention is given to gadolinium (Gd) because Gd-based contrast agents (GBCAs) are widely used in magnetic resonance imaging. The increase in Gd in the water supply has been observed in areas of high population density where hospitals extensively use GBCAs [14]. Another REE of environmental concern, Yttrium (Y) has been specifically identified as a strategic defence-critical mineral due to military requirements [10]. As a consequence, the input of Y into surface waters is high in areas situated near chemical-industrial complex [5]. Generally, the median level of Gd and Y in stream water in Europe according to the FOREGS database is 6.4 nM and 72 nM correspondingly [19].

Knowledge about the biological role and toxicity of REE for aquatic species is currently rather fragmentary and mostly represented by the data for marine bivalve molluscs [4]. Since REEs expected to compete with essential metals for their centers of binding in the biomolecules, their expected biological targets are metal sensitive sub-cellular organelles, like lysosomes, membrane ion-exchange channels and oxidative stress activities [1, 15]. In the surface water, it can be expected the combine pollution by REEs and pharmaceuticals that impact the physiological metals activities. The example of such pollutant is nifedipine (NFD). NFD is a calcium (Ca) influx inhibitor, which is widely used as a cheap antianginal and antihypertensive medicine. Correspondingly, it is a common pollutant in WWT plants effluents and surface waters and contained in the sewage effluents in the ten to thousands of ng L^{-1} [13]. Previously, the effect of NFD on the zinc (Zn) concentration and distribution, and redox-state in the bivalve molluscs was established [9, 12].

Bivalve molluscs are recognised as bioindicators of aquatic ecotoxicity, enabling long-term experiments at concentrations close to environmental levels [6]. However, available information on the effects of REEs in bivalves and other aquatic species mainly relates to acute exposures at unrealistic concentrations or long-term studies focused on the morphometric parameters and lethality [3, 11, 15, 17]. Therefore, the goal of this study was to study the effects of co-exposure to the REEs gadolinium (Gd) and yttrium (Y) with Ca-channel blocker nifedipine (NFD) on the essential metals Zn-dependent manifestations in bivalve mollusc *Unio tumidus* under the environmental level of contaminants.

Materials and methods

All reagents, except NFD, were at least Reagent grade and sourced from Sigma-Aldrich (St. Louis, MO, USA) or from SynbiaS (Ukraine). NFD was obtained from JSC "Lekhim" (UA/8603/01/01).

The adult specimens of *Unio tumidus* (length 8.9±0.4 cm and weight 58.8±5.5 g, mean±SD) were collected in summer (July 2024) from the middle streams of the Dniester River basin. After acclimation, molluscs were distributed to two groups: untreated molluscs (C-group), and groups treated with the mixture of Gd (30 nM), Y (30 nM) and NFD (10 µM) over 14 days at 18 ºC. After exposure, molluscs were immediately dissected on ice. The digestive gland tissues were utilised. The detailed description of the methods applied for the study is done in the recent works [18, 21]. For the redox state analysis, we assayed nicotinamide coenzymes NADH and NAD^+ and reduced and oxidised glutathione (GSH&GSSG) concentrations in the protein-free extract. The concentration of metallothionein protein (MTSH) was determined by analysing MT-related thiols and to determine Zn bound to metallothioneins (ZnMT), heat-denatured proteins were isolated by the chromatography on a

Sephadex G-50 column The concentrations of Zn in the tissue (Zn t) and in the merged MT-containing eluate (ZnMT) were determined in the reaction of the complexation of Zn(II) with 5-Br-PAPS. The levels of Gd and Y in the tissues were determined using a PerkinElmer Optima 7000 Dual View ICP-OES. To evaluate the level of oxidative damage, lipid peroxidation products were measured in the supernatant of a 10% (w/v) homogenate by the production of thiobarbituric acid-reactive substances (TBARS)

For the evaluation of biotransformation, the cytochrome P450 (CYP450) related ethoxyresorufin *O*-deethylase (EROD) activity was measured. The GTP-ase (EC: 3.6.5.5) activity was assayed to indicate the metabolic state. For the assessment of toxicity, the cholinesterase (ChE, EC 3.1.1.7) activity, lysosomal membrane stability and caspase-3 (EC 3.4.22.56)-related activity were determined.

For all traits, the sample size was eight individuals, except for Zn in MTs determination, where combined samples from five specimens were analysed in two iterations per group, each with four technical replicates and Gd and Y determination (n=4). Results were expressed as mean ± SD. Data were tested for normality and homogeneity of variance using the Shapiro-Wilk and Levene’s tests, respectively. Whenever possible, data were normalised using the Box-Cox transformation. A one-way ANOVA was used to test the effect of treatments, followed by post hoc tests. For data that were not normally distributed, non-parametric tests (Kruskal-Wallis ANOVA and Mann-Whitney U test) were performed. The IBM SPSS Statistics version 24 software for Windows was used for calculations.

Results and discussion

Analysis of REE concentrations in the tissue (Table 1) showed that only Gd was detectable in the exposed group, whereas Y was not detected in the samples.

Table 1

Gadolinium and yttrium concentrations (µg/g FW) in the digestive gland of *U. tumidus* after 14 days of exposure to mixture of Gd, Y and nifedipine. Data expressed as mean ± SD (n=4).

REE	Group	
	Control	Mix
Gd	<0.2	0.29±0.15
Y	<0.2	<0.2

Remark: n.d., not determined; <0.2, less than measurement limit correspondent to 5 µg/L.

The concentration of Zn in the tissue and in MT (ZnMT) was higher in the exposed group (Fig. 1) with the proportion of ZnMT in the total tissue Zn pool 28 - 32%.

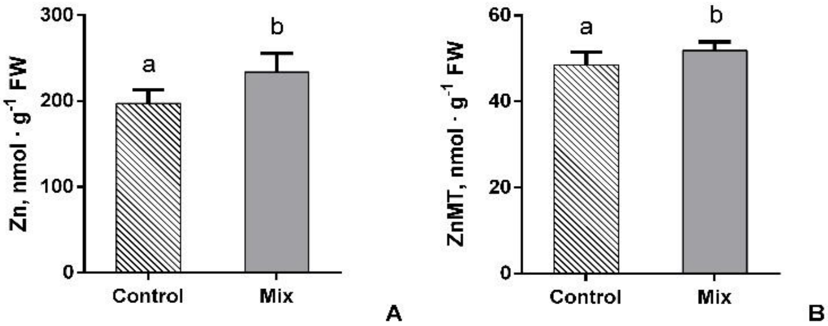

Fig. 1. Concentrations of zinc in the tissue (Zn) and metallothioneins (ZnMT) in the digestive gland of *U. tumidus* exposed to combination of Gd, Y and nifedipine over 14 days: A – Zn; B – ZnMT. Data are presented as mean ± SD (n = 8 from individual samples for Zn and n = 8 from four replicates of two independent chromatographic samples in each group. Here and on the Fig. 2,3,4, different letters above the columns indicate statistically significant differences (P < 0.05).

The evaluation of the low weight cellular thiols (Fig. 2) indicated that the exposure led to a remarkable increase in the concentrations of both GSH and GSSG without changing the RI GSH whereas the level of metallothionein protein (MTSH) remained similar to the control.

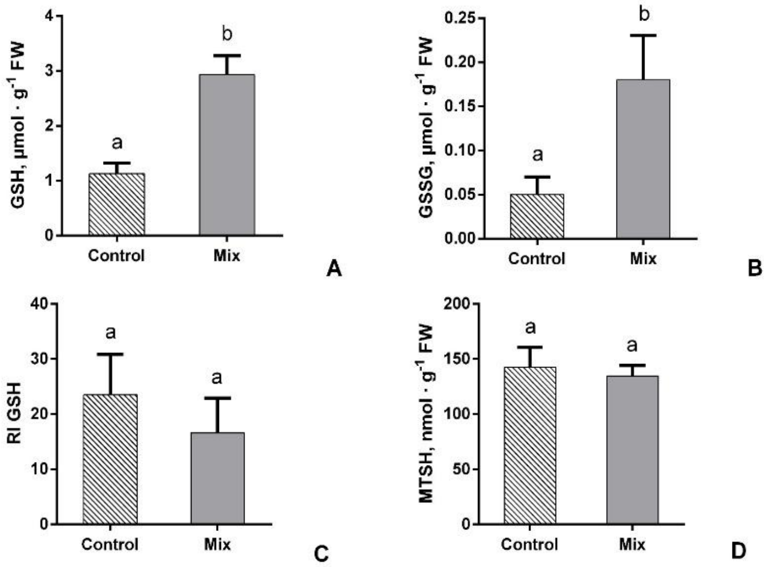

Fig. 2. Concentration of low molecular weight thiols in the digestive gland of *U. tumidus* after 14 days of experimental exposed to combination of Gd, Y and nifedipine: A – GSH concentration; B – GSSG concentration; C – redox index of glutathione (RI GSH); D – MTSH concentration. The level of Zn in the tissue and in MT increased, indicating a Zn-related mode of action. Data are presented as mean ± SD (n = 8).

The exposure increased the levels of nicotinamide coenzymes NAD^+ and, particularly, NADH, with a significant reductive shift in their ratio (Fig. 3A–C). The level of lipid peroxidation, as evaluated by TBARS, decreased compared to the control (Fig. 3D). The lysosomal membrane stability was not changed by the exposure. Caspase-3 activity increased compared to the control and cholinesterase activity decreased. Activities of EROD and GTPase increased prominently (Fig. 4).

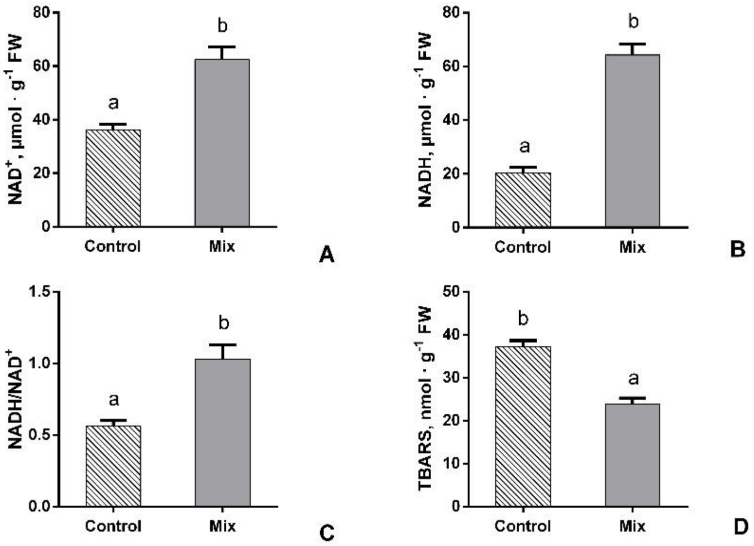

Fig. 3. Reductive-oxidative biomarkers in the digestive gland of *U. tumidus* after 14 days of experimental exposed to combination of Gd, Y and nifedipine: A – level of NAD^+; B – level of NADH; C – NAD^+/NADH concentration ratio; D – TBARS production. Data are presented as mean ± SD (n=8).

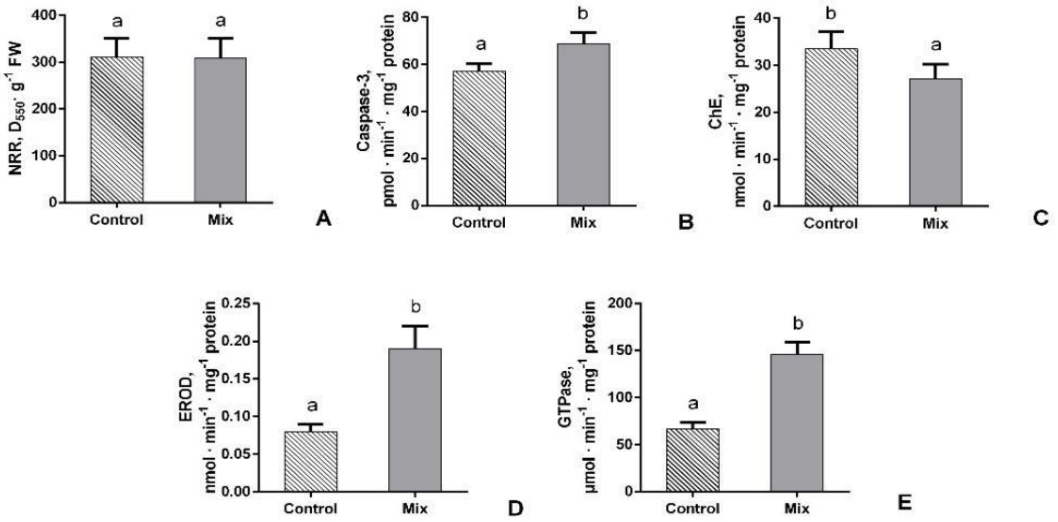

Fig. 4. Cytotoxicity and biotransformation parameters in the digestive gland of *U. tumidus* exposed to combination of Gd, Y and nifedipine: A – lysosomal membrane instability (NRR); B – caspase-3 activity; C – cholinesterase (ChE) activity; D – EROD activity; E – GTPase activity. Data are presented as mean ± SD (n=8).

Since the realistic surface waters represent so called "chemical cocktail", the multifactor exposures is the important step in the recognition of adaptivity of aquatic species to the polluted environment [20]. In the present study we distinguished two kinds of responses: the adaptive reductive shift and specific effects on the metal functionality and biotransformation.

The reductive shift detected directly from NADH/NAD^+ raise is a typical response to eustress in mussels [18, 21]. Its adaptive significance is attested by GSH&GSSG increase without changes in RI GSH that provides the reductive state and prevent the oxidative lesions. Indeed, the absence of destructive changes of lipids (TBARS) and lysosomes support this statement. The high redox state in cells can produce reduced MTSH and increased its ability to bound Zn, providing the reserve of this essential metal within the cells. The effect of REEs and NFD did not distort MT functionality. Similar results were shown in the single exposures mussels to NFD [9, 12]. The activation of GTP-ase can also be linked to general metabolic regularities under reductive-state control. Similarly, this effect was demonstrated for *U. tumidus* in response to caffeine, chlorpromazine, and microplastics separately and in combination, depending on the redox state [21]. Collectively, our data suggest a strong reductive effect of Gd and Y in the combination with NFD, evidenced by decreased lipid peroxidation levels, which indicates effective minimisation of oxidative damage. The antioxidant effect of REEs can be explained by the increased redox state in the tissue, including the utilisation of MTSH as an antioxidant. The available data on the impact of REEs on oxidative stress are contradictory, likely depending on the specific exposure [1, 2]. For example, the oxidative stress was caused by the acute exposure of *D. polymorpha* to extremely high concentrations (125 mg/L) of terbium, La, Gd and praseodymium [3].

Typical Zn effect is the inhibition of caspase-3 activity [7]. In opposite, its activity increased in the exposed group, similarly as it was reported for the effect of NFD alone [9, 12]. Probably, increased level of Gd can also cause this distortion. Our data on molluscs' ability to accumulate Gd in the digestive gland at a low concentration of 30 nM in water are supported by the results of Andrade et al. (2023a), who reported the detection of Gd in the tissues of *M. galloprovincialis* after exposure to 10 µg/L of Gd for 28 days [1]. Andrade et al. (2023b) also found an increased level of Y in the soft tissues of *M. galloprovincialis* after 28 days of exposure to 5 µg/L of Y [2]. However, they did not analyse the effect of REEs contained mixtures. Importantly, the mixture influenced biotransformation activity (EROD), confirming the data on the activation of cytochrome P-450 family member expression by NFD in higher vertebrates [22]. Despite the general evidence of adaptive response of mussels to the applied exposure, cholinesterase inhibition indicated the neurotoxicity as a result of multiple contaminants interaction.

Conclusions

Generally, the present study employed a simplified model of the real-world multiple-stressor effect by combining two REEs and a pharmaceutical at environmentally realistic concentrations. In this model, we demonstrate that multiple chemicals interaction reduces the typical manifestations of Zn functionality with Gd and NFD in the mixture contributing to this modulation. For the studied model, the freshwater mussel *U. tumidus* specific response to chemical combinations related to environmental conditions can be attributed to its adaptive ability as a facultative anaerobe to induce a reductive shift.

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[2]В. Хома, [1]К. Юнко, [1,3]В. Мартинюк, [2,4]Л. Гнатишина, [3]Є. Береженко, [5]Б. Гилите, [5]Р. Каритонас, [5]Л. Манусаджянас, [1]О. Столяр*

[1]Тернопільський національний педагогічний університет імені Володимира Гнатюка, Україна
[2]Тернопільський науково-дослідний експертно-криміналістичний центр, МВС України
[3]Тернопільський національний технічний університет імені Івана Пулюя, Україна
[4]Тернопільський національний медичний університет імені І. Я. Горбачевського, Україна
[5]Державний науково-дослідний інститут центр природничих досліджень, Вільнюс, Литва

СПІЛЬНИЙ ВПЛИВ ГАДОЛІНІЮ, ІТРІЮ ТА БЛОКАТОРА КАЛЬЦІЄВИХ КАНАЛІВ НІФЕДИПІНУ НА ДВОСТУЛКОВИХ МОЛЮСКІВ. МОДЕЛЬНИЙ ПРИКЛАД ВЗАЄМОДІЇ МНОЖИННИХ ЕКОЛОГІЧНИХ КОНТАМІНАНТІВ

Рідкісноземельні елементи (РЗЕ) стали мікрозабруднювачами, що викликають особливе занепокоєння, через їх стрімко зростаюче використання у сучасних технологіях, зокрема у військовій та медичній сферах, а також інтенсивним видобутком і переробкою. Така діяльність викликає занепокоєння щодо забруднення навколишнього середовища, особливо потрапляння РЗЕ у поверхневі води. Комбінації мікрозабруднювачів у поверхневих водах можуть спричиняти непередбачувані біологічні ефекти. Оскільки очікується, що РЗЕ впливатимуть на функціональність есенціальних металів, метою цього дослідження було вивчити ефекти спільного впливу РЗЕ – гадолінію (Gd) та ітрію (Y) у поєднанні з популярним фармацевтичним препаратом та блокатором кальцієвих каналів ніфедипіном (NFD) на цинк- та кальцій-залежні процеси есенціальних металів у двостулкових молюсків *Unio tumidus*. Молюсків піддавали дії сумішші гадолінію (Gd, 30 нМ), ітрію (Y, 30 нМ) та блокатора кальцієвих каналів ніфедипіну (NFD, 10 мкМ) протягом 14 днів. У травній залозі аналізували розподіл цинку (Zn) у тканині за участю металотіонеїнів (МТ), а також окисно-відновний стан та ознаки токсичності. Вплив суміші призводив до підвищення рівнів GSH, GSSG, МТ, NADH та NAD^+, а також співвідношення $NADH/NAD^+$, одночасно знижуючи перекисне окиснення ліпідів (TBARS), що вказує на відновний зсув. Рівень Zn у тканині та в МТ зростав, що вказує на цинк-залежний механізм дії. Суміш індукувала приблизно 2-кратне збільшення активності EROD, залежної від

Cyp450, ймовірно, через біотрансформацію NFD. Активність каспази-3 та ГТФази підвищувалася, що свідчить про апоптотичну та метаболічну активацію. Цілісність лізосом не була порушена, тоді як інгібування холінестерази свідчило про прояви нейротоксичності. Оскільки рівень Gd у тканині збільшувався, на відміну від рівня Y, його внесок у відповідь, імовірно, є більш значущим. Підсумовуючи, застосована модель взаємодії множинних забруднювачів навколишнього середовища відображає очікуваний вплив суміші на функціональність есенціальних металів, що призводить до адаптивних та специфічних реакцій водних організмів.

Ключові слова: рідкісноземельні елементи, ніфедипін, множинне забруднення, редокс-стан, цинк, двостулкові молюски, тіолвмісні сполуки.

Надійшла до редакції: 27.02.2026
Прийнята до друку: 13.03.2026
Опублікована: 30.03.2026