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Effects of Sub-Acute Exposure to Rhodium (as Rh (III) chloride hydrate) on Cytokines in Female Wistar Rats

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Abstract Quantitative changes in different cytokines were determined in serum of female Wistar rats exposed to Rhodium (III) chloride hydrate to evaluate its early effects on the immune system. Findings revealed an inhibitory effect of Rh salt since each cytokine, with the exceptions of IL-1α and IL-2 levels observed at the highest doses of exposure, was reduced compared to the controls and interestingly, the lowest doses induced the greatest inhibition. This generalized decrease of cytokine levels was not related to a specific cytokine pathway, and may suggest an anti-inflammatory role of Rh salt.

Keywords Rhodium · Immune system · Cytokines · Wistar rats · Biological monitoring · Effects

Some metals of the platinum group elements (PGEs) as platinum (Pt), palladium (Pd) and rhodium (Rh) are increasingly emitted into the environment since, in response to new emission standards, the introduction of automobile catalytic converters became mandatory in the U.S.A. (1975), in Europe (1993) and in other countries with large vehicle markets (Ravindra et al. 2004). The use of these elements in the modern "three-way catalysts" ensures the oxidative purification of toxic exhaust fumes from petrol/rich-burn engines removing more than 90 % of carbon monoxide and nitrous oxides and 80 % of unburned hydrocarbons and converting them into less harmful carbon dioxide, nitrogen and water vapour (Twigg 2007). In particular, Rh plays an important role in promoting the reduction of nitrous oxides being the most effective element in their conversion to nitrogen. In 2009 about the 86.5 % of the worldwide Rh production had been consumed by the catalyst manufacturing industry but this metal was also employed in the chemical, glass, and electrical sectors as alloying agent to harden Pt and Pd or electrical contact material and in the manufacturing of jewellery and optical instruments.

The wide use of Rh in vehicle exhaust catalysts, in addition to the other industrial applications, causes its anthropogenic emission and increases its concentrations in road dust, airborne particulate, soil and water ecosystem raising concerns about the environmental impact and toxicity of this metal (Iavicoli et al. 2008). However, despite its increasing use the health effects of Rh remain little known. Currently, Rh in metal form has not been found to play, or suspected to play, any biological role. In fact, if used in elemental form, rather than as compounds, this metal appears harmless. Nevertheless, exposure to Rh salts may result in some adverse health effects. Recently, an occupational immediate-type asthma and rhinitis due to Rh salts (sulphates, phosphates, chlorides, and others) was reported in a 27-year-old male employed in an electroplating plant (Merget et al. 2010). In 2008, a worker of a precious metal refinery developed an allergic contact dermatitis caused by a Rh solution containing H_3RhCl_6 and he

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showed a positive reaction to patch test conducted with rhodium (III) chloride hydrate (Goossens et al. 2011). Furthermore, in literature occupational allergic contact dermatitis has been described in subjects working in the jewellery trade and exposed to Rh salts (Goossens et al. 2011). Finally, some studies conducted on workers from Pt refineries and industries producing and recycling catalyzers, revealed skin prick tests positive to Pt, Pd, Rh, Ru and Ir salts (Cristaudo et al. 2005).

Limited literature is available concerning the in vivo and in vitro studies that investigated bioavailability, mode of penetration into live organisms and toxicity of Rh. The administration of Rh trichloride to adult male Sprague–Dawley rats and New Zealand white rabbits showed a low toxicity of the substance and revealed no pathological changes in the major organs of treated animals (Landolt et al. 1972). Low toxicity of Rh was confirmed by an in vitro study conducted on mouse fibroblasts L929 and a cell line of embryonic human lung tissue (L132) exposed to potassium pentachlororhodate (K_2RhCl_5) and ammonium hexachlororhodate [$(NH_4)_3RhCl_6$]. Results showed that Rh complexes were significantly less toxic than Pt and Pd compounds (Bünger et al. 1996). Similar results were obtained by Schmid et al. (2007) in human bronchial epithelial cells BEAS-2B but, Migliore et al. (2002), using a comet assay, demonstrated that Rh chloride is able to induce oxidative DNA damage. Finally, the study of interferon (INF)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-5 release in peripheral blood mononuclear cells (PBMCs), treated with different concentrations of Pt, Pd, and Rh salts, showed that Pd compounds are more immunotoxic than Pt and Rh salts (Boscolo et al. 2004).

Therefore, considering the increasing release of Rh into the environment from the use of catalytic converters and the ability of its compounds to induce immune responses in humans the aim of the present study was to evaluate the effects of Rh on the immune system of female Wistar rats, exposed for 14 days to different doses of Rh (III) chloride hydrate, by assessing possible quantitative changes in several cytokines (IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), INF-γ and TNF-α).

Materials and Methods

The Experimental Animal Production Plant of the Catholic University of Sacred Heart Rome, Italy supplied thirty-five female Wistar rats used in this study. At the start of the experiment, all the animals were approximately three months old. The mean weight for the animals was 265 g with individual weights within ±20 % of the mean, and no significant changes in body weight were observed at the end of the experiments. Before being treated with Rh (III) chloride hydrate, the animals were acclimated for two weeks and examined in order to confirm adequacy for the study. During the study the animals were individually housed in Macrolon® cages (Tecniplast S.p.A., Buguggiate, Italy). Environmental temperature and relative humidity were monitored and kept in the range of 19.9–25.1°C and 50 %–60 %, respectively, while a dark/light cycle of 12-h was maintained by an automatic timer. Animals were fed with the solid maintenance diet R (Altromin Rieper A. S.p.A., Vandoies, Italy). Diet was available to rats without restrictions, as well as pure water Rh (III) chloride hydrate spiked drinking water.

Thirty-five female Wistar rats were selected for the study and then they were randomly divided into seven groups of five rats each. The preparation of Rh solutions was performed by high-purity deionized water obtained by a double demineralization system: a mixed bed Culligan cartridge (Cadriano di Granarolo Emilia, Italy) and a MilliQ A10 apparatus (Millipore, Bedford, Massachussetts, USA) connected in series. The water had a resistivity of 18.2 Mcm compensated for temperature at 25°C and total organic compounds of 2 ppb measured by photoxidation. The solutions used for Rh administration had the following concentration of Rh (III) chloride hydrate (Alfa Aesar GmbH & Co., Karlsruhe, Germany) (as Rh): 0 (control group), 0.001, 0.01, 0.1, 0.25, 0.5, and 1 mg/L. The water solubility of the Rh salt used was sufficient to yield clear and homogeneous solutions. The actual concentration of the stock solution was checked by analyzing three replicates and results gave a maximum loss of the expected actual concentration <10 %, fully satisfactory for the aim of the study. The maximum concentration that we employed (1 mg/L) was the highest able to assure a stable solution in water. Water was given ad libitum to the animals of each group for the entire period of Rh administration, resulting in a daily ingestion of 19 ± 5 mL of Rh-containing drinking water (averaged on a total of 14 days) for each rat. Consequently, the treated rats assumed doses of approximately 19, 190, 1.900, 4.750, 9.500 and 19.000 ng Rh/day, respectively. The animals were sacrificed at the 14th day, at the end of the exposure period, following the experimental protocol approved by the ethical committee of the Catholic University of Sacred Heart of Rome, Italy.

On 14th day, rats were anesthetized with 0.5 mg/kg medetomine/kg and 75 mg ketamine/kg body weight. Blood was then collected from each of the thirty-five animals in a 1.5 mL vial (Eppendorf srl, Milan, Italy) by cardiac puncture. For the chemical analyses, sera were separated after centrifugation at 3,500 rpm per 15 min and stored at −20°C until analysis.

Urine was collected during a 24 h period in individual metabolic cages on day 14. During the collection of urine,

no food was supplied, as the experimental protocol scheduled only drinking water availability on the 24 h before sacrifice. After the urine sampling, rats were euthanized by exsanguinations by cutting both the abdominal aorta and vena cava. Urine samples were collected in 12 mL polyethylene tubes (Kartell, Milan, Italy) containing sodium azide (10 mg/100 mL) as preservative and frozen at −20°C within 2 h from collection. The polyethylene tubes were decontaminated by soaking overnight in ten percent HNO_3 (Suprapur grade, Merck, Darmstadt, Germany) and then washed with high purity deionized water (Idrolab-a-System, Idron, Rome,Italy).

A multiplex biometric enzyme linked immunosorbent assay (ELISA)-based immunoassay, containing dyed microspheres conjugated with a monoclonal antibody specific for a target protein, was used, according to the manufacturer's instructions (Bioplex Rat Cytokine 9-Plex A panel; BioRad Inc., Hercules, CA), for the simultaneous detection and quantitation of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, GM-CSF, INF-γ and TNF-α. Cytokine levels were determined using a Bio-Plex array reader an automated flow-based microfluidics device that uses a dual-laser fluorescent detector with real-time digital signal processing for quantitation (Luminex, Austin, TX, USA).

Quantification of Rh in urine and serum was performed using Inductively Coupled Plasma Mass Spectrometry (ICP-MS, ELAN® DRC-e ICP-MS (PerkinElmer, Shelton, CT USA).

Statistical analysis was carried out by SPSS software (Statistical Package for the Social Sciences, Inc., Chicago, Illinois, USA), ver 17.0. We assessed the response to six different levels (0.001, 0.01, 0.1, 0.25, 0.5, 1 mg/L) of Rh exposure and with respect to the control animals for the level of Rh in serum and urine. Levels of cytokines IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-10, GMC-SF, INF-γ, TNF-α have been measured before and after the six levels of exposure. Preliminary, the normal distribution of observed values was checked by the not parametric Kolmogorov–Smirnov Z test. One-way analysis of variance (ANOVA) was performed to test the significance of differences between the parameter means in the exposed and control rat group. Dunnett post hoc multiple comparison test was used to test the significance (p value Dunnett t test <0.05) of differences between the values for each parameter at different exposure levels against the control group. Boxplot or linear graphs were obtained for all analyzed parameters at different exposure levels.

Results and Discussion

Serum and urinary levels of Rh (μg/dL and μg/L respectively) and serum levels of cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, INF-γ, GM-CSF, TNF-α in rats after exposure to six different levels of Rh are presented in Table 1 and Figs. 1, 2 and 3. To our knowledge this is the first attempt to investigate in rats the toxic effects caused by the sub-acute oral administration of Rh salt. We used a wide dose range (from 0.001 to 1 mg/L) in order to obtain an adequate dose–response curve. The concentrations administered to the rats provided interesting results. In particular, at 0.1 and 0.25 mg/L doses of exposure, we observed Rh urinary and serum levels in the same order of magnitude of those observed by Cristaudo et al. (2007) and Petrucci et al. (2004) in workers involved in the assembly of catalysers and recycling metals and then moderately exposed to this metal. Furthermore, using higher doses of exposure we evaluated the occurrence of potential toxic effects correlated to unexpected or accidental exposure in the occupational settings. Unfortunately, it was not possible to use doses of exposure greater than 1 mg/L because the water solubility of the Rh salt was not sufficient to yield clear and homogeneous solutions. The results demonstrate that serum levels of Rh in rats exposed at 0.5 and 1 mg/L of Rh in drinking water are significantly higher than controls. Urinary levels of Rh confirm the substance assumption in rats exposed. Cytokines appeared to decrease after exposure and then to increase regularly at higher exposure levels never reaching the level observed in untreated rats.

One major concern regarding PGE exposure is sensitization potential, especially of their salts (Ravindra et al. 2004). Workers exposed to Rh salts show allergic symptoms ranging from sneezing and rhinorrhea to asthma, including contact dermatitis and urticaria (Merget et al. 2010; Goossens et al. 2011). Indeed, the investigation of the potential effects of Rh compounds on the immune system and in particular on the cytokine pattern is needed to better understand the mechanisms leading to such clinical manifestations. According to our knowledge, this is the first work reporting a modulatory effect of Rh salt on the immune system.

The oral administration employed was chosen for treating animals in order to avoid the potential for bias related to traumatic exposures. The stress of traumatic treatment could affect cytokine pathways for a stress-hormonal-immune response, preventing a clear interpretation of the results (Calcagni and Elenkov 2006). Moreover, the oral administration was also employed since it allows an accurate quantification of the dose consumed and permits a correlation with the corresponding effects. Each cytokine assessed showed alterations in serum concentrations compared to the control levels. All values were reduced compared to the controls and only in the case of IL-1α and IL-2, animals treated with the highest doses of Rh showed increased levels, although not significant, compared to the non-treated animals. Similar inhibitory effects of Rh on

Table 1 Mean levels (and standard error) of Rh in serum, urine and cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, INF-γ, GM-CSF, TNF-α of control rats and of six groups of female Wistar rats exposed to different levels of Rh (0.001, 0.01, 0.1, 0.25, 0.5, 1 mg/L)

Rh levels	Number of animals	0.001 mg/L (SE)	0.01 mg/L (SE)	0.1 mg/L (SE)	0.25 mg/L (SE)	0.5 mg/L (SE)	1 mg/L (SE)	Controls mg/L (SE)	*ANOVA F* test	*p* value ANOVA
Serum	5	0.018	0.031	0.083	0.173	0.640*	1.164*	0.018	30.6	<0.001
(μg/dl)		(0.0)	(0.0)	(0.0)	(0.0)	(0.1)	(0.2)	(0.0)		
Urine	5	0.12	0.14	0.54	1.70	4.24*	9.48*	0.20	39.9	<0.001
(μg/L)		(0.0)	(0.0)	(0.0)	(0.3)	(0.7)	(1.2)	(0.1)		
Cytokines	Number of animals	0.001 mg/L (SE)	0.01 mg/L (SE)	0.1 mg/L (SE)	0.25 mg/L (SE)	0.5 mg/L (SE)	1 mg/L (SE)	Controls mg/L (SE)	*ANOVA F* test	*p* value ANOVA
IL-1α	5	438.0	822.3	710.3	626.3	1238.2	1327.8	819.7	2.8	0.03
(pg/mL)		(93.3)	(112.6)	(74.0)	(177.3)	(354.0)	(198.3)	(176.8)		
IL-1β	5	605.0*	716.5	740.8	769.1	1065.7	1036.6	1353.6	2.1	0.08
(pg/mL)		(73.5)	(73.5)	(82.3)	(62.7)	(194.4)	(176.5)	(368.0)		
IL-2	5	2377.0	2651.8	3593.4	3362.3	5060.5	8481.7	6340.9	2.1	0.09
(pg/mL)		(375.1)	(258.6)	(343.4)	(282.9)	(670.7)	(3727.2)	(1391.4)		
IL-4	5	3030.4*	3468.4*	3934.4	3844.1*	4849.9	4798.6	5303.0	5.0	0.001
(pg/mL)		(239.3)	(233.0)	(211.1)	(174.6)	(373.5)	(133.7)	(784.8)		
IL-6	5	4313.5*	5025.5*	6493.7*	5932.6*	8852.1	8726.3	10681.0	5.0	0.001
(pg/mL)		(648.2)	(551.1)	(559.9)	(431.3)	(1184.2)	(316.0)	(2183.4)		
IL-10	5	1798.3*	2286.8*	2868.8	2620.0	3819.4	3401.1	4096.3	3.8	0.007
(pg/mL)		(267.0)	(188.3)	(158.0)	(319.6)	(628.2)	(223.4)	(776.5)		
INF-γ	5	272.2	297.1	413.4	328.5	556.6	445.5	594.8	2.2	0.07
(pg/mL)		(51.7)	(28.4)	(31.5)	(59.3)	(126.5)	(38.3)	(155.8)		
GM-CSF	5	1002.0*	1299.1*	1415.7*	1404.3*	2030.2	2033.1	2211.0	5.0	0.001
(pg/mL)		(125.7)	(140.2)	(107.1)	(111.3)	(208.7)	(168.4)	(401.2)		
TNF-α	5	1415.0*	1597.2*	1914.5	1798.3	2484.2	2505.3	2804.2	4.0	0.005
(pg/mL)		(154.1)	(150.5)	(149.4)	(121.3)	(310.4)	(74.3)	(543.9)		

ANOVA test and statistical significance (*p* value ANOVA)

Significance of the difference between mean in each exposed group and mean in the controls group: * *p* value <0.05

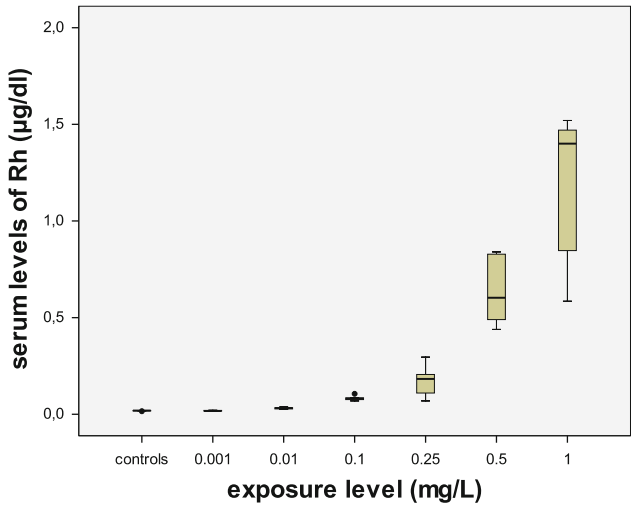

Fig. 1 Serum levels of Rh of control rats and of six groups of female Wistar rats exposed to different levels of Rh (0.001, 0.01, 0.1, 0.25, 0.5, 1 mg/L)

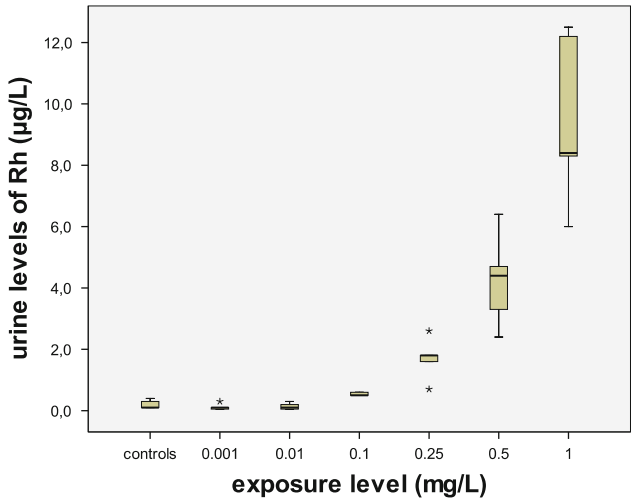

Fig. 2 Urine levels of Rh of control rats and of six groups of female Wistar rats exposed to different levels of Rh (0.001, 0.01, 0.1, 0.25, 0.5, 1 mg/L). *Asterisks* indicates measures three fold than that of the interquartile range (75° and 25° percentile)

cytokine release were demonstrated by Boscolo et al. (2004) in in vitro experiments with human PBMCs. In this work, both $(NH_4)_2[RhCl_6]$ and $RhCl_3$ significantly inhibited the phytohemagglutinin-stimulated IFN-γ, TNF-α and IL-5 release suggesting a toxic effect of Rh compounds on immune cells. However, this inhibitory effect was not confirmed by Paolucci et al. (2007) who demonstrated that Na_3RhCl_6 could play a crucial role in enhancing inflammatory reactions, particularly those triggered by allergen stimulation. In fact, the treatment of dendritic cells with the Rh salt increased the IL-5, IL-4 and IFN-γ production by co-cultured T lymphocytes. Moreover, in PBMCs collected

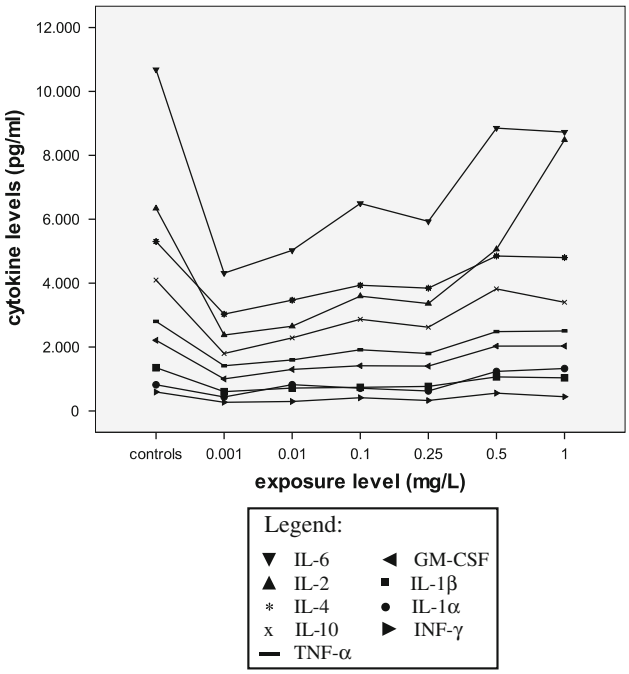

Fig. 3 Serum levels of cytokines IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, GM-CSF, INF-γ of control rats and of six groups of female Wistar rats exposed to different levels of Rh (0.001, 0.01, 0.1, 0.25, 0.5, 1 mg/L)

from individuals allergic to Ni and/or Pd and from healthy subjects, Na_3RhCl_6 exposure induced a clear IL-10 increase compared to controls, while not affecting IFN-γ levels (Bordignon et al. 2008).

Some critical experimental features, such as the different type of salt and cell-type employed, should be taken into account in evaluating the conflicting results reported by the previous studies (Boscolo et al. 2004; Bordignon et al. 2008), also in comparison with our in vivo findings. For example, the different Rh salts used could present a different toxicological profile due to the unknown intracellular distribution of each agent, and on the type of the cell treated. In fact, the active concentration of each compound may be affected by intracellular distribution, and its interaction with membrane and cytosolic proteins (Paolucci et al. 2007). The intrinsic characteristics of the individual, (i.e. genetic factors, gender, age, pregnancy status), or external factors such as habits (i.e. smoking and alcohol assumption), acute or chronic diseases, also affect the immune system and could create a different "host immunological background" able to modulate the response to xenobiotics, and to Rh. In this context, the central point in understanding the different effects of the metal compounds on the immune system could be the complex relationship between the "host" characteristics and the environmental exposure features, in terms of concentrations, duration of exposure/effect and co-stimulation with other substances.

When analysing the dose–response curve obtained in our study and that provided in vitro by Boscolo et al. (2004) a clear difference is evident. In our work the greater inhibition of cytokine release was inversely correlated with the dose of exposure, the lowest doses inducing the greatest inhibition. In the research of Boscolo et al. (2004) a positive dose–response correlation was observed when studying the inhibitory effect of Rh salt on cytokines. The surprising results of our work suggest the induction of a tolerance mechanism to the Rh effects due to an increasing dose of exposure. However, a definite conclusion is not possible and further studies are necessary to clarify the toxicological dose–response behaviour of the metal in vivo. However, it should be emphasized that our discussion is speculative since the in vitro situation previously detailed cannot thoroughly reflect the complexity of the in vivo exposure to the Rh salt we studied. Along this line, in vivo factors, e.g. modality of exposure, penetration of physiologic barriers (intestinal mucosa), solubility in biological media or metabolic modifications, can dramatically change the effect of challenging the immune system with a given concentration of a given substance. Thus, no simple direct prediction is possible between the in vitro and in vivo effects in a context suitable to formulate an appropriate risk assessment (Gerberick et al., 2005). However, in this preliminary phase of the Rh toxicity exploration, an in vitro and in vivo parallelism could be an useful tool to point out critical aspects of the metal toxicity that deserve greater attention.

Regarding a possible imbalance between T helper (Th)-1 and Th-2 cytokines, this was not evident in our results since the inhibitory effect determined was not related to a specific cytokine pathway, but resulted from a generalized response to a wide range of effect on molecules. This finding is surprising in view of the causative role of Rh salts in allergic disorders, being traditionally associated with a typical imbalance of the Th-1/Th-2 cytokines, with a greater preponderance of the latter pathway. Our findings are also unique in that the decreased cytokine levels in serum suggests an anti-inflammatory role of the Rh salt exposure. In this regard, the hypothesis, that Rh, as a persistent pollutant in densely populated metropolitan areas, may play a role in activation of the respiratory, gastrointestinal and cutaneous immune systems, particularly in genetically predisposed (atopic) individuals, should be revisited focusing on potential tolerance induction.

Future investigation should be focused on the mechanisms leading to the inhibition of the cytokine release. Several substances have also inhibited the immune system function, similar to that shown by the Rh salt in our work. Sulfur mustard induced injury of Th-1 and Th-2 lymphocytes and the consequent inhibition of the cytokine release according to its alkylating effect on cell DNA (Zabrodskii et al. 2007). The immunotoxic effect of sodium arsenite is related to the inhibition of monothiol and dithiol enzymes (e.g. dehydrolipoic acid of the pyruvate oxidase system) in immune cells, including Th-1 and Th-2 cells (Zabrodskii et al. 2007). Similarly, when cells were treated with prostaglandin (PG) I_2 analogs during the primary stimulation under Th-1 and Th-2 conditions, the production of IL-4, IL-5 and IFN-γ was inhibited while that of IL-10, considered an anti-inflammatory cytokine, was increased. Zhou et al. (2007) demonstrated that PGI_2 analogs (cicaprost and iloprost) inhibited the production of Th-1 cytokines (IFN-γ) and Th-2 cytokines (IL-4, IL-10, and IL-13) in a dose-dependent manner in previously activated and differentiated T cells. The inhibitory effect was partially dependent on the PGI_2 receptor signaling and was correlated with elevated intracellular cyclic adenosine monophosphate (cAMP) and down-regulated NF-kB activity. These different studies suggest that PGI_2 analogs may exert their anti-inflammatory action both between the up-regulation of IL-10 or inhibiting directly the cytokine production. Moreover, the cAMP inhibitory role was demonstrated also by other cAMP-elevating agents such as PGE_2, forskolin, cholera toxin and rolipram on T cell cytokine production (Ozegbe et al. 2004). In this context, the complexity of the potential mechanisms involved in cytokine modulation induced by Rh compounds exposure, seems an intriguing topic that deserves future attention.

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Conflict of interest The authors declare they have no actual or potential competing financial interests.

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