Archives of Immunology and Allergy

ISSN: 2639-1848

Volume 3, Issue 2, 2020, PP: 22-26

Heavy Metals Exposure and Risk of Autoimmune Diseases: A Review

K. P. Mishra[1*], Shashi Bala Singh[2]

[1]Defence Research and Development Organization (DRDO)-HQ, New Delhi, India.

[2]National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, India.

***Corresponding Author:** Dr. K. P. Mishra, Scientist-'E', Defence Research and Development Organization-HQ (DRDO), New Delhi, India.*

Abstract

Heavy metal exposure may lead to a variety of autoimmune diseases ranging from organ-specific to systemic disorders. Heavy metals such as mercury (Hg), silver (Ag) and lead (Pb) are associated with autoimmunity. The increased incidence of autoimmune diseases is due to an increase in industrial pollutants in the environment that contain high amount of heavy metals. Susceptibility to autoimmunity is determined by both heritable traits and environmental factors, and in this context it is possible that exposure to heavy metals may cause initiation and/or progression of autoimmune diseases. This review highlights the heavy metals exposure and cause of autoimmunity.

Keywords: *Heavy metal; Autoimmunity; IgA; nephropathy; self-peptides*

Introduction

Environmental agents interfere with cells and organs of the immune system at multiple sites, including thyroid and kidney and liver. The mechanism of eliciting autoimmunity for most of the heavy metal toxicants are not well established, however this information is not necessary to establish an association of exposure of heavy metals with autoimmune diseases. The manifestation of an autoimmune disease may indicate the production of autoantibodies, infiltration of destructive inflammatory cells into various target organs, and deposition of immune complexes in vascular sites. Some of the chemicals and therapeutic agents are associated with autoimmune phenomenon, although not always disease, in experimental animals/humans includes heavy metals such as mercury, silver, gold, and lead (Mirtcheva, et al., 1989; Goldman et al., 1991; Hultman et al., 1992, 1993; Griem and Gleichmann, 1995; Hanley et al., 1997; Bach et al., 2004).

Heavy metals and their compounds interact with the immune system in an antigen non-specific fashion. These metals exert direct toxicity upon the components of the immune system, which can lead to the malfunctioning of the system as a whole. The interaction of heavy metals with the immune system that may lead to immunodysregulation, may have consequences of allergy or autoimmunity (Gillespie et al., 1995, 1996; Oliveira et al., 1995; Prigent et al., 1995; Badou et al., 1997). The potential for adverse human health effects due to heavy metal exposure-induced alteration in the immune system has been a matter of increasing scientific and public concern. As such, there have been marked efforts in both basic research undertaken within this area as well as incorporation and development of appropriate test methods to assess the potential immunotoxicities in experimental animals, wild life studies and humans. Recent immunological findings suggest the involvement of innate immune receptors in the on-set of autoimmune diseases (Bach et al., 2004).

Heavy Metals and Autoimmunity

Reports of heavy metal induced autoimmunity in humans began to emerge over four decades ago (Barr et al., 1972; Bernard et al., 1987; Silva et al., 2004). Exposure to the heavy metal lead has been associated with the induction of autoantibodies and autoimmune diseases, though no precise mechanisms have been elucidated. The manner in which lead

affects the immune cells is not well understood as both immunosuppression *in vivo* and enhanced lymphocyte proliferation *in vitro* have been reported in addition to the various immunomodulatory actions of lead (Pb) on both cellular and humoral components of the immune system involving B-cells, T-cells, natural killer (NK) cells, and mediators like cyto-kines, chemokines, and nitric oxide (NO) (Mishra et al., 2003, 2006, 2009; Singh et al., 2003). Razani-Boroujerdi et al. (1999) demonstrated that, depending on the concentration of Pb, *in vitro* proliferation of splenic lymphocytes is either stimulated or inhibited, while Mishra et al. (2010) reported significantly lower CD4 and increased $CD45RA^+$ isoform levels in Pb-exposed subjects compared to controls and a correlation between higher blood lead level (BLL) and lower CD4 cell percentage (Mishra et al., 2010). It is thus probable that the adverse effects of Pb on the immune system may affect the kidneys especially in subjects with chronic exposure.

It has also been demonstrated that heavy metals may play a role in the pathogenesis of nervous system diseases including Multiple Sclerosis and Amylotrophic Sclerosis and Pb can aggravate diseases of nervous system by increasing the immune response against neuronal cell proteins (Waterman et al., 1994).

Mercury and Autoimmunity

Mercury (Hg) is a known heavy metal which aggravates autoimmune response (Lawrence, 1995; Pollard and Hultman, 1997). It was noted in the 1960s that Hg applied topically for the treatment of psoriasis led to nephritic syndrome (Turk and Baker, 1968; Li et al., 2010; Niu et al., 2017), and a similar pathology was observed in women using Hg-containing skin lightening cream (Barr et al., 1972). Another prominent source of Hg exposure is dental amalgam, which continuously releases small amounts of Hg vapor. Reports suggesting a role for this product in the onset of diseases like multiple sclerosis have been published (Aminzadeh and Mahyar, 2007; Tseng et al., 2020). Removal of Hg-based amalgam resulted in clinical improvements in patients with systemic lupus erythematosus (SLE), autoimmune thyroiditis, and multiple sclerosis. Furthermore, animal studies demonstrated that development of nephritis in Wistar rats injected with inorganic mercury (Druet et al., 1978).

Several factors likely work in concert with Hg leading to such desperate outcomes with respect to immune modulation. First, there is a clear gene/environmental interaction where genetic susceptibility factors linked to the MHC (major histocompatibility complex) as well as non-MHC linked genes contribute to Hg-induced systemic autoimmune disease. Mercury-mediated immunosuppression is also genetically influenced. Second, the mercury concentration with the chemical form enhances its immunotoxicity. Third, the cellular target (i.e., B-cells appear to be more sensitive than T-cells) and the activation state of the cells, influence the immunotoxicity of Hg at a given concentration (Lawrence, 1995; Pollard and Hultman, 1997).

Additionally, epidemiological studies support a linkage between Hg exposure and autoimmunity (Schrallhammer-Benkler et al., 1992; Dantas and Queiroz, 1997; Abedi-Valugerdi and Hansson, 2003; Abedi-Valugerdi, 2009) as well as many autoimmune diseases are also associated with abnormal lymphoproliferation and accumulation of autoreactive lymphocytes.

Silver and Autoimmunity

Silver (Ag) is a kind of metal which can induce AnolA/anti-fibrillarin autoantibodies in Hg-susceptible mouse strains with $I\text{-}A^s$ genotype. Interestingly, in most cases, Ag induced AnolA production resembled that of Hg-induced AnolA (Hultman et al., 1994, 1995; Johansson et al., 1997). The fact that Hg and Ag - as xenobiotic metals - are able to form strong chemical bonds with organic donors led the investigators to propose a general mechanism for induction of AnolA production by xenobi-otic metals in genetically-susceptible mice (Frausto da Silva and Williams, 1991).

Mechanism of Metal-Induced Autoimmunity

Xenobiotic metals such as mercury, gold, and silver - by having high affinity for different organic donors - bind tightly to several protein side-chains, thereby creating stable metal-protein complexes. Formation of metal-protein (i.e., Hg-fibrillarin) complexes results in an incomplete protein unfolding. Further enzymatic cleavage of this incomplete unfolded protein leads to the creation of cryptic self-peptides capable of binding to MHC (H-2 in the mouse) Class II mole-cules in susceptible mice (Hansson and Abedi-Valugerdi, 2003). Metal-induced cryptic self-peptides presented

to T cells induce activation in non-tolerant nucleolar-specific T-cells that, in turn, elicit an AnolA response (Hansson et al., 2003).

Conclusion

In spite of the recognition of environmental and occupational exposure to the heavy metals, the adverse health consequences of metal induced toxicity contribute significantly to the overall disease burden in many countries. This situation is worse in developing countries where programs for the control, prevention, and treatment of heavy metal exposure are none existent or poorly developed (Fewtrell et al., 2003). The role of environmental factors in the progression and modulation of autoimmune processes is now well established from a variety of epidemiological and experimental studies. Animal models of heavy metal-induced autoimmunity offer unique laboratory tools to reveal the mechanism by which heavy metals can lead to autoimmunity. Studies of the roles of T_H17 cells and toll-like receptors in heavy metal-exposed subjects are urgently required. Understanding of these mechanisms will lead us to appropriately find the solution of the problems exerted by the occupational or environmental heavy metal exposures.

References

[1] Abedi-Valugerdi, M. 2009. Mercury and silver induce B-cell activation and anti-nucleolar autoantibody production in outbred mouse stocks: Are environmental factors more important than the susceptibility genes in connection with autoimmunity? *Clin. Exp. Immunol.* 155:117-124.

[2] Abedi-Valugerdi and Hansson, 2003. Xenobiotic metal-induced autoimmunity: Mercury and silver differentially induce anti-nucleolar autoantibody production in susceptible H-2^s, H-2^q and H-2^f mice. *Clin. Exp. Immunol.* 131:405-414.

[3] Badou, A., Savignac, M., Moreau, M., Leclerc, C., Pasquier, R., Druet, P., and Pelletier L. 1997. $HgCl_2$-induced interleukin-4 gene expression in T-cells involves a protein kinase C-dependent calcium influx through L-type calcium channels. *J. Biol. Chem.* 272:32411-32418.

[4] Barr, R, D., Rees, P. H., Cordy, P. E., Kungu, A., Woodger, B. A., and Cameron, H. M. 1972. Nephrotic syndrome in adult Africans in Nairobi. *Br. Med. J.* 15:131-134.

[5] Bach JF, Bendelac A, Brenner MB, Cantor H, De Libero G, Kronenberg M, Lanier LL, Raulet DH, Shlomchik MJ, von Herrath MG. The role of innate immunity in autoimmunity. *J Exp Med.* 2004 Dec 20;200(12):1527-31.

[6] Bernard, A. M., Roels, H. R., Foidart, J. M., and Lauwerys, R. L. 1987. Search for anti-laminin antibodies in the serum of workers exposed to cadmium, mercury vapor or lead. *Int. Arch. Occup. Environ. Health.* 59:303-309.

[7] Dantas, D. C. and Queiroz, M. L. 1997. Immunoglobulin E and autoantibodies in mercury-exposed workers. *Immunopharmacol. Immunotoxicol.* 19:383-392.

[8] Druet, P., Druet, E., Potdevin, F., and Sapin, C. 1978. Immune-type glomerulonephritis induced by $HgCl_2$ in the Brown Norway rat. *Annal. Immunol.* 129:777-792.

[9] Fewtrell, L., Kautmann, R., and Pruss-Ustun, A. 2003. *Lead: Assessing the Environmental Burden of Disease at National and Local Levels.* WHO 2003 (WHO Environmental Burden of Disease Series, No. 2).

[10] Frausto da Silva, J. J., and Williams, R. J. (Eds.) 1991. *The Biological Chemistry of the Elements: The Inorganic Chemistry of Life. 1st Edition*. New York: Oxford University Press.

[11] Gillespie, K. M., Qasim, F. J., Tibbatts, L. M., Thiru, S., Oliveira, D. B., and Mathieson, P W. 1995. Interleukin-4 gene expression in mercury induced autoimmunity. *Scand. J. Immunol.* 41:268-272

[12] Gillespie, K. M., Saoudi, A., Kuhn, J., Whittle, C., J., Druet, P., Bellon, B., and Mathieson, P. W. 1996. T_H1/T_H2 cytokine gene expression after mercuric chloride in susceptible and resistant rat strains. *Eur. J. Immunol.* 6**:**2388-2392.

[13] Goldman, M., Druet, P., and Gleichmann, E. 1991. T_H2 cells in systemic autoimmunity: Insights from allogeneic diseases and chemically-induced autoimmunity. *Immunol. Today* 12:223-227.

[14] Griem, P., and Gleichmann, E. 1995. Metal ion induced autoimmunity. *Curr. Opin. Immunol.* 7:831-838.

[15] Hanley, G. A., Schiffenbauer, J., and Sobel, E. S. 1997. Class II haplotype differentially regulates

immune response in $HgCl_2$-treated mice. *Clin. Immunol. Immunopathol.* 84:328-337.

[16] Hansson, M., and Abedi-Valugerdi, M., 2003. Xenobiotic metal-induced autoimmunity: Mercury and silver differentially induce anti-nucleolar autoantibody production in susceptible H-2s, H-2q, and H-2f mice. *Clin. Exp. Immunol.* 131:405-414.

[17] Hultman, P., Bell, L. J., Enestrom, S., and Pollard, K. M. 1992. Murine susceptibility to mercury. I. Autoantibody profiles and systemic immune deposits in inbred, congenic, and intra-H-2 recombinant strains. *Clin. Immunol. Immunopathol.* 65:98-109.

[18] Hultman, P., Johansson, U., and Dagnaes-Hansen, F. 1995. Murine mercury-induced autoimmunity: The role of T-helper cells. *J. Autoimmun.* 8:809-823.

[19] Hultman, P., Johansson, U., Turley, S. J., Lindh, U., Enestrom, S., and Pollard, K. M. 1994. Adverse immunological effects and autoimmunity induced by dental amalgam and alloy in mice. *FASEB. J.* 8:1183-1190.

[20] Johansson, U., Sander, B., and Hultman, P. 1997. Effects of the murine genotype on T-cell activation and cytokine production in murine mercury-induced autoimmunity. *J. Autoimmun.* 10:347-355.

[21] Lawrence, D. A. 1995. Posited mechanisms of metal immunotoxicity. *Hum. Exp. Toxicol.* 14:114-116.

[22] Li SJ, Zhang SH, Chen HP, Zeng CH, Zheng CX, Li LS, Liu ZH. Mercury-induced membranous nephropathy: clinical and pathological features. Clin J Am Soc Nephrol. 2010 Mar;5(3):439-44.

[23] Mirtcheva, J., Pfeiffer, C., De Bruijn, J. A., Jacquesmart, F. and Gleichmann, E. 1989. Immunological alterations inducible by mercury compounds. III. H-2A acts as an immune response and H-2E as an immune "suppression" locus for $HgCl_2$-induced anti-nucleolar autoantibodies. *Eur. J. Immunol.* 19:2257-2261.

[24] Mishra, K. P., Singh, V. K., Rani, R., Yadav, V. S., Chandran, V., Srivastava, S. P., and Seth, P. K. 2003. Effect of lead exposure on the immune response of some occupationally-exposed individuals. *Toxicology* 188:251-259.

[25] Mishra, K. P., Chauhan, U. K., and Naik, S. 2006. Effect of lead exposure on serum immunoglobulins and reactive nitrogen and oxygen intermediate. *Hum. Exp. Toxicol.* 25:661-665.

[26] Mishra, K. P. 2009. Lead exposure and its impact on immune system: A review. *Toxicol. In Vitro* 23:969-972.

[27] Mishra, K. P., Rani, R., Yadav, V. S., and Naik, S. 2010. Effect of lead exposure on lymphocyte subsets and activation markers. *Immunopharmacol. Immunotoxicol.* 32:446-449.

[28] Niu HX, Li SH, Li HY, Chen YH, Liu WW, Li PL, Long HB. Clinicopathological features, diagnosis, and treatment of IgA nephropathy with minimal change disease related to exposure to mercury-containing cosmetics: a case report . Clin Nephrol. 2017 Apr;87 (2017)(4):196-201.

[29] Oliveira, D. B., Gillespie, K., Wolfreys, K., Mathieson, P. W., Qasim, F.,and Coleman, J. W., 1995. Compounds that induce autoimmunity in the Brown Norway rat sensitize mast cells for mediator release and interleukin-4 expression. *Eur. J. Immunol*. 25:2259-2264.

[30] Pollard, K. M., and Hultman P. 1997. Effects of mercury on the immune system. *Metal Ions Biol. Syst.* 34:421-440.

[31] Prigent, P., Saoudi, A., Pannetier, C., Graber, P., Bonnefoy, J. Y., Druet, P., and Hirsch, F. 1995. Mercuric chloride, a chemical responsible for T-helper cell (T_H)-2-mediated auto-immunity in Brown Norway rats, directly triggers T-cells to produce interleukin-4. *J. Clin. Invest.* 960:1484-1489.

[32] Razani-Boroujerdi, S., Edwards, B., and Sopori, M. L. 1999. Lead stimulates lymphocyte proliferation through enhanced T-cell-B-cell interaction. *J. Pharmacol. Exp. Ther.* 288:714-719.

[33] Schrallhammer-Benkler, K., Ring, J., Przybilla, B., Meurer, M., and Landthaler, M. 1992. Acute mercury intoxication with lichenoid drug eruption followed by mercury contact allergy and development of anti-nuclear antibodies. *Acta. Derm. Venereol.* 72:294-296.

[34] Silva, I. A., Nyland, J. F., Gorman, A., Perisse, A., Ventura, A. M., Santos, E. C., Souza, J. M., Burek, C. L., Rose, N. R., and Silbergeld, E. K., 2004. Mercury exposure, malaria, and serum anti-nuclear/anti-nucleolar antibodies in Amazon populations in Brazil: A cross-sectional study. *Environ. Health* 3:11.

[35] Singh, V. K., Mishra, K. P., Rani, R., Yadav, V. S., Awasthi, S. K., Garg, S. K. 2003. Immunomodulation by lead. *Immunol. Res.* 28:151-166.

[36] Takeuchi, K., Turley, S. J., Tan, E. M., and Pollard, K. M. 1995. Analysis of the autoantibody response to fibrillarin in human disease and murine models of autoimmunity. *J. Immunol.* 154:961-971.

[37] Tseng CF, Chen KH, Yu HC, Huang FM, Chang YC. Dental Amalgam Fillings and Multiple Sclerosis: A Nationwide Population-Based Case-Control Study in Taiwan. Int J Environ Res Public Health. 2020 Apr 12;17(8):2637.

[38] Turk, J. L., and Baker, H. 1968. Nephrotic syndrome due to ammoniated mercury. *Br. J. Dermatol.* 80:623-624.

[39] Waterman, S. J., el-Fawal, H. A., and Snyder, C. A. 1994. Lead alters the immunogenicity of two neural proteins: A potential mechanism for the progression of lead-induced neurotoxicity. *Environ. Health Perspect.* 102:1052-1056.

Citation: **K. P. Mishra, Shashi Bala Singh.** *Heavy Metals Exposure and Risk of Autoimmune Diseases: A Review. Archives of Immunology and Allergy. 2020; 3(2): 22-26.*