Medical Hypotheses (2006) **67**, 900–903

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Sympathetic nervous system plays an important role in the relationship between immune mediated diseases

Shahram Shahabi [a,*], Zuhair Muhammad Hassan [b], Nima Hosseini Jazani [a], Massoumeh Ebtekar [b]

[a] *Department of Microbiology, Immunology and Genetics, Faculty of Medicine, Urmia University of Medical Sciences, Road of Nazloo, Urmia, Iran*
[b] *Department of Immunology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran*

Received 18 March 2006; accepted 30 March 2006

Summary T helper (Th) lymphocytes have been classified into distinct subsets, Th1 and Th2 on the basis of the cytokines they produce. According to the cross-regulatory properties of Th1 and Th2 cells, one would assume that to be affected by a Th1 type disease increases susceptibility to a Th1 type disease and inhibits a Th2 type disease and vice versa about being affected by a Th2 type disease. However, the pattern of related diseases does not necessarily follow the conventional pattern of inhibitory effects of Th1 and Th2 immune responses on each other. For example, Mycobacteria including BCG, that induce Th1 immune responses; can modulate some Th1 type autoimmune diseases including MS, experimental autoimmune encephalomyelitis (EAE; an animal model for Multiple Sclerosis) and insulin-dependent diabetes mellitus (IDDM) thereby leading to an alleviation of their symptoms. Also BCG precipitates a syndrome similar to systemic lupus erythematosus (SLE), a Th2 type disease; in NOD mice. The coexistence of the major Th2-mediated atopic diseases such as asthma, eczema and allergic rhinitis with the Th1-mediated autoimmune conditions including; coeliac disease (CD), IDDM, rheumatoid arthritis (RA) and psoriasis is another example that is in apparent disagreement with counter-regulatory effects of Th1/Th2 phenotypes.
Hypothesis: SNS can be stimulated by pro-inflammatory cytokines, production of which is induced by mycobacteria including BCG. Although these cytokines can inhibit SNS activity in the site of inflammation and secondary lymphoid organs, they increase sympathetic tone in other places. Increased sympathetic tone can induce an anti-inflammatory and Th2 type milieu. This milieu can inhibit MS and IDDM and provide a susceptible environment for starting of SLE. Atopic diseases are Th2 type immune mediated diseases; therefore, they increase the production of Th2 type cytokine and decrease production of pro-inflammatory cytokines in the site of allergic reaction and also in secondary lymphoid organs. Therefore, atopic diseases decrease sympathetic tone in all tissues except in the sites of allergic reaction and secondary lymphoid organs. Decreased sympathetic tone results in a pro-inflammatory milieu and in such an environment, Th1 type autoimmune diseases can affect tissues.

* Corresponding author. Address: P.O. Box 14115-183 Tehran, Iran. Tel.: +98 2188011001x3565; fax: +98 2188013030.
E-mail addresses: shahabirabori@yahoo.com, s_shahabi@umsu.ac.ir (S. Shahabi).

0306-9877/$ - see front matter
doi:10.1016/j.mehy.2006.03.039

Introduction

T helper (Th) lymphocytes have been classified into distinct subsets on the basis of the cytokines they produce. Th1 cells primarily secrete IFN-γ, IL-2, IL-12 and TNF-β, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10 and IL-13, which promote humoral immunity. Naive CD4+ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells. Among the factors currently known to influence the differentiation of these cells toward the Th1 or Th2 subsets, cytokines present in the microenvironment and produced by the cells of the innate immune system are the most important. Thus, IL-12, produced by activated antigen presenting cells (APCs), is a major inducer of Th1 differentiation. Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN-γ inhibit Th2 responses, and IL-4 and IL-10 inhibit Th1 responses [1]. According to the cross-regulatory properties of Th1 and Th2 cells and since the balance of antigen-specific Th1/Th2 cells may dictate the clinical outcome of an immune system related disease [1], one could assume that to be affected by a Th1 type disease, would increase susceptibility to a Th1 type disease and inhibit a Th2 type disease and vise versa about being affected by a Th2 type disease. This is true regarding the pattern of certain diseases, for example, infection with BCG (a Th1 type disease) inhibits and/or attenuates Th2 type atopic diseases. However, this pattern does not stand for other diseases which do not seem to follow the pattern of inhibitory effects of Th1 and Th2 immune responses on each other. For example, Mycobacteria, including BCG, has been shown to alleviate the symptoms of MS and experimental autoimmune encephalomyelitis (EAE; an animal model for Multiple Sclerosis) [2—7] and insulin-dependent diabetes mellitus (IDDM) [6]. There apparently seems to be a paradox in that a Th1-promoting immune stimulus can demonstrate an alleviating effect on a supposedly Th1-mediated autoimmune disease [6]. Also the precipitation of a syndrome similar to systemic lupus erythematosus (SLE) by BCG in NOD mice [8,9] is another example that is unexplainable by the inhibitory effects of Th1/Th2 diseases on each other, because BCG, as a Th1 type disease, in this case precipitates a Th2 autoimmune disease [10] to start.

Coexistence of the major Th2-mediated atopic diseases such as asthma, eczema and allergic rhinitis with the Th1-mediated autoimmune conditions including coeliac disease (CD), IDDM, rheumatoid arthritis (RA) and psoriasis is another example that seems to be in discrepancy with the counter-regulatory effects of Th1/Th2 phenotypes [11,12].

Some mechanisms have been suggested to contribute to the modulation of MS and IDDM by Mycobacterium. These mechanisms include deletion of auto reactive T cells, induction of suppressor (regulator) T cells and redirected trafficking of activated auto antigen-specific T cells to the local inflammatory sites, induced by mycobacterial infection [2,5—7,13—15].

Also coexistence of the above mentioned Th1 and Th2 diseases has been attributed to certain mechanisms including the existence of a common environmental denominator behind the disease processes, sharing risk factors that increase the propensity of the immune system to generate both Th1- and Th2-mediated inappropriate responses to non-pathological antigens [11,12].

Some other mechanisms including counter regulation of Th2 responses by IL-10 and transforming factor beta (TGF-β) and contribution of Th2-type cytokines to the pathological mechanisms of several autoimmune diseases have been proposed as a solution to the above mentioned relationship between Th1 and Th2 type diseases [11].

Regarding the close relationship between the sympathetic nervous system (SNS) and immune system [16], particularly the expression of β2 adrenergic receptors on various types of immune cells including T, B and APCs also considering the effects of SNS on the Th1/Th2 paradigm [16] and autoimmune diseases [17], it can be hypothesized that SNS may play a role in the relation of Th1/Th2 type diseases.

Previously we have hypothesized that the SNS has a role in the beneficial effects of Mycobacteria on MS [18], and in this article we intend to extend that hypothesis to other disease conditions that seem to contradict the concept of counter-regulatory effects of Th1/Th2 phenotypes.

Hypothesis

Pro-inflammatory cytokines including TNF-α, IFN-γ, IL-12, IL-1β and IL-6 can inhibit local sympathetic tone, whereas they increase systemic sympathetic tone [16]. These cytokines are produced during the Th1 type immune responses [16], therefore systemic sympathetic tone is increased as a result of Th1 type immune response and due to the counter-regulatory effects of Th1/Th2 type immune responses [1], Th2 immune-deviation decreases systemic sympathetic tone.

Mycobacterium infection including BCG infection induces Th1 type immune responses and pro-inflammatory cytokines [19—22]. Since, APCs carry mycobacterium antigens to secondary lymphoid organs and activate naïve T lymphocytes in these places [23], there is a Th1 type and pro-inflammatory milieu both in the secondary lymphoid organs and the infection loci. Therefore, what appears during the infection by mycobacterium is the reduction of sympathetic tone in the infection loci and secondary lymphoid organs, accompanied by an increase in the tone in other places. Increased sympathetic tone can induce an anti-inflammatory and Th2 type milieu [16,17,24] in all the tissues except mycobacterium infection loci and secondary lymphoid tissues. This milieu can inhibit MS and IDDM which both are Th1 type autoimmune disease [17,18]. Increased sympathetic tone may inhibit these diseases via other mechanisms, mentioned in our previous article [18]. Therefore, the paradox that a Th1-promoting immune stimulus has inhibitory effects on purportedly Th1-mediated autoimmune diseases in certain aspects can be explained by the increased systemic sympathetic tone by mycobacterium infection.

The effect of BCG on SLE can be explained by the above mechanism, as well. BCG precipitates a syndrome like SLE in NOD mice [8,9]. This effect can be due to the increased systemic sympathetic tone as a result of the infection with BCG, since, SLE is a Th2 type disease, a sympathetic-induced Th2 type milieu can provide a susceptible environment for the emergence of this disease.

Coexistence of atopic diseases, as Th2 type diseases, with Th1 type autoimmune diseases like RA, IDDM, psoriasis and CD is explainable with the present hypothesis. As mentioned above, atopic diseases are Th2 type immune mediated diseases therefore; they increase the production of Th2 type cytokine and decrease the production of pro-inflammatory cytokines in the site of allergic reaction and also in secondary lymphoid organs. The latter is because of the circulation of T lymphocytes among the secondary lymphoid organs. As mentioned above, pro-inflammatory cytokines inhibit local sympathetic tone locally and increase systemic sympathetic tone; therefore, atopic diseases decrease sympathetic tone in all tissues except in the sites of allergic reaction and secondary lymphoid organs. Decreased sympathetic tone results in a pro-inflammatory milieu in all the tissues except the site of allergic reaction and the secondary lymphoid organs; and since the environment at the site of endogenous antigen has important impact on the pathogenic responses to self [25], therefore in such an environment, individuals with a favorable genetic background will be more susceptible to Th1 type autoimmune diseases.

Discussion

According to this hypothesis the discrepancies observed in the coexistence of certain immune mediated diseases can be attributed to the regulatory effects exerted by the SNS in addition to the direct counter-regulatory effects of Th1/Th2 immune responses on each other.

As mentioned above, BCG infection inhibits and/or attenuates atopic diseases but increases susceptibility to SLE in NOD mice. The immune responses in both atopic diseases and SLE are Th2 type, but why does BCG exert opposite effects on these diseases? The critical role of immunoglobulin E (IgE) in atopic diseases may be a suitable explanation. IgE has important role both in the sensitization phase of atopic diseases through binding to its receptors on the surface of APCs, and in the effector phase, by binding to its receptors on the surface of the effector cells like mast cells and basophiles. Switching from IgM to IgE happens in the secondary lymphoid organs and is strongly related to the environmental factors including cytokine milieu. As mentioned above, BCG induces a Th1 type cytokine milieu in the secondary lymphoid organs, therefore, despite sympathetic-induced Th2 type cytokine milieu in the site of allergic reaction, (due to systemic stimulatory effects of BCG on SNS) BCG inhibits and/or attenuates atopic diseases through the reduced production of IgE. IgE has no important role in the pathogenesis of SLE therefore; a systemic sympathetic tone induced Th2 type milieu produced by BCG can provide a susceptible environment for the starting of necessary immune reactions for SLE.

In brief, we hypothesized that in the relations between the above mentioned diseases, where it seems that the counter-regulatory effects of Th1/Th2 immune responses are not followed, in fact it is followed, but it is important to notice that because of the effects of SNS, a Th1 type disease may provide a Th2 milieu for an autoimmune disease. While in this article we have discussed the role of SNS in the relationship between coexisting Th1/Th2 immune mediated diseases, it is possible that other elements of the central and peripheral nervous system such as the vagus nerve and inflammatory reflex, hypothalamus-pituitary- adrenal (HPA) axis and endogenous opioid system may play a role too. Further studies on the cellular and molecular mechanisms involved in neuro-immune

pathways may also elucidate the etiology behind the apparently contradictory clinical observations discussed here.

References

[1] Elenkov IJ, Chrousos GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrin Met 1999;10:359–68.

[2] Christen U, von Herrath MG. Infections and autoimmunity–good or bad? J Immunol 2005;174:7481–6.

[3] Kamradt T, Goggel R, Erb KJ. Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection. Trends Immunol 2005;26:260–7.

[4] Sewell DL, Reinke EK, Hogan LH, et al. Immunoregulation of CNS autoimmunity by helminth and mycobacterial infections. Immunol Lett 2002;82:101–10.

[5] Ben-Nun A, Mendel I, Sappler G, et al. A 12-kDa protein of mycobacterium tuberculosis protects mice against experimental autoimmune encephalomyelitis. Protection in the absence of shared T cell epitopes with encephalitogenic proteins. J Immunol 1995;154:2939–48.

[6] Sewell DL, Reinke EK, Co DO, et al. Infection with mycobacterium bovis BCG diverts traffic of myelin oligodendroglial glycoprotein autoantigen-specific T cells away from the central nervous system and ameliorates experimental autoimmune encephalomyelitis. Clin Diagn Lab Immunol 2003;10:564–72.

[7] Ben-Nun A, Yossefi S, Lehmann D. Protection against autoimmune disease by bacterial agents. II. PPD and pertussis toxin as proteins active in protecting mice against experimental autoimmune encephalomyelitis. Eur J Immunol 1993;23:689–96.

[8] Baxter AG, Horsfall AC, Healey D, et al. Mycobacteria precipitate an SLE-like syndrome in diabetes-prone NOD mice. Immunology 1994;83:227–31.

[9] Baxter AG, Healey D, Cooke A. Mycobacteria precipitate autoimmune rheumatic disease in NOD mice via an adjuvant-like activity. Scand J Immunol 1994;39:602–6.

[10] Atta AM, Sousa CP, Carvalho EM, et al. Immunoglobulin E and systemic lupus erythematosus. Braz J Med Biol Res 2004;37:1497–501.

[11] Kero J, Gissler M, Hemminki E, et al. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. J Allergy Clin Immunol 2001; 108:781–3.

[12] Simpson CR, Anderson WJ, Helms PJ, et al. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. Clin Exp Allergy 2002;32:37–42.

[13] Grabie N, Wohl I, Youssef S, et al. Expansion of neonatal tolerance to self in adult life: I. The role of a bacterial adjuvant in tolerance spread. Int Immunol 1999;11(6): 899–906.

[14] Constant P, Davodeau F, Peyrat MA, et al. Stimulation of human gamma delta T cells by non-peptidic mycobacterial ligands. Science 1994;264:267–70.

[15] Muller D, Pakpreo P, Filla J, et al. Increased gamma-delta T-lymphocyte response to Mycobacterium bovis BCG in major histocompatibility complex class I-deficient mice. Infect Immun 1995;63:2361–6.

[16] Elenkov IJ, Wilder RL, Chrousos GP, et al. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev 2000;52:595–638.

[17] Bedoui S, Miyake S, Straub RH, et al. More sympathy for autoimmunity with neuropeptide Y? Trends Immunol 2004;25:508–12.

[18] Shahabi S, Hassan ZM, Jazani NH. Any beneficial effects of mycobacteria on Multiple Sclerosis and experimental autoimmune encephalitis may include stimulation of the sympathetic nervous system. Med Hypotheses 2006;67:164–8.

[19] Valone SE, Rich EA, Wallis RS, et al. Expression of tumor necrosis factor in vitro by human mononuclear phagocytes stimulated with whole mycobacterium bovis BCG and mycobacterial antigens. Infect Immun 1988;56: 3313–5.

[20] Peetermans WE, Raats CJ, Langermans JA, et al. Mycobacterial heat-shock protein 65 induces pro-inflammatory cytokines but does not activate human mononuclear phagocytes. Scand J Immunol 1994;39:613–7.

[21] Zhang Y, Doerfler M, Lee TC, et al. Mechanisms of stimulation of interleukin-1 beta and tumor necrosis factor-alpha by mycobacterium tuberculosis components. J Clin Invest 1993;91:2076–83.

[22] Peetermans WE, Raats CJ, van Furth R, et al. Mycobacterial 65-kilodalton heat shock protein induces tumor necrosis factor alpha and interleukin 6, reactive nitrogen intermediates, and toxoplasmastatic activity in murine peritoneal macrophages. Infect Immun 1995;63:3454–8.

[23] Jenkins MK, Khoruts A, Ingulli E, et al. In vivo activation of antigen-specific CD4 T cells. Annu Rev Immunol 2001;19: 23–45.

[24] Gold SM, Mohr DC, Huitinga I, et al. The role of stress-response systems for the pathogenesis and progression of MS. Trends Immunol 2005(Oct 6) [Epub ahead of print].

[25] King C, Sarvetnick N. Organ-specific autoimmunity. Curr Opin Immunol 1997;9:863–71.