NEUROTRANSMITTERS AND IMMUNITY: 2. CATECHOLAMINES

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INTRODUCTION

The catecholamines norepinephrine (NE) and epinephrine (EPI) have been implicated as important efferent immune modulators following exposure to stressors, often acting in concert with activation of the hypothalamic-pituitary axis (Maden, 2003; Hritcu et al., 2004a, 2004b; Hritcu et al., 2005; Hritcu, 2006). Catecholamines modulate a range of immune cell activities, including cell proliferation, cytokine and antibody production, lytic activity, and migration. In this manuscript we will summarize the evidence that catecholamine can enhance or suppress immune function.

CATECHOLAMINES AND IMMUNE RESPONSE

1. Sources of catecholamines

Cells of the immune system are exposed to catecholamines from intracellular and extracellular sources. Recently, NE and EPI and their metabolites have been detected in lymphocytes and macrophages that can be released by activating stimuli (Miller et al., 2000). These cells may synthesize catecholamines, or they may take up and store catecholamines from extracellular sources. Cells residing within lymphoid organs are also exposed to NE and colocalized neuropeptides, such as neuropeptide Y, released from sympathetic noradrenergic nerve fibers that can form direct synapse-like junctions with lymphocytes (Bellinger et al., 2001). It is likely that co-localized molecules potentate target cell signaling by NE upon sustained sympathetic activation. Under highly stressful conditions, EPI and NE are also released from the adrenal medulla to elevate plasma catecholamines. One such stressor is endotoxin, or lipopolysaccharide (LPS) (Qi et al., 1991; Hritcu et al., 2006). LPS-induced sympathetic activation and elevation of plasma catecholamines appears to maintain immune homeostasis.

2. Adrenergic receptor expression by cells of the immune system

NE and EPI stimulate cell surface α- and β-adrenergic receptors (AR) with differing affinities. β2-AR are present on almost all immune cell types, with the notable exception of Th2 clones (Sanders et al., 1997). A decrease in lymphocyte β-AR density and signaling has been reported at the time of peak lymphocyte proliferation (De Blasi et al., 1995), suggesting that removal of β-AR signaling capacity may be an intrinsic property of lymphocyte activation. In contrast to the ubiquitous expression of β-AR, lymphocyte α-AR are not easily detected under normal condition. α2-AR have been demonstrated on the surface of elicited macrophages (Spengler et al., 1990). Changes in lymphocyte AR expression have been reported in several human autoimmune diseases. α1-AR have been demonstrated on peripheral blood lymphocytes from children with a severe form of juvenile rheumatoid arthritis (Heijnen et al., 1996). β-AR density and signaling capacity are altered in peripheral blood lymphocytes from adults with rheumatoid arthritis and multiple sclerosis (Zoukos et al., 1994). Such alterations may reflect changes in sympathetic activity and catecholamine availability (Karaszewski et al., 1990), but it is also possible that the disease process itself elicits changes in lymphocyte AR expression that compensate for or exacerbate disease progression. These important issues need to be addressed experimentally before manipulation of AR signaling can be used therapeutically.

3. Altered catecholamine availability following immunization

Early reports demonstrated reduced NE concentration in lymphoid organs following immunization (del Rey et al., 1982), but it was not determined if the decreased NE levels reflected NE availability (Kohm et al., 2000). Other investigators have examined NE turnover in lymphoid organs as a means of assessing NE synthesis and availability during an immune reaction. Kohm and colleagues used severe combined immunodeficiency (SCID) mice that were reconstituted with antigen-specific B cells and Th2-type clones (Kohm et al., 2000). Intraperitoneal (i.p.) immunization with the antigen recognized by the donor cells, and not an unrelated antigen, increased turnover in the spleen, heart and bone marrow 18-24 after immunization. A sustained elevation in splenic NE metabolites in conjunction with reduced NE concentration was reported following i.p. immunization with a particulate antigen (sheep red blood cells), indicative of increased NE turnover (Fuchs et al., 1988). Similarly, increased NE turnover has been reported after administering LPS, in association with increased splenic nerve activity and elevated plasma NE and EPI (MacNeil et al., 1997). The biological impact of antigen induced alterations in NE turnover has not been directly assessed. The increased NE turnover following LPS administration reduces the pro-inflammatory response while enhancing the anti-inflammatory response (Elenkov et al., 1995; Suberville et al., 1996), indicative of a physiological mechanism to limit the magnitude of an inflammatory response. A careful examination of NE turnover over time following immunization with a variety of

antigen types, in conjunction with lymphocyte β-AR signaling capacity, will help determine the physiological significance of altered NE availability in immune physiology.

4. Evidence that catecholamines enhance and inhibit immune responses

The role of the SNS and AR signaling in immune regulation has been assessed in vivo by a variety of experimental approaches. Noradrenergic nerve ablation with the neurotoxin 6-OHDA (chemical sympathectomy) or treatment with the non-selective β-AR antagonist nadolol prior to immunization reduced a Th2-driven antibody response and decreased the delayed type hypersensitivity reaction to a contact sensitizing agent (Kohm & Sanders, 1999; Madden et al., 1989), suggesting that the SNS can enhance immune reactivity. Our experimental data demonstrated the effects of β-AR receptor blockade with propranolol in stress induce changes on haematological parametes of rats (Hritcu, 2006). However, in other studies we demonstrated that right-unilateral lesion of substantia nigra with 6-OHDA-induce changes of haematological parameters in Wistar rats, suggesting the implication of noradrenergic system in hematological processes regulation (Hritcu et al., 2007). In transgenic mice that lack one of the enzymes required to produce NE and EPI (dopamine β-hydroxylase), immune reactivity to infectious agents and a protein antigen was impaired (Alaniz et al., 1999). In vivo EPI administration prior to antigenic sensitization enhanced delayed type hypersensitivity and increased draining lymph node cellularity (Dhabhar & McEwen, 1999). Collectively, these results suggest that the SNS can enhance immune reactivity in vivo. By contrast, exposure to stressors or agents that activate the SNS reduced T cell responses, anti-viral immune reactivity, and NK cell activity; this immunosuppression was prevented by pretreatment with blockers or ganglionic blockade (Fecho, et al., 1996). In other experiments, chemical sympathectomy enhanced antigen-induced proliferation and Th1 and Th2 cytokine production in vitro (Kruszewska et al., 1998). Noradrenergic nerve ablation prior to i.p. immunization also increased serum antibody levels in rats and in C57BL/6 mice, but not BALB/c mice (Kruszewska et al., 1995). The discordance between these results and the reports of reduced cell-mediated immune reactivity following sympathectomy cited above demonstrate that genetic background (i.e., animal strain), the site of immunization, and the Th cells involved will influence outcome (Madden, 2001). These qualitative differences in catecholamine interactions with cells of the immune system in vivo suggest that a number of factors influence the outcome of SNS interactions with the immune system. Through in vitro studies with purified cell populations, investigators have begun to identify the mechanisms underlying catecholamine immunomodulation. Initial reports using unfractionated effector cells in vitro demonstrated β-AR-mediated enhancement of the generation of allo-reactive cytotoxic T lymphocytes and antibody secreting cells (Hatfield et al., 1986). Using antigen-specific B cells to present antigen and produce antibody and Th clones to provide help, β-AR stimulation increased antibody production when Th2 clones were provided as the source of T cell help (Sanders et al., 1997). Since Th2 clones do not express β-AR, B cell b-AR elicited the increased antibody production in this system. Subsequent experiments revealed that b-AR stimulation augmented antibody production by up-regulating B cell accessory molecule expression and by increasing B cell responsiveness to IL-4 (Kasprowicz et al., 2000; Hritcu et al., 2006). By contrast, when Th1 clones were exposed to b-agonists prior to antigen induced activation, the number of antibody forming cells decreased in conjunction with reduced IFN-c production (Sanders et al., 1997). These results suggest that Th1 responses are inhibited by b-AR stimulation, although Th1 responses also exhibit differential responsiveness to catecholamine stimulation. For example, when Th1 clones were activated with anti-CD3 instead of antigen, IL-2 production was reduced, but IFN-c production was unchanged in the presence of β-agonists (Ramer-Quinn et al., 1997). On the other hand, β-AR stimulation reduced monocyte- and dendritic cell-derived IL-12 production (Panina-Bordignon et al., 1997). These results demonstrate that the type of immune cell involved and its activational or maturational state contribute to the complexity of catecholamine interactions with the immune system. This complexity most likely reflects the important role of the SNS in fine-tuning a response with the goal of maintaining immune homeostasis.

5. Conclusions

The SNS and its primary neurotransmitter, NE, can enhance or inhibit immune reactivity depending on such factors as magnitude and timing of sympathetic activation relative to immunization, the lymphocyte subpopulations participating in the response, and the age and genetic background of the host. This complexity suggests that catecholamines are important in maintaining the balance between a rapid and effective response to a foreign antigen while minimizing destruction of normal tissue. Further work is necessary to elucidate the mechanisms by which catecholamines regulate immune function and to apply this knowledge to the therapeutic treatment of human immune-related diseases, including cancer.

REFERENCES

Alaniz, R. C., Thomas, S. T., Perez-Melgosa, M., Mueller, K., Farr, A. G., Palmiter, R. D., Wilson, C. B., 1999. *Proc. Natl. Acad. Sci. USA, 96, 2274–2278*

Bellinger, D. L., Lorton, D., Lubahn, C., Felten, D. L., 2001. *In R. Ader, D. L. Felten, & N. Cohen (Eds.), Psychoneuroimmunology (3rd ed., pp. 55–111). San Diego: Academic Press*

De Blasi, A., Parruti, G., Sallese, M., 1995. *J. Clin. Invest., 95, 203–210*
del Rey, A. E., Besedovsky, H. O., Sorkin, E., Da Prada, M., Bondiolotti, G. P., 1982. *Am. J. Physiol., 242, R30–R33*
Dhabhar, F. S., McEwen, B. S., 1999. *Proc. Natl. Acad. Sci. USA, 96, 1059–1064*
Elenkov, I. J., Hasko, G., Kovacs, K. J., Vizi, E. S., 1995. *J. Neuroimmunol., 61, 123–131*
Fecho, K., Maslonek, K. A., Dykstra, L. A., Lysle, D. T., 1996. *J. Pharmacol. Exp. Ther., 277, 633–645*
Fuchs, B. A., Campbell, K. S., Munson, A. E., 1988. *Cell. Immunol., 117, 339–351*
Hatfield, S. M., Petersen, B. H., DiMicco, J. A., 1986. *J. Pharmacol. Exp. Ther., 239, 460–466*
Heijnen, C. J., Rouppe van der Voort, C., Wulffraat, N., van der Net, J., Kuis, W., Kavelaars, A., 1996. *J. Neuroimmunol., 71, 223–226*
Hritcu, L., Horosanu, Daniela, Tiron, A., Maniu, C., Ungureanu, E., 2004a. *Analele Societatii Nationale de Biologie Celulara, vol. IX, nr. 2, 272-275*
Hritcu, L., Horosanu, Daniela, Tiron, A., Maniu, C., Ungureanu, E., 2004b. *Analele Societatii Nationale de Biologie Celulara, vol. IX, nr. 2, 2004, 276- 280*
Hritcu, L., Hefco, V., Neacşu, I., Maniu, C., 2005. *Analele stiintifice ale Universitatii Alexandru Ioan Cuza, Sectiunea Genetica si Biologie Moleculara, TOM VI, 2005, 65-68*
Hritcu, L., Clicinschi, M., Nabeshima, T., 2007. *Physiology & Behavior, 91(5):652-7*
Hritcu, L., Maniu, C., Campeanu, C., Clicinschi, M., 2006. *Analele SNBC, vol. XI, 307-311, 2006*
Karaszewski, J. W., Reder, A. T., Maselli, R., Brown, M., Arnason, B. G. W., 1990. *Ann. Neurol., 27, 366–372*
Kasprowicz, D. J., Kohm, A. P., Berton, M. T., Chruscinski, A. J., Sharpe, A., & Sanders, V. M., 2000. *J. Immunol., 165, 680–690*
Kohm, A., Sanders, V. M., 1999. *J. Immunol., 162, 5299–5308*
Kohm, A. P., Tang, Y., Sanders, V. M., Jones, S. B., 2000. *J. Immunol., 165, 725–733*
Kruszewska, B., Felten, S. Y., Moynihan, J. A., 1995. *J. Immunol., 155, 4613–4620*
Kruszewska, B., Felten, D. L., Stevens, S. Y., Moynihan, J. A., 1998. *Brain Behav. Immun., 12, 181–200*
MacNeil, B. J., Jansen, A. H., Janz, L. J., Greenberg, A. H., Nance, D. M., 1997. *Am. J. Physiol., 273, R609–R614*
Madden, K. S., Felten, S. Y., Felten, D. L., Sundaresan, P. R., Livnat, S., 1989. *Brain Behav. Immun., 3, 72–89*
Madden, K. S., 2001. *In R. Ader, D. L. Felten, & N. Cohen (Eds.), Psychoneuroimmunology (3rd ed., pp. 197–216). San Diego: Academic Press*
Madden, K.S., 2003. *Brain Behav. Immun., 17, S5-S10*
Miller, L. E., Hans-Peter, J., Scholmerich, J., Straub, R. H., 2000. *FASEB J., 14, 2097–2107*
Panina-Bordignon, P., Mazzeo, D., Di Lucia, P., D'Ambrosio, D., Lang, R., Fabbri, L., Self, C., Sinigaglia, F., 1997. *J. Clin. Invest., 100, 1513–1519*
Qi, M., Zhou, Z., Wurster, R. D., & Jones, S. B., 1991. *Am. J. Physiol., 261, R1431–R1437*
Ramer-Quinn, D. S., Baker, R. A., & Sanders, V. M., 1997. *J. Immunol., 159, 4857–4867*
Sanders, V. M., Baker, R. A., Ramer-Quinn, D. S., Kasprowicz, D. J., Fuchs, B. A., Street, N. E., 1997. *J. Immunol., 158, 4200–4210*
Spengler, R. N., Allen, R. M., Remick, D. G., Strieter, R. M., Kunkel, S. L., 1990. *J. Immunol., 145, 1430–1434*
Suberville, S., Bellocq, A., Fouqueray, B., Philippe, C., Lantz, O., Perez, J., Baud, L., 1996. *Eur. J. Immunol., 26, 2601–2605*
Zoukos, Y., Kidd, D., Woodroofe, M. N., Kendall, B. E., Thompson, A. J., Cuzner, M. L., 1994. *Brain, 117, 307–315*

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