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A Genetic Model of Stress Displays Decreased Lymphocytes and Impaired Antibody Responses Without Altered Susceptibility to Streptococcus pneumoniae

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Stress pathways affect immune function, the most notable of these pathways being activation of the hypothalamic-pituitary-adrenal (HPA) axis. Although HPA activation has generally been relegated to an immunosuppressive role, recent evidence suggests that stress and HPA activation can be immunoenhancing in certain situations. To investigate specific effects of stress on immune function, we used a genetic model of chronic stress wherein transgenic mice overexpress corticotropin-releasing hormone (CRH), a primary mediator of the stress response. In these mice, CRH is overproduced in the brain, leading to chronic activation of the HPA axis. We found that CRH-transgenic mice have decreased leukocyte numbers in lymphoid compartments, with preferential loss of B lymphocytes. They also exhibit decreased Ab production and impaired isotype switching in response to immunization with a thymus-dependent Ag, phosphocholine-keyhole limpet hemocyanin. Despite these deficits, immunization protected CRH-transgenic and wild-type mice equally well against lethal challenge with Streptococcus pneumoniae, an encapsulated Gram-positive bacterium known to require Ab-mediated opsonization for clearance. While IgG responses are severely depressed in these mice, IgM titers are only modestly decreased. This fairly robust IgM response may be sufficient to protect against S. pneumoniae. Additionally, while total leukocyte numbers are decreased in these mice, neutrophil numbers are increased. This increase in number of neutrophils may compensate for the depressed IgG response, allowing adequate host defense during chronic stress. The Journal of Immunology, 2001, 167: 691–698.
were subsequently back-crossed nine generations onto the C57BL/6 back-
Mice to chronic stress. CRH-tg mice exhibit increased anxiety, decreased exploration, learning impairment, and decreased reproductive behavior (26, 27). These behaviors exist in CRH-tg animals in the absence of exogenous stress and can be exacerbated further following exposure to stress (27).

Previous studies using these mice reported marked reductions in cell numbers in the spleen and thymus with a more modest reduction in the bone marrow (28, 29). Compared with other cell types, B lymphocytes were found to be preferentially depleted in the spleen and bone marrow, and CD44/CD8 double-positive (DP) T cell precursors were preferentially diminished in the thymus. Ab responses were also decreased in these mice. Adrenalectomy partially reversed these changes, making it unclear whether glucocorticoids are solely responsible.

These preliminary observations suggested that CRH-tg mice may be quite immunosuppressed. We hypothesized that this immunosuppression may be qualitative as well as quantitative and that adaptive immunity would be targeted. Therefore, we examined leukocyte populations in primary and secondary lymphoid organs. Because DP T cells were decreased in the thymus, and the bone marrow exhibited a profound loss of B cells, we suspected that certain B lymphocyte subsets may be targeted preferentially. Here, we show developmental alterations of B cell populations in the bone marrow, wherein pre-B cells are depleted preferentially. In investigating lymphocyte function by measuring Ab responses to primary and secondary immunizations, we found that CRH-tg mice display high preimmune IgM titers and mount robust IgM responses to immunization. However, these animals show poor secondary IgG Ab responses, indicating a predominant failure to undergo isotype switching. Finally, we tested whether such immune changes affect survival in the face of challenge with a bacterial pathogen. Despite the defects in B cell numbers and Ab response, immunization affords CRH-tg mice equal protection against challenge with Streptococcus pneumoniae compared with wild-type (WT) mice. This may be due, in part, to an enhancement of innate immunity, as we found augmented numbers of neutrophils in CRH-tg mice.

Materials and Methods

Mice

The creation of CRH-tg mice was previously described (23). CRH-tg mice were subsequently back-crossed nine generations onto the C57BL/6 back-ground. Mice were bred and housed in the specific pathogen-free facility at the Oregon Health Sciences University Department of Comparative Medicine. All procedures were approved by the Institutional Animal Care and Use Committee of Oregon Health Sciences University. Experiments were performed with minimal psychological and physical stress to the animals. Mice were used at 2–4 mo of age.

HPA response to restraint

Mice were housed overnight in pairs in shrouded cages to minimize environmental stress. Between 8 and 10 a.m. the following morning, mice were restrained for 10 min in 50 ml conical tubes equipped with airholes. Blood was collected from the retroorbital plexus at the following times: basal (unstressed), immediately after restraint, or 20 min following cessation of restraint. Results are the mean ± SEM of eight mice per genotype; each mouse was bled at one time point only. *, p < 0.05, CRH-tg vs WT; **, p < 0.05, CRH-tg 30 min vs CRH-tg basal; Newman-Keuls post hoc test.

FIGURE 1. CRH-tg mice have increased basal levels of CORT, which increase further in response to restraint stress. Mice were restrained for 10 min in 50 ml polypropylene conical tubes. Blood was collected from the retroorbital plexus at the following times: basal (unstressed), immediately after restraint, or 20 min following cessation of restraint. Results are the mean ± SEM of eight mice per genotype; each mouse was bled at one time point only. *, p < 0.05, CRH-tg vs WT; **, p < 0.05, CRH-tg 30 min vs CRH-tg basal; Newman-Keuls post hoc test.

Immunizations

For immunizations to examine both Ab titers and protection against S. pneumoniae, mice were injected i.p. with 70–100 μg phosphocholine coupled to keyhole limpet hemocyanin (PC-KLH) in 200 μl CFA (primary immunization, day 1) or IFA (secondary immunization, day 14). Blood was collected for Ab measurement at days 0, 7, 19, and 26, and serum was frozen at −20°C until the assay date.

S. pneumoniae challenge

Naïve or PC-KLH-immunized mice were infected with varying doses of S. pneumoniae, injected i.p. in 100 μl sterile saline. For PC-KLH-immunized mice, bacterial challenge occurred 7 days after the secondary immunization (day 21). Survival was analyzed statistically using χ² on collapsed doses, comparing total number of surviving mice: WT naive vs CRH-tg naive, WT immunized vs CRH-tg immunized, and naïve vs immunized within each genotype.

S. pneumoniae culture

S. pneumoniae (Wu-2, a generous gift from Dr. J. Kenny, National Institute on Aging, National Institutes of Health, Bethesda, MD) were periodically passed through WT mice to maintain a virulent stock. Bacteria were grown overnight on tryptic soy agar/5% blood agar plates (PML Microbiologicals, Wilsonville, OR). The following day, 5 ml of Todd-Hewitt’s broth supplemented with 0.5% yeast extract and 0.2% sheep blood were inoculated into an individual colony. This culture was incubated 12 h and then used to inoculate 125 ml of Todd-Hewitt’s broth supplemented with 0.5% yeast extract. Bacteria were collected at log phase, washed once, and dilutions were made in sterile PBS. Precise enumeration was calculated retrospectively by plating bacterial dilutions on thymic shared Ag/5% blood agar plates.

Leukocyte isolation

Bone marrow, spleen, and thymus were dissociated into single-cell suspensions, washed twice in PBS, and leukocytes were counted via trypan blue exclusion to determine viable cell numbers. After RBC lysis, peripheral blood leukocytes were washed three times in PBS and counted as above. These cells were then immunostained for FACS analysis as described below.

FACS analysis

Cells were preincubated with anti-CD16/CD32 (Fc block; BD Pharmingen, San Diego, CA) to decrease FcR-mediated background staining and subsequently incubated in PBS/3%FBS with the following panel of Abs or appropriate isotype controls: anti-CD3, anti-CD4, anti-CD8, anti-CD45R (B220), anti-CD43, anti-IgM, anti-IgD, anti-CD11b (Mac-1), and anti-Ly6G (1A8). B cell developmental stages were distinguished as follows: pro (B220⁺, CD34⁺), pre (B220⁺, CD34⁻), immature (IgM⁺, IgD⁻), and mature (IgM⁺, IgD⁺) (30–33). All Abs except 1A8 were purchased from BD Pharmingen as direct conjugates to FITC, PE, CyChrome, or biotin. 1A8 (a generous gift from T. Malek) is a rat mAb (IgG2a) that recognizes Ly6G (34), a differentiation marker restricted to neutrophils. The Ab bound to cells was detected with FITC-anti-rat IgG2a (BD Pharmingen). Cells were fixed in 1% paraformaldehyde and analyzed the following day by three-color flow cytometry on a FACScalibur (Becton Dickinson, Franklin Lakes, NJ).
Ab measurement

Serum obtained from retroorbital blood samples was stored at −20°C until the time of assay. Quantitative ELISA was performed to measure phosphocholine (PC-specific) or keyhole limpet hemocyanin (KLH)-specific Abs as previously described (35). Briefly, 96-well plates were coated over-night with PC-histone or KLH (1 μg/ml). Dilutions of individual or pooled sera were added and incubated at 1.5 h at room temperature, plates were washed, and samples were detected by incubation with isotype-specific alkaline phosphatase-conjugated secondary Abs (Zymed, San Francisco, CA). p-Nitrophenyl phosphate substrate (Sigma, St. Louis, MO) allowed color detection at OD 410. Standard curves generated with T15 idiotype (PC-specific) mAbs generated in our laboratory were used to determine the concentration of PC-specific Abs in serum dilutions. For IgG determination, a mixture of IgG1, IgG2a, IgG2b, and IgG3 T15 Abs was used. For PC inhibition studies, all wells contained 0.2 M free PC or control diluent (0.1 M phosphate buffer).

Results

CRH-tg mice have decreased cellularity and altered leukocyte populations in primary and secondary lymphoid organs

We analyzed the cellularity and leukocyte populations in primary and secondary lymphoid organs of naive CRH-tg and WT mice and found striking reductions in cellularity in the blood, spleen, thymus, and bone marrow of CRH-tg mice (Fig. 2). Spleen and thymus cell numbers were decreased 25- and 50-fold, respectively, consistent with effects previously reported with chronic HPA activation (36). Cellularity in the bone marrow and blood was also decreased, albeit to a lesser extent.

To test whether specific lymphocyte populations were preferentially decreased, we analyzed blood, spleen, and bone marrow by three-color FACS analysis to detect relative proportions of B and T lymphocytes and B lymphocyte precursors. The percentage of total B cells was decreased by 2- to 3-fold in the spleen and blood of CRH-tg mice (Fig. 3, A and B, left panels). Staining for IgM and IgD expression showed that this difference was primarily due to a loss of mature (IgD⁺) B cells, as seen when plotted as a percentage of total B cells (Fig. 3, A and B, right panels). We examined B cell precursors in the bone marrow to determine whether this loss of peripheral B cells might result from altered hematopoiesis. Total B cells in the bone marrow were decreased more dramatically (~6-fold) than in the periphery (Fig. 4B, left panel). We further identified pro (B220low CD43⁺), pre (B220low CD43low), immature (IgM⁺, IgD⁻), and mature (IgM⁺, IgD⁺) B cells using stage-specific markers (Fig. 4B, right panel) and found a near complete loss of pre-B cells in CRH-tg mice (Fig. 4A). In fact, as a percentage of total B cells, only the pre-B cell population was diminished (Fig. 4B). Thus, chronic HPA activation appears to affect mature B cells in the spleen and blood and developing B cells in the bone marrow as indicated by the loss in pre-B cells.

We also examined peripheral T cell populations because we were interested in T-dependent Ab responses. Unlike B lymphocytes, the percentage of circulating T cells was similar between WT and CRH-tg mice (Fig. 3B, left panel). Moreover, in the spleen CRH-tg mice had a greater proportion of T cells (Fig. 3A, left panel), although the absolute number of T cells was still decreased. The CD4:CD8 ratio was not altered in these mice (data not shown). Thus, alterations in T cell populations are unlikely to contribute to an Ab defect, although we have not ruled out the possibility of altered T cell function.

CRH-tg mice exhibit an altered Ab response to PC-KLH immunization

To investigate the reported defect in Ab production in CRH-tg mice, we examined primary and secondary Ab responses to a thymus-dependent Ag, PC-KLH. PC is an important antigenic component of cell-wall polysaccharides of numerous pathogens including Gram-positive bacteria (S. pneumoniae), Gram-negative bacteria (Haemophilus influenzae, Salmonella), protozoans (Leishmania, trypanosomes), and parasites (tapeworm, nematodes) (37). Abs against PC have been shown to be protective against pneumococcal and filarial infection (38–43). Thus, we elected to immunize mice with PC coupled to a protein carrier, KLH, which allowed us to examine thymus-dependent Ag responses and test whether immunization results in improved protection against a relevant pathogen, S. pneumoniae.

We found that preimmune titers of anti-PC IgM Abs were actually slightly higher (~2-fold) in CRH-tg mice than in WT mice (Fig. 5A). In addition, CRH-tg mice had primary (day 7) and secondary (days 19 and 26) anti-PC IgM responses that were robust, albeit somewhat lower (~3-fold) than WT mice. Primary (day 7) anti-PC IgG titers were low in both genotypes, but following secondary Ag challenge (days 19 and 26) WT mice mounted a strong IgG response. This response was severely decreased (10-fold below WT levels) in CRH-tg mice, indicating impaired isotype switching (Fig. 5B). This impairment is not due simply to delayed kinetics as IgG titers after immunization did not rise above levels

FIGURE 2. CRH-tg mice have decreased cellularity in lymphoid tissues. Spleen, thymus, and bone marrow were dissociated into single-cell suspensions and leukocytes counted by trypan blue exclusion. Results are the mean ± SEM of eight mice per genotype. *, p < 0.05; Student’s t test.
CRH-tg and WT mice are equally susceptible to infection with S. pneumoniae

The decrease in B lymphocytes and poor Ab responses after immunization suggested that CRH-tg mice would be more susceptible to infection with S. pneumoniae, a Gram-positive pathogen that requires opsonization for efficient clearance (45). We challenged CRH-tg and WT mice with various doses of a virulent strain of S. pneumoniae, Wu-2, to determine whether CRH-tg mice had increased susceptibility. Unexpectedly, survival was not different between naive mice of both genotypes (p > 0.3, χ², Table I). Furthermore, most animals died between 2 and 4 days after infection irrespective of genotype, indicating that the kinetics of death were similar between the two groups (data not shown). We then tested whether immunization with PC-KLH, which is known to induce protective Abs in WT mice (46, 47), would provide resistance against S. pneumoniae challenge in CRH-tg mice. Surprisingly, immunization protected CRH-tg and WT mice equally well (>100-fold compared with naive) (Fig. 6 and Table I). Again, there were no differences in survival between immunized CRH-tg and WT mice.

**Augmented neutrophils in CRH-tg mice**

It was unexpected to find that immunization afforded CRH-tg and WT mice equal protection against S. pneumoniae given the diminished B cell numbers and Ab responses. Abs are critical in clearing

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<td>WT</td>
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<td>CRH-tg&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> Number of mice that survived/number of mice infected.

<sup>b</sup> CRH-tg not statistically different from WT, p > 0.3, χ² test.
**FIGURE 6.** CRH-tg mice survive *S. pneumoniae* infection equally well compared with WT mice. PC-KLH immunized mice (9–10 mice per dose per genotype) were challenged i.p. with doses of 1, 10, 100, or 1000 *S. pneumoniae* organisms per mouse. There was no significant genotype difference in percent of mice surviving or average day of death. Both genotypes were significantly protected (~100-fold) by immunization (p < 0.05; $\chi^2$).

*Discussion*

Until recently, the immunological consequences of stress have been viewed as largely detrimental. It is becoming increasingly evident that this view does not convey the complete picture and is inaccurate in certain situations. Decreased lymphocyte numbers occur following acute and extended periods of stress, but such diminution does not always lead to suppressed functional outcomes of immune defense. Furthermore, new evidence supports the idea that exposure to acute stress can lead to enhanced immune responses (9, 10). Some have proposed that while acute stress can be immunoenhancing, chronic stress is detrimental (53). Our findings with susceptibility to *S. pneumoniae* suggest that this may not always be true. Thus, while stress-induced modulation of the immune response alters certain components of the immune system (e.g., cell numbers, population composition), the consequences on immune function need to be analyzed individually. Furthermore, effects of stress on innate and adaptive aspects of the immune response need to be considered individually. The magnitude and direction of the immunological consequences of stress can vary depending on the type and duration of stress, and the specific immune response being examined. **FIGURE 7.** CRH-tg mice have increased numbers of granulocytes. Single-cell suspensions of spleen, blood, and bone marrow were stained with mAbs to CD11b and Ly6G to distinguish monocyte/macrophages vs neutrophils (C, lower panels). Neutrophils were also distinguished by high side scatter (SSC; C, upper panels). CRH-tg mice had an increased proportion of monocyte/macrophages in the spleen (A) and increased proportion of neutrophils in all tissues examined (B and C). The absolute number of blood neutrophils was obtained by multiplying the percentage of neutrophils by the number of leukocytes per milliliter of blood (D). Results are the mean ± SEM of eight mice per genotype (*, p < 0.05; Student’s t test). FSC, Forward scatter.
system are not necessarily synchronous; thus, suppression of adaptive responses may be counterbalanced by enhancement of certain innate components.

Using a genetic model of chronic HPA activation, we found strong evidence for changes in both adaptive and innate components of the immune system. Stress-induced decreases in lymphoid numbers have been a fairly consistent finding among most models of stress and HPA activation. We found that CRH-tg mice exhibit decreased lymphoid numbers in all immune compartments examined. This may be due to increased glucocorticoids that have been shown to decrease the size of the spleen and thymus, although decreased cellularity has not been observed consistently in the blood and bone marrow (54–58). Furthermore, lymphocytes are known to be particularly sensitive to glucocorticoid-mediated apoptosis; thus, we speculate that the decrease in T and B lymphocytes in CRH-tg mice is due to increased basal levels of CORT (58–61). It is noteworthy that CRH-tg mice show a profound reduction in pre-B cells in the bone marrow, which to our knowledge is the first evidence that chronic HPA activation preferentially depletes pre-B cells. Again, this is likely due to excess glucocorticoids as del Rey and colleagues (62) showed that dexamethasone treatment induced widespread loss of pre-B cells, but had a lesser effect on pre- and mature B cells. Interestingly, DP T cells, which are at a developmental stage analogous to pre-B cells, are well known for their susceptibility to glucocorticoid-mediated apoptosis (59).

Precursor lymphocytes may be affected preferentially by glucocorticoids because these hormones play a role in lymphocyte selection. In the case of DP T cells, glucocorticoids antagonize TCR-mediated apoptosis, which allows selection of clones with low to moderate avidity for self Ags. Without glucocorticoid signaling at this stage, the threshold for positive selection is raised and T cells with low to moderate avidity for self Ags die (63, 64), although the total number of DP T cells generated in the thymus remains unchanged (65). In the case of pre-B cells, it is not known whether glucocorticoids influence B cell selection. However, our results showing that pre-B cells are particularly sensitive to chronic HPA activation raise this intriguing possibility. Furthermore, there is a marked difference in the Ag specificity of B cells induced by PC-KLH when comparing CRH-tg and WT mice. This difference in fine specificity quite likely indicates a difference in responding B cell clones and thereby suggests that the B cell repertoire may be altered during chronic HPA activation. Additionally, this observation is consistent with a failure to develop a strong memory response because NPPC-restricted Abs normally arise during secondary and memory responses to PC-KLH.

Depletion of mature B cells in the spleen was also evident among CRH-tg mice. This was unanticipated given that mature B and T cells are relatively resistant to glucocorticoid-mediated apoptosis (56, 57, 66). This could be a reflection of the decrease in B cell precursors, leading to fewer cells capable of entering the mature B cell pool. However, if this were the case, we would expect the proportion of immature B cells in the periphery to be similarly depleted. It is conceivable that hormones that act upstream of glucocorticoids such as CRH and ACTH may affect mature B cells in a manner that is independent of glucocorticoids (11, 13, 67, 68). In addition to direct effects on mature B cells, it is possible that chronic HPA activation leads to changes in specific factors necessary for B cell survival, thus indirectly limiting their development and/or expansion.

Adaptive responses are also impaired as measured by the ability of these mice to generate Ab responses to the Ag, PC-KLH. CRH-tg mice mount an IgM response to PC-KLH immunization but exhibit poor isotype switching. The precise mechanism underlying this impairment is not clear at this time. It is reasonable to speculate that B cells in these animals are unable to respond to appropriate signals needed to induce isotype switching or memory cell formation, perhaps due to altered expression of cytokine receptors or inhibition of signaling pathways (69). Lack of adequate T cell help, a critical component for isotype switching, may also be a factor. This could result from a decrease in T cell number, making cell-to-cell interactions infrequent. We think this is unlikely, because the T:B cell ratio is actually higher in the spleens of CRH-tg mice (data not shown). Instead, the T cells making up this population may be actively regulating B cell function. Alternatively, CRH-tg T cells may not express adequate levels of costimulatory molecules, such as CD40 ligand, or produce cytokines appropriate for class switching (70).

Surprisingly, immunization with PC-KLH provided CRH-tg and WT mice equal protection against S. pneumoniae. Given the low B cell numbers and poor Ab response, we predicted that immunization would be less beneficial to CRH-tg mice. However, because this was not the case, we need to consider that even the low level of Abs achieved in CRH-tg mice is sufficient to opsonize and clear S. pneumoniae. Immunization of WT mice with PC-KLH may elicit Ab titers that exceed those needed to protect against S. pneumoniae. However, previous studies have shown that when mice are immunized with pneumococcal polysaccharide, individual Ab titers correlated with survival in mice challenged with S. pneumoniae, indicating in that system Ab levels are not in great excess (71). It is also possible that IgM Abs play a more important role in bacterial clearance than has been appreciated previously. If this were the case, CRH-tg mice would be reasonably well protected given that their levels of anti-PC IgM were only modestly reduced. Indeed, an early study showed that S. pneumoniae preopsonized with IgM Abs obtained from pneumocococcus-immunized animals were cleared more rapidly from the bloodstream than those preopsonized with IgG (45). More recently, a number of studies have shown a critical role for IgM Abs in other models of bacterial infection (72–74). These observations, taken together with the recent isolation and identification of a novel FcR for IgM that enhances opsonic uptake (75), support a vital role for IgM in defense against bacterial disease, particularly in the early phases of infection that involve phagocytosis and clearance of bacteria.

It is also reasonable to speculate that augmented innate defenses may compensate for the lower Ab titers, allowing clearance of bacteria that are not opsonized optimally. We found that CRH-tg mice have increased numbers of circulating neutrophils, which may afford significant protection in the face of diminished Ab responses. The increase in neutrophils seen in these animals is likely due to elevated CORT levels because glucocorticoids have been shown to increase the production, release from the bone marrow, and half-life of neutrophils (76–79). Future studies are necessary to determine whether specific functions of innate immunity are enhanced in CRH-tg animals.

The idea that innate immune mechanisms may be augmented in CRH-tg mice is supported by other stress-related studies. Both stress and glucocorticoids have been shown to increase the phagocytic activity of neutrophils and macrophages (80–88). In addition, glucocorticoids induce molecules vital to opsonization such as complement and C-reactive protein, an acute-phase protein that binds PC and is protective against S. pneumoniae (89–94). Other products of the stress response, such as CRH, may also modulate innate immunity. Recent studies have shown that CRH receptors are expressed on splenic macrophages and can be induced on neutrophils following immunization or restraint stress (21, 95, 96). In the case of macrophage function, CRH has been shown to increase superoxide production (97), suggesting that an innate mechanism
of cytotoxicity could be enhanced by increased CRH production during stress.

Collectively our studies suggest that during stress, innate immune mechanisms are preserved while adaptive responses are clearly compromised. A balance appears to be achieved by these changes because CRH-tg mice develop an adequate immune response to protect against challenge with a lethal pathogen despite profound loss of B lymphocytes and diminished Ab responses. During periods of stress there are likely to be important demands on the immune system due to infection, thus stress regulation of the immune response may have evolved to provide a well-orchestrated immune defense to ensure survival.

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References


AB PRODUCTION AND HOST DEFENSE DURING CHRONIC STRESS


