Differential Effects of Growth Hormone and Prolactin on Murine T Cell Development and Function

By William J. Murphy,* Scott K. Durum,‡ and Dan L. Longo*

*From the Laboratories of *Leukocyte Biology and ‡Molecular Immunoregulation, Biological Response Modifiers Program, Division of Cancer Treatment, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, Maryland 21702*

Summary

DW/J dwarf mice have a defect in their anterior pituitary and are deficient in growth hormone (GH) and prolactin (PRL). These mice have been demonstrated previously to have a deficiency in CD4/CD8 double-positive thymocytes, which could be corrected by treatment of these mice with recombinant human GH. Since PRL has been implicated in T cell function and human GH can interact with the PRL receptor, DW/J dwarf mice were treated with either ovine GH (ovGH) (20 μg/d) or ovine PRL (ovPRL) (20 μg/d). The ovine hormones can only bind their own specific receptors in the mouse. After several weeks of treatment, it was found that these two hormones produced markedly contrasting effects on T cells. Phenotypic analysis of the lymphoid organs was performed by flow cytometry and the functional capability of the peripheral T cells was assessed by immunizing the mice and determining the extent of antigen-specific proliferation of T cells obtained from the draining lymph nodes or by determining splenic mitogen responses. The results indicated that ovGH administration to dwarf mice resulted in significant increases in thymic cellularity yet had little effect on peripheral T cell responses. In contrast, the administration of ovPRL resulted in a further decrease in thymic cellularity when compared with untreated dwarf mice. No thymic effects of either ovGH or ovPRL administration were detected on the normal +/? counterparts. However, ovPRL administration resulted in a significant increase in the number and function of antigen-specific peripheral T cells in both immunized dwarf and +/? mice. The adjuvant effects of PRL occurred even though the mice also received complete Freund's adjuvant. These results suggest that neuroendocrine hormones may act in concert in T cell development. GH appears to promote thymocyte proliferation, while PRL appears to decrease thymus size and yet augment the number and function of antigen-specific T cells in the periphery.

Neuroendocrine hormones have long been thought to play a role in T cell development and function (1). In particular, growth hormone (GH)[1] has been postulated to be a mediator important in thymic development (1, 2). Studies using neuroendocrine hormone–deficient dwarf mice have proven especially useful in dissecting the potential role of these hormones in T cell development (3, 4). DW/J dwarf mice have a defect in their anterior pituitary and, as a result, are deficient in the production of GH, prolactin (PRL), and other neuroendocrine mediators (4). Aside from the expected deficiencies in growth, these mice have also been reported to have deficiencies in T cell development and function (4, 5). We have recently found that these mice have deficiencies in $CD4^+CD8^+$ double-positive cells within their thymi and that treatment of these mice with either recombinant human (rh)GH or ovine (ov)GH could restore this T cell progenitor population within the thymus (6). Treatment with rhGH also resulted in an increase in thymic size and a modest increase in peripheral T cell function in these mice (6). These results suggested that GH can exert thymopoietic effects after in vivo administration and may be important for the maintenance of thymic function. However, rhGH can also bind the PRL receptor and can mediate effects associated with signal transduction through the PRL receptor (7). PRL has also been implicated in T cell development and has been suggested to be important for T cell function (8, 9). To address the role of PRL on T cell development, DW/J mice were given either ovGH, which cannot bind the murine PRL receptor (7), or ovPRL alone. We report here that these two closely related hormones in fact yield contrasting effects on T cells in dwarf mice. ovGH appears to act early during T cell development within the thymus whereas ovPRL appears to affect mature T cell function in the periphery. These results sug-

[1] *Abbreviations used in this paper:* GH, growth hormone; LNC, lymph node cells; ov, ovine; PRL, prolactin; rh, recombinant human.

gest that the neuroendocrine hormones exhibit diverse effects on T cells and may be of possible use in specific clinical settings where thymic or peripheral T cell stimulation might be indicated.

Materials and Methods

Mice. DW/J *dw/dw* mice and their control heterozygous littermates, consisting of *dw/+* and +/+ (abbreviated +/?), were purchased from The Jackson Laboratory (Bar Harbor, ME). The mice were not used until 8–9 wk of age and were kept under specific pathogen-free conditions until use. The mice were housed with control littermates, had food pellets placed on the bottom of the cages, and had water and food intake monitored. The mice were periodically tested for exposure to common murine pathogens before entering the colony at the National Cancer Institute, Frederick Cancer Research and Development Center (NCI-FCRDC) and were necropsied upon day of death to determine evidence for bacterial infection.

Antibodies and Flow Cytometric Analysis. Thymocytes, splenocytes, and lymph node cells (LNC) (brachial, inguinal, axillary, and mesenteric) were suspended in HBSS and incubated with the appropriate fluorochrome-conjugated antibodies. The single-cell suspensions were first counted using a cell counter (Coulter Electronics, Hialeah, FL), and a Student's *t* test was used to determine if the organ cellularities were significantly different. The cells were then fixed in 1% paraformaldehyde and analyzed using an EPICS flow cytometer (Coulter Electronics). Each two-color fluorescence study included controls of normal rat serum (NR-FITC and NR-PE). The primary antibodies were: anti-CD3-FITC, anti-CD8 (Lyt-2-FITC), and anti-CD4 (L3T4-biotinylated), which were purchased from Becton Dickinson & Co. (Mountain View, CA). All experiments were performed three to four times and had two to four mice per group with a representative mouse being shown.

Treatment with ovGH or ovPRL. Mice in some groups received 20 μg of ovGH or 20 μg of ovPRL (both provided by a hormone repository run by the National Institute of Diabetes and Digestive and Kidney Diseases, the Center for Population Research of the National Institute of Child Health and Human Development, the Agricultural Research Service of the U.S. Department of Agriculture (Bethesda, MD), and the University of Maryland School of Medicine, Baltimore, MD) resuspended in 0.2 ml PBS and injected intraperitoneally every day for 8 wk or until the mice were assayed. The percent of contamination of the hormones with each other was 0.03%. Control mice received 0.2 ml PBS daily. Mice were weighed weekly until termination of study.

Antigen-specific T Cell Proliferation and Splenic Mitogen Assays. Mice were immunized at the base of the tail with 100 μg of KLH (Calbiochem-Behring Corp., La Jolla, CA) in CFA (*Mycobacterium tuberculosis* strain H37Ra; Difco Laboratories, Detroit, MI). 7 d later the two draining lymph nodes (inguinal) from three to five mice were removed and single-cell suspensions were made. In some experiments, the B cells were removed by incubating the LNC suspension on 24-well cluster plates (Costar, Cambridge, MA) coated with goat anti-mouse Ig (a kind gift from Dr. James Kenny, Program Resources, Inc./DynCorp, NCI-FCRDC, Frederick, MD) for 1 h at 37°C at a concentration of 10^6 cells/ml. The nonadherent cells (5×10^5) were then cultured in RPMI 1640 supplemented with 0.5% fresh syngeneic serum and 50 μM 2-ME (Sigma Chemical Co., St. Louis, MO) in flat-bottomed microtiter wells (Costar). KLH (100 μg/ml) was then added to cultures. 4 d later proliferation was assayed by pulsing with 1 μCi (3.7×10^4 becquerels) of [^{3}H]thymidine (6.7 Ci/mmol) (New England Nuclear, Boston, MA) for 4 h and harvesting with a MASH II apparatus (Microbiological Associates, Bethesda, MD). In the splenic mitogen assay, splenocytes were obtained, counted, and cultured at 10^5 in 0.2 ml of the same medium described above in the LNC proliferation assay along with Con A (Sigma Chemical Co.) at a concentration of 5 μg/ml. After 2 d of incubation at 37°C, the cultures were pulsed for 3 h with [^{3}H]Tdr, harvested, and thymidine incorporation was quantitated as described in the LNC proliferation assay. All data are presented as means with standard deviation. A Student's *t* test was performed to determine statistical differences with *p* values <0.05 being considered significant.

Results

Administration of ovGH or ovPRL to Dwarf Mice Yields Opposite Effects on Thymic Cellularity. We have previously determined that rhGH exerted thymopoietic effects after in vivo administration to dwarf mice (6). We then wanted to determine if ovPRL also could exert effects on the dwarf thymus after in vivo administration in these mice since hGH can also bind the PRL receptor (7). Dwarf mice and their control +/? littermates were given 20 μg of either ovGH or ovPRL every day for 3 wk since the ovine hormones only can bind their respective receptors in the mouse (7). At this dose range, modest but not always statistically significant increases in growth occurred in the dwarf mice that were treated with ovGH (data not shown). No effects on growth were seen in any of the +/? littermates or *dw/dw* mice receiving ovPRL. Upon analysis, the thymi from untreated dwarf mice were markedly hypocellular, as has been previously described (3, 4, 6). Furthermore, administration of ovGH to these mice resulted in a significant ($p < 0.001$) increase in thymic cellularity (Fig. 1). In marked contrast, the administration of ovPRL resulted in a significantly ($p < 0.001$) decreased thymic cellularity in dwarf mice. No effect of ovGH or ovPRL was detected on the thymic cellularity of +/? control littermates (data not shown). Phenotypic analysis of the dwarf thymocytes was then performed. Untreated dwarf mice again displayed a modest decrease in CD4/CD8 double-positive thymocytes (Fig. 2 *a*), as has been previously reported (6, 10). The extent of the double-positive T cell deficiency is quite variable and may be related to the increased susceptibility of these mice to stress (6). However, treatment of these mice with ovGH resulted in a slight increase in double-positive cells (Fig. 2 *b*), which is also in agreement with previous reports (6). Interestingly, the administration of ovPRL resulted in further reduction of the double-positive cells, the residual being somewhat enriched for mature CD4 and CD8 single-positive thymocytes, particularly $CD4^+$ cells (Fig. 2 *c*). It appears therefore that ovGH can mediate increases in thymic cellularity and results in increases in double-positive cells, whereas ovPRL produces the opposite effects and results in decreases in both cellularity and the percentage of double-positive thymocytes in neuroendocrine-deficient dwarf mice. No effect of ovPRL or ovGH administration was detected on the thymic progenitor distribution of the normal control littermates (data not shown). Thus, the previously reported thymopoietic effects of rhGH in dwarf mice (6) appear to be mediated by the ability of human GH to bind the GH receptor and not the PRL

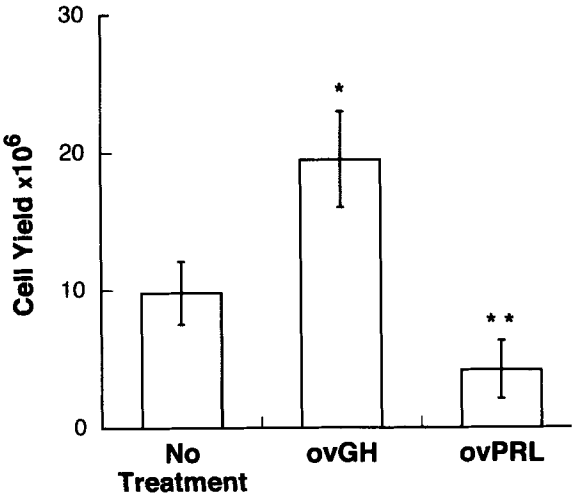

Figure 1. Thymic cellularity in dwarf mice after ovGH or ovPRL administration. Dwarf mice were treated with either 20 μg ovGH or 20 μg ovPRL daily for 8 wk as described in Materials and Methods. The data represent four experiments with three to four mice per group. Treatment with ovGH resulted in a significant ($*p < 0.001$) increase in thymic cellularity when compared with untreated controls. Treatment with ovPRL resulted in a significant ($**p < 0.001$) decrease in thymic cellularity when compared with untreated controls.

receptor since the ovine hormones produce contrasting effects on thymic cellularity in neuroendocrine-deficient dwarf mice.

Administration of ovPRL Increases Peripheral T Cell Function in Both dw/dw and +/? Mice. We then wanted to assess peripheral T cell content and function in mice as a consequence of either ovGH or ovPRL administration. There was no significant effect of ovGH or ovPRL administration on lymph node cellularity in unimmunized dwarf or +/? control mice (Fig. 3 *A*). Additionally, phenotypic analysis of the lymph nodes indicated that ovGH or ovPRL did not significantly alter the percentages of CD4 or CD8 cells in the dwarf mice (Fig. 2, *d–f*). CD4/CD8 double-positive T cells, which have previously been reported to occur in the periphery of these mice to a variable extent (6), were nonexistent in the lymph nodes of dwarf mice treated with ovPRL, while the lymph nodes of control and ovGH-treated mice did contain a small percentage of double-positive T cells (2–3% shown) (Fig. 2).

To ascertain the functional capability of the peripheral T cells in hormone-treated mice, we immunized the mice with KLH in CFA and 7 d later the draining lymph nodes were removed. The cells were then rechallenged with KLH in vitro and the extent of antigen-specific proliferation was determined. In some experiments lymph node B cells were removed be-

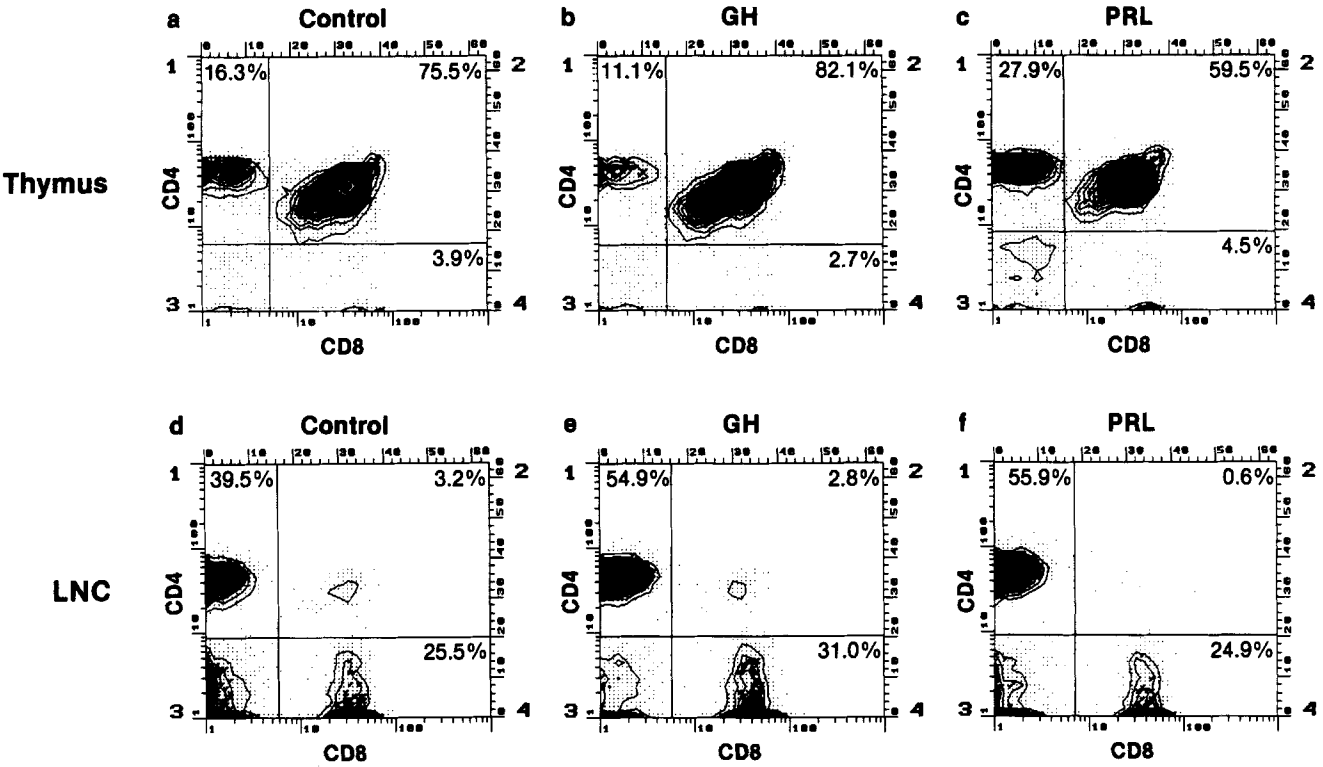

Figure 2. Phenotype of thymocytes and pooled LNC of *dw/dw* mice after treatment with ovGH or ovPRL. CD4 and CD8 staining was determined through flow cytometry and described in Materials and Methods. The data display a representative mouse selected from three to four experiments each with three to four mice per group. (*a*) Thymocytes from control animals; (*b*) thymocytes from ovGH-treated animals; (*c*) thymocytes from ovPRL-treated mice; (*d*) LNC from control animals (to include axillary, inguinal, mesenteric, and brachial lymph nodes); (*e*) LNC from ovGH-treated animals; (*f*) LNC from ovPRL-treated animals.

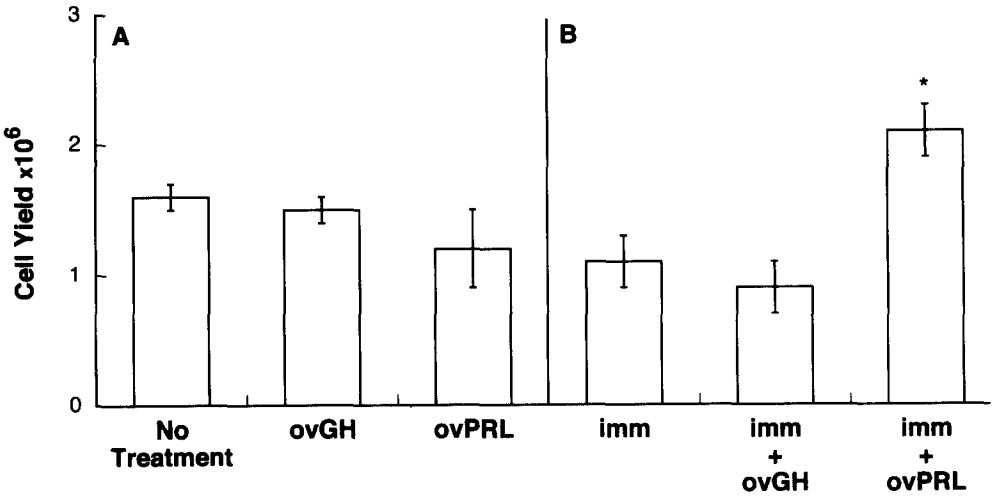

Figure 3. LNC cellularity in immunized and unimmunized *dw/dw* mice after treatment with ovGH or ovPRL. Mice were treated as described in Materials and Methods. (*A*) Total LNC cellularity (inguinal, axillary, mesenteric, and brachial) in *dw/dw* mice after ovPRL or ovGH administration. (*B*) Cellularity of draining (two inguinal) LNC in *dw/dw* mice that were immunized with KLH in CFA and treated with ovGH or ovPRL. There was an average of three to four mice per group.

fore culture to demonstrate that the proliferative responses were indeed T cell dependent. There were no significant differences in the proliferative responses between whole LNC and B cell–depleted LNC (data not shown). We have determined previously that 3–4-mo-old *dw/dw* mice do have functional T cells in their periphery, although at lower levels than their +/? littermates (6). The mice in these experiments were treated with ovGH or ovPRL for 2 mo and were 4 mo old at the time of assay. LNC from control *dw/dw* mice that were treated with saline injections before immunization displayed a modest proliferative response after being rechallenged with KLH (Table 1). Interestingly, ovGH did not significantly enhance the T cell responses in either *dw/dw* or +/? mice and the lymph node cellularity did not increase significantly (Table 1; Fig. 3 *B*). The increase in the extent of proliferation in the +/? recipients treated with ovPRL, while statistically significant in this experiment, was variable in others (data not shown). However, the results demonstrate that both immunized *dw/dw* and +/? mice responded to ovPRL administration with significantly ($p < 0.001$) higher LNC yields containing antigen-specific cells compared with either control or ovGH-treated mice (Table 1; Fig. 3 *B*). It is of particular interest that even the immunized +/? littermates responded to ovPRL.

To determine if the increase in peripheral T cell content in response to PRL treatment was due to an expansion of antigen-specific cells in the LNC or if ovPRL treatment caused an expansion of all peripheral T cells, splenic T cell mitogen responses were determined. The data demonstrate that splenic cellularity and mitogen-induced proliferative responses were not affected by ovPRL treatment in the immunized recipients (Table 2). Increases in splenic cellularity and total T cell number

Table 1. *Antigen-specific Responses of Peripheral T Cells in DW/J dw/dw and +/? Mice*

Strain	Treatment*	Cell yield‡	[³H]Thymidine incorporation	
			− KLH	+ KLH
		$\times 10^6$	*cpm*	
+/?	–	3.9 ± 2.9	4,495 ± 502§	24,796 ± 993
+/?	ovGH	1.7 ± 1.0	2,713 ± 255	22,167 ± 1,943
+/?	ovPRL	13.3 ± 3.7‖	3,303 ± 430	31,683 ± 1,893¶
dw/dw	–	1.1 ± 0.2	995 ± 141	2,240 ± 225
dw/dw	ovGH	0.9 ± 0.2	808 ± 161	1,323 ± 1,121
dw/dw	ovPRL	2.1 ± 0.2‖	1,871 ± 474	7,032 ± 1,463

* Mice were injected with 20 μg ovGH or ovPRL intraperitonally every day starting at 8 wk of age. Mice were analyzed 8 wk later.
‡ Average value from two inguinal LNC per mouse with three mice per group and with the proliferation assay performed as described in Materials and Methods.
§ Data presented as means with standard deviation.
‖ LNC cell yield significantly ($p < 0.001$) greater than mice not treated with ovPRL.
¶ Values significantly ($p < 0.001$) greater than mice not treated with ovPRL.

Table 2. *Effect of ovGH or ovPRL Administration of Splenic Mitogen Responsiveness*

Strain	Treatment*	Cells/spleen‡	−Con A	+Con A
		$\times 10^6$	*cpm*	
dw/dw	–	5.2 ± 1.5	1,436 ± 255§	15,104 ± 1,223
dw/dw	ovGH	15.1 ± 4.1	1,620 ± 414	9,752 ± 1,163
dw/dw	ovPRL	6.6 ± 4.3	1,197 ± 555	10,794 ± 4,217
+/?	–	61.0 ± 12.4	2,629 ± 466	10,453 ± 638
+/?	ovGH	58.8 ± 2.8	1,811 ± 416	9,786 ± 2,133
+/?	ovPRL	78.9 ± 9.8	1,481 ± 625	9,245 ± 1,536

Mitogen assay performed as described in Materials and Methods.
* Mice received either 20 μg of ovPRL or 20 μg of ovGH intraperitoneally every day for 8 wk.
‡ Average splenic cellularity of three mice per group.
§ Data are presented as means with standard deviation.

did occur after ovGH treatment however. The conclusion that ovPRL promotes the proliferation of antigen-specific T cells during a primary immune response is further supported by data demonstrating that PRL treatment had no effect on lymph node cellularity in unprimed mice (Fig. 2 *a*). Thus, it appears that ovPRL exerts a strong adjuvant effect on the antigen-specific priming of peripheral T cells in mice. Additionally, it appears that, while exerting significant thymopoietic effects in dwarf mice after in vivo administration, ovGH does not directly influence mature antigen-specific T cell function in the periphery. In marked contrast, administration of ovPRL produced the opposite effects, in which thymic size actually decreased and there was an increase in antigen-specific peripheral T cell number after immunization. Additionally, while the thymic effects of these hormones occurred only in *dw/dw* mice, the effects of ovPRL on peripheral T cell function occurred in both immunized *dw/dw* and normal +/? mice.

Discussion

The results presented here demonstrate that the neuroendocrine hormones GH and PRL can exert significant and diverse effects on T cell development and function in DW/J dwarf mice. GH appears to act early in T cell development as a thymopoietic agent, which results in an increase in thymic cellularity and restoration of CD4/CD8 double-positive progenitor cells within the thymi of dwarf mice. In contrast, PRL does not exhibit thymopoietic activity and in fact reduces the number of thymocytes in vivo. However, PRL exerts significant effects on increasing antigen-specific peripheral T cell proliferation in both dwarf and normal mice. While there is considerable evidence to demonstrate the proliferative effects of PRL on T cells in vitro (8, 9), the data presented here extend these findings and suggest that PRL can be used as an adjuvant in vivo. It is important to note that the adjuvant effects of ovPRL were detected in mice that were also given the adjuvant CFA. Since rhGH can bind both the GH and PRL receptor and mediate functions due to both of these binding activities (7), it may be of use clinically to promote T cell development since both the thymopoietic effects of GH and the peripheral T cell effects of PRL may be obtained. However, it has been recently reported that human T lymphocytes can synthesize hPRL (9). Murine T cells do not. It will be of interest to evaluate the effects of exogenous hPRL and hGH on human T cell function.

The mechanism underlying the thymopoietic effects of GH in dwarf mice is currently not known. We have previously shown that GH exerts significant hematopoietic growth-promoting effects in vivo (11, 12), and GH may cause an increase in the production of T cell progenitors from the bone marrow. Alternatively, GH may influence the thymus directly. We are currently examining the effect of ovGH on thymic stromal cells and thymic architecture.

The in vivo effects of PRL administration include decreasing thymic cellularity and augmenting antigen-specific peripheral T cell expansion in the lymph nodes. It has been previously demonstrated that PRL can augment T cell proliferation in vitro (9). It may be that PRL also plays a role in thymic selection by providing a similar activating signal. Due to the critical stage in thymic selection in which activation can result in apoptosis, an activating signal provided by PRL may be detrimental for T progenitor survival while optimal for peripheral mature T cell activation and expansion. However, the effects of ovPRL may also be indirect since it has been recently reported that thymic epithelial cells express PRL receptors (13). Indeed, preliminary results indicate that ovPRL does not induce apoptosis of thymocyte suspensions in vitro (our unpublished observations). However, it is also important to note that the thymic effects of the two hormones only occurred in the dwarf mice. It may be that prolonged neuroendocrine hormone deprivation predisposes the dwarf thymocytes to the effects of ovGH or ovPRL administration. DW/J dwarf mice congenitally lack the capability to produce GH and PRL as well as other neuroendocrine hormones. However, it has been established that maternal milk can provide some protective effects as the mice do not appear to demonstrate significant immunological and hematopoietic deficiencies until after weaning (4, 10).

PRL has been associated previously with autoimmunity (14). It has been shown recently that PRL accelerates autoimmune disease in autoimmune-prone mice, and treatment of these mice with drugs that inhibit PRL release delays the onset of the disease (15). As we have found that PRL administration increases peripheral T cell function, it may be that PRL allows for an expansion of autoimmune T cells in the periphery. Experiments are currently underway to assess Vβ gene usage of the T cells in mice after PRL administration. PRL may also act indirectly and affect APC in the periphery.

Thus, through studies on neuroendocrine hormone–deficient dwarf mice, it appears that GH and PRL are capable of exerting significant effects on T cell development. Although these two hormones are closely related, they produce diverse effects upon in vivo administration. In light of the minimal toxicities associated with their in vivo administration, these hormones and their antagonists may be therapeutic agents able to regulate T cell development and activation clinically.

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Address correspondence to William J. Murphy, Biological Response Modifiers Program, Division of Cancer Treatment, NCI-Frederick Cancer Research and Development Center, Building 567, Room 141, Frederick, MD 21702-1201.

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