Induction of Feline Acquired Immune Deficiency Syndrome by Feline Leukemia Virus: Immuno- and Neuroendocrine Dysfunctions (43715)

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Abstract. **Young cats, when chronically infected with feline leukemia virus (FeLV), developed feline acquired immune deficiency syndrome (FAIDS). The syndrome was associated with a sequence of dysfunctions in the hypothalamic-pituitary-gonadal (HPG) and the immune system, manifested in the reduction of luteinizing hormone-releasing hormone (LHRH), follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone in blood plasma. The average FSH and LH (in plasma or lymphocyte), testosterone, and LHRH concentrations in the 20 FeLV-infected cats were measured by radioimmunoassay. The results were compared with those of the 12 control cats that were not FeLV-infected. Four weeks after infection, the plasma LHRH concentration in the infected cats showed a 43% reduction. Five to six weeks after infection, the content of FSH and LH in lymphocyte was reduced by 50% and 28%, respectively, whereas, the plasma FSH and LH was reduced by 52% and 42%, respectively. A significant reduction in testosterone content was detected at Week 11 of infection. The onset of the immuno- and neuroendocrine dysfunctions in FAIDs cats followed this sequence: hypothalamus, lymphocyte, pituitary, adrenal gland, and gonads. Indirect immunofluorescence assay showed the presence of FeLV cytoplasmic antigens in the fibers of the hypothalamic preoptic region and the Leydig cells. The possible causal relationship between the dysfunction of the lymphocyte and HPG systems and the presence of FeLV was discussed.** [P.S.E.B.M. 1994, Vol 205]

Feline leukemia virus (FeLV) is a naturally occurring retrovirus discovered in 1964 by Jarrett *et al.* (1). It is one of the most well-studied causative agents for neoplastic and non-neoplastic diseases in the domestic cat (2). Over one million cats in the United States, representing approximately 2% of the total cat population, are infected with FeLV (3). FeLV causes a reduction in feline lymphocyte blast transformation, T-cell lymphomas, and a marked immunosuppression (4). The virus is also indirectly responsible for the typical opportunistic infections (2, 5). Recent studies show that many more FeLV-infected cats die from the consequences of an impaired immune system, than from the leukemia itself (6). This FeLV-associated immunodeficiency is very similar to the acquired immune deficiency syndrome (AIDS) in humans. Due to the parallels between these two systems, the domestic cat has become an important species in the study of retrovirus-induced AIDS (3, 4, 7).

In young cats, early infection with FeLV causes feline acquired immune deficiency syndrome (FAIDS), which is also associated with neuroendocrine dysfunction (8). Alterations in the content of plasma adrenocorticotropic hormone (ACTH), growth hormone (GH), and cortisol are found in the kittens

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after two to five weeks of FeLV infection (8, 9). Similar changes are also reported in the neuroendocrine system of humans with AIDS (10, 11). Current investigations on human male AIDS patients reveal that the disease suppresses the reproductive function (10–13). The associated clinical symptoms involve testicular failure, i.e., reduced sex steroid secretion, decreased spermatogenesis, Leydig cell hypoplasia, and germ cell tumors (14–19). These symptoms are attributed to the possible abnormality in the immuno-, neuroendocrine systems, involving lymphocytic and hypothalamic-pituitary-gonadal (HPG) dysfunction (20, 21). However, little is known about the function of these systems, and how and when they may be altered by the AIDS virus.

In the HPG axis, luteinizing hormone–releasing hormone (LHRH) is a key integrator between the neural and endocrine systems, whereas gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) serve as the mediator between the hypothalamus and the gonads (22, 23). In the vertebrate species, gonadotropins are released from two different sources, pituitary gland and lymphocyte (or immunoreactive FSH-, or LH-like factors) (24–25). The lymphocyte FSH and LH play a key role as the intercellular messengers, which act on their classic neuroendocrine target tissues and also serve as endogenous regulators of the immune system (26). In the past decade, it has been well established that the synthesis of neuropeptide hormones (i.e., ACTH, endorphins, etc.) in the lymphocyte is stimulated by the infection of micro-organisms (26–28). It is important to know whether the feline lymphocyte FSH and LH production is affected by FeLV. To aid in the study of the disease-related immuno-, neuroendocrine dysfunctions, we will report the changes in content of FSH and LH (from lymphocyte and plasma), plasma testosterone, and LHRH during the early stages of FAIDS.

Materials and Methods

Animals and Their Treatment. Thirty-two weanling male kittens (eight to 10 weeks old) with an average body weight of 0.8–1.0 kg (mean ± SEM, 0.9 ± 0.3 kg; Pearcroft Cattery, Beaufort, NC) were used for observation. The kittens were all FeLV-pathogen-free, housed in an individual cage under a 12L:12D cycle, and provided with Purina Cat Chow (Ralston Purina Co., St. Louis, MO) and water *ad libitum*. A group of 12 kittens was used as the control, and the other 20 kittens were inoculated intravenously with 8×10^4 focus-forming units (FFU) FeLV 'A' as assayed by clone 81 feline cell cultures (29) (ATCC-717, prepared in feline embryo fibroblasts [FEF] tissue culture fluid; American Type Culture Collection, Rockville, MD). The control cats were inoculated with tissue culture fluid from uninfected FEF.

Blood Sampling and Lymphocyte Preparation. Blood sampling (3 ml/kitten) was done just before and weekly after the inoculation of FeLV. All experiments were performed between 11:00–13:00 hr, and the samples were withdrawn by jugular venipuncture into syringe containing a drop of heparin and transferred to evacuated glass tubes with EDTA and placed on ice. Plasma was obtained by centrifugation at 1500*g* for 10 min and was immediately stored in −20°C. The sedimented layer from each plasma preparation was removed, diluted with 3 vol of normal saline, layered on top of 5 ml Histopaque 1077 density gradient and centrifuged at 1000*g* for 30 min at 25°C (30). The fraction containing the mononuclear lymphocytes was collected, washed with normal saline, and resuspended in RPMI-1640 medium containing 10 m*M* HEPES, 2 m*M* glutamine, 1 m*M* sodium pyruvate and 10% fetal bovine serum (FBS) (31). Lymphocytes were cultured in a 24-well plate with the presence of recombinant human interleukin-2 (100 μ/ml) in a humidified incubator at 37°C with 95% air plus 5% CO_2. At the end of the culture, the culture medium was removed by centrifugation at 500*g* for 10 min at 25°C and stored in −20°C until assayed. Cell-free cultures containing medium only were used as controls for potential nonspecific effects of FBS components.

Quantitative Determination of FSH, LH, Testosterone, and LHRH. FSH and LH were measured by direct radioimmunoassay (RIA) using an RIA kit (Simul TRAC LH[^{57}CO]/FSH [^{125}I]) from the Becton-Dickinson Co. (Orangeburg, NY). This assay consisted of a combined double antibody system. The percent of the cross-reactivities for FSH antibody were: 100% with FSH; 0.02% with LH; 0.9% with thyroid-stimulating hormone (TSH); 0.2% with hCG. The specificities of the antibody for LH were: 100% with LH; 5.5% with FSH; 4.8% with TSH, and 15.7% with hCG. The assay performance characteristics demonstrated intra-assay variations of 5.3% (FSH) and 4.9% (LH), and interassay variabilities of 9.3% (FSH) and 8.3% (LH). Plasma volume (or lymphocyte culture medium) used was 0.4 ml and each sample was assayed in duplicate. Concentrations of FSH (or LH) in plasma was determined by interpolation from the logit-log standard curve of % of trace binding versus either mIU FSH/ml or mIU LH/ml. The sensitivity of this assay was 0.3 mIU/ml for FSH and 1.0 mIU/ml for LH. Serial dilution and assay of cat plasma samples (or lymphocyte culture medium) containing FSH and LH concentration yielded displacement curves parallel to the standard curves (Fig. 1, a–c).

Testosterone levels were measured by RIA after ether extraction as according to Hodgson and DeKret-

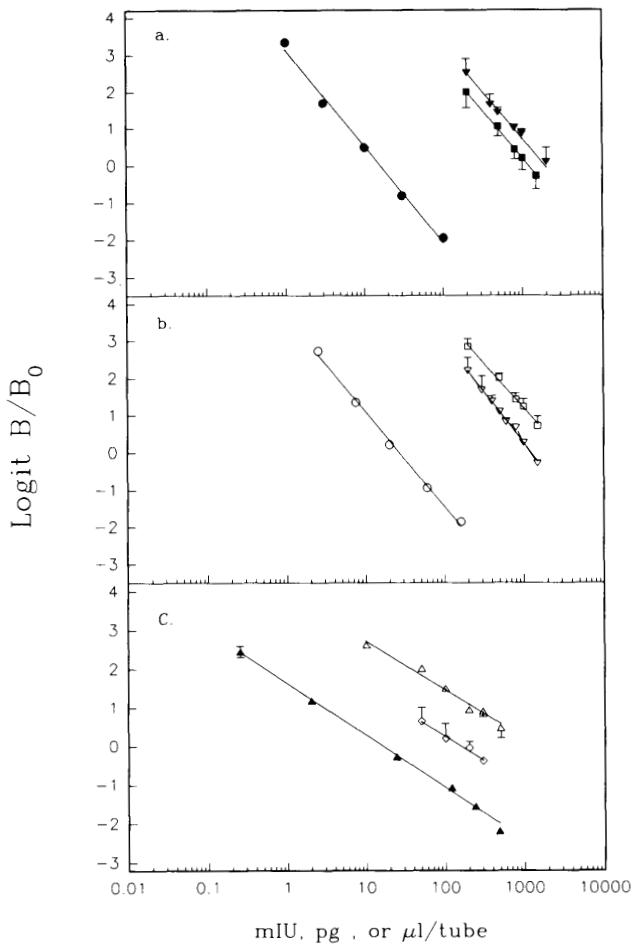

Figure 1. Parallelism between the standards and feline peptide hormones. a. Logit-log-response curves of the FSH standard in assay buffer (●—●, $n = 17$; $r = -0.99$, $Y = -2.61\times + 3.14$), for feline lymphocyte culture media (■—■, $n = 5$; $r = -0.99$, $Y = -2.43\times + 7.65$), and for feline plasma (▼—▼, $n = 14$; $r = -0.99$, $Y = -2.99\times + 9.19$). The FSH concentration used for standard is based on mIU/tube, whereas the sample volume used for lymphocyte culture media and plasma is based on μl/tube. Vertical bars refer to SEM from separate experiments. b. Logit-log-response curves of the LH standard in assay buffer (○—○, $n = 17$; $r = -0.99$, $Y = -2.54\times + 3.63$), for feline lymphocyte culture media (□—□, $n = 5$; $r = -0.99$, $Y = -2.44\times + 8.50$), and for feline plasma (▽—▽, $n = 14$; $r = -0.99$, $Y = -2.76\times + 8.56$). The LH concentration used for standard is based on mIU/tube, whereas the sample volume used for lymphocyte culture media and plasma is based on μl/tube. Vertical bars refer to SEM from separate experiments. c. Logit-log-response curves of the LHRH standard in assay buffer (▲—▲, $n = 9$; $r = -0.99$, $Y = -1.34\times + 1.21$), for feline plasma (◇—◇, $n = 5$; $r = -0.99$, $Y = -1.25\times + 2.75$), and for medial basal hypothalamus (MBH) extract (△—△, $n = 5$; $r = -0.99$, $Y = -1.29\times + 3.14$). The LHRH concentration used for standard is based on pg/tube, and the sample volume used for plasma and MBH extract is based on μl/tube. Vertical bars refer to SEM from separate experiments.

ser (32). The antiserum was kindly supplied by Dr. S. K. Wang (Yang-Ming Medical College, Taiwan, ROC) and was produced in rabbits against testosterone 3-carboxy-methyl-oxime conjugated to bovine serum albumin. Cross-reactivity of the antiserum with other steroids included 5α-dihydrotestosterone (7.5%), androstenedione (0.48%), androstenediol (0.096%), 5β-dihydrotestosterone (0.01%), and cholesterol (<0.01%). The inter- and intra-assay coefficients of variation were 7.6% and 4.3%, respectively. The minimum sensitivity for assay was 5 pg/tube.

LHRH was quantified in serum samples by RIA (33). The assay utilized an antiserum (rabbit anti-LHRH, Peninsula Lab, Inc., Belmont, CA) at a dilution of 1:15,000. Each assay tube contained 100 μl of diluted rabbit anti-LHRH serum, 400 μl assay buffer (50 m*M* sodium phosphate, 0.3% BSA, 10 m*M* EDTA, pH 7.2), 200 μl standard (synthetic LHRH, obtained from Sigma Chemical Co., St. Louis, MO) or unknown, and 100 μl [^{125}I] LHRH (10,000 cpm from Amersham Corporation, Arlington Heights, IL). The assay mixture was incubated at 4°C for 24 hr, and then added with 100 μl goat anti-rabbit IgG (1:400 dilution) and 100 μl of normal rabbit serum. After vortex mixing, the reaction mixtures were incubated for 24 hr at room temperature. The tubes were centrifuged at 1700*g* for 20 min, the supernatants were aspirated, and pellets were counted for 1 min. The amount of LHRH in serum was obtained on a log-logit standard curve. The curve constructed with synthetic LHRH was linear between 0.25–480 pg. Assay sensitivity was 0.5–1.0 pg/ml at 90% binding, with an interassay coefficient of variation of 10.7% and an intra-assay coefficient of variation of 7.2%.

Indirect Immunofluorescence Assay for FeLV Group-Specific Antigen. Hypothalamus (medial preoptic area) and testis from the control and infected cats were methanol-fixed, paraffin-embedded and sectioned at 4 μm according to Teng (8). Sections were placed on albumin-coated slides, air dried, and fixed in absolute methanol. Slides were overlaid with bovine anti-FeLV serum (Antibodies Incorporated, Davis, CA) diluted 1:5 in phosphate-buffered saline (PBS) or PBS-diluted normal bovine serum, or PBS alone, and incubated at 37°C for 1 hr. After washing with PBS (3X), the slides were overlaid with fluorescein isothiocyanate (FITC)-conjugated rabbit antibovine globulin (Cooper Biomedical Inc., Philadelphia, PA) diluted 1:10 in PBS and incubated at 37°C for 1 hr. The slides were subsequently washed with PBS, counterstained with 0.02% Evan blue, and then washed again with PBS and distilled water. The sections were air dried, mounted in glycerol (containing 50% PBS), and examined with a Leitz fluorescence microscope.

Statistical Analysis. Mean values were indicated as mean ± SEM. The mean data were tested statistically, using two-way analysis of variance (ANOVA), and the differences between specific means were tested for significance, using Scheffe's multiple range test (34). In some cases, the Mann-Whitney test was applied. A difference between the two means was con-

sidered to be statistically significant when the $P < 0.05$.

Results

Plasma FSH, LH, and Testosterone Content After Infection. The detection of feline plasma (or lymphocyte) FSH and LH depended on the radioimmunoassay kit. The standard of the test kit was developed for human clinical use. In order to verify its suitability for feline use, log-logit dose response lines were constructed. Increased volumes of plasma (or lymphocyte culture medium) from cats ran parallel with the standard in both the FSH and LH radioimmunoassay (Fig. 1, a and b). Because no difference in slope were noted among the logit-log dose response lines of FSH (or LH) from the standards, plasma, and lymphocyte media, the commercial test kit was used for the following studies.

The average amount of plasma FSH (and LH) in 20 infected cats was measured at various stages after FeLV infection and then compared with that of the 12 control cats (which were not infected with FeLV). The first stage was obtained from Week 0 (the starting time for FeLV injection) to Week 5 of infection; the amount of plasma FSH (and LH) in the infected and the control cats showed no significant difference (Fig. 2, a and b). The second stage was obtained from Week 5 to Week 7 of infection; the average amount of FSH (and LH) in the infected and the control cats was 0.8 (2.2) and 1.7 (3.8) mIU/ml, respectively. A 52% and 42% reduction in FSH and LH, respectively, was found in the infected cats (Fig. 2, a and b). The third stage was obtained from Week 9 to Week 11 of infection. At Week 11, the FSH (and LH) content in the infected and the control cats was 0.7 (1.5) and 1.1 (3.5) mIU/ml, respectively. A 35% and 57% reduction in FSH and LH, respectively, was detected in the infected cats (Fig. 2, a and b). Eleven weeks after infection, the average plasma FSH (and LH) content in the infected cats was reduced to 48% (and 46%) compared with that detected in the cats at Week 0.

The plasma testosterone level in the 20 infected cats was measured and compared with that of the 12 control cats. The plasma testosterone content in these two groups of cats remained constant (approx. 150 pg/ml) during Weeks 1–7 of the experimental period (Fig. 2c). The average amount of testosterone in the control cats increased gradually from 150 to 400 pg/ml during the seven to 11 weeks of investigation time. The increase was 167%. On the contrary, in this same time period, a slower increase of only 27% in testosterone was found in the infected cats (from 150 to 190 pg/ml), which was 84% less than that of the control cats.

FSH and LH content in the lymphocyte affected by FeLV. The FSH level in the lymphocyte was slightly increased in the control and infected cats during Week 1 and 2 of the experimental period. The content of FSH began reducing during the fifth and ninth week of investigation. During this time, the average amount of FSH in the infected lymphocyte dropped to 50% and 58%, compared with the control (Fig. 3a). The LH level in the lymphocyte also showed an increase in the control and infected cats, during the first two weeks of FeLV infection. However, once again, the content was reduced after the fifth to ninth week of infection. The average amount of LH in the infected lymphocyte was reduced to 28% and 51%, in comparison with the control (Fig. 3b).

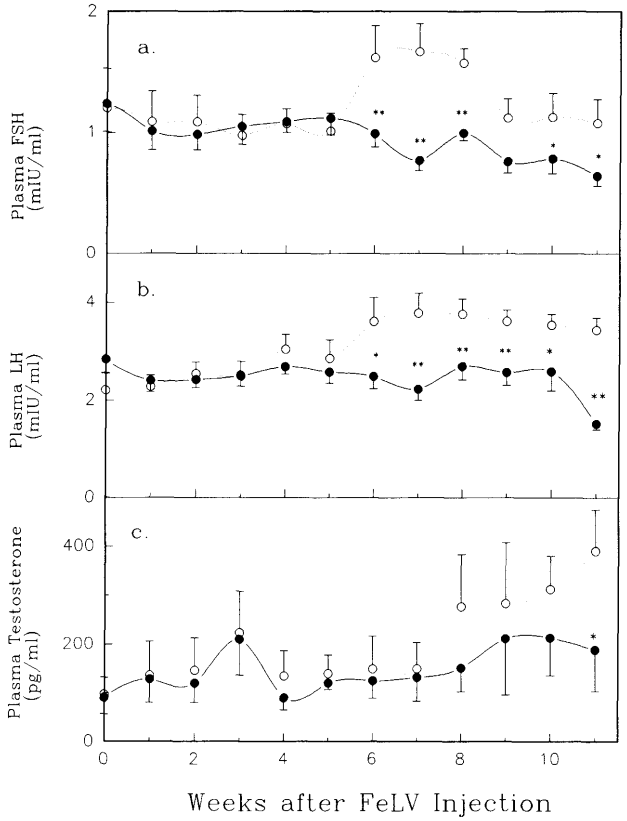

Figure 2. Plasma FSH, LH, and testosterone content detected by radioimmunoassay (RIA). FeLV was iv injected into cats on Week 0. All injected cats became viremic two weeks after injection as detected by an FeLV group-specific enzyme-linked immunosorbent assay [12]. Results presented in this figure were based on the experiments with 12 control cats and 20 infected cats. The content of FSH, LH, and testosterone was determined weekly by RIA as described in Materials and Methods. (a) Plasma FSH content; (b) plasma LH content; (c) plasma testosterone. (○) control cat; (●) infected cat. Each value represents mean ± SEM. $^{*}P < 0.05$; $^{**}P < 0.01$ (infected cats in comparison with control cats).

Change of plasma LHRH levels in the infected cats. Log-logit dose response lines presented in Figure 1 indicated that an increased volume of cat plasma ran parallel with the standard in the LHRH radioimmunoassay (Fig. 1c). The amount of plasma LHRH in control cats remained constant from Week 0–5 of the experimental period (from 26 to 29 pg/ml, respectively). In contrast, the plasma LHRH level showed a continuous reduction in the infected cats (from 24, 22,

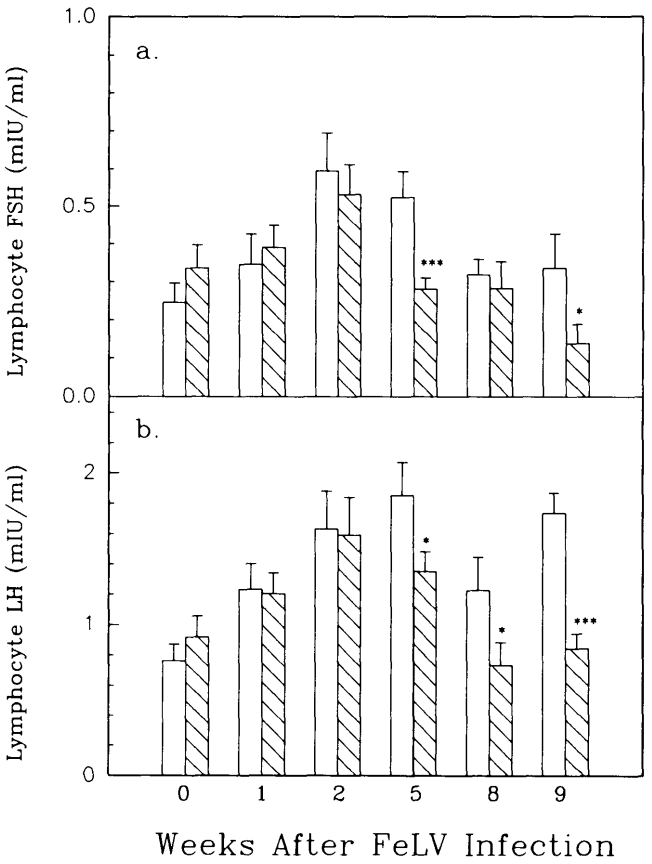

Figure 3. The effect of FeLV on the content of FSH and LH in the cultured lymphocyte. Lymphocytes purified from control (or infected) cats' blood samples were cultured at 10^6 cells/ml for 48 hr, according to the procedures described in Materials and Methods. The medium containing FSH (or LH) was determined by RIA. The results presented in this figure are the average of four determinations: (a) Lymphocyte FSH content; (b) lymphocyte LH content; (□) control; (▨) infected. *$P < 0.05$, ***$P < 0.001$ (infected cats in comparison with control cats).

17, 14, to 10 pg/ml in Week 0, 1, 2, 4, and 5 of infection, respectively). In comparison with the control cats, a significant reduction was found in the infected cats after four to five weeks of infection (from 43% to 67% reduction, respectively; Table 1).

Detection of FeLV group-specific antigens in the infected cats. Postmortem investigations in the hypothalamus and testes showed the presence of FeLV cytoplasmic antigens in the fibers of the hypothalamic preoptic region and the Leydig cells (Fig. 4, a and b). However, the same identification by indirect immunofluorescence assay in the control tissues showed a negative reaction (data not shown).

Discussion

Previously, the pituitary-adrenal dysfunction in FeLV-infected kittens has been studied by Teng (8). In order to further investigate the endocrine systems' dysfunctions and their association with early FAIDS virus infection, we have extended the studies to the HPG and the immune systems. These and previous studies were closely related to the sequences of viral replication in the infected young cats. The sequences were divided into six phases by Rojko and Hardy (35). Two to four weeks after infection (representing Phases 2–4; also defined as an acute FeLV infection), there was a significant suppression of the activity of the hypothalamus and the local lymphoid infection (5, 36, 37). Rojko *et al.* (38) were able to demonstrate the presence of FeLV gs antigens in the lymphocyte of the infected cats soon after exposure. We observed a similar phenomenon in the medial preoptic intrahypothalamic fibers (Fig. 4). These fibers were identified as the nonvascular routes that project the LHRH to portal vessels of the median eminence for the release of FSH and LH (39). The presence of FeLV in the fibers may affect the projection of LHRH. This manifested in a drastic reduction in the content of plasma LHRH, and a concomitant decrease in lymphocyte FSH and LH content as detected at Week 4 and 5 of infection.

Recent evidence showed cells of the immune system possess hormonal receptors and can synthesize biologically active neuroendocrine peptide hormones (e.g., ACTH, FSH, LH, etc.). On the other hand, the neuroendocrine hormones can influence immune functions (25, 26, 30, 31). This signaled a bidirectional communication that existed between the immune and neuroendocrine systems (30). The extrapituitary sites of FSH and LH production in the immune system are enhanced by the infection of micro-organisms (i.e.,

Table I. Effect of FeLV on Plasma LHRH

Treatment	Plasma LHRH (pg/ml) level (weeks after infection)				
	0	1	2	4	5
Without FeLV (Control)	26.77 ± 11.1	20.38 ± 6.2	18.47 ± 3.2	25.97 ± 6.1	29.28 ± 6.0
With FeLV (Infected)	24.34 ± 5.1	21.74 ± 6.4	17.18 ± 5.4	14.88 ± 4.1	9.60 ± 2.7
% Inhibition to control	ND	ND	ND	43%	67%
P value	NS	NS	NS	*P = 0.02	***P = 0.0007

FeLV was iv injected into cats on week 0.
Blood samples were collected weekly from jugular vein. The plasma LHRH was determined by RIA. The results presented in this table were based on the experiments with nine control cats and 20 infected cats. Values are expressed as mean ± SEM.
* $P < 0.05$; ***$P < 0.001$ (compared to control cats).
ND = nondetectable; NS = nonsignificant.

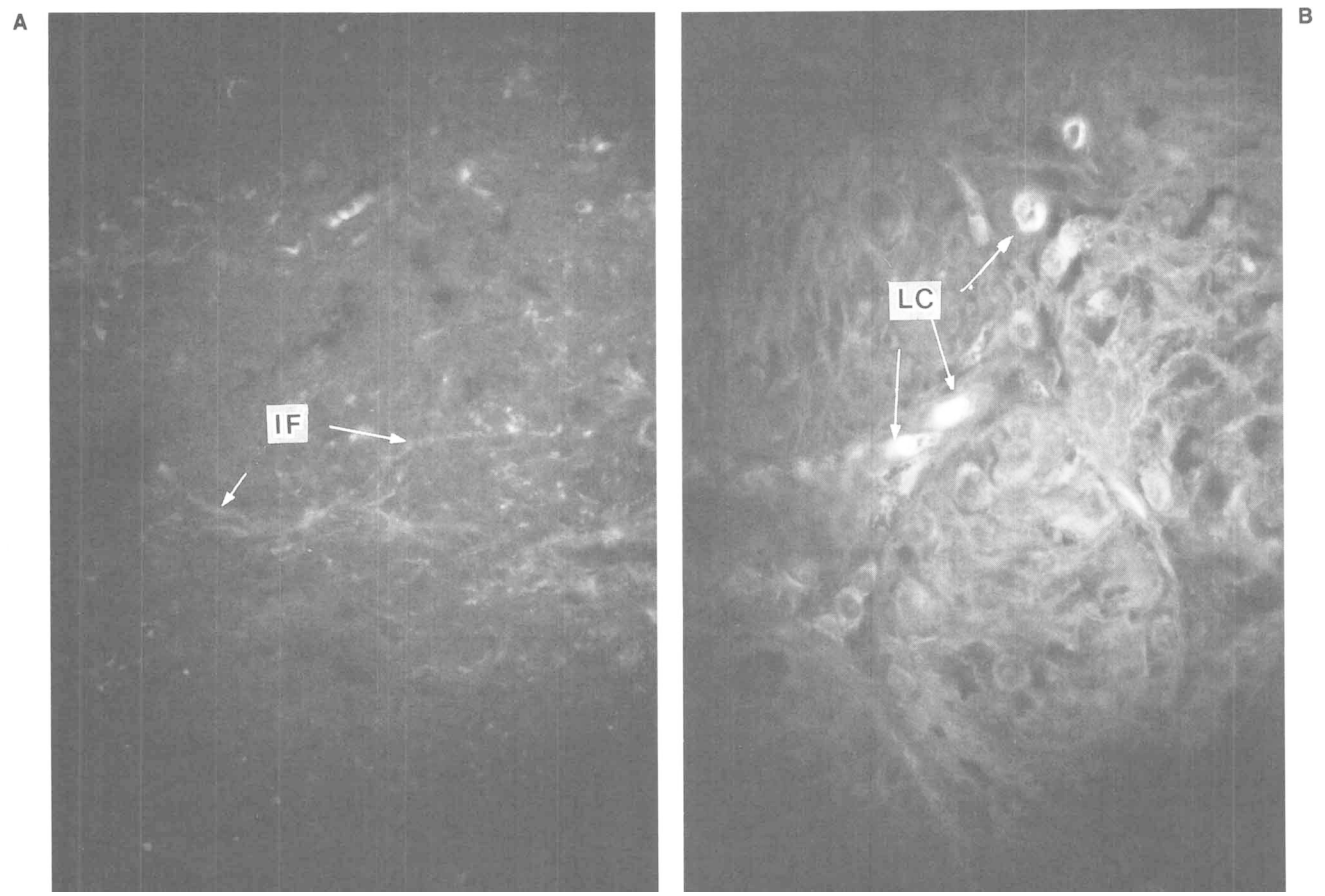

Figure 4. Detection of FeLV group-specific antigens in the infected tissues. The presence of group-specific antigen in the tissue was identified by indirect immunofluorescence assay as described in Materials and Methods. (a) The medial preoptic region of hypothalamus from a four-week infected cat; (b) Testes from a 12-week infected cat. IF, intrahypothalamic fiber; LC, Leydig cell; a and b: ×400.

bacteria and viruses). The infection of FeLV, however, inhibited the gonadotropins synthesis. The molecular mechanism behind this inhibitory effect is yet unknown. Our observations, however, suggested that the bidirectional communication in these two systems is interrupted. This could lead to a permanent dysfunction in HPG system.

Four to six weeks after FeLV infection (representing Phases 5 and 6; also classified as a protracted type of infection), important changes to the immune and endocrine systems take place (8, 9, 38). In this period, a protracted lymphopenia, neutropenia, anemia, and wasting syndrome were developed (40–43). Particularly, prior to the development of the wasting syndrome, there is an inhibition of growth hormone production in the pituitary gland (9, 44). This is accompanied by a viral infection of the anterior lobe of the pituitary gland and a reduction in the plasma ACTH (8). Current investigation shows that at the end of this period (six to seven weeks), the plasma gonadotropins (i.e., FSH and LH) were significantly reduced. These findings suggested that in the early stages of infection, both the acidophilic and the basophilic cells, as well as gonadotropes (which are responsible for FSH and LH secretion), may be suppressed by FeLV. In this regard, FeLV may suppress the synthesis of peptide hormones, or it may retard the process for hormone secretion. Investigations are now underway to determine which of the possibilities is valid.

Parallel observations were made in human AIDS patients, who also showed variations in plasma ACTH, FSH, and LH content when compared with non-HIV-infected humans (11, 13, 45). However, different results were presented, i.e., high (and low) level of plasma gonadotropins were observed after HIV infection (13, 21). The reason for the disparities in findings is not completely clear. Nevertheless, information compiled from the consequences of HIV and FeLV infection indicate that, in the infected patient, the function of HPG system is altered by the AIDS virus. The HPG dysfunction in human and cats may share the same causes. The possibilities are that (i) there is a functional disorder in the LHRH secretion (13, 21, 46); (ii) the virus causes the necrosis and/or fibrosis of the pituitary (47); (iii) pathological changes in the pituitary include involvement with opportunistic infections, i.e., Toxoplasma, cytomegalovirus, and pneumocystis (10, 14, 48); and (iv) the virus can induce the

Table II. The Progression of Immuno-, Neuroendocrine Dysfunction in FAIDS Cats

Immuno-, neuro-endocrine tissue	Appearance of dysfunction after infection (wk)	Hormones involved
1. Hypothalamus	4	LHRH
2. Lymphocyte	5	Lymphocyte FSH, and LH
3. Pituitary		
Acidophilic cell	5	GH [9]
Basophilic cell	6	ACTH [8]
Gonadotropes	6	FSH and LH
4. Adrenal cortex	4–5	Cortisol [8]
5. Gonads		
Leydig cell	8–11	Testosterone

secretion of factors from macrophages that alter hypothalamic-hypophyseal function (21, 49).

Seven weeks to one year after infection (representing Phase 6; also classified as persistent viremia) is the stage characterized by a severe immunosuppression (35). The reduction in plasma testosterone starts at Week 8, but is not statistically significant until Week 11 of infection. The drastic reduction of plasma testosterone content in the 20 infected cats is similar to observations made in men with AIDS (13, 21). They discovered that most of the men with AIDS (or AIDS-related complex [ARC]) were hypogonadal, and their serum testosterone concentrations were significantly less than that in asymptomatic (or normal) men. The mechanism(s) responsible for the decline in testicular testosterone secretion is not yet clear, but the presence of FeLV in the Leydig cells could account for the primary testicular failure. This will eventually lead to the following clinical symptoms, i.e., decreased spermatogenesis, Leydig cell hypoplasia, and germ cell tumors (15, 17, 18, 50).

The onset of the immuno-, neuroendocrine dysfunction in FAIDS cats follows the sequence in Table II.

In conclusion, the hormonal dysfunction in FAIDS involves various endocrine glands and is a manifestation of changes in the HPG and the immune systems. The alteration in these systems appears as a sequence of chain events. The types (or patterns) of this change in many ways are similar to those in most human patients with AIDS. As the number of subjects with AIDS increases, the demand for clinical treatment will also increase. Endocrine therapy may be an effective way of prolonging life. The FAIDS system established in young cats will provide a valuable testing system to evaluate which therapeutic and preventive measures will be the most beneficial for both humans and animals.

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