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Effect of lithium in immunodeficiency: improved blood cell formation in mice with decreased hematopoiesis as the result of LP-BM5 MuLV infection

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Abstract

Lithium salts have been demonstrated to induce the production of hematopoietic cells following administration in vivo and to minimize the reduction of these cells following treatment with either radiation, chemotherapeutic or antiviral drugs. We have previously demonstrated that lithium, when administered in vivo to immunodeficient mice infected with LP-BM5 MuLV (MAIDS) significantly reduced the development of lymphadenopathy, splenomegaly, and the lymphoma associated with late-stage immunodeficiency disease in this model, and increased the survival of these animals compared to virus-infected controls not receiving lithium. We report here

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the results of in vivo studies in the MAIDS model that determined the effect of lithium on peripheral blood indices and the number of myeloid (CFU-GM), erythroid (BFU-E) and megakaryocyte (CFU-Meg) hematopoietic progenitors from bone marrow and spleen harvested from immunodeficient mice receiving lithium carbonate (1 mM) placed in their drinking water compared to virus-infected controls not receiving lithium. Time-points evaluated were at weeks 1, 5, 9, 13, 17, and 21 postviral infection. Virus-control mice not receiving lithium demonstrated all the signs that are characteristic of MAIDS, i.e., splenomegaly, lymphadenopathy, hypergammaglobulinemia, reduced hematopoiesis, and death. Infected mice receiving lithium demonstrated diminished presence of splenomegaly, lymphadenopathy, hypergammaglobulinemia, no suppression of hematopoiesis nor mortality. Enhanced hematopoiesis was demonstrated by neutrophilia, lymphocytosis, thrombocytosis, and erythrocytosis that was evident by increased myeloid, erythroid, and megakaryocyte progenitor cells cultured from bone marrow and spleen. These studies further demonstrate that lithium influences the disease process in the MAIDS model and restricts the development of hematopoietic suppression that develops in this retroviral animal model of immunodeficiency.

Keywords: Lithium; Hematopoiesis; MAIDS; Retroviral infection; Immunodeficiency

1. Introduction

The human acquired immunodeficiency syndrome (AIDS) is a complex disease induced by the human immunodeficiency virus (Barré-Sinoussi et al., 1983; Popovic et al., 1984). Although much information has been generated on HIV and its life-cycle, the molecular and cellular mechanisms by which it induces immunodeficiency remain obscure. Part of this problem resides in the inability to perform studies using an effective animal model of human HIV-infection. Murine AIDS (MAIDS) is a disease that shares many similarities with human AIDS. Several immunological parameters of this disease have been analyzed, and genetic studies have mapped a gene (or genes) in the H-2 complex as important in viral disease pathogenesis. The etiologic agent of MAIDS is a defective murine leukemic virus that is capable of inducing a disease as a complex of B-tropic ecotropic and B-tropic mink cell focus-forming virus (MuLV) (Mosier et al., 1985). The similar features to human AIDS are polyclonal B-lymphocyte activation, hypergammaglobulinemia, lymphadenopathy and profound immunodeficiency (Mosier et al., 1985). In this murine model there is decreased helper T-cell function, and it most closely resembles the early phases of human AIDS. Differences between human AIDS and MAIDS do exist; most prominent is that MAIDS-infected mice die of respiratory failure due to mediastinal lymph node enlargement and not of recurrent infections as is commonly associated with human AIDS (Mosier, 1985).

The monovalent cation lithium has been an effective agent capable of influencing many aspects of immunohematopoiesis. Lithium has been demonstrated to have a consistent positive effect on lymphocyte-based host defense systems (reviewed in Gallicchio, 1991) such as: enhancing T-lymphocyte subsets; CD4CD8 ratios, following administration in normal controls and patients receiving lithium for manic depressive psychoses (Hart, 1987); enhancing T-lymphocyte-derived colony-stimulating activity through an effect upon T-suppressor cells (Wahlin et al., 1984); and elevating the

circulating granulocytes in clinical conditions such as cyclic neutropenia (Verma et al., 1982a,b); and congenital and acquired neutropenia (Gupta et al., 1975; Barret, 1980; Yassa and Arianth, 1981).

Lithium salts have been shown to influence viral infections. Manic depressive patients undergoing lithium therapy had fewer recurrences of herpes simplex virus (HSV) infections than did patients not receiving lithium (Lieb, 1979). Individuals who used topically applied ointment that contained 8% lithium succinate reported a reduced incidence and severity of recurrent genital HSV infection (Skinner, 1983). We have recently reported that lithium, in the form of lithium carbonate, administered in vivo in MAIDS mice produced a marked reduction in the development of lymphadenopathy and splenomegaly, which translated into significant survival compared to immunodeficient virus-infected mice not receiving lithium (Gallicchio et al., 1993). We report here the results of additional studies from MAIDS-infected mice administered lithium. Treated animals demonstrated significant hematopoiesis compared to the suppressed hematopoiesis associated with LP-BM5 MuLV infection in animals not receiving lithium.

2. Materials and methods

2.1. Mice

Female C57BL6 mice (8–10 weeks of age) were purchased from Harlan, Indianapolis, IN, USA. All animals were quarantined for a minimum of 1-week before experimental use. Animals were housed in plastic cages and fed Purina lab chow and water ad libitum.

2.2. Infection with LP-BM5 MuLV murine immunodeficiency virus

LP-BM5 MuLV isolate used in these studies was originally derived from a bone marrow stromal cell line (SC-1) harvested from animals infected with mink cell MuLV (Morse et al., 1992) and is routinely maintained in the laboratory. LP-BM5 MuLV is a retrovirus mixture containing replication-competent helper B-trophic ecotropic mink cell focus forming (MCF) virus and an etiologic 4.9-kb replication defective genome termed BM5-def, susceptibility to which depends on the presence of the FV-1b genotype permissive for B-trophic virus replication (Morse et al., 1992). Therefore, the viral pool consisted of a mixture of B-tropic ecotropic and B-tropic mink cell focus-inducing murine immunodeficiency virus (MuLV). The titers of ecotropic and MCF MuLV were determined by XC plaque assay in SC-1 cells or by SC-1 UV-mink assay. Virus pools on average contain $10^{5.1}$–$10^{5.8}$ XC-plaque-forming units and $10^{2.2}$–$10^{3.2}$ focus-forming units, respectively. To minimize exogenous infection, mice were maintained in microisolator cages and handled in accordance with the NIH Guide for the Care and Use of Laboratory Animals (NIH No. 85-23, 1985). Cages, bedding and food were autoclaved prior to use and all cages and animal handling or monitoring were performed in laminar

air flow hoods. Ventilation and air flow in the animal facility was set to 12 changes/h. Room temperatures were regulated at 72 ± 2°F and the rooms were on automatic 12-h light/dark cycles. One hundred and twenty mice were infected by i.p. injection of 0.25 ml of LP-BM5 MuLV virus-stock (10 μg of total protein) harvested from the SC-1 cell line following 3-day in vitro culture. The development of MAIDS induced by virus was monitored by physical findings (Morse et al., 1992). Early stage MAIDS develops 5 weeks postinfection. At this time, splenomegaly could be detected by palpation. Increased systemic levels of IgM were used to monitor the development of LP-BM5 MuLV-induced disease. Death from profound immunodeficiency usually ensued within 16–24 weeks after infection.

2.3. *Treatment of LP-BM5 MuLV immunodeficient mice (MAIDS) with lithium*

In order to evaluate the ability of lithium to influence hematopoiesis in immunodeficient virus-infected animals, the following studies were performed. One hundred and twenty mice infected with LP-BM5 were divided into two groups, i.e., 60 virus-infected mice served as virus controls and the other group was administered lithium carbonate (Li_2CO_3, ultra-pure; Alpha Therapeutics, Danville, MA, USA) placed in the drinking water at a concentration of 1 mM as previously described from this laboratory (Gallicchio et al., 1993). Lithium treatment was initiated 7 days prior to virus infection. This protocol has been previously determined to provide optimum protection from LP-BM5 MuLV-induced immunodeficiency (Gallicchio and Hughes, 1993). This protocol produces an individual animal lithium dose determined to be 18 mg Li_2CO_3/kg/day, based upon an average daily consumption of 5.3 ml of fluid per day (Gallicchio, 1991). Lithium was initiated 7 days before virus infection and was continued for the duration of the study. Plasma lithium levels from animals bled by cardiac puncture on the days of examination were monitored by use of flame photometry (Model no. 943, IL Instruments, Lexington, MA, USA). Virus-infected controls and virus-infected mice treated with lithium were serially sacrificed 1, 5, 9, 13, 17, and 21 weeks following virus inoculation for determination of lithium treatment on hematopoiesis following administration in LP-BM5 MuLV-infected animals.

2.4. *Assessment of hematopoiesis in LP-BM5 MuLV-induced immunodeficient mice receiving lithium*

In order to evaluate the effect of lithium on hematopoiesis following administration in vivo placed in the animals' drinking water, virus-infected mice treated with or without lithium on the days of sacrifice, i.e., weeks 1, 5, 9, 13, 17, and 21 were bled (400 μl by tail bleed) prior to sacrifice for determination of peripheral blood indices, i.e., packed red cell volume (hematocrit), WBC with differential to determine absolute values for neutrophils and lymphocytes, and platelets. Bone marrow and spleen cells were assayed for their progenitor cell content, i.e., erythroid (BFU-E), myeloid (CFU-GM), and megakaryocyte (CFU-Meg) using methodology as performed routinely in the laboratory (Gallicchio et al., 1981).

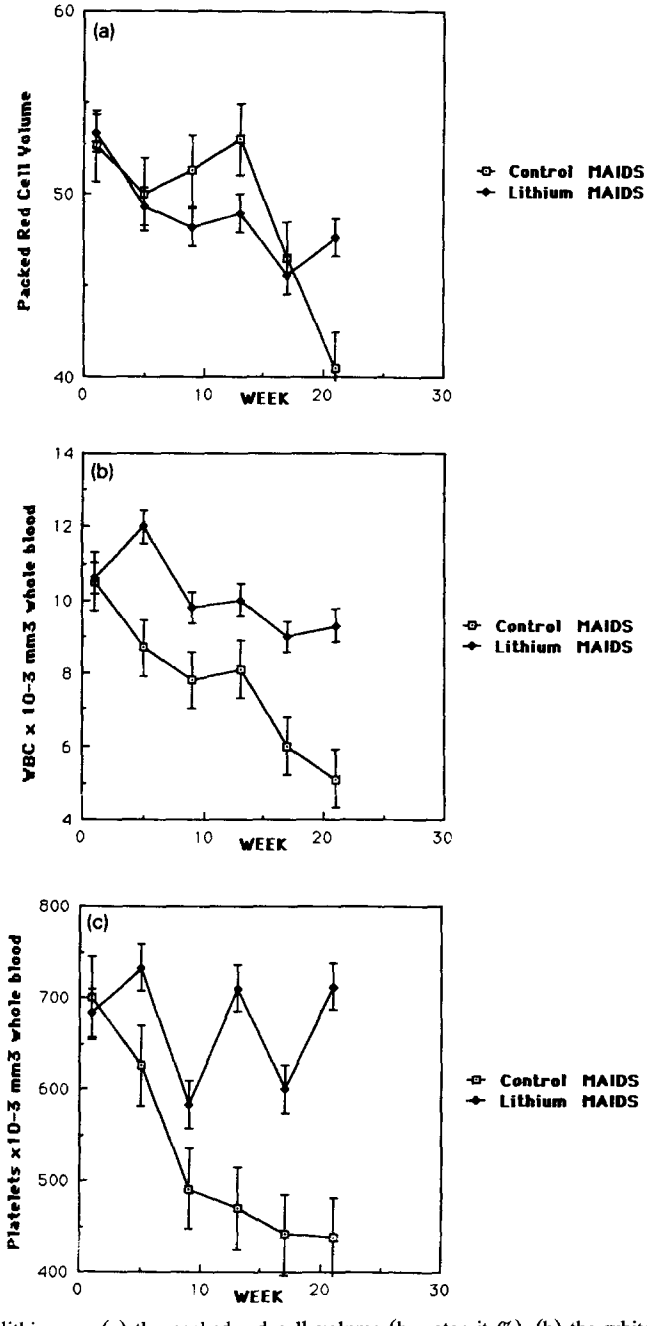

Fig. 1. Effect of lithium on (a) the packed red cell volume (hematocrit %), (b) the white blood cell count ($\times 10^3$) and (c) the platelet count ($\times 10^3$) administered to LP-BM5 MuLV immunodeficient animals. Controls received only sterile water. Minimum of 5 animals per group analyzed at time points 1, 5, 9, 13, 17, and 21 weeks postviral inoculation. Values $\pm$ S.E.M.

2.5. Statistical analysis of the data

Mean ± S.E.M. for values comparing virus control animals not receiving lithium to virus-infected animals receiving lithium from duplicate studies were determined and analyzed using the two-sample ranks test of Wilcoxan–White with a P-value < 0.05 used to determine significance.

3. Results

3.1. Effect of lithium administration on hematopoiesis in immunodeficient mice

Animals inoculated with LP-BM5 MuLV developed signs of immunodeficiency disease manifested by lymphadenopathy, splenomegaly, and hypergammaglobulinemia

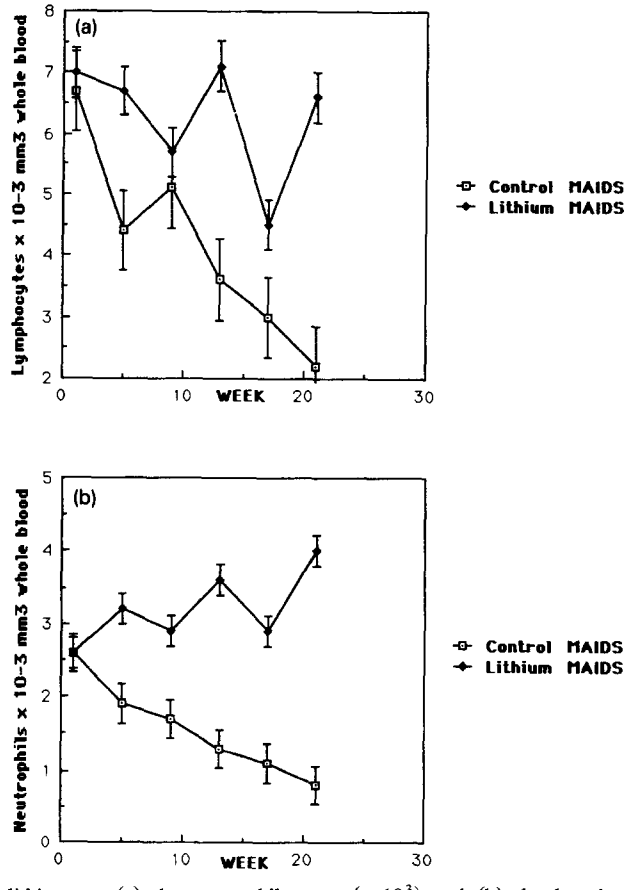

Fig. 2. Effect of lithium on (a) the neutrophil count ($\times 10^3$) and (b) the lymphocyte count ($\times 10^3$) administered to LP-BM5 MuLV immunodeficient animals. Controls received only sterile water. Minimum of 5 animals per group analyzed at time points 1, 5, 9, 13, 17, and 21 weeks postviral inoculation. Values ± S.E.M.

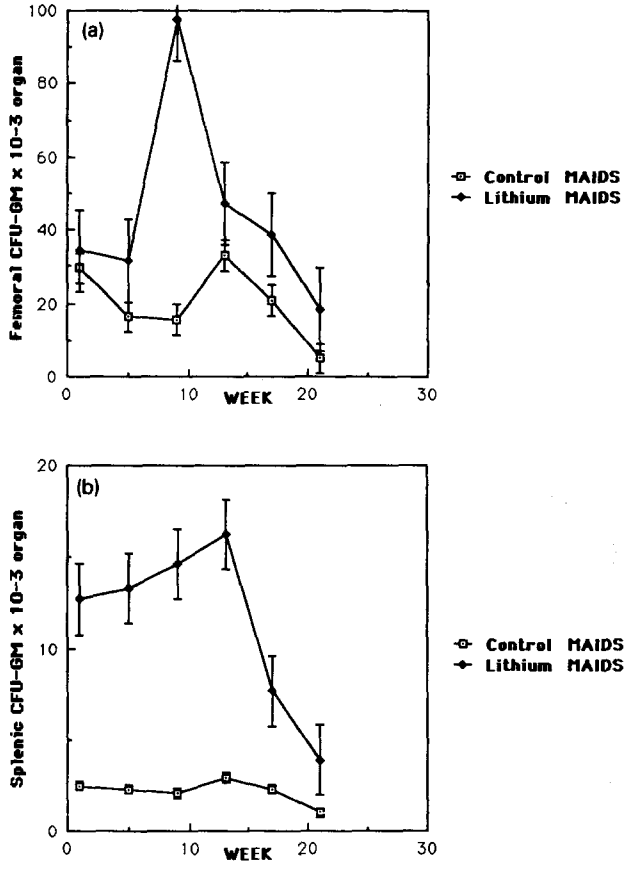

Fig. 3. Effect of lithium on (a) femoral myeloid progenitors (CFU-GM) ($\times 10^3$) and (b) splenic myeloid progenitors (CFU-GM) ($\times 10^3$) administered to LP-BM5 MuLV immunodeficient animals. Controls received only sterile water. Minimum of 5 animals per group analyzed at time points 1, 5, 9, 13, 17, and 21 weeks postviral inoculation. Values $\pm$ S.E.M.

by week 4–5 postviral infection (data not shown). Disease induction and monitoring of these findings have been previously published (Gallicchio et al., 1993; Gallicchio et al., 1994). The effect of lithium on influencing peripheral blood indices from LP-BM5 MuLV-infected animals is given in Fig. 1. Lithium decreased the reduction in packed red cell volume (hematocrit) (Fig. 1a), white blood cell count (Fig. 1b), and platelets (Fig. 1c) that is associated with virus infection when compared to the virus-control group not receiving lithium. To further demonstrate the effect of lithium on the WBC, the differential analysis produced absolute values for neutrophils (Fig. 2a) and lymphocytes (Fig. 2b) that indicated both were increased following lithium treatment compared to the virus control group. Virus-infected mice receiving lithium maintained a plasma lithium concentration of 0.4–0.8 mM, well within the therapeutic range known for

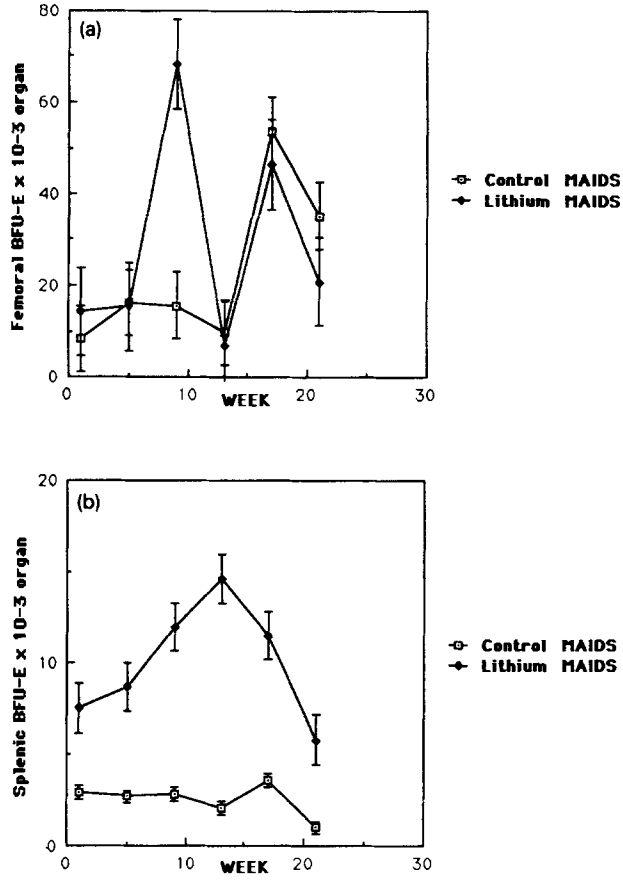

Fig. 4. Effect of lithium on (a) femoral erythroid progenitors (BFU-E) ($\times 10^3$) and (b) splenic erythroid progenitors (BFU-E) ($\times 10^3$) administered to LP-BM5 MuLV immunodeficient animals. Controls received only sterile water. Minimum of 5 animals per group analyzed at time points 1, 5, 9, 13, 17, and 21 weeks postviral inoculation. Values ± S.E.M.

lithium activity in humans. There were no demonstrable signs of lithium toxicity, i.e., tremor, in any mice receiving lithium treatment during the course of the study.

3.2. Effect of lithium administration on hematopoietic progenitor cells in LP-BM5 MuLV immunodeficient mice

The ability of lithium to influence hematopoietic progenitor cells cultured from bone marrow and spleen comparing lithium-treated versus viral control infected mice was determined. The effect on myeloid (CFU-GM) from bone marrow and spleen is given in Fig. 3 (bone marrow (a) spleen (b)). From bone marrow, lithium increased CFU-GM compared to viral controls that peaked on week 9, otherwise the slopes of CFU-GM response were very similar. Splenic CFU-GM from lithium-treated animals was signifi-

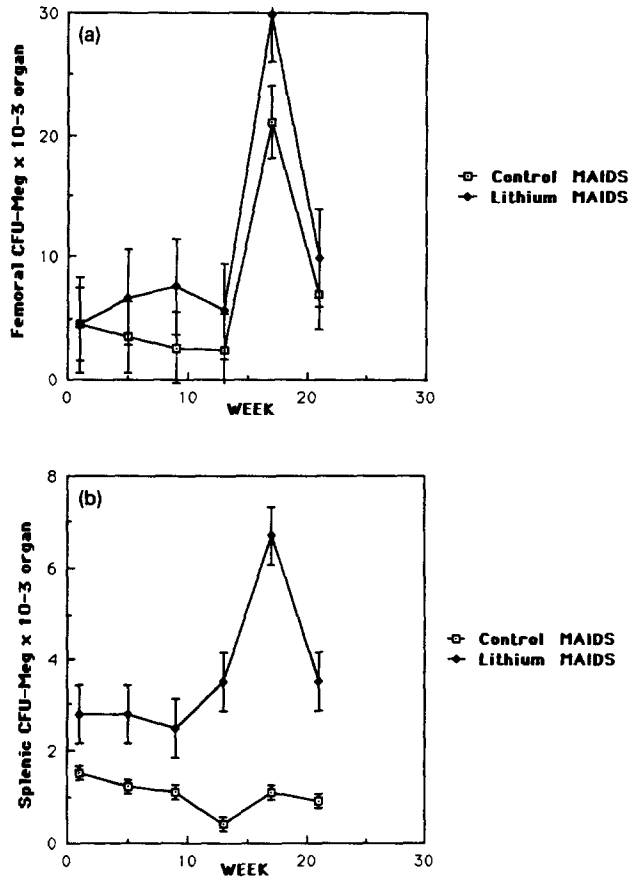

Fig. 5. Effect of lithium on (a) femoral megakaryocyte progenitors (CFU-Meg) ($\times 10^3$) and (b) splenic megakaryocyte progenitors (CFU-Meg) ($\times 10^3$) administered to LP-BM5 MuLV immunodeficient animals. Controls received only sterile water. Minimum of 5 animals per group analyzed at time points 1, 5, 9, 13, 17, and 21 weeks postviral inoculation. Values $\pm$ S.E.M.

cantly increased at all time points compared to viral controls. Fig. 4 depicts the effect of lithium on erythroid (BFU-E) progenitors from bone marrow (a) and spleen (b). As was observed for CFU-GM, lithium-treated virus-infected mice demonstrated increased BFU-E that peaked on week 9, all other points resembled the viral control group. Splenic BFU-E was increased at all time points examined from the lithium-treated virus-infected group. A similar response was observed for megakaryocyte progenitors (CFU-Meg) (Fig. 5). Bone marrow CFU-Meg (a) were increased, although not until week 17 of examination, compared to week 9 for both myeloid and erythroid progenitors, while from the spleen (b), at all time points examined, CFU-Meg were increased significantly, in response to lithium treatment.

4. Discussion

HIV-induced immunodeficiency disease has been associated with several aspects of infection which results in abnormal or insufficient hematopoiesis. Therefore, as the result of retroviral infection, pancytopenia can often develop and this condition can be exacerbated with the use of certain antiviral drugs such as zidovudine. Although several studies have identified hematopoietic progenitor cells decrease with time as the result of retroviral infection, the precise mechanism responsible for this effect has not been clearly elucidated. In the MAIDS model, results from our laboratory have recently implicated the role of the hematopoietic inductive microenvironment or stroma to be the key elements responsible for the depression of hematopoiesis associated with retroviral infection. This conclusion is based upon the observation that mice made immunodeficient as the result of LP-BM5 MuLV infection (MAIDS model), fail to establish an effective stroma capable of supporting hematopoietic progenitor cell proliferation and differentiation in vitro when evaluated in the long-term bone marrow culture system (Tse et al., 1993). Progenitor cells cultured from bone marrow harvested from LP-BM5 MuLV-infected mice responded in a normal fashion compared to marrow-derived progenitor cells from non-virus-infected control animals to the growth factors that regulate their proliferation and differentiation. Therefore, the reduced capacity to maintain normal hematopoiesis as the result of virus infection was due to an effect mediated via the microenvironment rather than to a defect in the progenitor cell population.

Several studies have demonstrated that lithium salts may possess antiviral properties against such viruses as herpes simplex virus and recently against HIV (Kinchington et al., 1993). Specifically, there have been several in vitro studies demonstrating lithium chloride, at concentrations ranging from 5 to 30 mM, inhibits herpes simplex virus replication by interfering with viral DNA synthesis (Skinner et al., 1980). Lithium γ-linolineate (Li-GLA) after 4-days incubation in the presence of H-9 cells that were chronically infected with HIV, where 90% killed compared to only 20% for the non-infected controls. The mechanism of cell killing correlated with the level of lipid peroxidation, as measured by the intracellular thiobarbituric acid-reactive material content.

We have previously demonstrated in the MAIDS model that lithium administration to virus-infected animals was associated with a marked reduction in their ability to develop both lymphadenopathy and splenomegaly (Gallicchio and Hughes, 1993). This response provided a significant increase in survival compared to virus-infected animals not receiving lithium. At 35 weeks postvirus infection, all lithium-treated mice were alive compared to 100% mortality by week 24 postvirus infection in virus-infected mice not receiving lithium. Lithium-treated virus-infected mice also failed to develop the characteristic lymphoma that is associated with late-stage MAIDS, even though lithium-treated animals still were positive for LP-BM5 MuLV as determined by electron microscopy when examined from infected tissues. This report also demonstrated that optimum protection from virus infection was associated when lithium was administered prior to virus when compared to the survival in MAIDS animals when lithium was initiated 5

weeks postviral infection. Although the percent survival in MAIDS mice administered lithium after virus infection differed when compared to when lithium was administered prior to virus infection, this could be potentially reversed with increased lithium dosing; however, this will require further testing to determine optimal dosing, being aware that increasing the lithium dose could induce undesired side effects. More recent studies from this laboratory have suggested lithium treatment in LP-BM5 MuLV immunodeficient animals may have been associated with an inhibition in viral pathogenesis that influences the reduced immune response induced as indicated by the reduction in the splenomegaly and hypergammaglobulinemia, i.e., IgM, that is associated with MAIDS (Gallicchio et al., 1994). These results confirm the ability of lithium to influence the pathogenesis of MAIDS when administered to virus-infected animals in vivo.

The monovalent cation lithium influences several functions that regulate the proliferation and differentiation of blood cells. Early undifferentiated pluripotential and committed progenitors of myeloid, erythroid and megakaryocyte lineages all respond to lithium (Gallicchio and Chen, 1980; Gallicchio et al., 1981). The subject of lithium and hematopoiesis has been reviewed previously (Gallicchio, 1991). Because of these properties, lithium has been demonstrated to induce hematopoietic recovery in animal models and in patients receiving myeloablative therapy for the treatment of malignant disease (reviewed in Gallicchio, 1991). This property of lithium has also been demonstrated when combined with the antiviral drug zidovudine (AZT) when administered in vivo (Gallicchio and Hughes, 1992) or in vivo (Gallicchio et al., 1993). Lithium not only effectively increased the number of hematopoietic progenitor cells derived from either bone marrow or spleen following administration in vivo, but also influenced the spatial location of these progenitor cells, i.e., within the endosteal marrow of the bone marrow cavity (Gallicchio et al., 1994). The population of cells demonstrating the greatest increase following lithium administration in MAIDS mice receiving zidovudine resided in the area of the endosteal bone marrow cavity containing the undifferentiated, i.e., pluripotential progenitor cell population, indicating lithium is capable of influencing the most undifferentiated cell population within hematopoietic tissue with the greatest proliferative potential.

The results described in this report confirm the ability of lithium to influence the development of hematopoietic suppression associated with MAIDS. The level of pancytopenia that developed in viral control animals was significantly reduced in virus-infected animals receiving lithium. Demonstration of increased neutrophilia and lymphocytosis was associated with lithium treatment as compared to the development of neutropenia and lymphopenia associated with MAIDS. Hematopoietic progenitor cells, i.e., erythroid, myeloid and megakaryocyte were all increased in response to lithium treatment compared to virus controls when examined from the spleen and at certain time points from the bone marrow. This is not an unexpected finding since following many perturbating agents that induce hematopoietic suppression, the spleen is the major organ responsible for hematopoietic reconstitution compared to the bone marrow. The bone marrow may provide the source of hematopoietic progenitor cells that use the spleen as the site of major reconstitution. Further studies are in progress to attempt to determine if the effect of lithium on hematopoiesis described in this report is the result of reduced viral proliferation or an effect on hematopoietic cells, and/or their ability to become

infected with virus or both. These data further indicate and support more intensive efforts to evaluate the use of lithium in human clinical trials.

There have been several reports demonstrating the effective use of lithium in HIV-infected patients to ameliorate the myelosuppression associated with the clinical use of zidovudine in humans (Herbert et al., 1988; Roberts et al., 1988; Amsterdam et al., 1990) and one report describing lithium use in three AIDS patients where one of three responded with neutrophilia (Worthington 1990). In one of these reports (Herbert et al., 1988), lithium was administered in order to achieve a serum lithium concentration of 0.6–1.2 mM, well within the therapeutic range observed in clinical psychiatry. Three of the 5 patients reported in this study demonstrated significant hematopoiesis and were capable of tolerating significantly higher doses of zidovudine (up to 1000 mg/day) without any observable signs of toxicity. There has been one report where lithium was administered to AIDS patients who were not receiving AZT (Parenti et al., 1988). In this study, 6 of 7 patients who received lithium for at least 4 weeks responded with neutrophilia; however, further lithium usage was limited due to the presence of lithium toxicity. In another report (Barrios et al., 1992) a 14-year-old male patient with severe Factor VIII deficiency was found to be HIV-positive in 1985. Treatment with zidovudine was initiated in March 1989, but was discontinued after 6 months due to the development of thrombocytopenia, neutropenia, and anemia. Because myelosuppression did not improve over the following 3 months, intravenous immunoglobulin therapy was initiated. Bone marrow examination revealed severe hypoplasia with absent megakaryocytes, and erythroid and myeloid precursors. The patient was administered intravenous methylprednisolone on a 5-day treatment course along with daily oral lithium carbonate (300 mg t.i.d.). Within 3 days, 'a remarkable rise' in both the absolute neutrophil and platelet counts was observed. Unfortunately, none of these clinical reports addressed the important question as to what effect, if any, did lithium have on virus production or pathogenesis.

Collectively, these results support the further testing of the antiviral properties of lithium as well as to further investigate its ability to improve the antiviral effectiveness of currently used antiviral therapies potentially by: (1) improving their efficacy by increasing their antiviral potency; (2) reducing their toxicity; or (3) both.

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