ELSEVIER

Journal of Neuroimmunology 86 (1998) 163–170

Journal of Neuroimmunology

The immune system can affect learning: chronic immune complex disease in a rat model

Steven A. Hoffman [a,*], David Wm. Shucard [b], Ronald J. Harbeck [c]

[a] *Department of Microbiology and Molecular and Cell Biology Program, Arizona State University, Tempe, AZ 85287-2701, USA*
[b] *Division of Developmental and Behavioral Neurosciences, Department of Neurology, State University of New York at Buffalo, Buffalo, NY 14203, USA*
[c] *Clinical Immunology, National Jewish Center, Denver, CO 80206, USA*

Received 27 June 1997; revised 14 October 1997; accepted 26 January 1998

Abstract

Evidence is presented that the immune system can affect central nervous system functioning, leading to changes in learning. Immune complex disease is induced in rats and their behavior tested using a Lashley maze. Significant differences in behavior were found between the animals with high disease activity and those with low disease activity and the non-disease controls. These changes were not due to uremia and are most likely due to the immune response. There is some evidence immune complex deposits in the choroid plexus may play some role, but not the sole or major role in the behavioral changes. This provides a model by which immunologic processes can cause neuropsychiatric manifestations in autoimmune diseases like lupus, as well as showing that immune processes can affect behavioral functioning.

Keywords: Neuro-immune interactions; Immune complex disease; Systemic lupus erythematosus; Behavior; Memory and learning

1. Introduction

There is good evidence for the immune system affecting mind, since it is not uncommon to find neurologic and psychiatric involvement associated with immunologic disorders. This occurs in diseases such as multiple sclerosis, Alzheimer disease and acquired immune deficiency syndrome. One of the best examples of neuropsychiatric manifestations associated with an immunologic disorder is systemic lupus erythematosus (SLE). In this autoimmune disease, CNS manifestations occur in approximately one third of the patients. These manifestations are equally divided between neurologic disorders, including seizures, pareses, and movement disorders, as well as pyschiatric involvement such as affective disorders, cognitive impairment and psychoses (including schizophreniform behavior). This association suggests an immune mediated genesis of some mental disorders (Schiffer and Hoffman, 1991).

We have tested the idea that the immune system can alter normal behavior, by manipulating the immune system in a model consistent with the pathogenic mechanisms involved in SLE. In the present study, we induced chronic immune complex (IC) disease in rats. The disease is an immunologic disorder where an antibody response is generated against an exogenous antigen. The antibody and antigen form circulating complexes which, if of the correct size, can deposit in various tissues. The immune system then attempts to eliminate these complexes and in so doing does damage to the organ containing the immune complexes. It is in this way that the glomerulonephritis associated with this disease occurs. There is, however, no gross damage to the CNS, although there is evidence that blood–brain barrier permeability, via the choroid plexus, may be affected (Hoffman and Harbeck, 1989; Hoffman et al., 1983; Harbeck et al., 1979; Peress and Tompkins, 1979; Peress et al., 1977a,b). Thus, if there are behavioral alterations associated with this model, it would not be due to gross damage to the brain, but rather to the transient effects on the brain associated with the influence of cytokines, complement components, antibodies, or related factors associated with immunologic processes. Indeed, many patients with diffuse neuropsychiatric manifestations fail to demonstrate pathologic brain lesions and show evidence of an autoantibody mediated pathogenesis (West et al., 1995; Denburg et al., 1988; Bluestein et al., 1981).

* Corresponding author. Tel.: +1 602 965-7024; fax: +1 602 965-0098; e-mail: atsah@asuvm.inre.asu.edu.

0165-5728/98/$19.00

Patients with focal manifestations, on the other hand, appear to primarily have a vascular mediated pathogenesis (Johnson and Richardson, 1968; Zvaifler and Bluestein, 1982; Harris and Hughes, 1985; McCune and Golbus, 1988; van Dam, 1991).

We tested the hypothesis that chronic immune complex disease could affect performance in a learning task and that this effect will be related to immunologic processes. We had previously shown (Hoffman et al., 1978) that behavior could be affected by chronic immune complex disease in an aversive learning paradigm (viz., in a shuttle box). In this behavioral paradigm experimental animals failed to extinguish a learned response as rapidly as the normal animals. In the current study, we used a behavioral paradigm different from an aversive one in order to test the generalizability of the phenomenon and test potential mechanisms involved. An appetitive task, using the Lashley maze, was used since it is complex, involving different types of behavior, including cognitive, affective and motor components, yet is a relatively simple task to perform. Thus, behavioral effects associated with IC disease would show that immunologic processes can affect behavior and provide additional information about the potential mechanisms of interaction between the immune system and brain.

2. Materials and methods

The study was conducted in two staggered sessions. An experimental and control group was included in each session. This procedure was followed for logistical purposes, so that an adequate sample size could be obtained for statistical evaluation. There was a difference between the sessions in several of the variables tested, although the control animals in each session were not different. The difference between sessions was due to the degree of immune complex disease in the experimental animals, with the animals in the second session in general displaying higher levels of immune complex disease than the experimental animals in the first session. Therefore, the control animals were combined and the experimental animals were separated into two groups, those with high immune complex disease and those with low immune complex disease, as defined by proteinuria levels. The combined data of the two sessions, with the high and low immune complex disease groups, is what is reported on here.

2.1. Animals

A total of 36 male Sprague–Dawley rats weighing between 200 and 250 g (39–44 days old) were used to form the experimental and control groups. The experimental group had a total of 22 animals and the control group had 14 animals at the end of the experiment.

2.2. Induction of chronic immune complex disease

Circulating immune complexes were induced using a two-part protocol similar to that previously reported (Hoffman et al., 1978). First, an immune response to antigen was produced in the experimental animals using either a low (first session) or high dose (second session) regimen designed to produce a weak or strong response. The animals were injected subcutaneously with either 1 mg (session 1) or 30 mg (session 2) of bovine serum albumin (BSA) in 0.1 ml of 50% Freund's incomplete adjuvant four or five times during a 36 or 50-day period with at least 10 days between injections. Control animals received saline instead of BSA. Ten days after the last injection, all animals were bled from the tail vein and the serum tittered for precipitating antibodies to BSA. Following this initial immunization period, experimental animals received either bi-weekly or tri-weekly intravenous injections of BSA. Equal volumes were injected into each animal and control animals received an equal volume of saline. Based on the animal's precipitating antibody responses, an attempt was made to keep the circulating level of antigen at 10 times excess.

To test the success of the above regimen to induce immune complex disease, weekly urine samples were collected from all animals. These samples were obtained while the animals were housed in metabolic cages overnight (15 h), without food but with free access to water. The urine samples were then assayed for protein using the Tsuchiya Method (Kracke and Parker, 1940). This procedure of weekly injections and proteinuria determination was followed throughout the experiment. When animals showed significant elevations in urine protein, an indication of disease activity, behavioral testing was begun. The time from the beginning of immunization (first subcutaneous injection) to the beginning of behavioral testing was between 7 and 9 months. At the beginning of behavioral testing, experimental animals had a wide range of urine protein values. Blood urea nitrogen values were determined at the beginning, middle and end of the experiment.

2.3. Behavioral testing

Behavioral testing was done using a Lashley III type maze, constructed according to the design of Lashley (1929), with four compartments, including eight cul-de-sacs, separating the start and goal box. In this task, the animal was to traverse a path from the start box to the goal box, without entering the cul-de-sacs and requiring five alternating left and right turns, for a food reward. Animals were initially trained to run for a food reward in a straight alley. After reaching a criterion of three consecutive trials in less than 10 s, they were then introduced to the Lashely Maze. The experimenters were blind as to the animals' group.

Animals were run for five trials per day, in the Lashley maze, up to 100 trials or until the criterion of 10 consecutive errorless trials was attained. Measures of speed, errors (entering cul-de-sacs and retracing) and the number of trials to criterion were obtained. Animals were gentled for one week prior to experimental manipulations (i.e., induction of immune complex disease) and behavioral testing by daily handling.

Preliminary training involved teaching the rats to run for a food reward in a straight alley. The straight alley dimensions were 156 cm × 12 cm and 20 cm deep. The start and goal box guillotine doors were set 28 cm from the ends of the runway. First the rat was placed in the goal box, which had 37 mg of food pellets. Prior to initial training animals were deprived of food for 48 h, with ad lib access to water. The animal was removed from the goal box 30 s after consuming the food, then returned to its home cage and the next animal was similarly trained. The apparatus was cleaned after each rat was removed from the behavioral apparatus. The goal box training was repeated five times/rat/day, until the animal learned to consume the food within 30 s. After this the animals were trained to run in the straight runway for the food reward. The animal was placed in the start box with its nose pointing away from the start door. When the rat turned around the door was opened after a 2 s delay, at which point timing of the run was started. The animal was allowed a maximum of 5 min to run to the goal box, then allowed 30 s to consume the food pellets once in the goal box. This procedure was repeated for five trials/day. These trials were repeated until the animals ran without hesitation (within 10 s) from start to goal box on three consecutive trials.

After preliminary training in the straight runway, the animals were trained and tested in the Lashley III maze. Once again, the animals were trained to consume food in the goal box of the maze for three trials. After the animals had gone through this training they were trained to run from the start box to the goal. The animal is placed in the start box as for the straight runway training. The rat is allowed a maximum of 5 min to reach the goal box, then another 30 s to consume the food reward. If the rat does not enter the goal box within 5 min, then it is placed in the goal box for 30 s. This trial occurred once per animal before behavioral testing began. Testing used the same procedure, except that data was recorded. Time between trials was 10 s between removal and placement of animals. Five trials per day were given for each animal. One hour after behavioral testing the animals were fed approximately 15 g of food and maintained at 80% of their original body weight.

2.4. Immunofluorescence staining

Upon completion of the behavioral testing, animals were sacrificed and kidneys and brains removed and frozen for immunofluorescent studies. Some of these tissues were lost and could not be used for data analyses. Fluorescein isothiocyante (FITC) conjugated rabbit antiserum to rat gamma-globulin was obtained from a commercial supplier (Cappel, Organon Teknika, Durham, NC). Fluoresceinated antisera to BSA was prepared according to previously described procedures (Weir et al., 1986). Frozen sections (6 μm) of brain and kidney were examined for fluorescence under a Leitz Ortholux Fluorescence Microscope equipped with an Osram HBO 100 W high pressure mercury vapor lamp. The intensity of staining in brain choroid plexus (CP) and renal glomeruli were graded on a scale from 0 to 4+ by two independent readers and the scores averaged. The ratings of the readers were always close to one another.

3. Results

The results indicated that there were significant differences in maze performance between animals that showed evidence of chronic immune complex disease and those that did not. A multivariate analysis of variance (SPSS 7.5 for Windows) was performed on three groups, experimental animals with high disease activity, as indicated by proteinuria levels (> 150 mg%), experimental animals with low disease activity (proteinuria < 150 mg%) and controls. Four measures of disease activity were compared, mean proteinuria during the behavioral testing, blood urea nitrogen levels and immune complex deposits in both the choroid plexus and kidneys. Three measures of behavioral variables were also compared, trials to reach criterion, the total number of errors made before reaching criterion and the total time it took to run the maze before reaching criterion (latency). A significant difference (Wilks' Lambda, $F = 7.653$; $df = 38$; $p < 0.001$) was indicated among the groups tested. The univariate F tests with (2,25) df, indicated that significant differences were found between the groups on the variables proteinuria ($F = 16.683$; $p < 0.001$), blood urea nitrogen ($F = 13.158$; $p < 0.001$), immune complex deposits in CP ($F = 8.984$; $p = 0.001$), and kidney ($F = 18.961$; $p < 0.001$), trials to criterion ($F = 9.144$; $p < 0.001$), total errors ($F = 5.642$; $p = 0.010$), but not latency per trial ($F = 2.599$; $p = 0.094$).

3.1. Behavioral effects of immune complex disease

It can be seen from Fig. 1 that it took animals with more severe immune complex disease, significantly fewer trials to reach criterion than both the low disease activity and control animals. A comparison of the number of errors made during maze performance (Fig. 2) also shows that the high disease animals made fewer errors during acquisition than either controls or low disease animals.

It is unlikely that uremia could have accounted for the behavioral changes. While there were statistically significant differences between the three groups, the high disease

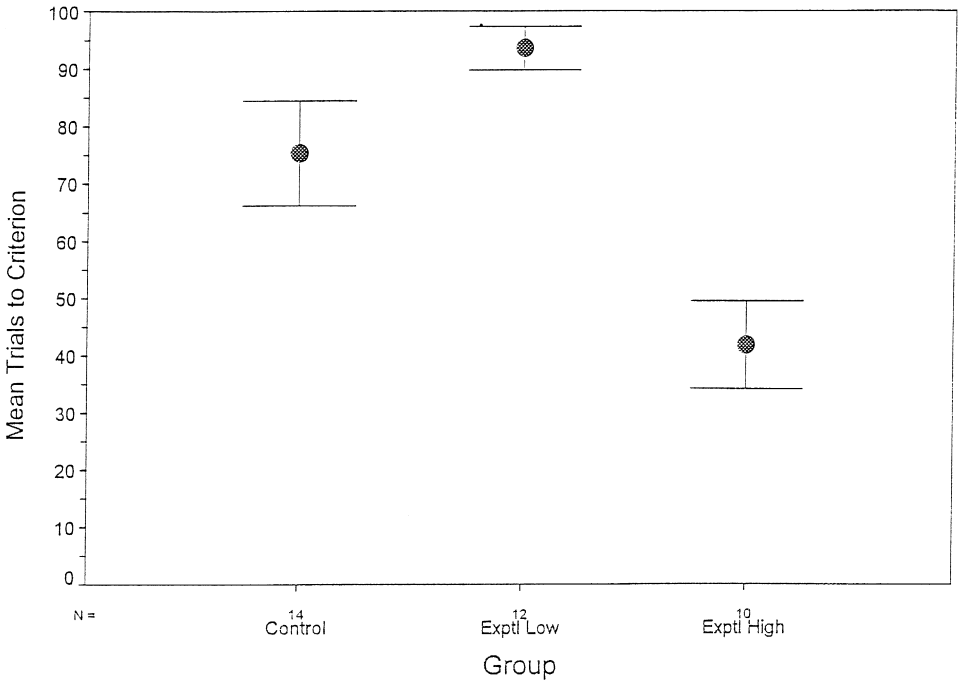

Fig. 1. Comparison of the mean for each group, of the total number of trials it took to reach the criterion of 10 consecutive, errorless runs. The maximum number of trials allowed was 100. Circulating immune complexes were induced in the experimental animals, but not in the controls. The experimental animals were further divided into those animals that developed either a high or low level of immune complex disease, as determined by proteinuria levels with a cutoff of 150 mg%. The number of animals in each group are shown on the figure ($N=$).

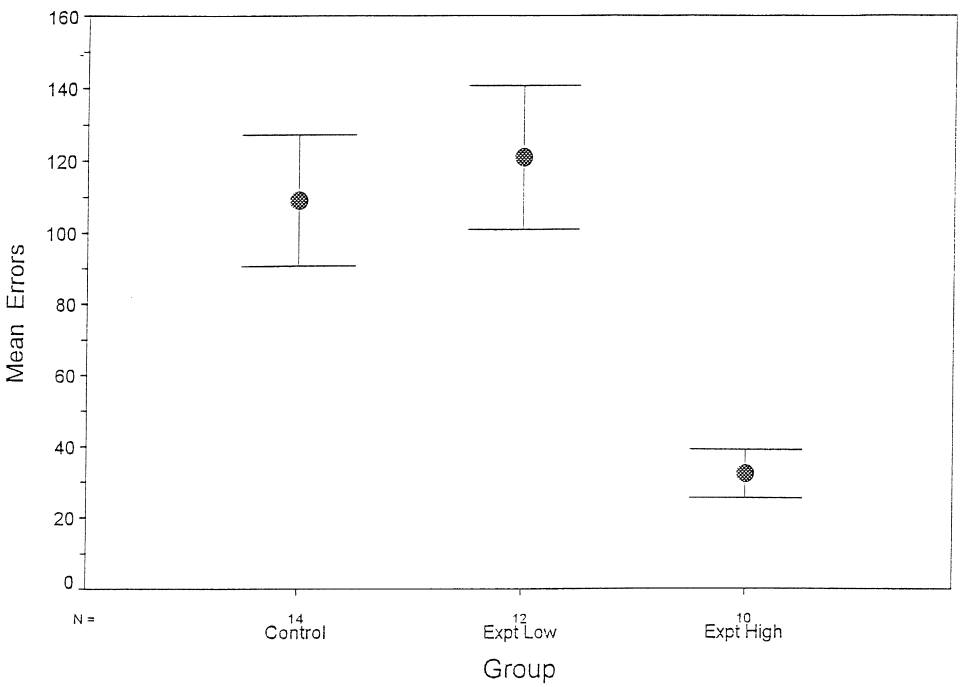

Fig. 2. Comparison of the mean errors made over the course of the behavioral testing by each group. The number of animals in each group was the same as in Fig. 1. An error was counted when the animals entered a cul-de-sac, made a wrong turn, or re-traced their path. An errorless run was when the animal went directly from the start box to the goal box.

activity experimental and control groups were not different from one another in blood urea nitrogen levels. Oddly enough, the low disease activity experimental group was significantly lower than the other two groups.

These data indicate that altered immunity can induce changes in behavioral performance, viz., learning. Cognitive impairment has been reported in human SLE (Hanly et al., 1993; Denburg et al., 1993), presumably as a consequence of immunologic processes. In the current experiment, both trials to criterion and errors were affected by induction of immune complex disease. That latency was not significantly different between the groups suggests that motor activity was not involved. Watching the animals run the behavioral tasks also did not suggest any motor differences between the groups. In addition, it is unlikely that motor activity accounts for the differences since the experimental group with more severe disease performed better on the task. This is an odd phenomenon, but would be the case if these animals were less attentive, or more stereotyped in their behavior. That is, the experimental animals with high disease activity may attend less to extraneous cues, or learn relatively simple tasks better than normal animals.

3.2. Immune complex deposits in choroid plexus and renal glomeruli

Immune complex deposits are known to occur in the choroid plexus of patients with systemic lupus erythematosus who have neuropsychiatric manifestations (Atkins et al., 1972; Sher and Pertschuk, 1974; Gershwin et al., 1975). We found IC deposits in both the CP and renal glomeruli of experimental animals, but not in controls. These deposits were granular, similar to those illustrated in our 1978 study (Hoffman et al., 1978). As in this first study, the IC fluorescent deposits in experimental animals were much stronger in the renal glomeruli (in the 3–4 + intensity rating range) than in the CP. There was a significant difference between the groups in IC deposits in both CP and kidney. As can be seen in Fig. 3, there was little difference between the mean fluorescence for IC deposits in the CP of the two groups of experimental animals, viz., low and high disease activity. The experimental low group had an average fluorescence intensity of about 1.0 for IC deposits in their CP, whereas the Experimental High group had an average fluorescence intensity of about 1.5. The controls had no evidence of IC deposits in their CP.

3.3. Immune complex deposition and behavior

It is possible that IC deposition in the CP could cause some of the behavioral alterations in this study. To test this we used Spearman's rank order correlation, one-tailed, between IC deposits in the CP and the behavioral measures of trials to criterion and total errors within the experimental animals. There was not a significant correlation between IC deposits in the CP and errors ($r = -0.143$, $n = 20$, $p > 0.05$), nor to trials to criterion ($r = -0.157$, $n = 20$, $p > 0.05$). Effects due to IC deposits in the CP would have been consistent with altered blood–cerebrospi-

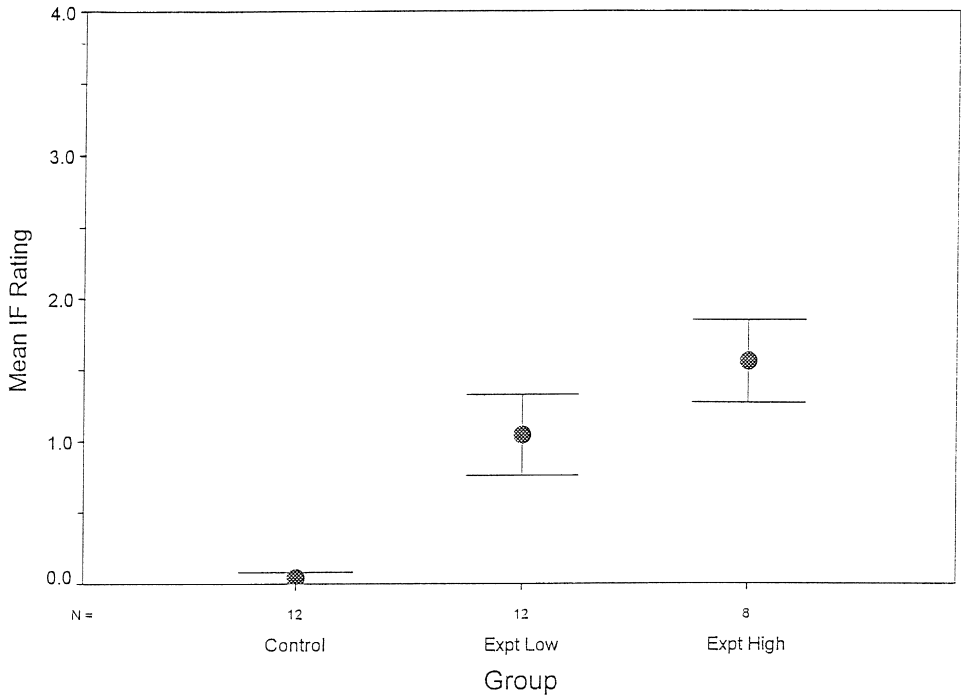

Fig. 3. Immune complex deposition in the choroid plexus, as determined by immunofluorescence, in each of the three groups of animals. Ratings were made by two independent investigators, blind to the animal groups, on a scale from 0 to 4 + and the scores averaged.

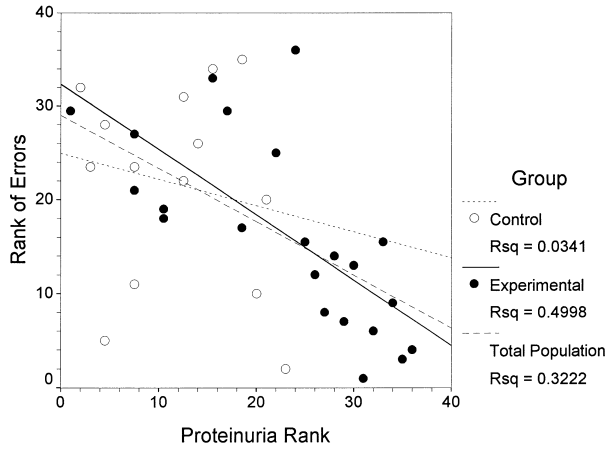

Fig. 4. Correlation of errors to disease activity (as defined by proteinuria). These measures were rank ordered. Experimental animals (including both low and high disease activity) are shown as closed circles, while control animals (no immune complex disease) are shown as open circles. The regression line for experimental animals is solid, whereas the regression lines for the total animal and control populations are shown as dashed lines.

nal fluid barrier permeability, leading to the observed behavioral changes.

When disease activity (based on proteinuria) was correlated to behavior (Fig. 4) within the experimental animals, one-tailed, there was a highly significant association, both with trials to criterion ($r = -0.778,\ n = 22,\ p < 0.001$) and errors ($r = -0.814,\ n = 22,\ p < 0.001$). It can also be seen that there was no correlation, as would be expected, in the controls (Rsq = 0.034). Thus, it is unlikely that the behavioral effects were due to the immune complex deposits in the choroid plexus, although they may play some role.

4. Discussion

The above data provide strong evidence that the immune system can alter behavior, particularly since uremia was not the cause of the behavioral changes. More specifically, it was shown that changes in learning could be induced by immune complex disease in an appetitive learning paradigm, in addition to the previously tested aversive paradigm (Hoffman et al., 1978). The changes in learning seen in the animals are a good model for the neuropsychiatric manifestations seen in patients with CNS-SLE. In two completely different behavioral paradigms we have now seen changes associated with chronic immune complex disease, which are most likely due to immunologic processes. In the first study we noticed a decline in learning and memory, in the animals with chronic immune complex disease, as manifested by the failure to extinguish a previously learned response. Although, in these animals, the initial ability to learn the behavioral task was as good as the control animals. In the present study, the experimental animals appeared to perform the appetitive task better than the control animals, although this is probably a paradoxical effect associated with a deficiency in cognitive flexibility. The key point is not, however, whether the behavior appears to be improved in the experimental animals compared to the controls, but that the behavior is altered. This implies that immunological processes can alter behavior, although we may not currently know exactly what those mechanisms are by which the behavior is altered.

Improved behavioral performance in a simple appetitive task, has been seen in animals with hippocampal lesions (Wickelgren and Isaacson, 1963; Gustafson, 1975; Xavier et al., 1990). In these tasks, rats with hippocampal lesions ran a straight alley runway, with distracting stimuli, better than the controls. It had been proposed that the improved performance was due to the inability of the experimental animals to attend to distal cues. That is, the lesioned animals perform more stereotyped behaviors better because they cannot be easily distracted. What is most interesting in the discussions associated with these articles, it is mentioned that animals with hippocampal lesions have also been found to fail to extinguish a previously learned task as rapidly as controls. Although the explanation for this behavior, viz., that animals with hippocampal lesions are incapable of relinquishing the effects of prior learning has been challenged (Harley, 1979), the phenomenon exists and is similar to what we saw in our aversive paradigm with chronic immune complex rats. In another study (Packard et al., 1989), it was shown that fornix lesioned rats performed a ‘win–stay’ task, in an eight-arm radial maze better than controls, whereas caudate nucleus lesioned animals performed more poorly than the controls. The authors argued that different types of memory are mediated by different systems of the brain. Other information on hippocampal lesioned animals showing improved performance exists. Another example is in spatial learning, where hippocampal lesioned rats are normally impaired, but they perform better than controls in conflict situations. That is, when a second test is in conflict with the first, normal rats with good memories show proactive inhibition, where a high rate of error in learning the second test occurs because the memory for the first competes with the learning of the second. In animals with hippocampal lesions, this conflict does not occur because of the impaired memory for the first task and they perform better on the second task. Our two studies support the idea that even though individuals may appear to display normal cognitive behaviors, more in depth testing can show impaired, or altered, performance. This is apparently the case in SLE patients, where cognitive deficit is difficult to detect, but can be found (Denburg et al., 1993, 1994a,b, 1997). It would be interesting to test the hypothesis that the hippocampus is involved with some of the behavioral phenomena we are seeing in the chronic immune complex model. Based upon the above stories, it may be that the

immunological processes are affecting hippocampal functioning.

Although immune complex deposits in the choroid plexus could lead to altered blood–brain barrier functioning, we could not provide strong evidence that such deposits were involved. In addition to immune complexes mediating the behavioral changes, antibodies, complement components and cytokines may also have an effect on brain functioning. That antibodies can mediate CNS changes is currently being studied by several different laboratories, including our own (Hoffman et al., 1988; Forster and Lal, 1990; Sakic et al., 1993; Schrott and Crnic, 1994; Vogelweid et al., 1994; Lutomski et al., 1995; Miller and Rodriquez, 1995; Crimando et al., 1997). Most of the autoantibody studies focus on reactivity with antigens of brain, interfering with CNS functioning. Although it is possible that the antibody response generated in our model had an effect on brain functioning, this is unlikely, since they were not brain reactive. It is, however, possible that brain reactive antibodies were generated through idiotypic interactions.

It has been shown that complement components can mediate behavioral changes (Schupf and Williams, 1985). The anaphylatoxins C3a and C5a, can alter normal neurotransmitter release (Schupf et al., 1983; Williams et al., 1985). It is possible that elevations in these complement components during the induced immune response could lead to altered neurotransmitter functioning within the CNS. This in turn could lead to the behavioral effects seen in the present study.

Cytokines can also mediate changes in CNS functioning. It has been shown that cytokines administered centrally (Dafny et al., 1988; Katafuchi et al., 1991; Lapchak, 1992; Fukata et al., 1993; Shintani et al., 1993), or even peripherally (Bartholomew and Hoffman, 1993; Zalcman et al., 1994) can have an effect on neuronal functioning within the brain. It is also known that cytokines can alter normal behavior (Maes et al., 1990; Crestani et al., 1991; Zalcman et al., 1995). There is evidence that in CNS-SLE, cytokines play a role in the neuropsychiatric manifestations (Yeh et al., 1994; Shiozawa et al., 1992; Hirohata and Miyamoto, 1990). Further evidence suggesting cytokines play a role in the CNS, report altered cytokine receptor expression in the brains of autoimmune mice (Tehrani et al., 1994).

The immune system and nervous system influence one another during the course of normal physiologic processes. Evidence from many areas support the notion that there is a neuroimmunologic circuit whereby the CNS and immune system can communicate with one another and modulate one another's functioning. Based on this model, a perturbation in the normal immunologic status of an individual, such as that caused by immune complex or autoimmune disease, could alter normal immune system signaling of the CNS so as to lead to altered CNS functioning and behavior. However one views the cause, whether it be by pathophysiologic mechanisms or by a perturbation of normal physiologic processes, the current data provides interesting evidence that the immune system can alter normal neurobehavioral processes.

References

Atkins, C.J., Kondon, J.J., Quismorio, F.P., Friou, G.J., 1972. The choroid plexus in systemic lupus erythematosus. Ann. Int. Med. 76, 65–72.

Bartholomew, S.A., Hoffman, S.A., 1993. Effects of peripheral cytokine injections on multiple unit activity in the anterior hypothalamic area of the mouse. Brain Behav. Immunol. 7, 301–316.

Bluestein, H.G., Williams, G.W., Steinberg, A.D., 1981. Cerebrospinal fluid antibodies to neuronal cells: association with neuropsychiatric manifestations of systemic lupus erythematosus. Am. J. Med. 70, 240–246.

Crestani, F., Seguy, F., Dantzer, R., 1991. Behavioural effects of peripherally injected interleukin-1: role of prostaglandins. Brain Res. 542, 330–335.

Crimando, J., Cooper, K., Hoffman, S.A., 1997. Inhibition of inward sodium channel currents by antineuronal autoantibody from autoimmune mice. In: Moore, P. (Ed.), Neuropsychiatric Manifestations of Systemic Lupus Erythematosus. New York Academy of Sciences, New York.

Dafny, N., Lee, J.R., Dougherty, P.M., 1988. Immune response products alter CNS activity: interferon modulates central opioid functions. J. Neurosci. Res. 19, 130–139.

Denburg, J.A., Denburg, S.D., Carbotte, R.M., Long, A.A., Hanly, J.G., 1988. Nervous system involvement in systemic lupus erythematosus. Isr. J. Med. Sci. 24, 754–758.

Denburg, S.D., Denburg, J.A., Carbotte, R.M., Fisk, J.D., Hanly, J.G., 1993. Cognitive deficits in systemic lupus erythematosus. Rheum. Dis. Clin. N. Am. 19, 815–831.

Denburg, S.D., Behmann, S.A., Carbotte, R.M., Denburg, J.A., 1994a. Lymphocyte antigens in neuropsychiatric systemic lupus erythematosus—relationship of lymphocyte antibody specificities to clinical disease. Arthritis Rheum. 37, 369–375.

Denburg, S.D., Carbotte, R.M., Denburg, J.A., 1994b. Corticosteroids and neuropsychological functioning in patients with systemic lupus erythematosus. Arthritis Rheum. 37, 1311–1320.

Denburg, S.D., Carbotte, R.M., Denburg, J.A., 1997. Psychological aspects of systemic lupus erythematosus: Cognitive function, mood and self-report. J. Rheumatol. 24, 998–1003.

Forster, M.J., Lal, H., 1990. Animal models of age-related dementia—neurobehavioral dysfunctions in autoimmune mice. Br. Res. Bull. 25, 503–516.

Fukata, J., Imura, H., Nakao, K., 1993. Cytokines as mediators in the regulation of the hypothalamic–pituitary–adrenocortical function. J. Endocrinol. Invest. 16, 141–155.

Gershwin, M.E., Hyman, L.R.H., Steinberg, A.D., 1975. The choroid plexus in CNS involvement of systemic lupus erythematosus. J. Ped. 87, 588–590.

Gustafson, J.W., 1975. Distractibility and reactivity under different response conditions following hippocampal lesions in rats. Behav. Biol. 15, 479–484.

Hanly, J.G., Walsh, N.M., Fisk, J.D., Eastwood, B., Hong, C., Sherwood, G., Jones, J.V., Jones, E., Elkon, K., 1993. Cognitive impairment and autoantibodies in systemic lupus erythematosus. Br. J. Rheumatol. 32, 291–296.

Harbeck, R.J., Hoffman, A.A., Hoffman, S.A., Shucard, D.W., 1979. Cerebrospinal fluid and the choroid plexus during acute immune complex disease. Clin. Immunol. Immunopathol. 13, 413–425.

Harley, C.W., 1979. Nonreversal and reversal shifts in the hippocampectomized rat. Phys. Behav. 22, 1135–1139.

Harris, E.N., Hughes, G.R.V., 1985. Cerebral disease in systemic lupus erythematosus. Springer Sem. Immunopathol. 8, 251–266.

Hirohata, S., Miyamoto, T., 1990. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. Arthritis Rheum. 33, 644–649.

Hoffman, S.A., Arbogast, D.N., Day, T.T., Shucard, D.W., Harbeck, R.J., 1983. Permeability of the blood cerebrospinal fluid barrier during acute immune complex disease. J. Immunol. 130, 1695–1698.

Hoffman, S.A., Harbeck, R.J., 1989. CNS lupus and the blood–brain barrier. In: Neuwelt, E.A. (Ed.), Implications of the Blood–Brain Barrier and Its Manipulation Volume 2 Clinical Aspects. Plenum Medical, New York, pp. 469–494.

Hoffman, S.A., Narendran, A., Shucard, D.W., Harbeck, R.J., 1988. Autoantibodies, immune complexes, and behavioral disorders: Neuropsychiatric involvement in systemic lupus erythematosus. Drug Dev. Res. 15, 237–251.

Hoffman, S.A., Shucard, D.W., Harbeck, R.J., Hoffman, A.A., 1978. Chronic immune complex disease: behavioral and immunological correlates. J. Neuropathol. Exp. Neurol. 37, 426–436.

Johnson, R.T., Richardson, E.P., 1968. The neurological manifestations of systemic lupus erythematosus: a clinical–pathological study of 24 cases and review of the literature. Medicine 47, 337–369.

Katafuchi, T., Hori, T., Take, S., 1991. Central administration of interferon-alpha enhances rat sympathetic nerve activity to the spleen. Neurosci. Lett. 125, 37–40.

Kracke, R.R., Parker, F.P., 1940. Textbook of Clinical Pathology. Williams and Wilkins.

Lapchak, P.A., 1992. A role for interleukin-2 in the regulation of striatal dopaminergic function. Neuroreport 3, 165–168.

Lashley, K.S., 1929. Brain Mechanisms and Intelligence: A Quantitative Study of Injuries to the Brain. University of Chicago Press, Chicago.

Lutomski, D., Caron, M., Bourin, P., Lefebure, C., Bladier, D., Joubert-Caron, R., 1995. Purification and characterization of natural antibodies that recognize a human brain lectin. J. Neuroimmunol. 57, 9–15.

Maes, M., Bosmans, E., Suy, E., Vandervorst, C., Dejonckheere, C., Raus, J., 1990. Immune disturbances during major depression: upregulated expression of interleukin-2 receptors. Neuropsychobiology 24, 115–120.

McCune, W.J., Golbus, J., 1988. Neuropsychiatric lupus. Rheum. Dis. Clin. N. Am. 14, 149–167.

Miller, D.J., Rodriquez, M., 1995. A monoclonal autoantibody that promotes central nervous system remyelination in a model of multiple sclerosis is a natural autoantibody encoded by germline immunoglobulin genes. J. Immunol. 154, 2460–2469.

Packard, M.G., Hirsh, R., White, N.M., 1989. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J. Neurosci. 9, 1465–1472.

Peress, N.S., Tompkins, D.C, 1979. Rat CNS in experimental chronic serum sickness: Integrity of the zonulae occludentes of the choroid plexus epithelium and brain endothelium in experimental chronic serum sickness. Neuropathol. Appl. Neurobiol. 5, 279–288.

Peress, N.S., Miller, F., Palu, W., 1977a. The immunopathophysiological effects of chronic serum sickness on rat choroid plexus, ciliary process and renal glomeruli. J. Neuropathol. Exp. Neurol. 36, 726–733.

Peress, N.S., Miller, F., Palu, W., 1977b. The choroid plexus in passive serum sickness. J. Neuropathol. Exp. Neurol. 36, 561–566.

Sakic, B., Szechtman, H., Denburg, S., Carbotte, R., Denburg, J.A., 1993. Brain-reactive antibodies and behavior of autoimmune MRL-1pr mice. Physiol. Behav. 54, 1025–1029.

Schiffer, R.B., Hoffman, S.A., 1991. Behavioral sequlae of autoimmune disease. In: Ader, R., Felten, D., Cohen, N. (Eds.), Psychoneuroimmunology. Academic Press, New York, pp. 1037–1066.

Schrott, L.M., Crnic, L.S., 1994. Sensitivity to foot shock in autoimmune NZB×NZW F1 hybrid mice. Physiol. Behav. 56, 849–853.

Schupf, N., Williams, C.A., 1985. Effect of immune complex-forming reactants on catecholamine-modulated behaviors in the rat hypothalamus. J. Neuroimmunol. 9, 13–27.

Schupf, N., Williams, C.A., Hugli, T.E., Cox, J., 1983. Psychopharmacological activity of anaphylatoxin C3a in rat hypothalamus. J. Neuroimmunol. 5, 305–316.

Sher, J.H., Pertschuk, L.P., 1974. Immunoglobulin G deposits in the choroid plexus of a child with systemic lupus erythematosus. J. Ped. 85, 385–387.

Shintani, F., Kanba, S., Nakaki, T., Nibuya, M., Kinoshita, N., Suzuki, E., Yagi, G., Kato, R., Asai, M., 1993. Interleukin-1B augments release of norepinephrine, dopamine and serotonin in the rat anterior hypothalamus. J. Neurosci. 13, 3574–3581.

Shiozawa, S., Kurcki, Y., Kim, M., Hirohata, S., Ogino, T., 1992. Interferon-alpha in lupus psychosis. Arthritis Rheum. 35, 417–422.

Tehrani, M.J., Hu, Y., Marquette, C., Dietrich, H., Haour, F., Wick, G., 1994. Interleukin-1 receptor deficiency in brains from NZB and (NZB/NZW)F1 autoimmune mice. J. Neuroimmunol. 53, 91–99.

van Dam, A.P., 1991. Diagnosis and pathogenesis of CNS lupus. Rheumatology 11, 1–11.

Vogelweid, C.M., Wright, D.C., Johnson, J.C., Hewett, J.E., Walker, S.E., 1994. Evaluation of memory, learning ability and clinical neurologic function in pathogen-free mice with systemic lupus erythematosus. Arthritis Rheum. 37, 889–897.

Weir, D.M., Herzenberg, L.A., Blackwell, C., Herzenberg, L.A., 1986. Handbook of Experimental Immunology. Blackwell, Oxford.

West, S.G., Emlen, W., Wener, M.H., Kotzin, B.L., 1995. Neuropsychiatric lupus erythematosus: a 10-yr prospective study on the value of diagnostic tests. Am. J. Med. 99, 153–163.

Wickelgren, W.O., Isaacson, R.L., 1963. Effect of the introduction of an irrelevant stimulus on runway performance of the hippocampectomized rat. Nature 200, 48–50.

Williams, C.A., Schupf, N., Hugli, T.E., 1985. Anaphylatoxin C5a modulation of an alpha-adrenergic receptor system in the rat hypothalamus. J. Neuroimmunol. 9, 29–40.

Xavier, G.F., Stein, C., Bueno, O.F.A., 1990. Rats with dorsal hippocampal lesions do react to new stimuli but not to spatial changes of known stimuli. Behav. Neural. Biol. 54, 172–183.

Yeh, T.S., Wang, C.R., Jeng, G.W., Lee, G.L., Chen, M.Y., et al., 1994. The study of anticardiolipin antibodies and interleukin-6 in cerebrospinal fluid and blood of Chinese patients with systemic lupus erythematosus and central nervous system involvement. Autoimm. 18, 169–175.

Zvaifler, N.J., Bluestein, H.G., 1982. The pathogenesis of central nervous system manifestations of systemic lupus erythematosus. Arth. Rheum. 25, 862–866.

Zalcman, S., Nance, D.M., Greenberg, A.H., 1995. Behavioral activating effects of interleukin (IL)-2 and IL-6. Soc. Neurosci. Abstr. 21, 884.

Zalcman, S., Green-Johnson, J.M., Murray, L., Nance, D.M., Dyck, D.G., Anisman, H., Greenberg, A.H., 1994. Cytokine-specific central monoamine alterations induced by interleukin (IL)-2, IL-2 and IL-6. Brain Res. 643, 40–49.