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EFFECT OF CEREBELLAR FASTIGIAL NUCLEUS LESION ON IMMUNITY IN WISTAR ALBINO RATS

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ABSTRACT

The aim of the present study was to investigate the role of cerebellum in immunomodulation as cerebellum was thought traditionally to play an important role in voluntary motor activities. Rats weighing about 200-220 gm were subjected to bilateral electrolytic lesion of fastigial nucleus and following immune parameters were assessed- leucocyte migration inhibition test, foot pad thickness, antibody titre and estimation of cytokines – IL-2, IL-4 and IFN-γ respectively in immunized animals. Rats were divided in to three groups, namely control immunized, sham immunized and lesioned immunized groups. The sham group was strictly considered for evaluation of lesion effect as superficial structures during surgical procedure gets damaged and could also influence on immunomodulation. The significance was fixed at $P<0.05$. There was significant increase in migration index with concomitant decrease in foot pad thickness in bilateral lesion immunized groups. Significant alterations in cytokine levels were observed in lesion immunized groups when compared with its respective control groups.

INTRODUCTION: The existence of bidirectional cross talk between the neuroendocrine and the immune system has prompted many investigators to examine the mechanisms modulating the immune functions and vice-versa. Recent advances in the field of neuroimmunomodulation and in psychoneuro-immunology have shown that the nervous system and the immune system are closely linked and do not work independently [1, 2]. The knowledge of physiological function of cerebellum has long been confined to its voluntary control of motor activities and is less well documented in immunoregulation. Since there are no direct connections existing between the cerebellum and the immune system, some studies have reported cerebellar influence on immune function via pathways that are largely unknown.

The bidirectional connections existing between the cerebellum and the hypothalamus are named as cerebello-hypothalamic and hypothalamo-cerebellar projections [3, 4, 5]. The spinocerebellum is a functionally organized region of the cerebellum that includes the vermis at the midline and the intermediate part of the cerebellar hemispheres [6].

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The fastigial nucleus, one of the main output nuclei of spinocerebellum, receives and conveys information of spinocerebellum to its target nuclei or regions within the central nervous system [7]. Neuroanatomical researches [8, 4] by retrograde and anterograde tracings have identified direct and indirect projections from cerebellum to hypothalamus from all the three deep cerebellar nuclei and they terminate in those areas of hypothalamus which is extensively involved in autonomic activities [3, 4, 5, 6, 9, 10, 11, 12, 13].

Many studies have been documented the important role of hypothalamus in modulating immune functions [14,15] as well as mediating cerebellar modulation of visceral activities [3, 4, 5, 10, 11, 12, 13]. A study on a neurological mutant strain of reeler mice having an abnormally high concentration of cerebellar norepinephrine, showed a suppressed T cell and macrophage function, suggesting a close relationship between the cerebellum and immune function [16]. Electrolytic lesion of the vestibulocerebellum has been shown to decrease the peripheral blood leukocyte concentration, neutrophil myeloperoxidase response and antibody titer to sheep red blood cells [17]. Studies have predominated on expression of cytokines and their receptors in the cerebellum [18, 19, 20, 21].

Bilateral kainic acid lesion of the cerebellar fastigial nucleus caused an increase in Con A-induced lymphocyte proliferation and NK cell cytotoxicity [6]. In the present study, we investigated the role of cerebellar fastigial nucleus in immunomodulation. Adaptive immunity is capable of recognizing and selectively eliminating specific foreign antigens. Unlike innate immune responses, adaptive immune responses are not the same in all members of a species but are reactions to specific antigenic challenges. The major agents of adaptive immunity are T lymphocytes and B lymphocytes which are involved in cell mediated immunity and humoral mediated immunity respectively.

Previous studies have assessed only kainic acid lesion effect of fastigial nucleus on lymphocyte functions. Hence, the effect of bilateral electrolytic lesion of the cerebellar fastigial nucleus lesion on adaptive immunity was assessed in adult male Wistar albino rats by challenging them with sheep red blood cells which is a T cell dependent antigen.

MATERIALS AND METHODS:

Ethical approval: The study was approved by the Institute's Animal Ethical Committee (IAEC No. 08/034/07) and the Committee for the Purpose of Control and Supervision of Experiments on Animals, University of Madras, Chennai, India.

Animals: Healthy adult male Wistar albino rats weighing about 200-220 g have been used for this study and allowed to have food and water *ad libitum*. The animals were maintained in appropriate environmental conditions of temperature and humidity on an alternative 12- hour light/dark cycle. Since the interested site of lesion is not on the surface, inevitably the cortical structures above are also destroyed. There are reports that these structures influence the neural modulation of immunity [22]**.** Hence, the sham animals are considered as the strict control to evaluate the lesion effect. To avoid variations in the measured results due to circadian rhythm, stress free blood samples collections were done between 8:00-10:00 am [23].

Experimental groups: Animals were divided into three groups with six animals in each group. Group I: Control immunized animals; Group II: Sham operated immunized animals; Group III: Bilateral Fastigial Nucleus lesioned immunized animals.

Fastigial Nucleus Lesion: Rats were anaesthetized with Pentathol Sodium (40 mg/kg bw). The hair on the scalp was removed and the animal was fixed to the stereotaxic apparatus. The coordinates for fastigial nucleus from Bregma minus 10 mm, 1.10 mm lateral, 4.80 mm from dura (depth) [24]. Appropriate holes were made and using stainless steel electrode of 0.22 mm diameter, anodal electric lesions were made on both sides of the cerebellum with direct current of 2mA at 100 volts for 10 seconds. The lesioned as well as the sham lesioned animals were allowed to recover for 10 days postoperatively and then subjected for immune studies on 15th day. The brain of the lesioned animals were removed immediately and preserved in buffered formalin. The tissue pieces were dehydrated by passing through ascending grades of alcohol and cleared by chloroform. Impregnation and embedding were done using paraffin wax and sections of 20 µ were taken using a rotary microtome and stained using cresyl violet [6].

Immunization: Sheep red blood cells were collected in sterile Alsever's solution and washed three times with pyrogen free normal saline and then adjusted to $5x10^9$ cells/ml saline. On 10^{th} day after the surgery, the animals were then immunized by intra-peritoneal injection of 1 ml of the sheep red blood cell suspension. On 15^{th} day all the immunological parameters were studied [22].

Leukocyte Migration Inhibition Test: This test was used to assess the cell mediated immune responses in animals. Sensitized T lymphocytes in the presence of the corresponding antigen produce migration inhibition factor (MIF), as well as Migration enhancing factor and the balance determine the migration of leucocytes from capillary tubes [25]. Alteration in these mediators is the indictor of altered cell mediated immunity. Thymocytes were used as a migrating population to study the effect of migration inhibition factor released by lymphocytes of spleen in the presence of sheep red blood cells. On 15^{th} day postoperatively, the animals were sacrificed by cervical dislocation.

Spleen and thymus were removed, weighed individually and single cell suspension was prepared by teasing and pressing through the mesh in a Petri dish containing medium. Erythrocytes were removed from the spleen cell suspension using 0.83% of ammonium chloride solution. Spleen and thymus cell suspensions were washed thrice with medium and counts were adjusted. Thymocytes (migrating population) and lymphocytes of spleen (effector cells) which produce migration inhibition factor were mixed approximately 1:3 so as to provide a migrating cell density of $80x10^6$ cells. This was divided into two parts. To one part 1.5 x 10^6 SRBC/ml was added. The resulting suspensions were mixed well and drawn into the capillary tube. At one end it was heat sealed and centrifuged (2000 g) for 3 minutes at room temperature. Capillaries were cut just below the cell liquid inter phase and mounted in the sealed end chamber with the help of silicon grease.

Immediately the chamber is filled with medium taking great care to exclude air bubbles. The plates were incubated in an incubator at 37°C over night (15 to 18 hours). After incubation the migration area from the capillary was projected to a screen with the help of Camera Lucida and the area of migration was plotted in a paper. Using planimeter, the area of migration was calculated. The average of 4 to 6 capillaries was taken as the mean area of migration. The migration index was calculated as follows:

Migration index =

$$\frac{\text{Mean area of migration in the presence of antigen}}{\text{Mean area of migration in the absence of antigen}}$$

Foot Pad Thickness: Cutaneous Foot pad thickness (FPT) is delayed type hypersensitivity (DTH) reaction initiated when CD4+ memory T cells are activated by Langerhan cells and other antigen presenting cells to release lymphokines, which recruit the effector cytotoxic killing cells to the site of antigen administration[25]. The monocyte / macrophage and T cells are thought to serve as effectors cells in the FPT reaction. Activated effector cells mount an inflammatory response which results in the elimination of antigen and the extravasations of plasma accompanied by swelling at the site of challenge.

FPT was studied only in the immunized animals as this needs sensitization. The day of immunization of the rat using 20% SRBC was considered as day '0'. Four days later the left hind foot pad was challenged by an injection of 0.1ml of 20% SRBC subcutaneously suspended in normal saline. The right hind paw received 0.1 ml of normal saline alone. The increase in foot pad thickness was measured 24hrs after SRBC challenge by Vernier caliper.

Foot pad thickness ratio =

$$\frac{\text{Thickness of SRBC injected foot pad}}{\text{Thickness of Saline injected foot pad}} \times 100$$

Antibody Titre: This test was done to assess humoral immunity. The direct haemagglutination reaction is that commonly performed by mixing various dilutions of antiserum with a suspension of particulate material containing surface antigens[26]. The reaction between the antigen and antibody is manifested by agglutination / clumping or aggregation of particles in a well. Serial dilution of sera was performed in 0.15M phosphate buffer solution and aliquoted into "U" bottom microtiter plates.

1% SRBC suspended in phosphate buffer solution was dispensed into each well and mixed. The plates were incubated for 2 hours at 37°C and then observed visually for haemagglutination. The highest dilution of the test serum giving haemagglutination was taken as haemagglutination titer.

Cytokines Estimation: Serum cytokine levels of Interleukin-2 (IL-2), Interleukin-4(IL-4) and Interferon-γ(IFN-γ) was analyzed using standard rat ELISA immunoassay kit by Bender MedSystem, Austria. BMS 634 (IL-2), BMS 628 (IL-4), BMS and BMS 621 (IFN- γ).

Statistical Analysis: All the data from various groups were analyzed for the individual parameters by ANOVA followed by Tukey's multiple comparison. The significance was fixed at P<0.05.For understanding the lesion effect, the sham group was considered as strict control and was compared with controls. All the animals were healthy and no significant weight loss was observed in any of the group.

RESULTS: The histology of the cerebellum revealed the Fastigial nucleus lesion by loss of nissl bodies in the neuronal bodies when compared with its respective control animals. Animals placed with lesion in wrong place were discarded from the study. The data from different groups are shown in **Figure 1 and Table 1**.

Leucocyte Inhibition Test: The migration index of the bilateral lesioned immunized animals showed a marked increase (df 4, F 58) when compared to immunized control and immunized sham animals The respective sham-immunized animals showed no variation from control-immunized animals.

Footpad Thickness: Footpad thickness in bilateral lesioned immunized groups showed a significant decrease when compared with control, and sham immunized groups (df 4, F 19). The respective sham immunized group showed no significant variation from control immunized animals.

Humoral immunity:

Antibody Titre: Bilateral lesioned immunized animals showed a significant decrease in the circulating antibody titre (df 4, F 66), when compared with their immunized control animals and respective sham immunized animals. The respective sham immunized group remained similar to control immunized animals.

Serum cytokines:

Interferon γ: The level of IFN-γ in the serum bilateral lesioned immunized animals showed significant decrease (df 4, F 24) when compared to immunized control and respective sham immunized operated animals. The sham immunized groups were similar in their IFN γ levels when compared to control-immunized animals.

Interleukin-4: The level of IL-4 in the serum of bilateral lesioned immunized animals was significantly (df 4, F 23) increased when compared to control and respective sham operated immunized animals. The sham immunized group showed similar levels of IL-4 compared to control immunized animals.

Interleukin -2: The level of IL-2 in the serum of bilateral lesioned immunized animals is significantly decreased (df 2, F 67.5) when compared to immunized control and respective sham operated immunized animals. The sham operated immunized groups did not show any change when compared to the control immunized groups.

TABLE 1: FASTIGIAL NUCLEI LESION ON IMMUNE PARAMETERS IN WISTAR ALBINO RATS

	Group I	Group II	Group III
LMI	0.427 ± 0.024	0.423 ± 0.035	0.717 ± 0.052*@
FPT	27.51±1.35	26.43±2.14	18.36±0.71*@
Antibody titre	10.17±0.56	10.29±0.64	6.63±0.27*@
Interferon γ	366.6±15.59	374.0±14.9	313.0±16.92*@
Interleukin 4	48.5±2.16	46.5±2.94	54.66±2.16*@
Interleukin 2	453.83±2.89	448.16±19.34	341.00±16.34*@

Values are Mean ± SD. * indicates significant when compared with control immunized group (Group I); @ indicates significant when compared with Sham operated group (Group II); p<0.05 is considered significant.

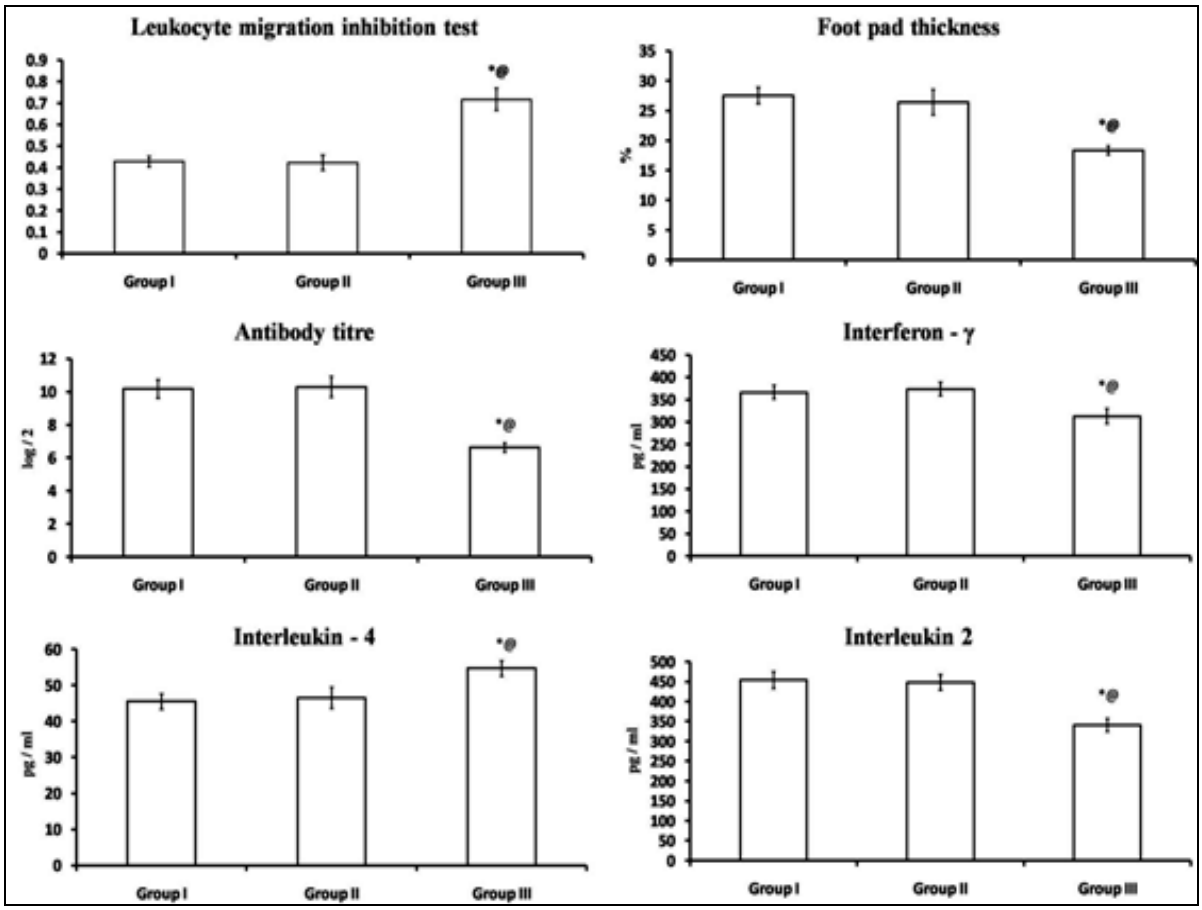

FIGURE 1: FASTIGIAL NUCLEI LESION ON IMMUNE PARAMETERS IN WISTAR ALBINO RATS

Values are Mean ± SD. * indicates significant when compared with control immunized group (Group I); @ indicates significant when compared with Sham operated group (Group II); p<0.05 is considered significant.

DISCUSSION AND CONCLUSION: From the data, it is clear that cerebellum have a role in immunomodulation. The sham animals are considered as a strict control to assess the lesion effect. Because in sham surgical procedure, the electrode pathway inevitably destroys certain brain regions above the area of interest which has also been reported to have the impact on the neuroimmunomodulation [22]. Neural modulation of immunity is supported by many experimental investigations [27, 28, 29].

The data from the present study also substantiates the presence of neural modulation of immunity. In this study, care has been taken to have consistent reproducible results and therefore electrolytic lesions were preferred. According to several histopathological findings, not all brain regions are equally injured following kainic acid administration. Moreover, several lines of evidence indicate that the neurochemical changes following kainic acid application, appears to be highly region specific [30, 31].

An increase in prostaglandin formation in rat brain following systemic application of kainic acid has also been reported [32]. Since these mediators may interfere with the immune parameters, in the present study kainic acid lesion was avoided.

The lesioned animals were allowed to recover post operatively for 10 days and only on the 10th day, the immunization (SRBC administration) was carried out in lesion and sham immunized groups. The control animals were immunized on 0 day and tested for all the parameters on the 5th day of immunization. The experimental procedures were performed on 15th day to assess the immunity status of the animals. It has been reported that in lesions produced in the caudate nucleus and also in hypothalamus of rats by passing direct anodal current through sterotaxically inserted electrodes, the apparent lesion size increases during the first postoperative day and then decreases progressively after the first postoperative week with contraction of the central cavity and disappearance of neuroglia cells [33].

Acquired immune responses are based on the proliferation of antigen-specific B and T cells, which also occurs when the surface receptors of these cells bind to antigen. B cells secrete the antigen-specific antibodies responsible for eliminating extracellular microorganisms. Hence, the cell mediated and humoral immunity is discussed together.

In this study, the bilateral lesioned immunized animals showed a significant increase in migration index with a decrease in antibody titer. In most biological situation, balance is achieved by the opposing actions of these two factors namely Migration stimulation factor (MStF) and Migration Inhibition Factor [34]. Further, Fox and Rajaraman [35], showed the release of Migration stimulation factor (MStF) from the suppressor cells and Migration Inhibition Factor (MIF) from the helper cells. Further, he also reported the existence of two different distinct membrane receptors for the reception of these factors.

During the cell-mediated immune response the sensitized T-lymphocytes, on being challenged with the antigen secrete a number of lymphokines including Leukocyte Migration Inhibition (LMI) factor [36]. These lymphokines attract scavenger cells to the site of reaction, which are then immobilized to promote an effective defense reaction. According to Talwar and Gupta [37], the sensitized T-lymphocytes, on being challenged with the antigen secrete a number of lymphokines including LMI factor.

Further, there is an inverse correlation existing between LMI and FPT. In this study, the balance between MIF and MStF is altered in the lesioned immunized animals as indicated by the increase in the migration index. The decrease in FPT with an increase in LMI also again reflects the inverse correlation between LMI and FPT. The enhanced migration is pointing towards the decrease in the activity of T helper cells. Such enhanced migration and altered cell population after the electrolytic lesion of dorsal hippocampal region was also reported [38]. Similar decrease in antibody titer and decrease in plaque forming B cells after ventral hippocampal lesion was also reported [29].

DTH reaction requires a specific antigenic substance which will release cytokines by activation with T-lymphocytes [39]. Normally, Th_1 immune response is characterized by secretion of pro-inflammatory cytokines (IL-2, IL-12, TNF-α, IFN-γ) that promote the cellular immune response. A Th_2 immune response is characterized by the secretion of cytokines (IL-4, IL-10, TGF-β1) that modulate the cellular immune response [40, 41]. IFN-γ preferentially inhibits the proliferation of Th2 but not Th1 cells, indicating that the presence of IFN-γ during an immune response will result in the preferential of Th1 cells[42]. This is well in agreement with our present study with a decrease of IL-2 and IFN-γ and altered cell mediated immune responses.

IL-4 lymphokine also has a variety of stimulatory and inhibitory actions on B and T cells[43,44,45]. The marked increase in the IL4 observed in bilateral immunized lesioned animals again supports the increase in Th2 cell activity. Further, this points out the imbalance occurred between Th1:Th2 cells. In addition, IL-4 can inhibit the production of TNF-α, IL-1 and IL-6 by macrophages[46]. The changes observed in the adaptive immune responses after bilateral fastigial nucleus lesion may be evoked by the imbalance of the cytokine pattern which links the immune and neuroendocrine system. IL-1, IL-6, TNFα, nerve growth factor, IFNγ, and in some cases IL-2 have been shown to stimulate the hypothalamic-pituitary-adrenocortical axis [47, 48].

Cytokines also influence neurotransmitter activity [49]. In summary, the lesion of the fastigial nucleus by electrolytic lesion causes an alteration in cell mediated as well as humoral immune responses with an imbalance in the Th1:Th2 cells and their cytokine pattern. Thus, the changes of lymphocyte functions induced by the FN lesions may be mediated by the cytokines and further exploration of the functional pathways mediating these changes need to be observed. These findings strongly suggest the cerebellar role in modulating adaptive immune responses.

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