Immune Effects of Intracerebral Infection with Mouse Hepatitis Virus[a]

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Previous studies with mouse hepatitis virus type 4 (MHV-4), a neurotropic strain of murine coronavirus, demonstrated that there is involution of the thymus within 3-5 days after intracerebral inoculation of susceptible strains of mice. This involution is in part due to the direct infection of lymphocytes, epithelial cells, and macrophages of the thymus by the virus.[1] The degree of involution following intracerebral inoculation is better appreciated when compared with the limited changes observed after even 1,000-fold more virus delivered into the peritoneal cavity. The present series of experiments was undertaken to investigate potential mechanisms by which this difference could be explained.

Mice of the susceptible CXJ-8 strain,[2] in groups of four, were inoculated intracerebrally, under Avertin anesthesia, with 100 plaque-forming units (PFU) of MHV-4 in a volume of 0.05 ml. Control CXJ-8 mice received an equal volume of medium without virus. Another group of CXJ-8 mice were inoculated intraperitoneally with 0.1 ml of either 10,000 PFU of the virus or control medium. A group of unmanipulated CXJ-8 mice of the same 6-8-week age group were also studied. Only males were used for these studies. Plasma was collected from all mice at the time of sacrifice, 5 days after infection, for determination of corticosterone levels by radioimmunoassay.

Data on the thymic and splenic weights in the different groups at 5 days after treatment are presented graphically in FIGURE 1. Following virus intracerebrally (V-IC), there is involution of the thymus and spleen. Mean thymic weight in the V-IC group was 0.007 g compared with 0.036 g for the unmanipulated mice (NT = not treated). Mean splenic weight was 0.059 g compared with 0.190 g when untreated. The mean thymic weight following intraperitoneal inoculation of virus (V-IP) was 0.029 g. After intracerebral inoculation of medium (M-IC), mean thymic weight was 0.021 g, and after intraperitoneal inoculation of medium (M-IP) it was 0.041 g. The mean splenic weight following intraperitoneal injection of virus (V-IP) was 0.218 g, whereas following intracerebral injection of medium (M-IC) it was 0.132 g. After the intraperitoneal injection of medium (M-IP), the mean splenic weight was 0.161 g.

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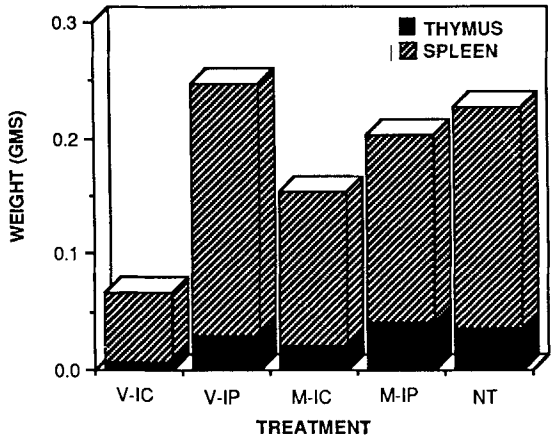

FIGURE 1. The mean weight of thymus (*solid*) and spleen (*hatched*) from groups of four mice each that were injected with virus intracerebrally (V-IC) or intraperitoneally (V-IP), injected with medium intracerebrally (M-IC) or intraperitoneally (M-IP), or not treated (NT).

Although the thymus did show some involutional changes at 5 days after intraperitoneal inoculation with MHV-4, the spleen does not involute. In fact, it appeared enlarged compared with spleens from unmanipulated or medium-inoculated mice. The thymus and spleen did show some effect from the intracerebral injection of medium, and therefore a response to stress by measuring corticosterone levels in the plasma of these mice was performed.

The corticosterone levels in three different groups of the mice are presented in FIGURE 2. These results demonstrate that the plasma corticosterone level is substantially higher in mice that had received virus intracerebrally (V-IC). There is also elevation after injection of the brain with medium alone, although it is not statistically

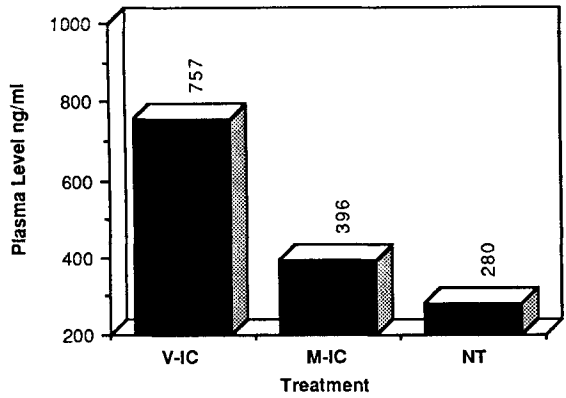

FIGURE 2. The mean plasma levels of groups of four mice each that were injected with virus intracerebrally (V-IC), medium intracerebrally (M-IC), or not treated (NT). The V-IC corticosterone level is significantly elevated over M-IC or NT at $p < 0.01$.

significant compared with the increase in unmanipulated mice. Therefore, intracerebral infection with MHV-4 appears to lead to involution of the lymphoid compartment both by direct infection, as previously demonstrated, and by a component due to a dramatic increase in corticosterone levels. The mechanism of this increase is currently under analysis.

This study demonstrates that there is involution of the central components of the immune system (thymus and spleen) following intracerebral, but not intraperitoneal (systemic), infection with MHV-4. Although this virus does infect the immune cells of the thymus and spleen directly, the infection alone does not account for the degree of involution observed. In mice that were intracerebrally infected with MHV-4, but not in controls receiving an intracerebral injection of medium alone, there was a significant elevation in plasma corticosterone levels. The combination of MHV-4 infection of immune cells with the hormonal milieu induced by intracerebral but not systemic virus infection suggests that virus replication in the brain can have a dramatic impact on the integrity of the immune system. This model will therefore be useful to investigate potential mechanisms by which virus replication in the brain can influence the development of acquired immunodeficiency syndrome.

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