Abstract: The pathogenesis of influenza encephalopathy or encephalitis is poorly understood. This review summarizes our recent studies of the roles played by inflammatory cytokines, inducible nitric oxide synthase (iNOS), adhesion molecules and mini-plasmin in influenza encephalitis. After the intranasal infection of newborn mice with the non-neurotropic strain of influenza A virus (IAV) Aichi/2/68/H3N2, encephalitis and severe brain edema were observed within 3-5 days. IAV-RNA and abnormalities in the blood-brain barrier permeability were detected in association with an increase in the mRNA expressions of endothelin-1, iNOS, and tumor necrosis factor-α. Furthermore, the accumulation in the brain capillaries of mini-plasmin, which proteolytically induces the viral envelope fusion activity and allows the virus to enter the cells, changes the brain from non-susceptible to susceptible to non-neurotropic IAV multiplication. The accumulation of mini-plasmin was markedly greater in newborn mice with an impaired mitochondrial fatty acid metabolism. These inflammatory mediators and the accumulation of mini-plasmin in the brain may play an important role in the onset and progression of IAV encephalitis. J. Med. Invest. 50: 1-8, 2003

Keywords: influenza encephalitis; cytokines; nitric oxide synthase; mini-plasmin
Orthomyxoviridae

in vivo
D. Yao et al.  **Pathogenesis of influenza encephalitis**

The image contains a chart showing the expression levels of various genes and proteins after infection. The chart includes lines representing different treatment groups: Control, IAV, and IAV+Delt. The y-axis indicates the concentration in pg/mg. The x-axis represents days after infection, with Day 3 and Day 5 shown.

The chart illustrates the changes in gene expression and protein levels over time for different treatments. The y-axis is labeled with concentrations ranging from 0 to 120 pg/mg. The chart includes a legend that distinguishes between the Control, IAV, and IAV+Delt groups. The specific gene and protein expressions are not detailed in the chart, but the graph allows for a comparison of how each treatment group responds over time.
A. iNOS Expression in Brain

<table>
<thead>
<tr>
<th></th>
<th>GAPDH</th>
<th>iNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>104bp</td>
<td>208bp</td>
</tr>
</tbody>
</table>

B. NOS Activity in Brain

C. Role of NO in Host-defense
Pathogenesis of influenza encephalitis

A. ET-1(1-21) in lungs

B. ET-1(1-31) in lungs

C. ET-1(1-21) in brains

D. ET-1(1-31) in brains

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