2010

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Publication Details
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Keywords
model, schizophrenia, neuregulin, immune, 1, factors, knockout, mouse

Disciplines
Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

This conference paper is available at Research Online: http://ro.uow.edu.au/hbspapers/643
Immune factors in the Neuregulin-1 knockout mouse model of schizophrenia

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BACKGROUND

Schizophrenia

- Neurodevelopmental disorder affecting 1% of the population
- Complex gene x environment interaction
- Neuregulin-1 (Nrg1) gene mutation highly associated in genetic linkage studies
- Neuregulin-1 heterozygous knockout (Nrg1 KO) mice are an established model of schizophrenia

Schizophrenia and Cytokines

- Cytokines
  - modulate peripheral immune response
  - can penetrate the blood-brain-barrier (BBB)
  - regulate complex behaviours in healthy brain
- Altered cytokine levels in schizophrenia patients in both blood and CSF
- Cytokine levels correlated with symptom severity
- Epidemiological link between schizophrenia and lower incidence of autoimmune and inflammatory diseases

AIMS

- To determine the basal Nrg1 KO mouse peripheral cytokine profile as observed in schizophrenia patients
- To determine if the peripheral cytokine profile in Nrg1 KO animals is altered following a chronic immune stimulus compared to wild type litter mates

METHODS

Nrg1 KO mouse with a heterozygous knockout of the Nrg1 transmembrane protein domain on C57/Bl6 background

1. Spleen samples obtained:
   a) Adult (PNF161) (n=6-15)
2. Plasma samples obtained:
   a) Late adolescence/early adulthood (PNF356) (n=3)
3. Immune challenge:
   a) B16F0 melanoma cell line injected subcutaneously (3x10^6 cells per mouse) (Nrg1 KO and WT littermates; n=8)
   b) Control - PBS injections (Nrg1 KO and WT littermates; n=8)
   c) Late adolescence/early adulthood (PNF356)
   d) Sacrifice after 10 days (PNF665)

- Spleen cells analyzed using BD Biosciences fluorescent conjugated antibodies against T and B cell surface markers on LSRII flow cytometer
- Plasma samples analyzed with multiple flow cytometry bead array to determine levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-6, KC (murine IL-6), IL-10 and IL-13, IP-10

RESULTS

- Basal
  - Plasma Cytokine Levels in Nrg1 KO mice compared to WT litter mates
  - Under basal conditions, with no additional immune stimuli, Nrg1 KO mice showed a significant increase in cytokine levels compared to WT KO mice (N=8, P<0.05). Cytokine levels in Nrg1 KO mice were not detected in wild type litter mates (n=8) (P<0.05).

- Immune Challenge
  - A tendency towards increased TNF-α, IL-2 and KC (murine IL-6) indicated a potential pro-inflammatory state in Nrg1 KO animals in the absence of an immune stimulus
  - A trend towards decreased IL-10 and IFN-γ in the presence of possible increased TNF-α suggested dysfunction of cytokine regulation
  - This was consistent with data of schizophrenia patients.

DISCUSSION

- IL-6 is produced in the periphery as well as the brain
- IL-6 crosses the blood-brain-barrier from blood to brain via saturable transport mechanisms
- Neurons are responsive to IL-6 signalling - role in neurite outgrowth, differentiation and survival of neurons as well as cognition
- Membrane bound IL-6 receptor has been shown on adult murine and human neurons
- Soluble IL-6 receptor is produced endogenously in brain
- Signal transduction component (gp130) widely distributed in the brain

Relevance to Schizophrenia:

- Patients have consistently demonstrated increased plasma levels of IL-6
- Higher plasma levels of IL-6 have been correlated with worse symptomology
- Anti-psychotics reduce plasma IL-6 levels
- First genetic neurodevelopmental mouse model of schizophrenia that mimics the neuro-immunology of the illness.

FUTURE DIRECTIONS

- Acute immune stimulus (LPS)
- Cytokine Microdialysis:
  - measure central IL-6 changes
  - following LPS treatment in Nrg1KO mice
\[ \text{Baseline} \]

References:


Measuring IL-6 in the brain using microdialysis

Plasma/CSF Correlation by ELISA

Spleen/Plasma Correlation by ELISA

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