Influence of Maternal Glutamatergic Stress Response on Dyadic Behavior and the Neurobiology of the Offspring

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Early life stress may lead to a hyperglutamatergic state and neuronal compromise. MRSI of variable foraging demand (VFD) offspring exhibited increased Glx (a glutamate/glutamine surrogate) in the anterior cingulate cortex versus controls. High Glx signal correlated inversely with NAA concentrations, an indicator of neuronal integrity. We directly examined maternal CSF glutamate and glutamine and CRF in response to VFD stress.
Glutamate and CRF

• Recent studies using NMDA antagonist, such as ketamine, or antiglutamatergics, such as riluzole, have served to emphasize the important role of glutamate in mood and anxiety disorders.

• Previous biological models of anxiety and mood disorders have outlined a critical role of central CRF system overactivity.

• There is evidence of interaction of these systems in the brain, with glutamate, an excitatory amino acid, providing a major excitatory input stimulating release of CRF.

• Microinjection of glutamate into the rat amygdala results in increased plasma corticosterone, suggesting glutamatergic facilitation of CRF release from the median eminence (Gabr et al, 1995)
Glutamate & other Systems

- Medial prefrontal cortex (mPFC) glutamatergic projections to the dorsal raphe exist. Stimulation of the mPFC causes release of serotonin in the dorsal raphe.
- The dorsal raphe extracellular serotonin by acting on 5HT\textsubscript{1A} somatodendritic autoreceptors inhibits serotonergic neuronal firing which decreases serotonin release in the projection areas.
- Serotonin is associated with dopamine metabolism via modulation of VTA and norepinephrine metabolism via modulation of the locus ceruleus.
- Glucagon-like Peptide (pGLP-1) is an insulin analogue, an incretin, which reduces body mass, is neuroprotective and stimulates neurogenesis. It is elevated following VFD-rearing.
- We explored the relationship of offspring GLP-1 in relation to maternal CSF glutamate change to VFD and prediction of future neurogenesis.
Early Life Stress, Dorsal Raphe 5-HT “Flooding” and Shutdown of Serotonin Neurotransmission

Model of DR activity:

NK1 receptors activates a population of glutamatergic neurons in the DR that subsequently drives a population of 5-HT neurons, triggering inhibition of neurons throughout the nucleus via 5-HT1a receptor activation – Valentino et al, J Neurosci, 2003.

Third replication of high CSF 5-HIAA in VFD

Mathew et al, 2002 Stress

CSF 5-HIAA IN VFD-REARED BONNETS

* p < .02

Average Age ~ 24 months
Cross-sectional Analysis of VFD-exposed versus non-exposed Dyads

- 18 mother-infant dyads were examined, nine of whom had been exposed to the VFD paradigm (5 males) whereas as the remaining subjects served as unstressed controls (3 males).
- No differences between groups were noted for either CSF glutamate or CSF glutamine concentrations.
- There were no group differences for maternal age, body mass, sex distribution or dominance status and therefore these were not used as covariates.
Baseline Differences

Table 1. Comparison of Maternal Independent and Dependent Variables in VFD-exposed versus unstressed dyads.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-VFD Mean (N=9)</th>
<th>Std. Dev.</th>
<th>VFD Mean (N=9)</th>
<th>Std. Dev.</th>
<th>t-value</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF glutamate (ng/ml)</td>
<td>1.21</td>
<td>0.86</td>
<td>1.20</td>
<td>0.27</td>
<td>0.04</td>
<td>16</td>
<td>0.97</td>
</tr>
<tr>
<td>CSF glutamine (ng/ml)</td>
<td>542.53</td>
<td>50.90</td>
<td>527.19</td>
<td>44.89</td>
<td>0.68</td>
<td>16</td>
<td>0.51</td>
</tr>
<tr>
<td>Mother Weight (kg)</td>
<td>4.90</td>
<td>0.95</td>
<td>5.16</td>
<td>1.14</td>
<td>-0.51</td>
<td>16</td>
<td>0.62</td>
</tr>
<tr>
<td>Mother Age (days)</td>
<td>3435.11</td>
<td>1371.15</td>
<td>2624.22</td>
<td>752.63</td>
<td>1.56</td>
<td>16</td>
<td>0.14</td>
</tr>
<tr>
<td>Maternal Rank 1 = dominant</td>
<td>3.67</td>
<td>2.00</td>
<td>3.89</td>
<td>2.37</td>
<td>-0.22</td>
<td>16</td>
<td>0.83</td>
</tr>
</tbody>
</table>
**Prediction of Maternal CSF CRF**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>df</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFD Effect</td>
<td>1</td>
<td>10.92</td>
<td>.005</td>
</tr>
<tr>
<td>Glutamate</td>
<td>1</td>
<td>15.64</td>
<td>.001</td>
</tr>
<tr>
<td>VFD Effect * glutamate</td>
<td>1</td>
<td>16.35</td>
<td>.001</td>
</tr>
<tr>
<td>Error</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current effect: $F(1, 14) = 10.91, p = .005$

(Computed for covariates at their means)

Vertical bars denote 0.95 confidence intervals

Covariate means:
- glutamate: 1.20 ng/ml

Maternal CSF CRF (ng/ml)
Maternal CSF Glutamate is positively associated with CSF CRF in VFD-exposed vs. Non-exposed Mothers (VFD Exposure x Glutamate Interaction)
Longitudinal Analysis

• All subjects were VFD exposed mothers, VFD offspring or interacting VFD-exposed mothers and infants.

• Comparison controls are lacking in this within-subject design

• N of subjects is not consistent but follow-up is across the Lifecycle

• Appropriate precautions in interpretation are necessitated.
Maternal CSF CRF Increases on VFD Exposure is associated with Glutamine Depletion

$\text{r} = -0.64, \text{N} = 13; \text{p} = 0.013$
Maternal CSF Glutamate Increase Associated with Increased Dyadic Distance

$r = 0.70, N = 13; p = 0.007$
Maternal CSF Glutamate increase predicts high CSF 5-HIAA in the offspring

$r = 0.77, p = 0.024$
Maternal CSF Glutamate Increases predicts Offspring CSF HVA Increases

$r = 0.77, p = 0.02$
Maternal Glutamate Increases to VFD Exposure Predicts increased Offspring CSF MHPG

\[ r = 0.93, \text{N= 8, p = 0.0007} \]
An Inverse Relationship is Noted between CSF-5-HIAA and CSF HVA and Hippocampal Volume supporting the Hypothesis that high peri-raphe 5-HT is associated with Reduced Serotonin Neurotransmission
Maternal CSF Glutamate Change to VFD Exposure predicts Decreased pGLP-1

$r = -0.70, p = 0.035$
“High” Adult Neurogenesis is predicted by High Adolescent pGLP-1

![Graph showing the relationship between Adolescent plasma GLP-1 (umol/l) and Adult Dentate Gyrus Doublecortin Staining. The graph indicates a significant difference with F(1,12) = 11.64, p = 0.005. The mean values are presented as bars with error bars indicating ±1.96*SD for both "high" and "low" groups.]
Conclusions

- Maternal CSF Glutamate /Glutamine response in response to VFD exposure is associated with alterations in stress-related behavior and physiology of the mother, the mother-infant dyad, and in the offspring. Its effect is thus trans-generational.

In the cross-sectional comparison, VFD exposure was associated with increased maternal CSF CRF concentrations and the effect is positively associated with glutamate relative increase in response to VFD exposure.

- Within-VFD exposure mothers, glutamine depletion was associated with increased maternal CSF CRF concentrations.

- A relative increase in maternal glutamate in response to VFD exposure predicts high CSF 5-HIAA, CSF HVA and CSF MHPG in juvenile offspring.

- High monoamine metabolites in VFD inversely predicts young adult right hippocampal volume.
Conclusion Continued

• Relative increases in maternal glutamate in response to VFD exposure inversely predicts adolescent GLP-1.
• Low GLP-1 is associated with reduced mature adult Neurogenesis.
• Relative increases in maternal glutamate in response to VFD exposure is associated with an absence of increased dyadic proximity crossing from the final HFD to LFD phase, a potential opportunity for mothers to rebond with their infants post-HFD.
• By contrast, relative increases in maternal glutamate in response to VFD is associated with a decrease in maternal-infant proximity, suggesting failure of compensatory attachment mechanisms.