EFFECTS OF EARLY LIFE EXPERIENCES ON BRAIN STRUCTURE AND FUNCTION: NEUROGENESIS & DECISION MAKING

M. Loi1; L. de Visser1; S. Koricka1; M.J. Kas1; P.J. Lucassen2; M. Joels1
1Department of Neuroscience and Pharmacology, Rudolf Magnus Institute, University Medical Center Utrecht, The Netherlands;
2Center for Neuroscience, Swammerdam Institute of Life Sciences, University of Amsterdam, The Netherlands
Contact info: m.loi@umcutrecht.nl

Background

- During early life, brain structures involved in cognitive processing are still developing.
- Exposure to stress during perinatal life can enhance stress responsiveness and lead to increased vulnerability for psychiatric disorders later in life.
- In animal models of early life stress, we can study the biological basis of stress-induced structural and behavioral alterations that may contribute to an enhanced risk for psychopathologies later in life.
- Maternal deprivation (MD) is a well-established animal model for early life stress. MD leads to increased levels of corticosterone and disrupts the stress hyporesponsive period.
- Early life stress affects both neurogenesis and hippocampal plasticity.
- This is thought to be mediated by glucocorticoid receptors, which can be blocked by mifepristone (see previous results below).

Aim

- Investigate the effects of a brief period of MD on brain structure and function during adolescence and adulthood.

Methods

- We used Wistar rats.
- Animals were exposed to 24 h maternal deprivation at postnatal day (PND) 3.
- From PND21 onwards, pups were group-housed in pairs by gender and treatment group.
- From PND 26-28 half of the maternally deprived and control groups received either mifepristone or vehicle, administered through an oral syringe directly into the stomach.

Experiment 1

At PND29 the females were sacrificed and perfused. The number of young, differentiating neurons were identified with an antibody against the microtubule-associated protein doublecortin (DCX; ongoing experiments, not shown).

Immunohistochemistry for Ki-67 was used to assess cell proliferation.

Experiment 2

To assess the functional effects of maternal deprivation, 12 week old male rats performed the Rodent Iowa Gambling Task (r-IGT).

To study the neural substrates underlying decision-making, we measured expression of the immediate early gene c-fos in the medial prefrontal cortex directly after the task.

Results

Table: BODY WEIGHT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Female/no-MD</th>
<th>Male/no-MD</th>
<th>Female/MD</th>
<th>Male/MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PND 26-28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>70 ± 3</td>
<td>75 ± 4</td>
<td>65 ± 2</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Male</td>
<td>60 ± 3</td>
<td>65 ± 4</td>
<td>55 ± 2</td>
<td>50 ± 2</td>
</tr>
</tbody>
</table>

Note: *p<0.05 as revealed by Bonferroni testing.

Figure 1: Averaged body weight in the maternally deprived groups (females and males) is reduced. Error bars indicate SEM.

Table: CELL PROLIFERATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Female/no-MD</th>
<th>Male/no-MD</th>
<th>Female/MD</th>
<th>Male/MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PND 26-28</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1000 ± 100</td>
<td>1100 ± 110</td>
<td>900 ± 90</td>
<td>800 ± 80</td>
</tr>
<tr>
<td>Male</td>
<td>800 ± 80</td>
<td>900 ± 90</td>
<td>700 ± 70</td>
<td>600 ± 60</td>
</tr>
</tbody>
</table>

Figure 2: Mean number (+ SEM) of Ki-67 positive cells in the hippocampal hilus per 10 sections. We observed no differences between the groups.

Figure 3: MD male rats showed a lower fraction of visits to the advantageous arm, compared to control animals. This was prevented by mifepristone treatment at PND 26-28.

Figure 4: MD rats had a tendency (ANOVA=0.08) to make visit empty arms more often than controls. Mifepristone treatment at PND 26-28 normalized this.

Figure 5: Levels of c-fos expression (number of positive cells per mm²) in the dorsomedial striatum. The number of c-fos+ cells was increased in MD compared to controls rats. This was reversed by mifepristone treatment at PND 26-28.

Conclusions

- Male and female maternally deprived rats had lower body weights at PND26 compared to the non-deprived groups.
- At PND29, maternally deprived female rats showed a trend towards a lower number of Ki-67 positive cells in the hippocampal hilus, compared to controls. Treatment with mifepristone resulted in a comparable number of Ki+ cells as in controls.
- Male MD rats had a tendency to avoid empty arms and had a significantly lower fraction of visits to the advantageous arm compared to non-deprived rats, when tested in a rIGT at 3 months of age. This deficit was fully reversed by mifepristone treatment at PND 26-28.

These preliminary data support that treatment with mifepristone in adolescence can lastingly reverse adverse effects of early life stress.