Wistarr-Kyoto rats as a model of treatment resistant depression

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Introduction
Major Depressive Disorder (MDD), is a common, chronic and serious recurrent mental illness. Existing treatments improve the quality of life for the majority of patients with MDD. However there are a significant number of patients for whom treatment is ineffective and are considered as having treatment-resistant depression (TRD). Clearly this population represents an area of unmet clinical need.

The Wistar-Kyoto (WKY) rat displays a number of depression-like behaviors that are resistant to treatment with existing MDD treatments, thereby providing a potential preclinical model of TRD (see Ivarsson et al., 2005, EJP 522:63-71).

Aims
In this study we investigated the differences in sleep architecture and EEG power spectra between WKY rats and Sprague-Dawley (SD) rats (n =9), using radio-telemetry electroencephalography (EEG). EEG sleep-wake represents an excellent translational model of neuropharmacological activity due to the high conservation of both the sleep-wake and EEG architecture across species.

Methods
EEG signals were recorded from electrodes over the frontal-parietal cortex using intracranial electrodes, with the positive electrode at 2mm left of the mid-line, 2mm anterior of Bregma and the negative electrode 2mm left of the mid-line, 2mm anterior of lambda. Nuchal EMG was recorded to enable sleep stage scoring. Signals were recorded from the onset of the light period for 24hrs. The animals were dosed vehicle (saline i.p.) 30min following the onset of the light period, and the light period for 24hrs

Power spectra bands were calculated from the raw EEG signal using Fast Fourier Transformation and the following frequency banding:

<table>
<thead>
<tr>
<th>Spectral Band</th>
<th>Frequency Range (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td>0.25 to 4</td>
</tr>
<tr>
<td>Theta</td>
<td>4 to 8</td>
</tr>
<tr>
<td>Alpha</td>
<td>8 to 13</td>
</tr>
<tr>
<td>Beta</td>
<td>13 to 40</td>
</tr>
<tr>
<td>Gamma</td>
<td>40 to 80</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.

Results

Figure 1: Effect of strain on Hypnogram

Figure 2: Effect of strain on Periodogram

Conclusion
As previously described WKY rats have a disrupted PS sleep pattern compared with an outbred strain. We demonstrated clear changes in PS in the WKY rat compared with the Sprague-Dawley rat. Not only was the amount of PS increased in the WKY rats, but latency to the first bout of PS and fragmentation of PS were also increased in the WKY rats. These effects were most pronounced during the dark (active) phase of the light cycle.

These data suggest that the assessment of PS sleep in WKY rats may provide a novel signature of TRD that is translatable to the clinic. Further work is needed to fully validate the model, using a range of agents effective in MDD.

References

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