Cortical gamma oscillations: mechanistic insights from *in vitro* studies

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Introduction

The human brain is known to generate electrical activity (oscillations) of various sizes in different conditions by activating different subunits of the N-methyl- D- aspartate (NMDA) receptor. Neuronal oscillations are described as the rhythmic fluctuations of the firing rate of nerves in the brain. In particular, gamma (γ) frequency oscillations have been identified in numerous brain areas *in vivo*. However, there is a need to understand the mechanisms of this activity *in vitro* in the cortical regions of the brain.

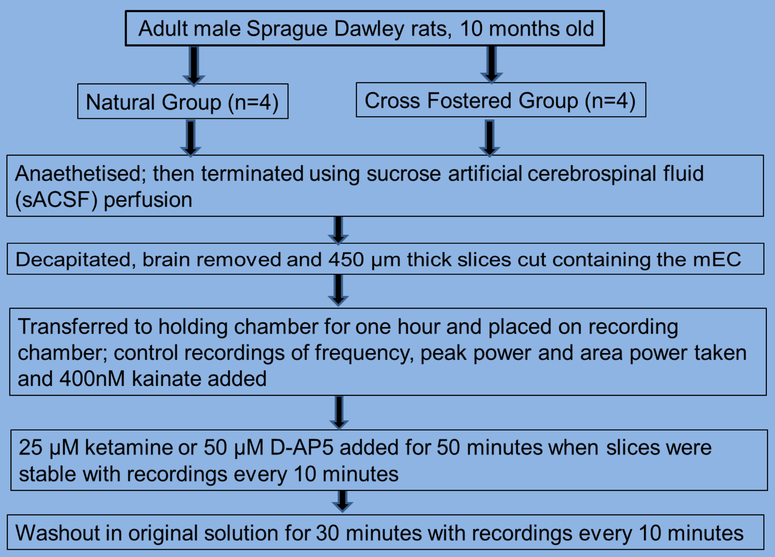
Previous studies have shown a decrease in the level of protein expression and mRNA of the NMDA receptor (NMDAR) subunits NR1 and NR2B in rats and mice on increasing age compared to their younger counterparts.

We were able to achieve some insight into gamma range oscillations by undertaking a pharmacological study using two groups of aged rats (one group who were raised by their natural mother from birth and the other group who were raised by a foster mother) in order to compare any differences in oscillations (and possibly NMDAR subunits) generated in the medial entorhinal cortex (mEC) by these two groups and their subsequent response on exposure to the drugs tested.

Aims

- To verify how subunits of the NMDAR, and hence oscillation generation and maintenance in the mEC, vary between the two groups of aged experimental animals (natural and cross fostered).

Methods



Results

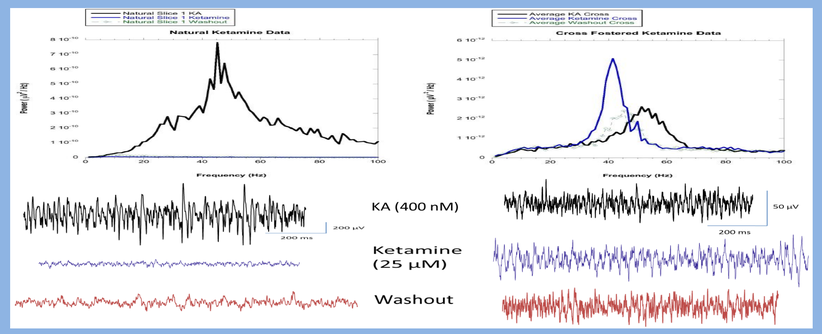


Figure 1: Comparison of the Effect of Ketamine on Gamma Oscillations of Natural and Cross Fostered Rats. Pooled power spectra graphs of oscillation power vs. frequency (above) and raw data traces (below) for each pharmacological treatment. Results representative of n=2 cross fostered rat brain slices and n=1 natural rat brain slice.

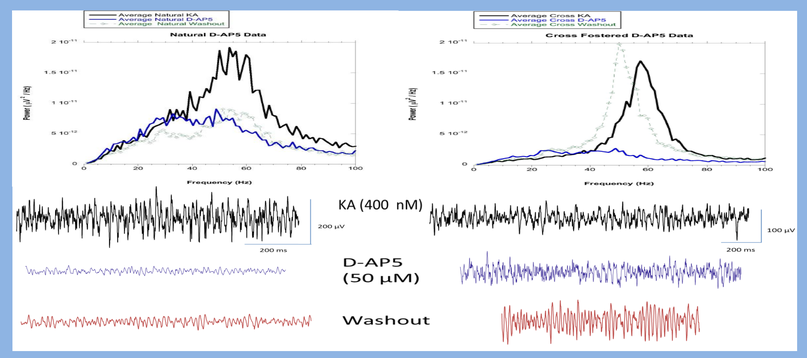


Figure 2: Comparison of the Effect of D-AP5 on Gamma Oscillations of Natural and Cross Fostered Rats. Pooled power spectra graphs of oscillation power vs. frequency (above) and raw data traces (below) for each pharmacological treatment. Results representative of n=2 cross fostered rat brain slices and n=2 natural rat brain slices.

In Figure 1, the addition of ketamine is seen to have contrasting effects between natural and cross fostered rat oscillations, with ketamine abolishing the oscillation with no significant recovery on washout compared to a shift increase in power but a similar decrease in frequency which returns to previous levels on washout.

For Figure 2, D-AP5 decreases both frequency and peak power of both sets of oscillations. However, there is a steeper return to the original oscillation parameter values upon washout for the cross fostered rat slices whereas the natural rat slices produce washout oscillations with no significant difference to those elicited after the drug application.

Interestingly, in both treatments, the natural rat slices produced larger oscillations and hence are evidenced to be more sensitive to the drugs applied to them compared to their cross fostered counterparts, who generally responded more robustly to the drug applications.

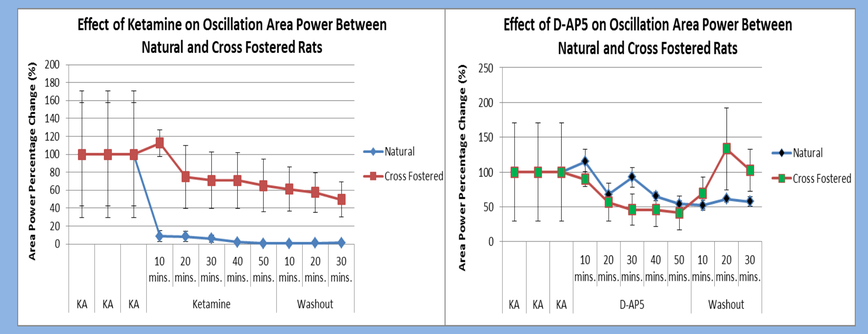


Figure 3: Time Series Comparison of the Effect of Ketamine and D-AP5 on Gamma Oscillation Area Power of Natural and Cross Fostered Rats. Results representative of n=2 cross fostered rat brain slices and n=1 natural rat brain slice for ketamine and n=2 cross fostered rat brain slices and n=2 natural rat brain slices for D-AP5.

Similar effects as of those for frequency and peak power are shown for area power of both groups of oscillations for both ketamine and D-AP5.

The major limitation of this project was the low number of rat brain slices which became sufficiently stable to be able to perform experiments on them. As a result of this, no statistical analysis was conducted on the results to determine significance of the data.

Nevertheless, these preliminary results seem to suggest that not only is there a deficit in NR1 and NR2B NMDAR subunits in both aged rat groups, but also an additional difference in NMDAR composition and therefore sensitivity to drug treatments, which in turn influences the relative ease of generation and stability of gamma oscillations.

Conclusions

- The results from this project initially indicate that there is perhaps an added difference in NMDAR subunit composition other than those stated previously between aged natural and cross fostered rats which leads to the observed variety between responses to the drug treatments used in this project.
- However, due to the low numbers of viable rat brain slices from the experimental animals, further work will need to be carried out in this area.

References

- Clayton DA and Browning MD (2001) 'Deficits in the expression of the NR2B subunit in the hippocampus of aged Fisher 344 rats' *Neurobiology of Aging* **22**: 165-168
- Liu P, Smith PF and Darlington CL (2008) **'**Glutamate Receptor Subunits Expression in Memory-Associated Brain Structures: Regional Variations and Effects of Aging**'** *Synapse* **62**:834–841

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