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Research Report

Investigation into the effect of the general anaesthetic etomidate on local neuronal synchrony in the mouse neocortical slice

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ABSTRACT

How general anaesthetic drugs cause unconsciousness is a topic of ongoing clinical and scientific interest. It is becoming increasingly apparent that they disrupt cortical information processing, but the effects appear to depend on the spatial scale under investigation. In this study we investigated whether the intravenous anaesthetic etomidate synchronises neuronal activity on a sub-millimetre scale in mouse neocortical slices. In slices generating no-magnesium seizure-like event (SLE) field activity, we analysed the morphology of field potential activity recorded with 50 μm extracellular electrodes. The analysis was based on the understanding that the amplitude and sheerness of field potential oscillations correlates with the synchrony of the underlying neural activity. When recorded from the region of the slice initiating SLE activity, etomidate consistently increased both population event amplitude (median(range) 85(24–350) to 101(30–427) μV) and slope 16.6(1.5–106.2) to 20.2(1.7–111.1) μV/ms ($p=0.016$ and $p=0.0013$, respectively). The results are consistent with an increase in neuronal synchrony within the receptive field of the recording electrode, estimated to be a circle diameter of 300 μm. In conclusion, the neocortical slice preparation supports *in vivo* data showing that general anaesthetics increase neuronal synchrony on a local scale and provides an ideal model for investigating underlying mechanisms.

1. Introduction

The biological basis of consciousness remains one of the most important unsolved mysteries in science. The practice of anaesthesia, which involves the controlled switching on and off of consciousness, provides a unique, accessible and perhaps under-utilised research tool for exploring this most complex of brain functions. Increasingly, anaesthetic disruption to cortical information processing is being recognised as an important mechanism by which these drugs ablate consciousness. Interestingly, the effects depend on the spatial scale under observation. Thus, 'long-range' integration of

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information between widely separated cortical regions is disrupted (Ferrarelli et al., 2010; Mhuircheartaigh et al., 2010; Ku et al., 2011; Schrouff et al., 2011); while 'local' connectivity appears to be enhanced (Li et al., 2013). The former implies a loss of information integration due to an interruption to functional connectivity; and the latter a reduction in information capacity through enhanced neuronal synchronisation. Both are potential unifying mechanisms to explain anaesthesia-induced unconsciousness (Alkire et al., 2008).

One of the difficulties with investigating spatial characteristics across species of different size is the interpretation of equivalence of scale. Thus, 'long-range' and 'local' in a sheep brain will be on a different scale to that in a mouse. To circumvent this issue, we have been investigating the effect of anaesthetics on long- and short-range spatial dynamics of 'no-magnesium' seizure-like event (SLE) field activity in mouse neocortical slices. In this model, removal of magnesium from the artificial cerebrospinal fluid (aCSF) unblocks N-methyl-D-aspartate (NMDA) receptors. This activates the tissue and precipitates generation of SLE activity (Tsau et al., 1998)—recordable as population field potential activity using extracellular electrodes (Voss et al., 2012). The activity characteristically initiates from two or three confined loci and propagates widely throughout the slice (Tsau et al., 1998; Voss et al., 2012).

Previously we have shown that the general anaesthetic etomidate 'decouples' widely separated cortical regions by interrupting the propagation of SLE activity across the slice (Voss et al., 2012). The question that naturally follows is whether this break-down in long-range connectivity in the slice is associated with increased connectivity and synchronisation on a local scale. To answer this we have used the same mouse neocortical slice model to investigate the effect of etomidate on field potential dynamics on a sub-millimetre spatial scale—using the receptive fields of single electrodes. The results show that etomidate synchronises neuronal activity at the SLE initiation focus, confirming that this anaesthetic differentially affects long- and short-range cortical dynamics.

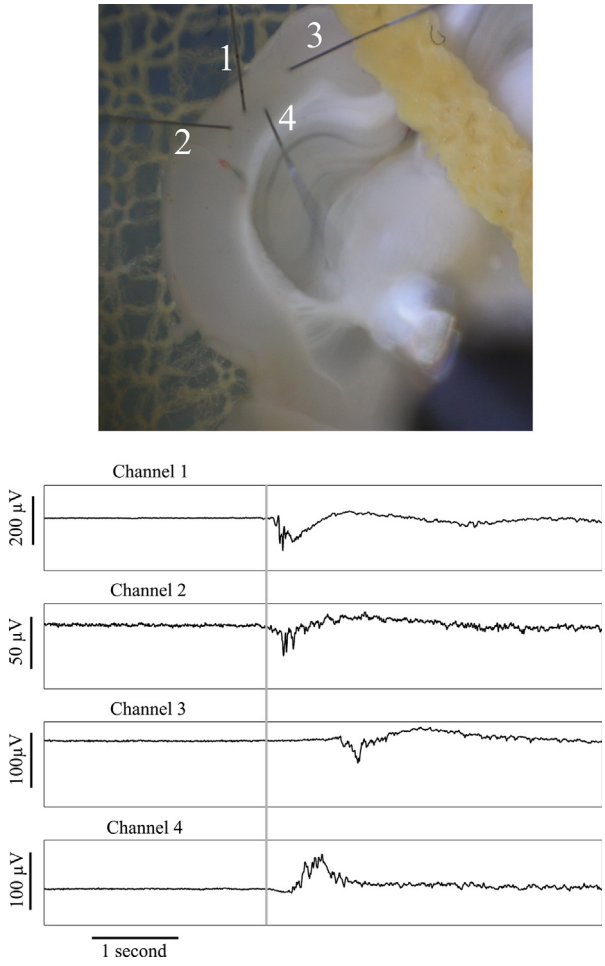

Fig. 1 – Photograph (top) showing the electrode locations from one slice and the corresponding recorded SLE activity (bottom). The vertical line in the bottom graph shows that the SLE source was located very close to electrodes 1 and 2, spreading to electrode 4 and subsequently, electrode 3. In this example, the source and distant locations were defined as channels 2 and 3, respectively.

2. Results

2.1. *SLE activity*

SLE activity was reliably generated in all slices by removing magnesium from the aCSF. The pattern of activity is illustrated in Figs. 1 and 2. Each event was characterised by a sharp deflection in the field potential recording, followed on occasion by an 8–10 Hz oscillation up to 3 s in length. Events were separated by quiescent periods of variable length of approximately 10–60 s.

2.2. *Source localisation*

Etomidate perfusion reliably effected a reversible reduction in SLE frequency at both source and distant recording locations (Table 1), reflecting the anticipated drug-induced reduction in tissue excitability. Importantly, an increase in SLE amplitude was seen at the source electrode in all slices tested (median (range) 85(24–350) µV before anaesthetic compared to 101(30–427) µV during anaesthetic, $p=0.016$ Wilcoxon test). This is illustrated in Fig. 3a. The amplitude effect was not seen at the electrode distant to the activity source ($p=0.81$ Wilcoxon test) (Table 1), indicating that neuronal activity was synchronising at the locus of SLE generation.

The mean(SD) numbers of SLEs that were averaged for each comparison were 11(8) during baseline and 36(16) during etomidate delivery for source recordings; and 10(7) for baseline and 33(19) for distant recordings. The larger number of events during the etomidate period reflects the longer analysis window used (20 min) compared to baseline (3.5 min).

2.3. *Slope of the SLE population response*

The slope of the SLE field potential increased during etomidate delivery (median(range) 16.6(1.5–106.2) µV/msec during baseline recording compared to 20.2(1.7–111.1) during drug delivery, $p=0.0013$, Wilcoxon test) (Fig. 3b) and was highly