Regional anaesthetic brain susceptibility to propofol is linked with local $GABA_A$ receptor density

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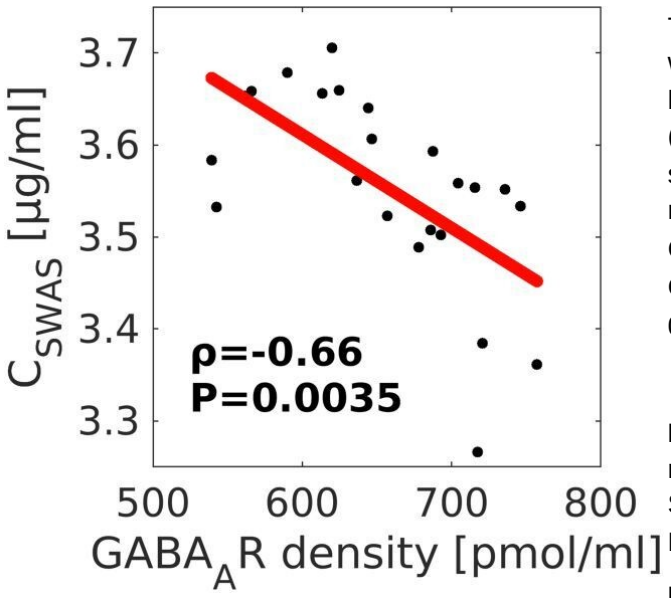
Propofol is a GABAergic anaesthetic causing neuronal hyperpolarisation leading to large-scale cortical up/down oscillations. In humans, this is observable as slow waves (~1Hz) on the electroencephalogram (EEG). EEG slow-wave activity saturation (SWAS) has been proposed as an individualised loss of perception measure suitable for depth of anaesthesia monitoring [1].

Methods

Analysis used previously reported 32-channel EEG collected in N=16 healthy volunteers (8 female, age 28.6±7 years) during IV propofol induction to 4 µg/ml effect-site concentration [1]. After re-referencing to scalp average and artifact rejection, slow-wave activity was extracted as spectral power in 0.5Hz-1.5Hz band (4s windows, 3s overlap; MATLAB, Math Works Inc.). A 4-parameter sigmoid dose-response curve was fitted to slow-wave activity on each electrode [1]. Propofol concentration to achieve SWAS (C_{SWAS}) was identified as the propofol concentration at 95% power saturation. Subjects that did not reach SWAS (N=2) due to insufficient dosing were excluded. Next, an in vivo atlas of $GABA_A$ receptor density ($GABA_AR$D) previously obtained with [^{11}C]PET [2] was projected onto N=26 EEG cortical locations using FSL v6.0. Correlation between C_{SWAS} and local $GABA_AR$D was tested with Spearman rank and its permutation P-value.



Results

The concentration required to achieve maximal slow-wave activity (C_{SWAS}) varied across the scalp, with highest doses needed across centro-temporal regions (Figure 1; mean C_{SWAS}=3.50(0.42)µg/ml across all subjects and brain regions, mean between-brain-region variability ΔC_{SWAS} = 0.60(0.45)µg/ml). Mean C_{SWAS} for a brain region significantly correlated with $GABA_AR$D in that projected region (Spearman ρ=-0.66, P=0.0035).

Figure 1. Correlation between group-average brain regional variation of propofol dose needed to achieve SWAS (C_{SWAS}) and scalp-projected $GABA_AR$D. Dots=individual electrodes; line=linear best fit.

Discussion

We have demonstrated regional brain differences in susceptibility to propofol. Whole-brain slow-wave saturation may be required for complete unconsciousness. Thus, varying anaesthetic susceptibility across the brain means commonly used clinical frontal EEG monitoring may underestimate propofol doses needed. Linking local $GABA_A$ expression and C_{SWAS} suggests slow waves link to neurobiology important during anaesthesia.

Acknowledgements

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References

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