A Selective $GABA_A$-Slow Agonist Produces a Unique EEG Profile

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Background/Introduction: Anesthetic agents like propofol increase power in slow delta frequencies (1 to 4 Hz), with a general decrease in EEG frequencies above 30 Hz. Propofol is non-selective for $GABA_A$ response subtypes, enhancing all three $GABA_A$-subtypes (slow, fast, and tonic). A new anesthetic, BB, selectively targets $GABA_A$-slow synapses to depress brain responsiveness. We hypothesized that a selective GABAA-slow agonist, BB, would produce a different EEG signature compared to the broad spectrum $GABA_A$ agonist (propofol), and tested this using rat EEG recordings.

Methods: Male rats were used following IACUC approval from the US Army Medical Research Institute of Chemical Defense or the University of Michigan. Rats were anesthetized using isoflurane (3-5% induction, 1-3% maintenance; with oxygen @ 0.5-1.0 L/min. Stainless steel screws were used to capture cortical EEG activity.

Results: Propofol administration generated increased power in slow delta frequencies (1 to 4 Hz) and a general decrease in EEG power above 30 Hz at loss of righting reflex (LORR). By contrast, BB administration increased theta activity markedly (5 - 8 Hz), and slightly increased delta power, but did not depress high frequency responses above 30 Hz. Neither agent produced burst suppression activity at LORR. Both anesthetics produced a characteristic flattening of time-delayed embeddings, similar to volatile and dissociative anesthetics at LORR. Propofol's EEG effects were in agreement with those seen in previous studies across individuals and species. At LORR a generalized slowing in EEG was seen with increased power in frequencies below 4 Hz. BB produced a markedly different EEG pattern, with a selective increase observed in the theta frequency range.

Conclusion: Increased theta frequencies are interesting because $GABA_A$ slow synapses have previously been suggested to underlie theta frequency oscillations, while fast synapses control high, gamma frequency oscillations (30-60 Hz). Tonic $GABA_A$ responses produce a generalized depression of neuronal activity across all frequencies. BB and propofol share the ability to flatten EEG time-delayed embeddings at LORR. Flattened embeddings are also observed in humans and thought to reflect a decrease in EEG information content at LORR. It appears that propofol's effects on fast and/or tonic responses contribute to its respiratory and cardiovascular unwanted side effects, since these were not produced by BB.

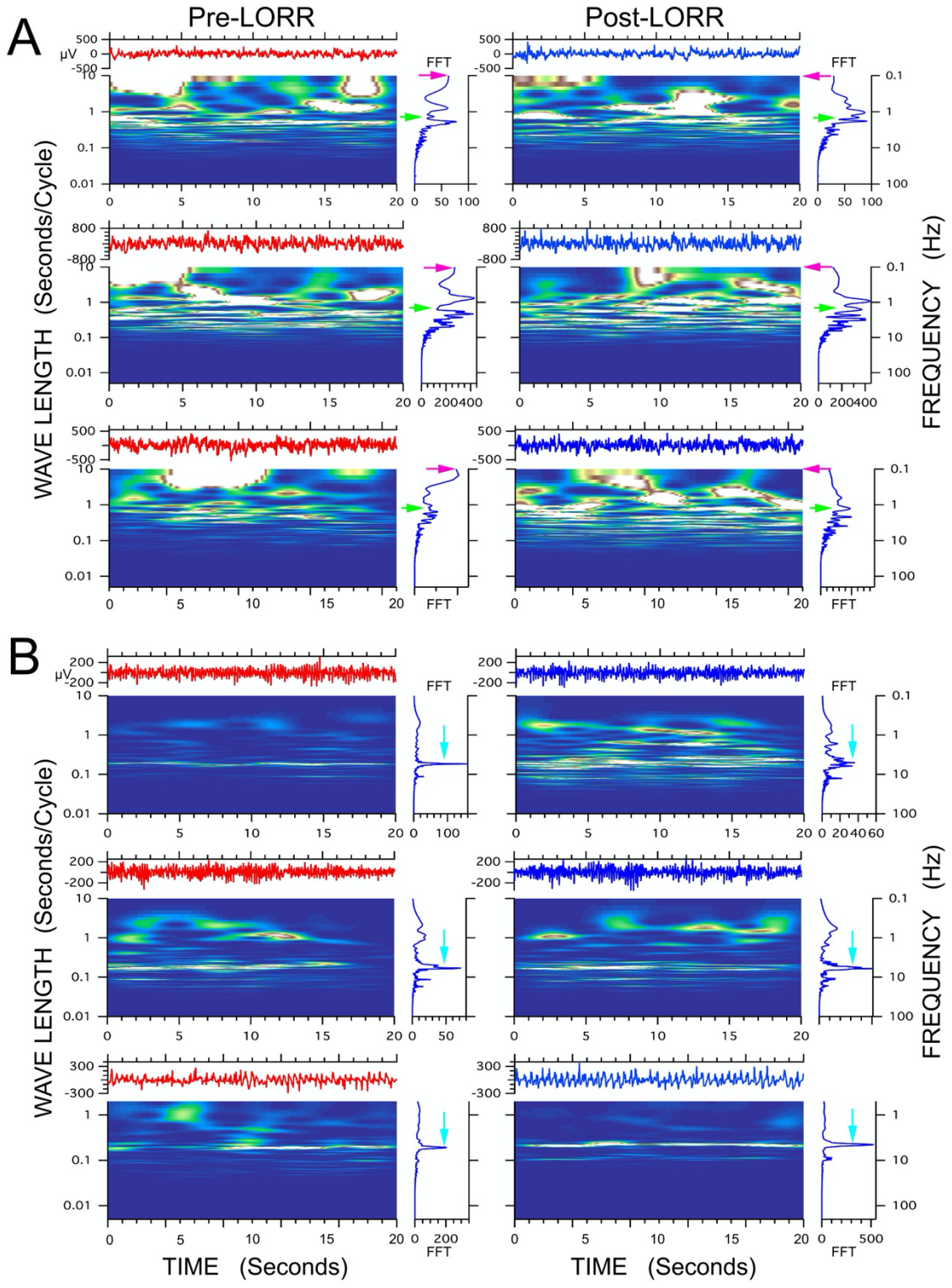

Figure 1. Frequency analysis comparing effects produced by propofol (A) and BB (B) on EEG recordings 20 seconds before loss of righting (LORR) and after. Propofol produced a decrease in

slow wave (0.1 Hz – pink arrows in FFT graphs) rhythms together with an increase in delta rhythms (1-3 Hz – green arrows). BB produced a selective increase in theta frequencies (B – blue arrows in FFT), produced by prolonging GABA-slow synaptic inhibition at loss of righting. Each row presents data from individual animals, together with EEG recordings used to create spectrograms and fast-Fourier transforms (FFT).