Lack of Tolerance With Repeat Dosage of Dexmedetomidine in Rat for 21 Days as Measured by EEG

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Background

- Sublingual dexmedetomidine is approved for the treatment of agitation associated with schizophrenia or bipolar disorder I or II in adults.
- Dexmedetomidine is a selective, full agonist at α2-adrenergic receptors (ADRA2A) expressed widely in the central nervous system.
- Dexmedetomidine activates the ADRA2A receptor and modulates norepinephrine release from locus coeruleus (LC) neurons, thereby reducing sympathetic arousal.
- Chronic activation of ADRA2A receptors could lead to tolerance, thereby reducing drug efficacy or rebound effects upon cessation of drug use

Objective

Here we examine if:

1) Repeat dosing of dexmedetomidine will lead to tolerance, and
2) Discontinuation of repeated dexmedetomidine dosing results in withdrawal symptoms or rebound agitation.

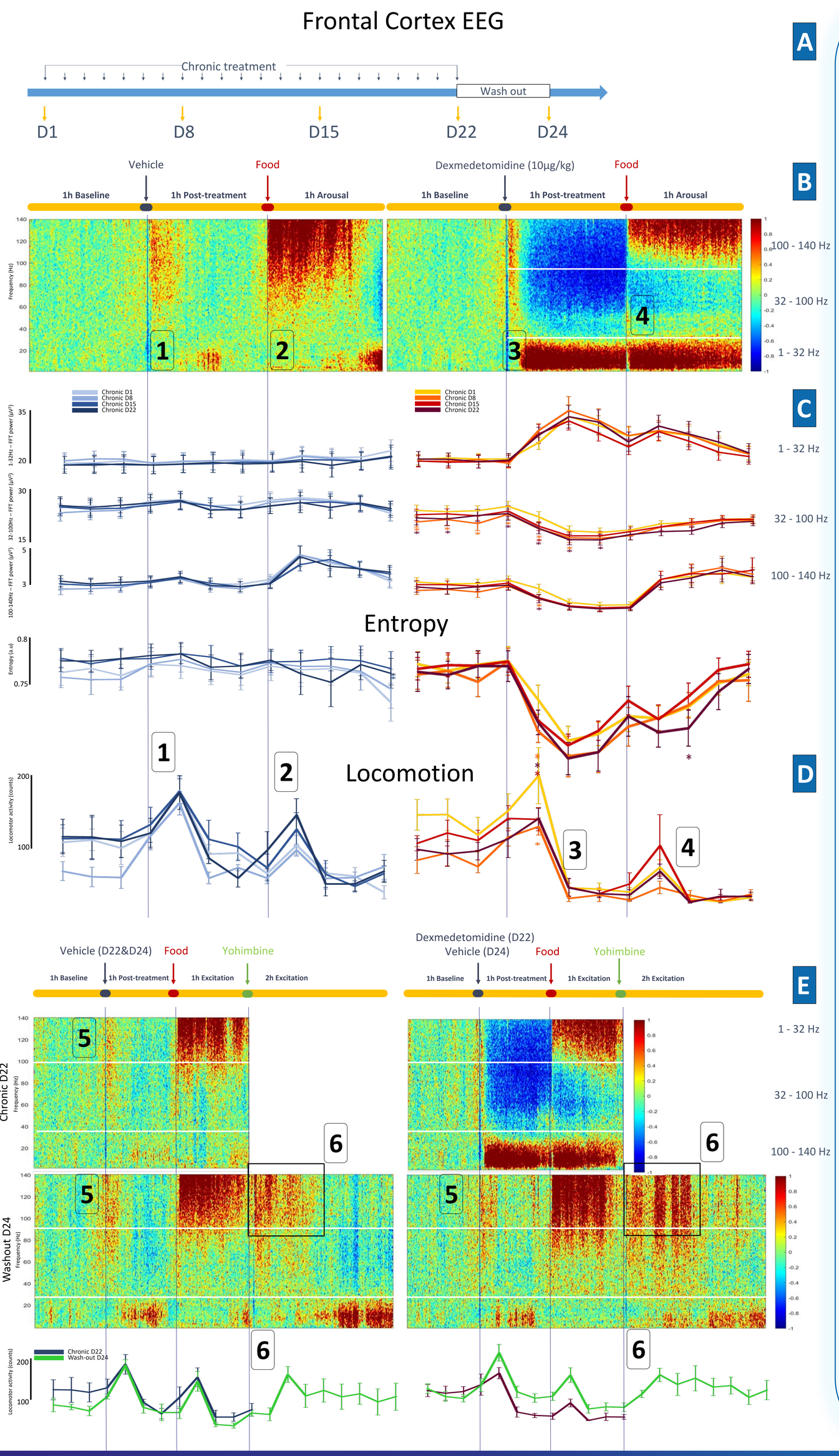
Methods

- Studies were carried out at a preclinical neuroscience CRO (SynapCell, France).
- 24 Sprague-Dawley 3-month-old male rats were implanted with electrodes in the frontal and parietal cortices and connected to an intraperitoneal telemetry transmitter.
- Rats were dosed with 10 µg/kg of dexmedetomidine intramuscularly (IM) and kept on a restricted diet to maintain weight. Treatment groups are n=8 and follow a balanced cross-over protocol with a 7-day washout.
- EEG responses were quantified with time-frequency (TF) decompositions and fast Fourier transform (FFT) power spectra plotted relative to baseline values.
- Spectral entropy (SE) calculations were based on power spectra calculated using FFT. Spectra were first normalized to obtain the probability distribution of frequencies, then the SE was calculated for the frequency range 1 to 140Hz.

Statistics

- Individual time points were compared using 2-way ANOVA with a post-hoc Dunnett test. Asterisks indicate statistical significance compared to Day 1.
- Curves were also compared by calculating the AUCs for each recording segment; Baseline (BL); Stimulus (Veh or Dex); Food (FD) and Yohimbine (Yoh), for all recoding days, 3 frequency bands: 1-32; 32-100; 100-140 Hz and Spectral Entropy. 2-way ANOVA significance levels for multiple comparisons were corrected using Tukey's or Sidak; NS = No Significance.

Stimulus	Compared to	Significance	Notes
Dex	Veh or BL	P<0.01	For each Day. Not for 100-140Hz
FD	BL	P<0.01	For each Day. Not for 100-140Hz
Dex	Dex	NS	Between each Day (D1;D8;D15;D22)
FD	FD	NS	Between each Day (D1;D8;D15;D22)
Yoh	Yoh	NS	D24 between Dex and Veh groups
Veh	Veh	NS	D24 between Dex and Veh groups and D22 Veh group
Yoh	BL	P<0.01	Both in Dex and Veh Group only in Spectral Entropy



Results

A) Stimulus Paradigm: Dexmedetomidine (Dex) was dosed daily in rats at 10 µg/kg IP for 22 days followed by a 2 day wash out. EEG and locomotion recording days are indicated

B) Averaged spectrograms (n=8) of frontal cortex EEG. Day 1 acute dosing.

1) **Vehicle injection itself is associated with high frequency and locomotor activity lasting up to 20 min**
2) **Adding food to the cage causes arousal in the rats as reflected by a marked increase in higher frequencies and locomotion.**
3) **In contrast, Dex injection reduces the duration of agitation, shifts the EEG power distribution to lower frequencies and reduces locomotion.**
4) **Addition of food to the cage in Dex injected animals still causes arousal and increases locomotion but superimposed on the lower frequency bands.**

C) The Dex EEG response is characterized by quantifying the power distribution over 3 frequency bands : 1-32Hz; 32-100Hz and 100-140Hz (white lines in B) on D1, D8, D15 and D22. The spectral complexity of the signals is quantified by plotting the spectral entropy. Repeat dosing does not significantly change the overall response patterns to either vehicle, Dex or food stimulus.

D) Locomotion recorded following vehicle, Dex or food stimulation. Dex reduces locomotion but not fully. No significant changes between the curves for D1, D8, D15 and D22.

E) EEG spectrograms on D22 and D24.

5) **Following washout, responses to vehicle injections on D24 in Dex treated rats are similar to vehicle control groups on D22 and D24, arguing against a Dex rebound effect.**
6) **The responses to the ADRA2A receptor antagonist Yohimbine both in EEG (shift to higher frequencies) and locomotion (increased) is similar between vehicle and Dex treated groups, suggesting absence of any homeostatic compensation to prolonged Dex exposure.**

Conclusion

In rats, repeat dosing of dexmedetomidine for 22 days does not cause tolerance as measured in CNS. Consistent with these observations we also found no evidence of hyperlocomotion or EEG excitability following dexmedetomidine treatment cessation (rebound effect).

These results suggest that dexmedetomidine's efficacy in reducing agitation should not diminish after multiple, consecutive doses or cause withdrawal symptoms.

References 1. Preskorn SH et al., JAMA 2020. 2. Citrome L, et al., J Clin Psychiatry 2020

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