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Evaluation of Selective Muscarinic M4 Agonists on Cortical Oscillations: a Sleep-EEG Study in Rats

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CONCLUSIONS

- EEG reveals dose-dependent pharmacodynamic effects on cortical oscillations following M4 activation
- Whereas activation of dopaminergic receptors results in increased higher frequencies such as alpha, beta, and gamma oscillations, antipsychotics commonly decrease alpha and gamma oscillations
- Data generated with these M4 activators align with an antipsychotic profile and suggest selective activation of M4 may be an effective treatment for the neuropsychiatric or neurobehavioral symptoms components associated with CNS disorders

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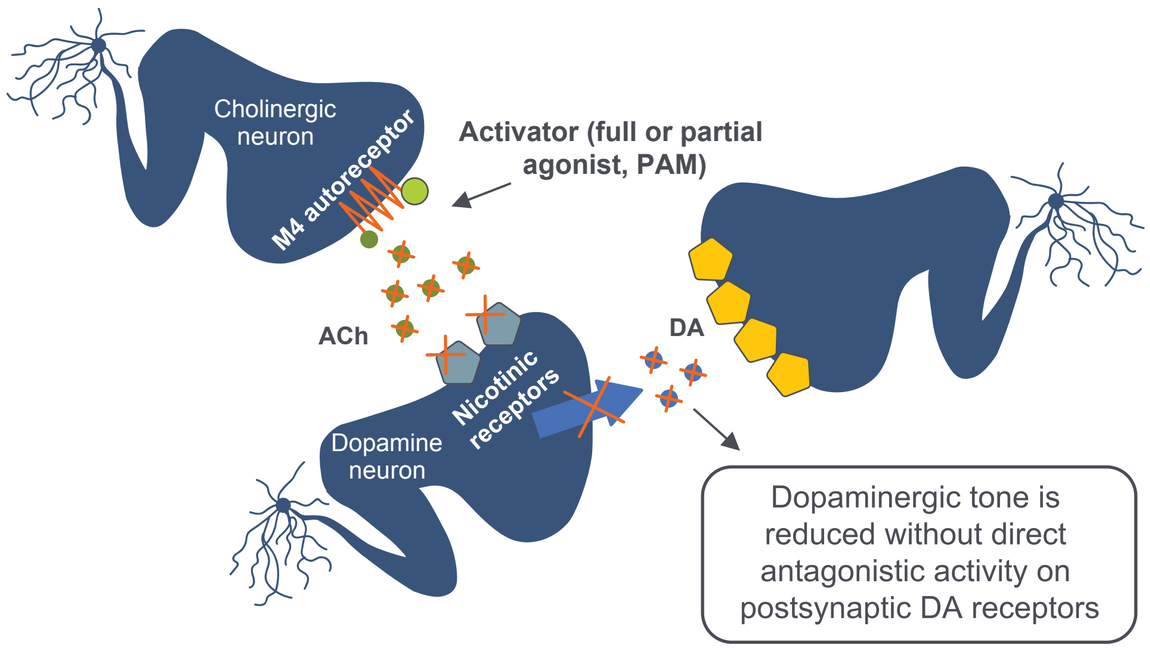
INTRODUCTION

- A primary role for the M4 muscarinic acetylcholine receptor (M4 mAChR) is to function as an inhibitory autoreceptor
- Activation of M4 receptors decreases acetylcholine, which in turn decreases levels of dopamine (DA) or DA-receptor function without the direct receptor blockade



METHODS

- Polysomnographic electroencephalography (sleep-EEG) study was carried out using radiotelemetry in unanesthetized Sprague Dawley rats following subcutaneous compound administration (n=8 rats per treatment per crossover study). EEG was recorded using PhysioTel HD-S02 transmitters (DSI, St. Paul, MN, USA) sampled at 500 Hz and analyzed using conventional methods: spectral power was determined using NeuroScore (DSI) for each 1-Hz bin for every 10 seconds and averaged into frequency bands, temporal epoch, sleep stage, and treatment group

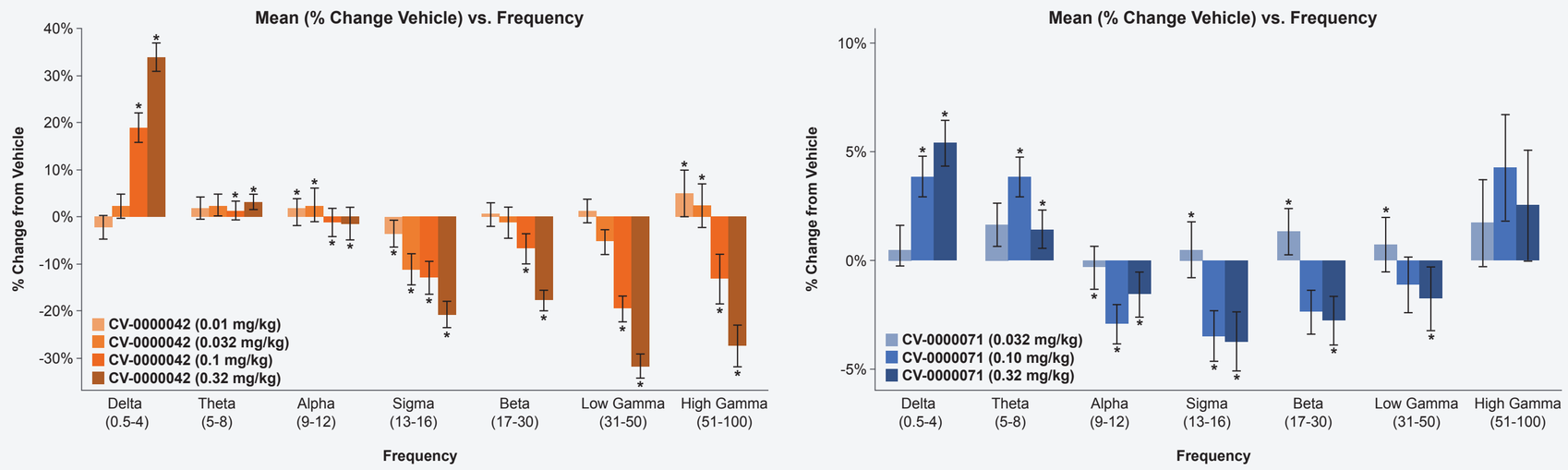
Table. Full and Partial M4 Agonists Used in Study

Compound	Dose (mg/kg)	Change in cAMP, %
CV-0000042 full agonist	0.032	12
	0.1	30
	0.32	58
CV-0000071 partial agonist	0.0032	15
	0.1	35
	0.32	63

RESULTS

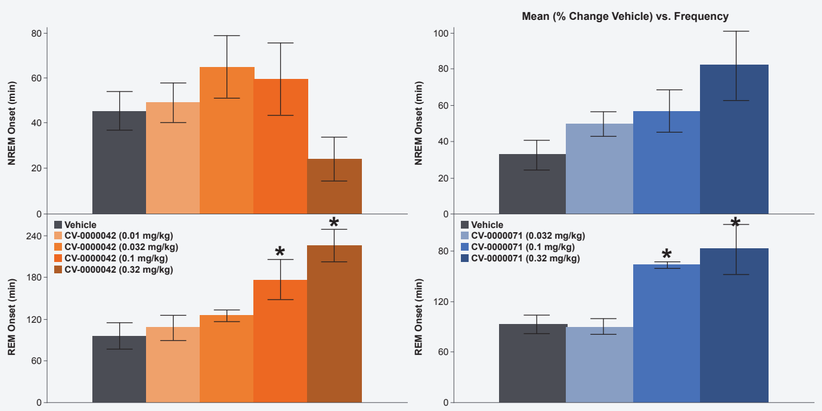
- Full and partial M4 agonists showed similar profiles on cortical oscillations but with clear differences in the magnitude of changes (full > partial)

Figure 1. Relative power.



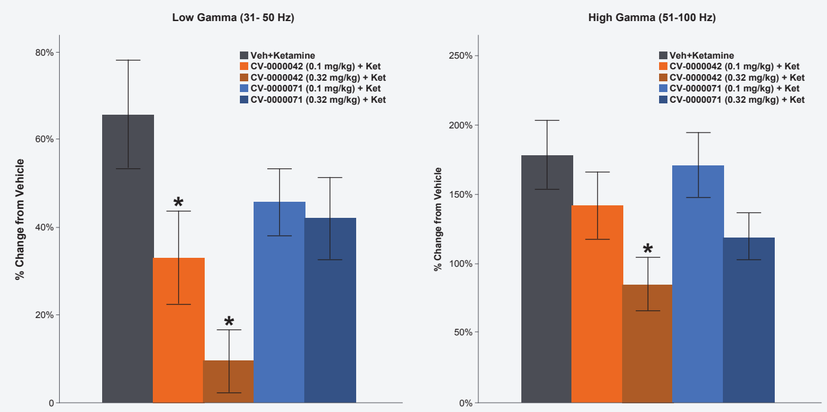
Relative power, as represented by the percent change from vehicle 0-1 hours post dose. CV-0000042 dose-dependently increased delta, suppressed power in higher frequencies. CV-0000071 dose-dependently increased delta, suppressed power in higher frequencies (except high gamma) to a lesser extent than the full agonist. Data are presented as mean ± SEM. Statistical analysis performed on Relative Power (not shown) by frequency band and 1 hour bin using one-way ANOVA followed by Dunnett's test (*P<0.05 vs vehicle).

Figure 2. NREM and REM onset latencies.



CV-0000042 and CV-0000071 dose-dependently increased the latency to REM onset without significantly changing non-REM (NREM) onset. Data are presented as mean ± SEM. Statistical analysis performed using one-way ANOVA followed by Dunnett's test (*P<0.05 vs vehicle).

Figure 3. Ketamine challenge.



CV-0000042 dose-dependently decreased ketamine-induced gamma. CV-0000071 decreased ketamine-induced gamma but did not reach significance at the doses tested. Data are presented as mean ± SEM of the percent change of relative power from vehicle 0-1 hours post dose. Statistical analysis performed on relative power (not shown) using one-way ANOVA followed by Dunnett's test (*P<0.05 vs vehicle ± ketamine).