COMMUNICATION FROM THE CEREBELLUM TO THE NEOCORTEX DURING SLEEP SPINDLES

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Introduction

Surprisingly little is known about neural activity in the sleeping cerebellum. 5. 17 Using long-term wireless recordings, we have made routine recordings of local field potentials (LFPs) and action potentials for the entirety of natural sleep in non-human primates.

Methods

We were able to record simultaneously from the primary motor cortex (M1), the thalamus and the cerebellum using both rigid multi-contact linear electrode arrays and flexible microwires. 17. 12 Recording for the entirety of the natural sleep was achieved using a custom-made wearable device.

Results

We find that the M1 and cerebellum communicate with each other during sleep, 13. 14 with cerebellum-to-M1 signals passing via the thalamus. We find that both M1 and cerebellar neuronal firings are broadly synchronous and phase-locked to the sleep cycle. 7 Additionally, both spikes and LFPs in M1 and cerebellum also show coherence at slow (<1Hz), delta (1-4Hz) and alpha (7–15Hz) frequencies. 8. 15. 16 We also see phase-locking between the spikes of M1 and the LFPs of the cerebellum (and vice versa) at these same frequencies. Using Granger causality analysis on the LFPs we were able to observe directed connectivity from motor cortex to the cerebellum in deep sleep. This suggested a neocortical origin of slow oscillations. By contrast, sleep spindles (in the alpha frequency range) in light sleep revealed a causal influence from the cerebellum to motor cortex, going via the thalamus.

Discussion

Our results shed new light on the mechanisms of sleep spindle generation 9 and show that the cerebellum is an active participant of sleep. We postulate that the cerebellum-thalamo-neocortical pathways is implicated in sleep-dependent consolidation of procedural learning. 1. 3. 4. 6. 18. 20

REFERENCES

Discussion  This study suggests that a ‘one-size fits all’ approach to mattresses may not be appropriate and contrasting body types need different levels of support to improve overall spinal alignment. The use of simple anthropometric measurements could make the selection of the most appropriate mattress easier for the public.

P003  RANDOMISED, PLACEBO-CONTROLLED STUDY OF SOLRIAMFETOL FOR EXCESSIVE DAYTIME SLEEPINESS IN NARCOLEPSY TYPES 1/2

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Introduction  Solriamfetol (formerly JZP-110), a dopamine and norepinephrine reuptake inhibitor, has been approved in the United States to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy (75–150 mg) or obstructive sleep apnoea (OSA; 37.5–150 mg). A Marketing Authorisation Application for these indications is under review with the European Medicines Agency. This phase 3 study assessed safety and efficacy of solriamfetol in participants with narcolepsy types 1 and 2 (NT1/2).1

Methods  In this 12-week, double-blind, randomised, placebo-controlled study, participants with or without cataplexy were randomised to solriamfetol 75 mg, 150 mg, 300 mg, or placebo. Eligibility criteria: NT1/2 diagnosis; mean sleep latency <25 minutes on Maintenance of Wakefulness Test (MWT); Epworth Sleepiness Scale (ESS) score ≥10. Exclusion criteria: medications that could affect EDS or cataplexy; night-time or variable shift work; other conditions affecting EDS. 236 participants received ≥1 dose of solriamfetol (67.2% female; 80.2% white). Baseline MWT mean sleep latency: 7.5 minutes; baseline ESS score: 17.2. Solriamfetol significantly increased MWT sleep latency at week 12 (P<0.0001 for 300 mg and 150 mg); least squares (LS) mean change: 12.3 minutes for 300 mg, 9.8 for 150 mg, 4.7 for 75 mg, and 2.1 for placebo. Solriamfetol significantly decreased ESS scores at week 12 (P<0.0001 150 mg and 300 mg; P<0.05 75 mg). LS mean change in ESS: -6.4 for 300 mg, -5.4 for 150 mg, -3.8 for 75 mg, and -1.6 for placebo. Most common treatment-emergent adverse events (TEAEs; ≥5%): headache, nausea, decreased appetite, nasopharyngitis, dry mouth, and anxiety. Discontinuations due to TEAEs were more frequent in solriamfetol 150 mg and 300 mg groups.

Discussion  Solriamfetol improved wakefulness and reduced EDS in participants with NT1/2. Most AEs were mild to moderate.

Support  Jazz Pharmaceuticals.

REFERENCE

P004  SOLRIAMFETOL FOR EXCESSIVE DAYTIME SLEEPINESS IN OBSTRUCTIVE SLEEP APNOEA: A RANDOMISED CONTROLLED TRIAL

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Introduction  Obstructive sleep apnoea (OSA) is often associated with persistent excessive daytime sleepiness (EDS) despite sleep apnoea therapy. There are currently no approved treatments in the European Union for the treatment of EDS in this population. Solriamfetol (formerly JZP-110), a dopamine and norepinephrine reuptake inhibitor, has been approved in the United States to improve wakefulness in adults with EDS associated with narcolepsy (75–150 mg) or OSA (37.5–150 mg). A Marketing Authorisation Application for these indications is under review with the European Medicines Agency. This study evaluated the efficacy and safety of solriamfetol for treatment of EDS in participants with OSA and current or prior sleep apnoea treatment.

Methods  In this double-blind, placebo-controlled, parallel-group phase 3 trial, participants with OSA and associated EDS were randomly assigned to solriamfetol 37.5 mg, 75 mg, 150 mg, or 300 mg or placebo for 12 weeks.

Results  Of 476 randomised participants, 459 were included in the prespecified efficacy analyses. Co-primary endpoints (Maintenance of Wakefulness Test sleep latency, Epworth Sleepiness Scale score) were met at all solriamfetol doses (P<0.05), with dose-dependent effects observed at week 1 and maintained over the study duration. All doses except 37.5 mg resulted in significantly higher percentages of participants reporting improvement on Patient Global Impression of Change (key secondary endpoint; P<0.05). Adverse events (AEs) were reported in 47.9% of placebo- and 67.9% of solriamfetol-treated participants; 5 participants experienced serious AEs (2 [1.7%] placebo, 3 [0.8%] solriamfetol); none were deemed related to study drug. The most common AEs with solriamfetol were headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7.0%), and nasopharyngitis (5.1%).

Discussion  Solriamfetol significantly improved wakefulness and reduced sleepiness in participants with OSA and EDS. Most AEs were mild or moderate.

Support  Jazz Pharmaceuticals.

REFERENCE