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KYNURENINE AMINOTRANSFERASE II INHIBITION IMPROVES SLEEP ARCHITECTURE IN ADULT MALE AND FEMALE RATS EXPOSED TO KYNURENIC ACID ELEVATION DURING DEVELOPMENT

Snezana Milosavljevic[1], Katherine Rentschler[1], Courtney Wright[1], Ana Pocivavsek[1]
University of South Carolina School of Medicine [1]

Introduction: Dysregulated sleep and cognitive impairments are commonly reported in individuals with psychotic disorders, including schizophrenia (SZ) and bipolar disorder (BPD). Emerging evidence implicates the kynurenine pathway (KP) of tryptophan catabolism in the pathophysiology of psychotic disorders. Kynurenic acid (KYNA), a KP metabolite synthetized by kynurenine aminotransferases (KATs) from its biological precursor kynurenine, is elevated in brain tissue and the cerebrospinal fluid of patients with SZ and BPD. KYNA is hypothesized to play a key role in sleep disturbances, thus, we presently investigate if pharmacological inhibition of KAT II to reduce brain KYNA formation may overcome sleep.
Methods: We employed the embryonic kynurenine (EKyn) paradigm to induce KYNA elevation in the fetal brain (Pocivavsek et al 2014 Psychopharm). Wistar dams were fed either kynurenine (100 mg/day) (EKyn) or control wet mash (ECon) from embryonic day (ED) 15 to ED 22. Adult (postnatal day 56-85) male and female offspring were used in sleep studies (EEG/EMG telemetry) to evaluate the effectiveness of PF-04859989 (30 mg/kg, s.c.), an irreversible KAT II inhibitor. Each subject was treated at zeitgeber time (ZT) 0 with either vehicle or PF-04859989 and rapid-eye movement (REM) sleep, non-REM (NREM) sleep, and wakefulness parameters were assessed.
Results: KAT II inhibition significantly increased REM duration during the second half of the light phase in both male ($P<0.01$) and female ($P<0.05$) EKyn compared to vehicle treatment. PF-04859989 increased NREM duration and reduced wakefulness during the latter part of the dark phase in both ECon and EKyn male rats, accompanied with significant decrease in relative cage activity, but no differences were determined in female rats across 24 hr. Light phase analysis of spectral power during NREM sleep in EKyn rats revealed significant frequency by treatment interaction ($P<0.0001$) in males only, with enhanced delta power (0-4 Hz) after PF-04859989 treatment.
Conclusion: Acute decrease in brain KYNA mitigates sleep deficits and elicits higher quality sleep in male EKyn offspring, suggesting KAT II inhibition as a novel mechanistic approach to treating sleep deficiencies in a translationally-relevant preclinical paradigm.
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THE ODDS RATIO PRODUCT AS A MARKER OF SLEEP HOMEOSTASIS

Darion Toutant[1], Magdy Younes[1], Marcus Ng[1]
University of Manitoba [1]

Introduction: Classic EEG markers of sleep homeostasis (process S) usually study the level and amount of slow wave activity (SWA). In recent years, the odds ratio product (ORP) has been described as a novel quantitative measure of sleep depth (and conversely, arousability), which is derived from a four-digit permutation of the power in four respective frequency bands. Therefore, we sought to determine whether the ORP can also be used as a novel quantitative marker of process S.
Methods: Utilizing C3/C4 electrodes with TP9/TP10 reference, ORP was calculated from 25 nights in 15 patients. We used ORP from REM and NREM1-3 segments/bouts in each person's night(s) with varying number of data points per REM segment(s) in each night(s). Artifacts and wake segments were discarded from analysis. Average ORP is calculated for an individual bout per night per patient. Generalized Estimating Equation (GEE) modelling used GEEQBOX MATLAB toolbox to identify change in sleep depth over bouts. Resultant beta (β) values represented change in nightly sleep depth over sequential NREM/REM segments per patient. Significance was $p\leq0.000833$.
Results: From 15 people in the epilepsy monitoring unit, 3 did not have epilepsy. In NREM, the average ORP for C3/C4 is 1.26/1.19 (n=146307/125709). Average number of nightly NREM segments for C3/C4 are 4.64/4.9 (n=1261.27/1282.74 average ORP values per nightly segment). In REM, the average ORP for C3/C4 is 1.44/1.44 (n=47629/43528). Average number of nightly REM segments for C3/C4 are 4.36/4.38 (n=418.68/453.33 average ORP values per nightly segment). Signifying the change in sleep depth the beta values from C3/C4 were consistently positive: REM (epilepsy 0.033/0.018, non-epilepsy 0.096/0.053), NREM (epilepsy 0.047/0.053, non-epilepsy 0.026/0.064).
Conclusion: As a marker of sleep homeostasis, SWA decreases across a period of sleep. Consistently positive beta values derived from ORP in both REM and NREM are comparable because they demonstrate shallower sleep depth (i.e. greater arousability) across segments over nights as sleep debt is repaid. Also as expected, REM has a higher ORP than NREM. Furthermore, our findings of positive beta values are robust against sleep stage and pathology (i.e. epilepsy). Therefore, these findings may represent a novel quantitative marker of sleep homeostasis that includes REM.
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