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ACTIVATION OF NOCICEPTIN/ORPHANIN-FQ PEPTIDE (NOP) RECEPTORS PRODUCES AN INCREASE IN NON-REM SLEEP IN RATS AND CONSTITUTES A NOVEL AND ATTRACTIVE TARGET FOR THE TREATMENT OF INSOMNIA

Whiteside, G. T.[1] Hummel, M.[2] Knappenberger, T.[2] Hiroyama, S.[3] Itoh, T.[3] Takai, N.[3] Kyle, D. J.[2]

[1]Imbrium Therapeutics, Stamford, CT, [2]Purdue Pharma L.P., Stamford, CT, [3]Shionogi & Co., Ltd., Osaka, JAPAN.

Introduction: Treatments for insomnia have targeted GABA, histamine, serotonin, melatonin and orexin receptors. The nociceptin/orphanin-FQ peptide (NOP) receptor is widely expressed in the nervous system. High doses of NOP agonists administered systemically or locally into the CNS can result in sedation, however, the utility of targeting this receptor to treat insomnia has not been fully described.
Methods: V117957 is a recently described investigational oral, potent and selective NOP receptor partial agonist. We determined the brain Kp in whole brain and multiple sub-regions (50mg/kg) and receptor occupancy in the hypothalamus (30, 300mg/kg) via *in vivo* displacement using [^{3}H]-NOP-1A. EEG/EMG were determined in rats chronically implanted with electrodes (cortex and dorsal neck muscle) and recorded via telemetry following dosing (3, 30, 300mg/kg); sleep stage was determined from visual analysis of EEG level. Sleep parameters were also assessed in NOP receptor knock-out rats (300mg/kg). The side-effect profile for V117957 was determined by functional observation battery, whole-body plethysmography, Morris water maze (MWM) (up to 600mg/kg) and conditioned place preference (CPP) assay (up to 300mg/kg).
Results: V117957 displayed limited distribution into the CNS but achieved a high level of receptor occupancy (75% at 30mg/kg). Administration of V117957 produced dose-dependent and statistically significant increases in non-REM sleep with a minimally efficacious dose of 30mg/kg; a coincident dose-dependent and statistically significant decrease in wakefulness and a non-dose-dependent effect on REM sleep occurred. These changes were not seen in knock-out animals demonstrating effects are via NOP receptors. At doses higher than those that increased non-REM sleep, V117957 had no effects in a functional observational battery, did not affect escape latency in MWM or produce CPP; additionally, V117957 did not affect respiratory parameters.
Conclusion: We conclude that activation of NOP receptors decreases wakefulness and increases non-REM sleep in rats with an improved preclinical profile compared to historical profiles of current treatments and, therefore, may represent a novel and attractive target for the treatment of insomnia.
Support: Funded by Shionogi and Imbrium Therapeutics, a subsidiary of Purdue Pharma L.P.

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DECREASED CONCENTRATION OF KLOTHO AND INCREASED CONCENTRATION OF FGF-23 IN THE CEREBROSPINAL FLUID OF PATIENTS WITH NARCOLEPSY

Oliveira, G. P.[1,2] Elias, R. M.[3] Fernandes, G. B.[1] Moyses, R.[3] Tufik, S.[1] Bichuetti, D. B.[1] Coelho, F. M.[1]

[1]Universidade Federal de São Paulo, São Paulo, BRAZIL, [2]Universidade Federal do Piauí, Teresina, BRAZIL, [3]Universidade de São Paulo, São Paulo, BRAZIL, [4]Universidade Federal de São Paulo, São Paulo, BRAZIL.

Introduction: Narcolepsy is a disorder characterized by hypersomnolence, cataplexy, sleep paralysis, hallucinations and sleep fragmentation. Patients with type 1 narcolepsy have cataplexy and/or hypocretin-1 deficiency. Klotho is a protein expressed by kidneys and choroid plexus, with anti-aging properties. Fibroblast growth factor 23 (FGF-23) is a hormone secreted by osteocytes with actions on mineral metabolism. The purpose of study was to explore the status of concentration of klotho and FGF23 in the cerebrospinal fluids (CSF) of patients with narcolepsy.
Methods: 59 patients with narcolepsy and 17 individuals were enrolled. We used a radioimmunoassay technique, human klotho enzyme-linked immunosorbent assay (ELISA), human intact FGF23 ELISA and spectrophotometry to measure hypocretin-1, klotho, FGF-23 and phosphorus, respectively. T-Student Test was used to compare klotho and phosphate concentrations and Mann-Whitney U Test was used to compare FGF-23 levels between groups. ANOVA Test was used to compare klotho and phosphate CSF concentrations among narcolepsy patients with CSF hypocretin-1 <110pg/ml (HCRT-) and narcolepsy patients with CSF hypocretin-1 >110pg/ml (HCRT+) versus control subjects.
Results: Klotho and phosphorus CSF levels were lower in narcoleptic patients than in control (908.18 ± 405.51 versus 1265.78 ± 523.26 pg/ml; p=0.004 and 1.34 ± 0.25 versus 1.58 ± 0.23 mg/dl; p= 0.001, respectively). We found higher median FGF-23 levels in narcoleptic patients (5.51 versus 4.00 RU/ml; p= 0.001). Klotho and phosphorus CSF levels were lower in both HCRT-/HCRT+ than controls (892.63 ± 388.34/ 925.95 ± 430.76 versus 1265.78 ± 523.26 pg/ml; p=0.014 and 1.35 ± 0.28/ 1.33 ± 0.22 versus 1.58 ± 0.23 mg/dl; p= 0.004). Moreover, we found higher median FGF-23 levels in both HCRT-/HCRT+ groups versus controls (5.51/ 6.02 versus 4.00 RU/ml in controls), p= 0.009.
Conclusion: Patients with narcolepsy have decreased CSF concentration of klotho and increased CSF levels of FGF-23. These findings may play a role in understanding the pathogenesis of narcolepsy.
Support: .

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LGI1 AND CASPR2 AUTOIMMUNITY: SLEEP SYMPTOMS, POLYSOMNOGRAPHY, AND QUANTITATIVE REM SLEEP WITHOUT ATONIA

Devine, M. F. Feemster, J. C. Lieske, E. A. McCarter, S. J. Sandness, D. J. Steele, T. Boeve, B. F. Silber, M. H. McKeon, A. St. Louis, E. K.

Mayo Clinic, Rochester, MN.

Introduction: Sleep disturbances, including rapid eye movement (REM) behavior disorder (RBD), are known manifestations of voltage-gated-potassium-channel-complex VGKC-IgG seropositivity (VGKC+). Discovery of leucine-rich, glioma inactivated protein 1 (LGI1) and contactin-associated protein 2 (CASPR2) have refined our understanding of VGKC+. VGKC+ without LGI1/CASPR2-IgG ("double-negative") has lost its clinical significance. Previous detailed sleep analysis of these subtypes has been limited.
Methods: We performed a retrospective study to characterize clinical and polysomnographic features of LGI1/CASPR2 seropositive (LGI1+/CASPR2+) and VGKC double-negative patients, including quantitative REM sleep without atonia (RSWA). Quantified RSWA was compared to matched controls and normative RSWA percentiles.