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A1

Development and pharmacological characterisation of bifunctional CGRP-PACAP receptor antagonists in transfected cells and spinal cord cultures

D. Hay[1], Z. Tasma[2], A. Siow[2], M. Brimble[2], P. Harris[2], C. Walker[2]
[1]University of Otago, Dunedin, New Zealand; [2]University of Auckland, Auckland, New Zealand
Correspondence: D. Hay
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Question: The neuropeptides calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating peptide (PACAP) are both implicated in migraine. Blocking the activity of these peptides simultaneously may provide a clinical advantage over individual blockade. One strategy is to develop a bifunctional ligand, capable of antagonizing both systems at once. As a starting point we utilized the known antagonism imparted by CGRP and PACAP peptide fragments, exploring different lengths of PACAP. From this, we selected $CGRP_{8-37}$ and $PACAP_{6-38}$ to attach together and assessed these molecules as bifunctional antagonists.
Methods: Peptides were synthesized in-house and $CGRP_{8-37}$ was linked to $PACAP_{6-38}$ using 1,3-dipolar cycloaddition at amino acid positions 21, 34 and 38. The potency of these peptides as bifunctional antagonists was then tested, and compared to the parent fragments. We tested antagonism against CGRP at the human CGRP and AMY_1 receptors and against PACAP-27, PACAP-38 and VIP at the human PAC_1, $VPAC_1$ and $VPAC_2$ receptors in Cos7 cells (cAMP production). Translational relevance was assessed by measuring antagonism of agonist-stimulated cAMP production in primary rat spinal cord cultures.
Results: The bifunctional antagonists generally displayed similar antagonist activity to $CGRP_{8-37}$ and $PACAP_{6-38}$ in receptor transfected Cos7 cells and spinal cord cultures. Interestingly, linking $CGRP_{8-37}$ to position 38 of $PACAP_{6-38}$ generated a peptide with greater antagonist potency than $CGRP_{8-37}$ at CGRP and AMY_1 receptors in Cos7 cells.
Conclusions: This study provides proof-of-concept that bifunctional antagonists capable of blocking both CGRP and PACAP activity can be generated.

A2

Crosstalk between cannabinoid and vanilloid systems: role of CB receptors in the capsaicin-induced relaxation responses in human coronary arteries

E. Rivera- Mancilla[1], A. van den Bogaerdt[2], A. H. J. Danser[1], C. M. Villalón[3], A. Maassen van den Brink[1]
[1]Erasmus Medical Center, Division of Vascular Medicine and Pharmacology, Department of Internal Medicine, Rotterdam, Netherlands; [2]ETB-BISLIFE, Heart Valve Department, Beverwijk, Netherlands; [3]Cinvestav-Coapa, Pharmacobiology, Mexico City, Mexico
Correspondence: E. Rivera- Mancilla
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Background: The use of cannabis and its derivatives has increased during the last years due to their therapeutic potential. However, the exact mechanisms of action of cannabinoids are still limited. It has been suggested that cannabinoids can exert their effects via the activation of cannabinoid receptors (*i.e.* CB_1 or CB_2 receptors) and/or transient receptor potential vanilloid 1 (TRPV1) channels, suggesting an interaction between both systems. We investigated the role of CB receptors in the vasodilatory effects induced by capsaicin in human isolated coronary arteries (HCAs).
Methods: In HCAs (female, n=5; 56±5 years and male, n=4; 57±4 years), the vasodilatory responses to capsaicin (TRPV1 channel agonist) were evaluated in the absence or presence of the antagonists capsazepine (TRPV1, 5 μM); AM6545 (CB_1 receptor, 1 μM); AM630 (CB_2 receptor, 1 μM); O-1918 (putative endothelial CB receptor, 10 μM) or cannabidiol (GPR55 receptor, 1 μM) to obtain the maximum contractile response (E_{max}).
Results: Capsaicin induced concentration-dependent relaxation responses (E_{max} 109±8%), which were significantly reduced by AM6545 (E_{max} 87±4%) or cannabidiol (E_{max} 86±3%), but not by capsazepine (E_{max} 103±6%), AM630 (E_{max} 100±3%) or O-1918 (E_{max} 93±5%). Moreover, pilot experiments (n=2) showed that the maximal response induced by N-arachidonoylethanolamine, (ACEA, a CB_1 receptor agonist; E_{max} 43±7%) is inhibited by AM6545 or capsazepine: E_{max} 16±3% and 21±4%, respectively.

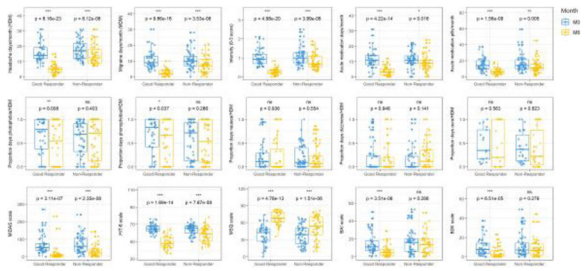

Fig. 1 (abstract P145). See text for description

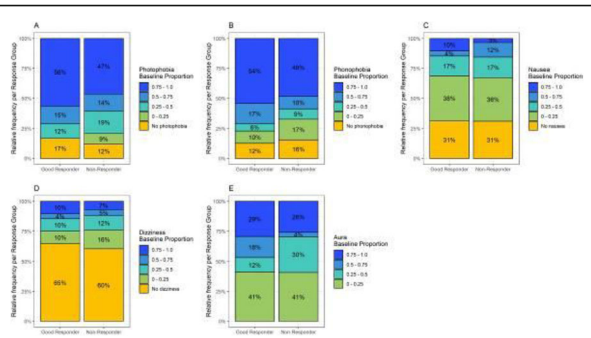

Fig. 2 (abstract P145). See text for description

P146

Mapping Migraine Minds: A cross-sectional survey to compare the difference in the level of treatment expectations and satisfaction for migraine among Indian male & female patients

S. Singh[1], R. L. Narasimhan[2], A. Gupta[3], J. Sharma[4], U. Sundar[5], S. Thakur[6], A. Thorat[6]
[1]Artemis Hospital, Neurology, Gurgaon, India; [2]Madras Medical College, Neurology, Chennai, India; [3]Army Hospital, R&R New Delhi, New Delhi, India; [4]Base Hospital, Neurology, New Delhi, India; [5]Sion Hospital, Neurology, Mumbai, India; [6]Novartis, Medical, Mumbai, India
Correspondence: S. Thakur
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Objectives: To assess the difference in the level of treatment expectations and satisfaction for migraine among Indian male(M) and female(F) patients.
Methods: A survey was conducted from 20th April 2022 – 21st June 2022 in 300 adult male and female (1:1) migraine patients. Survey questionnaire was validated by a steering committee of 10 Indian neurologists. Data was collected by using telephonic and face to face interview mode.
Results: On an average, female migraine patients had higher expectations from migraine treatment compared with males [60%(F); 51%(M)]. Higher proportion of females wanted aggressive therapy for rapid relief [68%(F); 52%(M)]. Higher proportion of females expected symptom relief [53%(F); 41%(M)] & more females did not want their migraine to worsen [48%(F); 36%(M)]. Overall average treatment satisfaction level was lower in females than that in males for both acute [73%(F); 77%(M)] & preventive therapies [81%(F); 87%(M)].
Conclusion: This study has demonstrated that there is a difference in the level of treatment expectations & satisfaction with both acute & preventive therapies with female patients demanding more from their current migraine therapies. An individualized approach towards migraine care for both male & female patients comprising of realistic expectations from therapy, lifestyle modification, trigger management & early use of targeted advanced pharmacotherapy would improve clinical outcomes. A focused attention towards female migraine patients in India is warranted where females are also the caregivers, & their migraine could impact their families too
Key words: Migraine; Treatment satisfaction; Treatment expectation; Genders

P147

Migraine, chronic neck pain and endurance muscle cervical test - a controlled study

A. Rodrigues[1], M. Mendes Bragatto Scornavacca[1], L. Lima Florencio[2], L. Bigal[3], M. Bigal[4], D. Bevilaqua Grossi[1]
[1]University of São Paulo, Health Sciences, Ribeirão Preto, Brazil; [2]Universidad Rey Juan Carlos, Madrid, Spain; [3]University of North Carolina, Chapel Hill Gillings School of Global Public Health, North Chicago, IL, United States; [4]Ventus Therapeutics, Montreal, Canada
Correspondence: A. Rodrigues
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Objective: To verify if the cervical pain observed in patients with migraine may occur due to cervical muscle dysfunction, the presence of pain during the cervical muscle endurance test or a combination of both. **Methods:** Sample consists of 100 women, stratified by diagnosis (migraine, cervical pain, both and none) and self-reported pain during the cervical muscle endurance test (with or without headache and / or cervical pain during the endurance test). The resistance test for cervical flexion and extension was evaluated and immediately after each resistance test, the participants were asked if they had neck and / or head pain during the test. Pain was classified according to the numerical pain rate scale (NPRS, 0-10). **Results:** As for the diagnosis, during the endurance test in flexion, migraine patients with cervical pain presented less endurance when compared to the control ($p = 0.02$). In the extension endurance test, the cervical pain groups with or without migraine, had a shorter sustaining time than the control group ($p < 0.01$). As for the report of pain during the endurance test in flexion and extension, those who had headache sustained less time than those without headache during the test. Similar results were seen when comparing those with head and neck pain versus no pain during the test ($p < 0.05$). **Conclusion**: The clinical diagnosis was not decisive for the performance of muscular endurance. Instead, the presence of headache associate or not neck pain during the test is what caused the endurance time to decrease.

P148

Effects of Rimegepant 75 mg on Monthly Migraine Days: a 52-Week, Open-Label Extension Study

J. Ailani[1], D. Kudrow[2], T. Smith[3], R. Lipton[4], A. C. Thiry[5], C. M. Jensen[5], L. Kamen[5], V. Coric[5], R. Croop[5]
[1]Medstar Georgetown University Hospital, Washington, DC, United States; [2]California Medical Clinic for Headache, Santa Monica, CA, United States; [3]Study Metrix Research, Saint Peters, MO, United States; [4]Albert Einstein College of Medicine, Bronx, NY, United States; [5]Biohaven Pharmaceuticals, New Haven, CT, United States
Correspondence: C. M. Jensen
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ObjectiveAssess the effects of rimegepant 75 mg on monthly migraine days (MMDs) through 52 weeks of open-label treatment when dosed every other day (EOD) for preventive treatment plus as needed (PRN) for acute treatment on nonscheduled dosing days.**Methods**Open-label extension phase of a 12-week, randomized, double-blind, placebo-controlled study evaluating rimegepant 75 mg EOD for preventive treatment of migraine in adults aged ≥18 years with a history of 4-18 moderate-severe monthly migraine attacks. Subjects completing a 4-week observation period and 12 weeks of double-blind treatment could continue with open-label rimegepant 75 mg EOD for preventive treatment for 52 weeks. On nonscheduled dosing days, subjects could take rimegepant 75 mg up to once per day PRN for acute treatment. **Results**Of 741 subjects who received double-blind treatment, 603 (81.4% [rimegepant n=301, placebo n=302]) were treated in the open-label phase (mean age 42.6 years, 82.7% female, hx of 7.9 monthly mod-sev attacks). Mean (SD)