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Conference report

Proceedings of Neuropeptides 2004, the XIV European Neuropeptides Club meeting

The XIV Annual Meeting of the European Neuropeptides Club (ENC) was held in the Complejo Residencial "Pérez-Mateos", in Alicante (Spain), 9–12th of May 2004. The meeting was supported by the Spanish Ministerio de Ciencia y Tecnología (SAF2002-11881-E), Novartis, Springer, Menarini Ricerche, Ipsen, and the local financial institutions CAM and Bancaja, as well as the Municipal Tourism Board of Alicante, and the University Miguel Hernández. The main scientific topics were (1) sensory neuropeptides and pain; (2) control of body functions and behaviour by different neuropeptides; and (3) hot topics and last advances. The organizing committee decided to maintain the name of Prof. Manfred Zimmermann for the main recognition of the ENC, to acknowledge his strong support to the development of the Club and the Annual Meeting since 1989. The "Manfred Zimmermann Award" of the ENC was given to Prof. Janos Szolczányi (University of Pécs, Hungary), as a recognition for his pioneering studies on pain and a lifetime devoted to neuroscience. The Special Plenary Lecture of Prof. Szoclzányi, entitled "Forty years in capsaicin research for sensory physiology and pharmacology" is published together with this report.

The major scientific topics were structured in keynote lectures and symposia. Among the lectures, the first one by Carmen de Felipe (Instituto de Neurociencias, UMH–CSIC, Spain) focused on the role of sensory neuropeptides in addiction. Using NK1 knockout mice, de Felipe and co-workers showed evidence that SP mediates the rewarding effects of different opiates, amphetamine, alcohol and nicotine. Eliminating NK1 positive neurons with SP conjugated with the neurotoxin saporin, de Felipe showed evidences that the amygdala is important for the control of the anxiety-related behaviours that follow opiates withdrawn. In his lecture, Riccardo Patachini (Department of Pharmacology, Menarini Ricerche, Firenze, Italy) presented an overview of distribution, biological effects and possible contribution to human diseases of urotensin-II (U-II). U-II is a cyclic dodecapeptide isolated in the mid 60s from the urophysis of the goby fish. More recently U-II isoforms have been identified in peripheral and central tissues of different mammalian species, including man, where they produce preferentially a strong vasoconstriction. Two compounds that possess high antagonist potency at the specific UT receptors have recently been described: urantide (peptidic) and ACT-058362 (nonpeptidic). As U-II levels have been found elevated in hypertension, heart failure and diabetes, these antagonistic compounds are expected to be useful tools to investigate the physiological and possibly pathological role of h-U-II in mammals, as well as for future therapeutic uses. The lecture of Luis de Lecea (Scripps Research Institute, CA, USA) focused on the effects of different neuropeptides, namely hypocretins and cortistatin, on the sleep–wakefulness cycle. Injection of hypocretin into the CNS increases the wakefulness and suppresses REM sleep, while injection of cortistatin alters sleep architecture. De Lecea has developed a mice strain lacking cortistatin. Those animals show an increase of sleep episodes in the dark cycle of the circadian rhythm. De Lecea also introduced new peptides that he discovered with region specific expression in the brain.

Among the symposia, the symposium on the role of CGRP in nociception and headache was chaired by Karl Messlinger (Institute of Physiology and Experimental Pathophysiology, Erlangen, Germany). Insights into the mechanisms of CGRP release in different in vitro and in vivo preparations were presented by Susane Sauer and Richard Carr (from the same institution), who respectively analysed the role of TRPV1 receptor and extracellular sodium on CGRP release from sensory nerves and terminals. Nociceptor sensitisation by CGRP, and the reduction of activity of brainstem neurons with dural input, by the non-peptidic CGRP receptor antagonist BIBN4096BS were presented, respectively, by Katharina Zimmermann and Michael Fischer (from the same institution). Kirsten Arndt

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(Boehringer–Ingelheim Pharma, GmbH, Biberach, Germany) presented the first clinical results of BIBN4096BS, that has been recently shown as effective as the triptans in the management of migraine attacks.

At the symposium chaired by Girolamo Caló (Department of Experimental and Clinical Medicine and Neuroscience Center, Ferrara, Italy) the therapeutic opportunities of novel ligands of the receptor for nociceptin/orphanin (NOP) were analyzed. Jean-Claude Meunier (Institut de Pharmacologie et de Biologie Structurale, CNRS, Toulouse, France), who first identified the peptide, presented several modes of differential binding of the peptide to the receptor using several photolabile NOP ligands, and suggested novel strategies for the rational design of NOP ligands. John McDonald (Department of Cardiovascular Sciences, Pharmacology and Therapeutics Group, University of Leicester, UK) presented the in vitro pharmacological profile at the human recombinant NOP receptor of a novel series of N/OFQ related peptides designed and synthesised by the research group of S. Salvadori (Department of Medicinal Chemistry, University of Ferrara, Italy). The NOP receptor antagonists UFP-101 and J-113397, as well NOP receptor knockout mice were used by Niall P. Murphy (RIKEN Brain Science Institute, Hirosawa, Japan) for the investigation of the relationship between the N/OFQ system and the rewarding properties of drugs of abuse, in particular morphine, alcohol and methamphetamine; by Girolamo Caló for demonstrating that blockade of N/OFQ-NOP receptor signalling causes antidepressant-like effects in rodents; and by Michelle Morari (Department of Pharmacology, University of Ferrara, Italy) for the investigation of the role of this system in modulating motor behaviour in physiological and pathological conditions (Parkinson disease models).

Illana Gozes (Sackler Medical School, Tel Aviv University, Israel), and Mario Delgado (Institute of Parasitology and Biomedicine, CSIC, Granada, Spain) co-chaired a symposium in which the role of different neuropeptides (the VIP/PACAP family, substance P, somatostatin cortistatin) in immunity was studied. Eberhard Weihe (Department of Molecular Neuroscience, Philipps University Marburg, Germany) gave an overview of the immune functions and dysfunctions in which neuropeptides are thought to be involved. Mario Delgado presented VIP as a molecule involved in the reciprocal neuroendocrine communications, both in health and disease, and suggested the potential therapeutic applications of VIP as immunomodulator. A practical approach of the immunomodulatory effects of VIP was presented by Rosa Gomáriz (Department of Cellular Biology, Complutense University, Madrid, Spain) in a model of Crohn's disease. Javier Leceta and co-workers (Department of Cellular Biology, Complutense University, Madrid, Spain), used gene microarrays to demonstrate the effects of VIP on the inhibition of expression of a wide number of cytokines, chemokines and their receptors in the joints of arthritic mice. James Washeck and co-workers (University of California at Los Angeles, Los Angeles, CA, USA) showed data on a facial nerve injury model in immunocompetent and immunodeficient mice, as well as in mice with targeted mutations of the genes encoding VIP and PACAP. Their results suggest that VIP/PACAP could act as bi-directional signaling molecules between injured neurons and immune cells. John Quinn and co-workers (Departments of Physiology and Human Anatomy and Cell Biology, University of Liverpool, UK) used a transgenic mice strain expressing a yeast artificial chromosome for the human PPT-A, in which they induced a pulmonary infection with a MHV-68 virus. In this context they were able to find substance P expression in a variety on non-neuronal cells at the lung and spleen.

The symposium entitled "Hot topics and last advances" was co-chaired by John Taylor (IPSEN Group, Milford, MA, USA), and Daniel Hoyer (Novartis Institutes for Biomedical Research, Basel, Switzerland). This symposium was aimed to present some recent developments on receptors pharmacology and neuropeptides expression regulation. Using a combination of binding assays and in vivo experiments, John Taylor presented evidences suggesting the existence of a novel, non-GHS-1a receptor for Ghrelin, that could be a major player of the stimulating effects of Ghrelin in feeding and weight gain. This putative receptor could open a new way for investigating antiobesity strategies. Daniel Hoyer presented data on the in vivo effects of two new somatostatin receptor antagonists in development by Novartis. SRA880 is an orally available and brain penetrant sst1 receptor antagonist that seems to reduce aggressive behaviour, enhance social recognition, and improve short-term memory in different animal models in vivo. ACQ090 is a sst3 receptor antagonist, also orally available and brain penetrant, that displays anxiolytic-like activity, and also seems to improve memory and/or learning. In order to clarify more in detail the neuroprotective effects of VIP/PACAP, Illana Gozes and co-workers presented data on vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP) that are implicated in neuronal survival. Inhibition of the expression of the PAC1 receptor-HOP2 splice variant produced neuronal death in cell culture. Further results showed that knocking out the VIP/PACAP responsive, activity-dependent neuroprotective protein (ADNP), results in impaired brain formation and embryonic death in vivo and cell death in vitro. NAP, (an 8 amino acid fragment of ADNP) which is neuroprotective in vitro and in vivo at subfemtomolar concentrations, binds tubulin, to promote microtubule polymerisation. Thus, NAP interacts (downstream to VIP) with the microtubular network to provide cellular protection. John Quinn and co-workers

used functional genomics in vivo and in vitro, as well as bioinformatics to demonstrate a major role for the transcription factors NRSF and bHLH in mediating tachykinin gene expression to NGF, NOS and VIP. Their findings can contribute to a better understanding of the plasticity of neurotransmitter expression that occurs in different psychological and neurological disorders. Jerzy Nowak (Polish Academy of Sciences, and Medical University, Lodz, Poland) showed data on the interspecies differences in signaling pathways of the peptide histidine–isoleucine (PHI) and peptide histidine–methionine (PHM) and the more typical neuropeptides VIP and PACAP. All of them seem to share a neuromodulator role in the vertebrate CNS, but PHI/PHM seem to be less potent in avian brain.

A last special symposium co-chaired by Adolfo Aracil and Juana Gallar (Instituto de Neurociencias, UMH–CSIC, Alicante, Spain) was arranged with a series of free communications that were sent by young investigators, and were selected by the organizing committee to be presented as papers. Valeria Camarda and co-workers (Department of Pharmacology, University of Ferrara, Ferrara, Italy) presented data on the effects of urantine, urotensin II and [Orn8]U-II on recombinant UT-II receptors. Marcelo Trevisani and co-workers (Interdisciplinary Center of Excellence for the Study of Inflammation, University of Ferrara, Ferrara, Italy) presented data on the CGRP release from spinal cord slices, induced by menthol, an agonist of the TRPM8 receptor (the so-called ''cold receptor''). Jason McDougall (Department of Physiology and Biophysics, University of Calgary, Calgary, Canada), showed that intraarterial endomorphin-1 losses its antinociceptive effects in a rat chronic arthritis model, possibly reflecting the downregulation and/or desensitisation of μ-opioid receptors during chronic inflammation. Victor Chaban (Department of Neurobiology and Center for Neurovisceral Science and Women's Health, University of California at Los Angeles, Los Angeles, CA, USA), showed a potential pro-nociceptive effect of estrogen acting through membrane-associated estrogen receptors (ER) in cultured DRG neurons. Activation of ER can attenuate the cellular responses to μ-opioid receptors. Jessica J. Hawes and co-workers (Department of Psychiatry, Yale University of School of Medicine, New Haven, CT, USA), demonstrated that GalR1 receptor for galanin is upregulated in the locus coeruleus by neuronal activity and changes in cAMP levels, a mechanism that can explain the effects underlying the role of galanin in opiate addiction. Catalina Abad (Department of Cellular Biology, Complutense University, Madrid, Spain) studied the effects of VIP on the mRNA levels of different proinflammatory mediators by real time PCR, in a colitis model in mice. VIP ameliorated colitis and inhibited the expression of a wide range of proinflammatory molecules. Vincent Lelievre and co-workers (David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA) presented the preliminary results of the phenotyping and genotyping of a double mutant strain for the patched gene (ptc) and PACAP gene that they have generated. Lacking of both genes increase dramatically the frequency of appearance of medulloblastoma. Tumor cells displayed high levels of PAC1 receptor, that is involved in inhibition of cell proliferation, thus suggesting a potential future role for PACAP as therapeutic agent for medulloblastoma.

In addition to the symposia, another 35 free communications were accepted for poster presentation at the meeting. Abstracts of all the communications presented at the meeting are published together with this report.

Neuropeptides 2005 will be held in Riga (Latvia) under the sponsorship of the Latvian Academy of Sciences, and will be chaired by Prof. Mara Pilmane.

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