BELGIAN SOCIETY OF

PHYSIOLOGY AND PHARMACOLOGY

NATIONAL COMMITTEE OF PHYSIOLOGY AND PHARMACOLOGY

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Spring Meeting

Friday, May 10th 2019

PROGRAMME AND ABSTRACT BOOK

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Venue

Palace of the Academies
Royal Academy of Medicine of Belgium
"Rubens room"
Rue Ducale / Hertogstraat 1
1000 Brussels

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Local host

Prof. Dr. Julien Hanson
Laboratory of Molecular Biology – GIGA Institute
ULiège
Belgium

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with support of the

Royal Flemish Academy of Belgium for Science and the Arts

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Oral Communications

10.00-10.15 EFFECT OF KETAMINE ON THE EXCITABILITY OF DORSAL RAPHE NEURONS
Cyrine Hmaied, Stanislav Koulchitsky, Dominique Engel, Vincent Seutin (ULiège)

10.15-10.30 TREATMENT WITH A TNAP INHIBITOR PREVENTS THE DEVELOPMENT OF VASCULAR MEDIA CALCIFICATION
Britt Opdebeeck (UAntwerp)

10.30-10.45 GPR101 ORPHAN RECEPTOR: A NOVEL CAUSE OF GROWTH HORMONE DEREGULATION
Dayana Abboud, Adrian Daly, Nadine Dupuis, Céline Laschet, Pierre Geubelle, Bernard Pirotte, Albert Beckers, Julien Hanson (ULiège, CHU of Liège)

10.45-11.00 A SCREENING-COMPATIBLE NANOLUCIFERASE COMPLEMENTATION ASSAY FOR THE DETECTION OF GPCR-G PROTEIN INTERACTIONS
Céline Laschet, Nadine Dupuis, Stéphanie Vandevoorde, Dayana Abboud, Julien Hanson (ULiège)

Key note lecture

11.00-12.00 “TIME IS OF THE ESSENCE”. THE KINETICS OF DRUG ACTION.
Ad P. IJzerman **(**Leiden Academic Centre for Drug Research, Division of Drug Discovery and Safety, Leiden University, PO Box 9502, 2300RA Leiden, The Netherlands)

12.00-13.00 **Lunch – Guided Poster Session**

Posters

(height 120 cm – width 100 cm)

1. DMPK PROMOTER SILENCING BY CRISPRi AS A NEW THERAPEUTIC STRATEGY IN MYOTONIC DYSTROPHY TYPE 1
   F. Porquet, S. Ormenese, F. Giroulle, L. Massotte, S. Freeman, A. Revnic, H. Gazon, D. Furling, E. Di Valentin, N. Gillet, A.F. Klein, V. Seutin, L. Willems. (ULiège, Sorbonne Universités UPMC Univ Paris 06, UNamur)

2. GABA-ERGIC TRANSMISSION IN ALZHEIMER’S DISEASE
   Anna Kreis, Nathalie Pierrot, JN Octave, Philippe Gailly (UCL)

3. ETHANOL-INDUCED LOCOMOTOR SENSITIZATION MODULATES HYPERAROUSAL IN DBA/2J MICE
   Thierry Matonda-ma-Nzuzi, Vincent Didone, Vincent Seutin, Ezio Tirelli, Etienne Quertemont (ULiège)

4. SOMATOSTATIN ANALOGUE RESISTANCE IN X-LAG SYNDROME - IDENTIFICATION OF THE UNDERLYING MECHANISMS
   Stéphanie Vandevoorde, Dayana Abboud, Céline Laschet, Julien Hanson, Adrian F. Daly, Albert Beckers (ULiège)

Oral Communications

13.00-13.15 CKD PROGRESSION IS HALTED BY METFORMIN TREATMENT
Raphaëlle Corremans, Anja Verhulst, Benjamin A. Vervaet, Patrick C. D'Haese (UAntwerp)

13.15-13.30 ANCESTRAL IP3 RECEPTORS ARE MODULATED BY BCL-2
Nicolas Rosa, Hristina Ivanova, David Yule, Geert Bultynck (KU Leuven)

13.30-13.45 INVERTING THE COUPLING BETWEEN ACTIVATION AND INACTIVATION GATING IN KV2.1 AND KV3.1 CHANNELS
Laura Coonen, Evy Mayeur, Nicolas De Neuter, Dirk J. Snyders, Luis G. Cuello, Alain J. Labro (UAntwerp Texas Tech University)

Coffee – Tea

Key note lecture

“Time is of the essence”. The kinetics of drug action.

Ad P. IJzerman

Leiden Academic Centre for Drug Research, Division of Drug Discovery and Safety, Leiden University, PO Box 9502, 2300RA Leiden, The Netherlands

In early drug discovery one strives to optimize the properties of drug candidates for a given therapeutic target, usually focusing on standard pharmacological parameters of affinity, potency and intrinsic activity. There is mounting evidence, however, that the often ignored *kinetic* aspects of the interaction between a drug and its target in the body are highly relevant for *in vivo* efficacy and clinical success. This ignorance may be one of the reasons for the high attrition rates in drug discovery, as it has been analyzed that quite a few recently marketed drugs had indeed improved kinetic profiles.

In this presentation I will provide an overview of our own recent efforts in this respect, while addressing a particular class of drug targets, G protein-coupled receptors. I will first introduce some concepts of receptor kinetics, after which I will present two case studies, focusing on pharmacological and physiological principles. Ultimately our efforts may lead to a better understanding of structure – kinetics relationships (SKR) to be used in the design of kinetically appealing molecules.

ORAL 1

EFFECT OF KETAMINE ON THE EXCITABILITY OF DORSAL RAPHE NEURONS

Cyrine Hmaied, Stanislav Koulchitsky, Dominique Engel, Vincent Seutin

Laboratory of Neurophysiology, GIGA Neurosciences, ULiège

INTRODUCTION | The non-competitive NMDA antagonist ketamine is an old drug that traditionally has been used as an anesthetic with a unique profile of "dissociative anesthesia". More recently, it has been repeatedly shown that a single infusion of a subanaesthetic dose of ketamine is able to quickly relieve major depressive symptoms (including suicidal thoughts) in severely affected patients. We therefore tested the hypothesis that ketamine and/or its metabolites acutely modulate the synaptic inputs of serotoninergic (5HT) neurons.

METHODS | Whole-cell patch clamp recordings were performed in brainstem slices from juvenile rats. 5HT neurons were identified as cells generating an outward current > 30 pA in voltage clamp at -60 mV during superfusion of 100 nM of the 5HT1A agonist 8-OH-DPAT.

RESULTS | We first tested the effect of ketamine on isolated spontaneous excitatory postsynaptic currents (sEPSCs). We found that 10 µM ketamine increases AMPA EPSCs in terms of amplitude and frequency in ~ half of 5HT neurons (N total = 18).This effect was not observed when recording from non-5HT neurons (N = 6). The same effect was observed with its metabolite 2,6 hydroxynorketamine (HNK).

CONCLUSION | Ketamine and its metabolite HNK robustly and specifically enhance AMPA EPSCs onto a subgroup of pharmacologically identified 5HT neurons. It remains to be determined what is the mechanism of this effect and whether this subgroup projects to specific targets, given that subpopulations of DR 5HT neurons have been shown to have specific and non-overlapping projections.

ORAL 2

TREATMENT WITH A TNAP INHIBITOR PREVENTS THE DEVELOPMENT OF VASCULAR MEDIA CALCIFICATION

Britt Opdebeeck

University of Antwerp, Department of Biomedical Sciences, Laboratory of Pathophysiology

INTRODUCTION | Arterial media calcification (AMC) is frequently seen in elderly and patients with diabetes and chronic kidney disease. Tissue non-specific alkaline phosphatase (TNAP), which is highly expressed in calcified arteries, degrades extracellular pyrophosphate, a well-known calcification inhibitor, into phosphate ions, by which pyrophosphate loses its ability to block AMC. We aimed to evaluate whether a TNAP-inhibitor is able to prevent the development of AMC in a rat model of warfarin-induced AMC.

METHODS | To induce AMC, rats received a diet containing 0.30% warfarin and 0.15% vitamin K1 and were subjected to vehicle(n=10) or 10mg/kg/day TNAP-inhibitor(n=10) for 7 weeks The aortic mRNA expression of osteo/chondrogenic marker genes was analyzed by qPCR. At sacrifice, AMC was evaluated by measurement of the total calcium content in the arteries and quantification of the area% calcification on Von Kossa stained sections of the aorta.

RESULTS | Warfarin exposure resulted in distinct calcification in the aorta and peripheral arteries in vehicle treated rats. Importantly, daily treatment with a TNAP-inhibitor significantly reduced AMC as indicated by a significant decrease in calcium content in the arteries and a distinct reduction in area% calcification on Von Kossa stained aortic sections as compared to vehicle treated controls. Treatment with a TNAP-inhibitor did not modulate the mRNA expression of osteo/chondrogenic marker genes runx2, TNAP, SOX9, collagen 1 and 2.

CONCLUSION | Treatment with a TNAP-inhibitor significantly reduced the development of AMC in the aorta and peripheral vessels of warfarin exposed rats. Further research will explore the signaling pathways by which this TNAP-inhibitor inhibits AMC.

ORAL 3

GPR101 ORPHAN RECEPTOR: A NOVEL CAUSE OF GROWTH HORMONE DEREGULATION

ABBOUD Dayana (1,2), DALY Adrian (3), DUPUIS Nadine (1,2), LASCHET Céline (1,2), GEUBELLE Pierre (1,2), PIROTTE Bernard (2), BECKERS Albert (3), HANSON Julien (1,2)

(1) ULG, Laboratory of Molecular Pharmacology, GIGA-Molecular Biology of Diseases, CHU, tour GIGA (+4), 11, av. de l'hôpital, 4000 Liège, Belgium (2) ULG, Laboratory of Medicinal Chemistry, CIRM, CHU, B36 (+5), 11, av. de l'hôpital, 4000 Liège, Belgium (3) Department of Endocrinology, CHU of Liège

INTRODUCTION | GPR101 is an orphan GPCR. Recently, a clinical study showed that GPR101 is strongly associated X-linked acrogigantism syndrome, a rare disorder characterized by excessive growth hormone secretion. The GPR101 function in growth regulation is elusive and this lack of precise information precludes its validation as a drug target. Therefore, we sought to characterize GPR101 signalling pathways.

METHODS | We cloned in expression vector the human GPR101 fused to an N-terminus FLAG epitope and we generated cells stably expressing FLAG-GPR101. Subsequently, we determined the receptor precise cellular localization and trafficking by using flow cytometry and microscopy. We then used several pharmacological transduction assays and we developed a bioluminescent β-arrestin complementation test to decipher GPR101 signalling pathways. We also generated several mutants that can increase and/or alter GPR101 activity.

RESULTS | GPR101 is characterized by a very high constitutive activity. We detected important constitutive cAMP production that was linked to Gs activity, and we completed our study with an examination of receptor coupling to other G proteins and pathways. We also demonstrated that the basal recruitment of β-arrestins leads to constitutive internalization of the receptor. We also applied targeted mutagenesis and identified putatively important residues for constitutive signalling.

CONCLUSION | The characterization of GPR101 signalling pathways constitute an absolute prerequisite to establish a strong mechanistic link between GPR101 activation in the pituitary and gigantism.

ORAL 4

A SCREENING-COMPATIBLE NANOLUCIFERASE COMPLEMENTATION ASSAY FOR THE DETECTION OF GPCR-G PROTEIN INTERACTIONS

Céline Laschet, Nadine Dupuis, Stéphanie Vandevoorde, Dayana Abboud, Julien Hanson

ULiège, Laboratory of Molecular Pharmacology, CIRM, GIGA-Molecular Biology of Diseases, CHU, tour GIGA (+4), 11, av. de l'hôpital, 4000 Liège, Belgium

INTRODUCTION | Although it is one of the most characterized protein-protein interactions, a flexible and screening-compatible GPCR-G protein interaction assay is still missing.

METHODS | We set up a novel technique to detect ligands inducing a G protein-GPCR interaction. This complementation assay is based on the recently described ultra-bright and small nanoluciferase.

RESULTS | We demonstrated that our system can be used to profile compounds with regard to the G proteins they activate through a given receptor. Furthermore, we established the proof of applicability of our procedure with the dopamine receptor D2, a prototypical class A aminergic receptor whose coupling to Gαi/o family has been extensively studied. We conducted the screening of a library of known drugs on the D2-Gαi1 and D2-Gαo interactions and could fish five agonists used as antiparkinsonian medications. We performed further profiling of the ligands and demonstrated that piribedil and pergolide were, relatively to dopamine, full agonists in the Gαi1 assay while being partial agonists for Gαo.

CONCLUSION | Therefore, this novel assay could be used for drug discovery programs aiming at the discovery of molecules able to selectively modulate a particular G protein pathway and increase their therapeutic effect or mitigate their unwanted reactions

ORAL 5

CKD PROGRESSION IS HALTED BY METFORMIN TREATMENT

Raphaëlle Corremans, Anja Verhulst, Benjamin A. Vervaet, Patrick C. D'Haese

Laboratory of Pathophysiology, University of Antwerp

INTRODUCTION | Metformin, the first-line drug for type-2 diabetes mellitus, also exerts multiple benign pleiotropic actions on different organs. Recent preclinical and clinical data point towards a beneficial impact of metformin on the kidney. Chronic kidney disease (CKD) is a worldwide recognized public health problem and represents a progressive loss of renal function. To date effective treatment for CKD is lacking. To investigate whether metformin is able to attenuate the progression of established CKD, the rat model of adenine-induced-CKD was used.

METHODS |Metformin or vehicle treatment (daily oral gavage) was initiated after 4 and 5 weeks of adenine administration, respectively, and continued during 4 weeks until the end of the study (i.e. week 8 and 9). Renal function (serum creatinine) and morphology (PAS staining) were examined.

RESULTS | Serum creatinine levels dramatically rose in vehicle-treated rats: from 0.6±0.1 mg/dL to 5.7±0.6 mg/dL after 8 weeks and to 4.8±1.1 mg/dL after 9 weeks. This increase was almost completely prevented in the metformin-treated CKD rats (significantly lower serum creatinine after 8 (2.0±0.5mg/dL) and 9 (2.9±0.5mg/dL) weeks compared to vehicle treatment). Histological examination of the kidney revealed that vehicle-treated rats showed tubular dilation, epithelial flattening, brush border loss, basement membrane thickening, and tubulointerstitial cellular infiltration, all being less severe in metformin treated rats. Compared to vehicle-treated rats, the tubulointerstitial area percentage, consisting of both extracellular matrix and infiltrating cells, significantly decreased with 33% and 23% in rats receiving metformin from week 4 and 5, respectively.

CONCLUSION | Metformin is able to slow down progression of pre-existing CKD.

ORAL 6

ANCESTRAL IP3 RECEPTORS ARE MODULATED BY BCL-2

Nicolas Rosa, Hristina Ivanova, David Yule, Geert Bultynck

Laboratory of Molecular and Cellular Signaling, KU Leuven

INTRODUCTION | Calcium signalling is an important feature in all living systems. In complex eukaryotes, Ca2+ is released from the endoplasmic reticulum (ER) via the inositol 1,4,5-trisphosphate receptor (IP3R). The properties of IP3R channels are tightly regulated by several factors, including the B-cell lymphoma-2 (BCL-2) family of proteins. Bcl-2 is an anti-apoptotic protein, which is evolutionary conserved. Bcl-2 inhibits IP3R through complex interactions, one of which involves the central, modulatory region of IP3R, in particular a stretch covering the residues 1389-1408 (according to mouse IP3R1). Strikingly, this stretch is highly conserved among the different IP3R isoform during evolution, even in species that do not express any BCL-2 family members.

METHODS |Here, we focused on one of the most ancestral IP3R orthologues present in the unicellular organism Capsaspora owczarzaki (co).

RESULTS | Sequence analysis revealed that the residues 1389-1408 of mouse IP3R1 were largely conserved in coIP3R, suggesting that coIP3R could serve as a target for human Bcl-2. Exploiting a HEK293 triple knockout cells, lacking any endogenous IP3R expression, but re-expressing coIP3R, we show that coIP3R is an active channel, able to release Ca2+ in response to agonist and BCL-2 overexpression reduces coIP3R-mediated Ca2+ release. In cellulo, BCL-2 and coIP3R form native protein complexes and biotin-BH4-Bcl2 peptides are able to interact with co-IP3Rs.

CONCLUSION | These data demonstrated that ancestral IP3Rs already hold the signature for Bcl-2 binding and thereby their ability to be regulated by Bcl-2 precedes the actual appearance of BCL-2 in evolution.

ORAL 7

INVERTING THE COUPLING BETWEEN ACTIVATION AND INACTIVATION GATING IN KV2.1 AND KV3.1 CHANNELS

Laura Coonen, Evy Mayeur, Nicolas De Neuter, Dirk J. Snyders, Luis G. Cuello, Alain J. Labro

Molecular, Cellular and Network Excitability, University of Antwerp, 2610 Antwerp, Belgium, and Cell Physiology and Molecular Biophysics, Center for Membrane Protein Research, Texas Tech University Health Sciences Center, Lubbock, TX 79430 USA

INTRODUCTION | Voltage gated potassium (Kv) channels display several inactivation processes, including N, C- and U-type. C-type inactivation is attributed to a non-conductive conformation of the channels' selectivity filter (SF). Moreover, as conformational changes in the activation gate (AG) affect the SF structure and vice versa, it is said that an allosteric coupling is present. The second threonine of the SF signature sequence (e.g., TTVGYG) has been proven essential for this allosteric coupling. Conversely, the molecular determinants of U-type inactivation are less well characterized.

METHODS |To study the role of the SF in U-type inactivation, we substituted the second threonine of the TTVGYG sequence by alanine in hKv2.1 and hKv3.1 channels, which are known to display U-type inactivation.

RESULTS | For hKv2.1-T377A, the U-type inactivation profile was inverted. I.e. hKv2.1-T377A displayed closed state inactivation and channel opening recovered conductivity. This recovery was accelerated by increasing extracellular K+ concentration. For hKv3.1-T400A, U-type inactivation was not inverted but abolished during prolonged depolarizations. Increasing the extracellular K+ concentration did increase the current amplitude, suggesting that also hKv3.1-T400A adopted a particular inactivated state when the channels were closed. The behaviour of both hKv2.1-T377A and hKv3.1-T400A are similar to what has been reported for Shaker and hKv1.5 T to A mutants.

CONCLUSION | Our data support a significant role of the SF in U-type inactivation, which can be inverted (abolished) by the T to A substitution. By extension, an allosteric coupling between the SF and the AG seems present in U-type inactivation as is observed for C-type inactivation in Shaker-type Kv channels.

POSTER 1

DMPK PROMOTER SILENCING BY CRISPRi AS A NEW THERAPEUTIC STRATEGY IN MYOTONIC DYSTROPHY TYPE 1

Porquet F.[1,2], Ormenese S.3, Giroulle F.4, Massotte L.[2], Freeman S.[3], Revnic A.[4], Gazon H.[1], Furling D.[5], Di Valentin E.[4], Gillet N.[6], Klein A.F.[5], Seutin V.[2]*and Willems L.[1]*

1. Mol Cell Epigenetics, 2. Neurophysiol, 3. In Vitro Imaging, 4.Viral Vectors, all at GIGA, ULiège; 5. Institut de Myologie, Sorbonne Universités UPMC Univ Paris 06. 6. URVI, UNamur (Belgium) * These authors contributed equally to this work.

INTRODUCTION | Myotonic dystrophy type 1 (DM1) is a life threatening disease that causes severe physical and mental disabilities. Unfortunately, there are currently only symptomatic treatments for this condition. Therefore, our team aims at elaborating a new curative approach which consists in the silencing of the promoter of the gene with pathogenic excessive repeats (Myotonin-protein kinase or DMPK) using the CRISPRi system.

METHODS | The ability of our CRISPRi system to inhibit the promoter of DMPK was tested in immortalized myoblasts from DM1 patients. For this purpose, lentiviral particles were produced using CRISPRi plasmids with their own sgRNAs. Next, these myoblasts were transduced and selected with blasticidin. Total DMPK mRNA was subsequently titrated by RT-qPCR and the density/size of nuclear DMPK RNA foci (ribonucleoproteic particles that are a hallmark of the disease) were determinated by FISH.

RESULTS | Two out of 12 sgRNAs led to ~70% inhibition of DMPK transcription as well as a significant reduction in the intensity/number of foci in the cells. Other sgRNAs were less efficient or completely devoid of any activity.

CONCLUSION | Our CRISPRi system is able to efficiently prevent the production of DMPK mRNA and formation of foci in pathological myoblasts. Further experiments will test whether functional abnormalities in pathological myocytes derived from the myoblasts can be rescued by our two most efficient CRISPRi constructs.

POSTER 2

GABA-ERGIC TRANSMISSION IN ALZHEIMER'S DISEASE

Anna Kreis, Nathalie Pierrot, JN Octave, Philippe Gailly

Université Catholique de Louvain

INTRODUCTION | Alzheimer's disease (AD) is the most common neurodegenerative disorder characterized by cognitive impairment and neuronal loss due to formation of senile plaques containing amyloid-β peptide, a cleavage product of the amyloid precursor protein (APP) and tau pathology. However, arising evidence suggests that a disruption between inhibitory and excitatory neurotransmission is present decades before clinical symptoms become evident. GABA is the predominant inhibitory neurotransmitter in the brain, functionally dependent on the electrochemical chloride gradient in neurons. Chloride concentration in neurons is regulated by KCC2 (Cl- extruder) and NKCC1 (Cl- importer). Previous observations of the group of JN Octave (UCL) revealed a KCC2 decrease, but not NKCC1, in cultured cortical rat cells overexpressing wild type human APP, leading to a disruption in GABAergic transmission.

METHODS | Using a mouse model that overexpresses human APPwt we analyzed the effect of APP on GABAergic transmission in two different age groups.

RESULTS | Behavioral experiments revealed impairment in spatial memory in hAPPwt in both age groups (6 and 12 months). Western blot analysis of hippocampal lysates revealed no changes in KCC2 but surprisingly a significant decrease in NKCC1 in hAPPwt mice at 12 months. A downregulation of main GABAAR subunits (α-1, α-3), GABABR as wells as AMPA and NMDA subunits was present as well in hAPPwt mice (12 months).

CONCLUSION | Due to evident changes in excitatory neurotransmission the induction and maintenance of memory is impaired alongside with downregulation of main proteins involved in inhibitory neurotransmission, leading to abnormal signaling in hAPPwt mice.

POSTER 3

ETHANOL-INDUCED LOCOMOTOR SENSITIZATION MODULATES HYPERAROUSAL IN DBA/2J MICE

Thierry Matonda-ma-Nzuzi, Vincent Didone, Vincent Seutin, Ezio Tirelli, Etienne Quertemont

Laboratory of Neurophysiology, GIGA Neurosciences, Liège University, B-4000 Sart Tilman, Liège

INTRODUCTION | Co-occurrence of substance use disorder (SUD) and post-traumatic stress disorder (PTSD) is common. These last years a growing body of literature were devoted to the influence of SUD on PTSD symptoms. Animal studies on this topic are scarce. Two of the latest studies on this topic have used drug-induced locomotor sensitization as an animal model of drug addiction. These two studies concluded that ethanol-induced locomotor sensitization (EILS) and cocaine-induced locomotor sensitization modulate the sensitized fear of a PTSD-like condition (PTSDLC). With respect to the alcohol study, sensitized fear was overexpressed in stressed mice beyond theoretical period of EILS (< 4 weeks). To better understand the modulating effect of EILS on this PTSDLC symptom the present study assessed sensitized fear at different time intervals following an EILS.

METHODS | Female DBA/2J mice were submitted to an EILS procedure with a daily ethanol dose of 2 g/kg administrated during 10 days and then, 7 days later, they underwent the PTSDLC procedure with an electric foot-shock paradigm. Sensitized fear and conditioned fear were assessed 2, 4 and 6 weeks after the electric footshock.

RESULTS | Statistical analyses show that EILS increased sensitized fear and conditioned fear till 5 weeks after the last ethanol administration. In contrast, 7 weeks after the last ethanol administration, the modulating effect of EILS was strongly decreased for sensitized fear and became non-significant for conditioned fear.

CONCLUSION | The present study confirms the modulating effect of EILS on sensitized fear. This modulating effect persists beyond the theoretical period of EILS.

POSTER 4

SOMATOSTATIN ANALOGUE RESISTANCE IN X-LAG SYNDROME - IDENTIFICATION OF THE UNDERLYING MECHANISMS

Stéphanie Vandevoorde, Dayana Abboud, Céline Laschet, Julien Hanson, Adrian F. Daly, Albert Beckers

Laboratoire de Pharmacologie Moleculaire, Université de Liège, Avenue de l'Hôpital 1, B34 (+4), B-4000 Liège

INTRODUCTION | X-Linked Acro-Gigantism (X-LAG) Syndrome is a rare genetic disorder caused by a microduplication on the X-chromosome of an array of genes comprising gpr101. This disorder leads to a pituitary adenoma secreting since early childhood high levels of growth hormone, via elevated cAMP levels inside the somatotrophes of the adenoma. However, X-LAG patients cannot be treated by somatostatin analogues (SSA), such as octreotide, and present only a minor decrease in cAMP in response to pasireotide.

METHODS & RESULTS | In heterologously transfected GH3 cells, cAMP levels do not decrease in presence of GPR101 in response to SSA treatment because the coupling of Gαi-proteins to the somatostatin receptors expressed in the pituitary adenoma (i.e., SSTR2 and SSTR5) is decreased in presence of GPR101. Moreover, due to a decreased arrestin-coupling to SSTR2 in presence of GPR101, SSTR2 is less endocytosed after stimulation.

CONCLUSION | GPR101 quenches the signalling pathways of SSTR2 and SSTR5. However, further studies are necessary to determine the underlying cause of the patients' resistance to SSA