

International Workshop on cAMP signaling and phosphodiesterases: from genetics to function in adrenal physiology and diseases”

Paris, France, July 11-12, 2013

SCIENTIFIC REPORT

SUMMARY

The international Workshop on cAMP signaling and phosphodiesterases: from genetics to function in adrenal physiology and diseases” was held in Paris, at Cochin Medical School within the Paris Descartes University Conference room and The Cochin Hospital on July 11-12, 2013. Despite the fact that the Conference room and the Poster session and lunch rooms were made available at no charge by the University and the Hospital the meeting was made only possible by the generous support from the European Science Foundation through the ENSAT program.

It gathered 96 participants mainly from Europe and also North America that discussed around 25 oral presentations, one plenary conference and 8 posters addressing the cAMP signaling pathway in adrenal cortex physiology, its genetics and its implication in adrenal disorders.

It clearly allowed to establish contact between clinician and basic researchers and to stimulate international collaborations.

SCIENTIFIC CONTENT

The cAMP signaling pathway as explained below plays a major role in adrenal cortex physiology and diseases, especially cortisol secreting tumors. This signaling pathway is ubiquitous and is the focus of major basic research. However due to the rarity of adrenal diseases only few basic researchers are studying specifically the adrenal gland. One of the major aims of the meeting was to bring together clinical researchers working on adrenal tumors and basic researchers working on the cAMP signaling pathway. The Workshop was built to answer this important need by offering a meeting place for basic and clinical scientists interested in PKA, phosphodiesterases (PDEs) and related topics studying its physiology and its alterations in human diseases, especially adrenal disorders and tumors. It stimulated international collaborations and served as an incubator for interdisciplinary exchanges in the fields covered by the participants. One of the major successes of the meeting was also that students and post-docs attended the meeting which in the long term will be an important thing for the development of research on adrenal tumors.

The cAMP pathway plays a major role in the control of the adrenal cortex. The pituitary hormone ACTH signals mainly through the second messenger cAMP to stimulate adrenal steroid synthesis and secretion. In absence of this signal the adrenal cortex undergoes apoptosis and is atrophic. On the other hand chronic oversecretion of ACTH is responsible for adrenal hypertrophy and cortisol

excess as observed in Cushing's disease. Activation of the cAMP pathway have been demonstrated in various types of endocrine tumors: pituitary, thyroid, adrenal, gonads. In the adrenal cortex illegitimate expression of membrane receptors coupled to G protein have been describe in patients with adrenal Cushing due to macronoduloar adrenal hyperplasia. Several of these receptors activate the cAMP pathway. Activating mutations of the Gs protein have been observed in patients with Mc Cune Albright. When the somatic mosaic mutation is present in the adrenal cortex Cushing syndrome due to macronodular hyperplasia is observed. The multiple endocrine neoplasia syndrome Carney complex is an autosomal dominant disease. The main manifestation of Carney Complex is adrenal Cushing due to primary pigmented nodular adrenal cortical disease, a form of bilateral benign adrenal tumor. The Carney complex gene is the regulatory sub-unit of the Protein Kinase A, a central component of the cAMP pathway and the major target of cAMP itself. Inactivating mutations of the phosphodiesterases PDE11A4 and PDE8B have been also observed in patients with adrenal Cushing due to micronodular adrenal hyperplasia. The physiology of the cAMP signaling is complex due to the fine tuning of this important signaling pathway. The subcellular localization of each component of the pathway and its dynamic trafficking is an important aspect. Considering the importance of the cAMP patwahy in adrenal disease there is an important need for merging the gap between the genetic and clinical observations and the knowledge of the cellular and molecular physiology of the cAMP pathway.

The scientific program contained talks on structure, function and regulation of the components of the cAMP pathways important in adrenal physiology: seven transmembrane receptors, G protein, phosphodiesterases, protein kinase A. Both the structural biology, molecular genetics and cellular physiology aspects were presented. New technologies like FRET that have been recently developed to study this pathway and their potential to investigate genetic alterations observed in human diseases were presented and discussed. Sessions were specifically dedicated to the pathophysiology of adrenal diseases and tumors associated with genetic alterations of this pathway. A special emphasis was put on cortisol secreting tumors due to alterations of key component of the pathway. Potential therapeutic perspective by targeting the pathway were discussed as well as current development due to the progress of genomics to identify cAMP signaling genetic alterations in adrenal tumors.

PARTICIPANTS

The workshop attracted 108 participants from 7 countries from Europe and the USA. There were 32 speakers or chairpersons, among them 21 were invited.

There was no registration fee in order to allow students and post-doc to participate actively.

PARTNERS

The principal partner and the single one to give specific financial support to the meeting organizers was the European Science Foundation. Co-partners were The Paris-Descartes University-Cochin Medical School (conference room at no charge), the Cochin Hospital (Lunch room at no charge) and the NIH (direct support of the travel of the speakers coming from the NIH/USA).

MEETING PROGRAM

Thursday July 11th (a.m.)

8h30-8h50: **Registration**

8h50: **Introduction:** Anna Spada, Jérôme Bertherat, Constantine Stratakis,

cAMP signaling networks (I)

Session I Moderators : **Antonio Feliciello and Rodolphe Fischmeister**

- 9h00 - A PKA-ezrin-connexin 43 signaling complex controls gap junction communication in cell fusion, *Guillaume Pidoux*, Paris, France
- 9h25 - Cytoskeleton in GPCR targeting and signaling, *Erika Peverelli*, Milano, Italy
- 9h50 - Role of Epac-1 in beta adrenergic-mediated signals in the heart, *Frank Lezoualc'h*, Toulouse, France
- 10h15 - PKA network and GPCR cascades, *Eduard Stefan*, Innsbruck, Austria

10h40 - 11h30 - COFFEE BREAK AND POSTERS VISIT (Cloître)

- P1- Epac 2 is involved in the inflammatory and migratory response of trans-differentiated Vascular Smooth Muscle Cells. Amélie Vromman/ Isabelle Limon. Paris, France
- P2- Paternal *GNAS* mutations lead to severe intrauterine growth retardation (IUGR) and provide evidence for a role of XL α s in fetal development. Nicolas Richard/ Marie-Laure Kottler. Caen, France .
- P3- PKA induced phosphorylation inhibits its own association to A-kinase anchoring proteins
Pepijn P. Burgers/Arjen Scholten. Utrecht, Netherlands
- P4- Dendritic tree confers nonlinearity in signaling pathway integration from dendrite to nucleus.
Nicolas GERVAS/ Jean-Antoine GIRAULT. Paris, France

Session II Moderators : **Marie-Laure Kottler and Paolo Beck-Peccoz**

- 11h30 - The role of alterations in cAMP levels in the deformability and adhesion of Plasmodium falciparum-infected red blood cells, *Gordon Langsley*, Paris, France
- 11h55 - The role of cAMP signaling bone and adrenal pathophysiology and physiology, *Michael Collins*, Bethesda, USA
- 12h20 - Role of G Proteins in Central Regulation of Energy and Glucose Metabolism, *Lee S Weinstein*, Bethesda-USA
- 12h45 - Proteomic analysis of the cAMP/PKA signaling, *Paul Insel*, San Diego, USA

13h10-14h10 - LUNCH (Cloître)

Thursday July 11th (p.m.)

cAMP signaling networks (II)

Session III Moderator : **Xavier Bertagna and Constantine Stratakis**

- 14h10 - Spatiotemporal dynamics of cAMP signaling in the functional genomics era, *Kjetil Tasken*, Oslo, Norway
 14h35 - cAMP regulation of adrenal steroids by Rho effector proteins and the cytoskeleton, *Marion Sewer*, San Diego, USA
 15h00 - cAMP signaling and aberrant receptors in adrenal tumors, *Hervé Lefebvre*, Rouen, France
 15h25 - cAMP signaling and aberrant receptors in primary aldosteronism, *Franco Mantero*, Padova, Italy

15h50 - 16h40 - COFFEE BREAK AND POSTERS VISIT (Cloître)

- P5- PKA RI α Homodimer Structure Reveals Intermolecular Interface with Implications for Cooperative cAMP Binding and Carney Complex Disease (CNC) Jessica G.H/Susan S. Taylor San Diego, La Jolla, California, USA
 P6- Investigating the role of cAMP phosphodiesterases in the regulation of K⁺ channels in rat coronary smooth muscle. Boris Manoury/Véronique Leblais . Châtenay-Malabry, France
 P7- Differential control of cytoplasmic and nuclear protein kinase A activity by phosphodiesterases and Ser/Thr protein phosphatases in cardiac myocytes. Zeineb Haj-Slimane / Grégoire Vandecasteele. Châtenay-Malabry, France
 P8- Viagra makes *Plasmodium* stiff: a new way to block transmission? Ghania Ramdani/Catherine Lavazec. Paris, France

Session IV Moderator : **Pierre Vincent and Kjetil Tasken**

- 16h40 - Dynamic and spatial regulation of adenylyl cyclase by calcium, *Demot Cooper*, Cambridge, UK
 17h05 - Imaging of cAMP signaling in endocrine cells, *Davide Calebiro*, Wuerzburg, Germany

Plenary Conference

Moderator : **Jérôme Bertherat**

- 17h30-18h20** - How PKA is activated: the dynamic interactions between the catalytic and regulatory subunits,
Susan Taylor, San Diego, USA
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Friday July 12th

Protein Kinase A and Phosphodiesterases

Session V Moderators : **Anna Spada and Hervé Lefebvre**

8h30 - PKA alterations in adrenal Cushing, *Jérôme Bertherat & Bruno Ragazzon*, Paris, France

8h55 - The use of FRET to study the consequences of PRKAR1A inactivation on cAMP signaling in adrenal Cushing, *Grégoire Vandecasteele*, Chatenay Malabry, France

9h20 - PRKAR1A inactivation in the adrenal cortex: mice models, *Antoine Martinez*, Clermont Ferrand, France

9h45 - Altered PRKAR1A and PDE4D in human hormone resistance and bone disorders, *Agnes Linglart & Caroline Silve*, Paris, France

10h10 - The interactions between the catalytic subunit and mutants of PRKAR1A observed in human diseases, *Eric Clauser*, Paris, France

10h35 - The use of next generation sequencing to identify genetic alterations of signaling pathways in adrenal tumors, *Felix Beuschlein*, Munich, Germany

11h00-11h25 - COFFEE BREAK (faculté)

Session VI Moderators : **Rossella Libe and Guillaume Pidoux**

11h25 - Ubiquitination and compartmentalized cAMP signaling in physiology and endocrine tumors, *Feliciello Antonio*, Naples, Italy

11h50 - PDE11A and adrenal Cushing in mice and human, *Constantine Stratakis*, Bethesda, USA

12h15 - Development of PDE11A selective antagonist acting on cortisol secretion, *Charlie Hoffman*, Chestnut Hill, USA

12h40 - PDE8B deficiency: human disease and mouse model of cortisol and other steroid hormone production, *Eva Szarek*, Bethesda, USA

13h05 - Imaging the cAMP/PKA signaling cascade in the striatum: what is the functional role of PDE10 and what implications in schizophrenia treatment, *Pierre Vincent*, Paris, France

13h30 - CONCLUSION: Anna Spada, Jérôme Bertherat, Constantine Stratakis

13h40 - LUNCH - (Faculté)

LISTS OF PARTICIPANTS

NOM

Ajuria
Assié
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BANDJE
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Bertagna
Bertherat
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Bram
Brenner
Bruystens
Burgers
Calebiro
Castro
Clauser
Coculescu
Collins
Cooper
Decouture
Delon
Dorseuil
Drougat
Duchez
Dumaz
Echebli
El Hage
El Nemer
Espiard
Feliciello
Felouzis
Feuillet
Fischmeister
Fraudeau
Gerbaud
Gervasi
Groussin
Guellich
Guiot
Haidar
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