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Australasian Paediatric
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Asia Pacific Paediatric
Endocrine Society (APPES)

African Society for Paediatric and Adolescent
Endocrinology (ASPAAE)

British Society for Paediatric Endocrinology
and Diabetes (BSPED)

Canadian Pediatric Endocrine Group (CPEG)

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(ESPE)

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Japanese Society for Pediatric Endocrinology
(JSPE)

The Lawson Wilkins Pediatric Endocrine
Society (LWPES)

Sociedad Española de Endocrinología
Pediátrica (SEEP)

Sociedad Latino Americana de Endocrinología
Pediátrica (SLEP)

Early and lifelong remodelling of our epigenomes by nutrition

Claudine Junien. Genetics and Epigenetics of Metabolic Diseases, Neurosensorial Diseases and Development, Hospital Necker - Enfants Malades, Paris, France

The phenotype of an individual is the result of complex interactions between genome, epigenome and current, past and ancestral environment leading to a lifelong remodelling of our epigenomes. The genetic information expression contained in the genome is controlled by labile chromatin-associated epigenetic marks. Epigenetic misprogramming during development is widely thought to have a persistent effect on the health of the offspring and may even be transmitted to the next generation. The epigenome serves as an interface between the environment and the genome. Dietary factors - including folate involved in the one-carbon metabolism - and other social and lifestyle exposures have a profound effect on many aspects of health including ageing and do so, at least partly, through interactions with the genome which result in altered gene expression with consequences for cell function and health throughout the life course. Depending on the nature and intensity of the environmental insult, the critical spatiotemporal windows and developmental or lifelong processes involved, epigenetic alterations can lead to permanent changes in tissue and organ structure and function, or to phenotypic changes that can (or cannot) be reversed using appropriate epigenetic tools. Moreover, the flexibility of epigenetic marks may make it possible for environmental, nutritional and hormonal factors, or endocrine disruptors to alter — during a particular spatio-temporal window in a sex-specific manner — the sex-specific methylation or demethylation of specific CpGs and/or histone/chromatin modifications underlying sex-specific expression of a substantial proportion of genes. Moreover, genetic factors, the environment and stochastic events change the epigenetic landscape during the lifetime of an individual. Epigenetic alterations leading to gene expression dysregulation accumulate during ageing are important in tumorigenesis and age-related diseases. Given several encouraging trials, prevention and therapy of age- and lifestyle- related diseases by individualized tailoring to optimal epigenetic diets or drugs are conceivable. However these interventions will require intense efforts to unravel the complexity of these epigenetic, genetic and environmental interactions and to evaluate their potential reversibility with minimal side effects.

The GH receptor: Update on mechanism and actions

Michael J Waters. Institute for Molecular Bioscience, University of Queensland, St Lucia, Queensland, Australia

Until recently, the accepted model for GH-dependent activation of the receptor was hormone induced dimerization, which brought two JAK2 tyrosine kinase molecules bound to the receptor cytoplasmic domain together, so that they could cross-activate as for tyrosine kinase receptors. However, a wealth of data now supports the existence of a constitutive receptor dimer, which mandates a conformational change/receptor realignment as the mechanism of activation. We determined the crystal structure of the extracellular domain in the absence of hormone and compared it to the published structure of the bound form in order to identify the conformational change. The only salient difference was a change in the disposition of a loop in the lower beta-sandwich domain (see below), but mutation of this loop did not influence signalling through JAK2. It appeared that activation must involve subunit realignment, and we were able to show that relative rotation of subunits can activate the receptor, but not fully. To identify additional conformational changes we have used three approaches (1) cysteine crosslinking down the transmembrane domain of the full length receptor (2) replacing the extracellular domain with a jun zipper, which holds the receptor extracellular domain in manageably fixed orientations and (3) FRET with fluorophores placed just below the transmembrane domain. These approaches led us to conclude the activation mechanism involves a rotation coupled with a drawing together of the extracellular domain, resulting in (surprisingly) movement apart of the receptor subunits just below the membrane, which we suggest displaces the inhibitory pseudokinase domain of one JAK2 from the catalytic domain of the other JAK2 and vice versa. Mutation of the loop referred to above abrogated ERK signalling, but not JAK2/STAT5 activation. This led us to identify a second tyrosine kinase signalling system directly activated by the receptor, involving a Src family kinase and ERK, acting via PLC γ and increased cytosolic calcium. We could show this pathway in cells lacking JAK2 and in mice with a mutation in the box 1 sequence which abrogates their ability to activate JAK2. Using microarray analysis we have identified transcripts specific to this pathway in mice, and have identified liver regeneration as a process critically dependent on this pathway. Studies are in progress to identify the target of GH-dependent ERK signalling responsible.

Human ALS deficiency: clinical, endocrine and metabolic consequences

Horacio M Domené. Centro de Investigaciones Endocrinológicas (CEDIE-CONICET), Hospital de Niños R. Gutiérrez, Buenos Aires, Argentina

The majority of IGF-I (and IGF-II) circulates in the serum as a complex with IGFBP-3 or IGFBP-5, and an acid labile subunit (ALS). The well-established function of ALS is to prolong the half-life of the IGFs-IGFBP-3/IGFBP-5 binary complexes. From the description of the first case of ALS deficiency, the number of mutations identified in the *IGFALS* gene has rapidly increased, suggesting that ALS deficiency may be prevalent in a subset of patients with extraordinarily low serum levels of IGF-I and IGFBP-3 that remain abnormally low upon GH stimulation. Fourteen different mutations of the human *IGFALS* gene have been identified in the seventeen patients identified to date. Eleven patients were found to be homozygous and six were compound heterozygous. The mutations showed an autosomal recessive pattern of inheritance.

Postnatal growth was clearly affected. Commonly, height SDS before puberty was between -2 and -3, and were approximately 1.4 SD shorter than the midparental height SDS. Adult height SDS was higher than prepubertal height, but still 1.0 SD lower than the midparental height SDS. Pubertal delay was found in 50% of the male patients, while in the remaining, puberty started relatively late. Human ALS deficiency results in a peculiar IGF-I deficiency. Whereas circulating levels of IGF-I decrease dramatically, local production appears to be preserved. In addition to IGF-I other members of the circulating IGF system are also affected. Circulating IGF-II, IGFBP-1, -2, and -3 levels were all reduced, with the greatest reduction observed for IGFBP-3. Insulin resistance, characterized by normal glucose levels, hyperinsulinemia and low levels of IGFBP-1, was a common finding. In addition, some patients presented low bone mineral density (BMD). The pathophysiological mechanisms explaining these findings are still only partially understood. In summary, human ALS deficiency, the first monogenic defect involving an insulin-like growth factor binding protein, represents a unique condition in which the lack of ALS protein results in the disruption of the entire IGF circulating system. Despite a profound circulating IGF-I deficiency, there is only a mild impact on postnatal growth. Perhaps, the preserved expression of locally produced IGF-I under the stimulation of normal or even increased GH levels, might be responsible for the preservation of linear growth near or within normal limits.

The consensus conference on insulin resistance in children: definition, measurement, risk assessment, treatment and prevention

Claire Levy-Marchal, Alan R Sinaiko, Silva Arslanian, Wayne Cutfield, Francesco Chiarelli, The Consensus Conference on Insulin Resistance in Children. U690, INSERM, Paris, France; Pediatrics, University of Minnesota, Minneapolis, Minnesota, United States; Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, United States; Department of Pediatrics, University of Auckland, Auckland, New Zealand; Department of Pediatrics, University of Chieti, Chieti, Italy

Insulin resistance (IR) in adults has been recognized for decades as a cardinal feature in the development of type 2 diabetes mellitus and as a strongly associated factor in the pathogenesis of cardiovascular risk. It has also become clear, based on substantial evidence from pediatric studies that IR is significantly related to obesity and levels of cardiovascular and metabolic risk factors in children and adolescents. In addition, there are some unique features for IR in childhood, with relation to puberty, children born small for gestational age, prematurity, some developmental syndromes and treatment with glucocorticoids or growth hormone. Screening for insulin resistance requires information about prevalence, potential adverse effects on child health and treatment; and sensitivity, specificity and cost of the tests used. It is generally agreed that it is not practical to use the hyperinsulinemic euglycemic clamp — the gold standard —, FSIVGTT or OGTT to screen large groups of children. Fasting insulin measurement is simple, safe and relatively inexpensive, but there is significant variability among assays and among ethnic groups, genders and pubertal stages, and a lack of sensitivity and specificity in diagnosing IR. The prevalence of IR in children is unknown, but there are high-risk populations, e.g. polycystic ovary disease and obesity. Because of the strong tracking effect of obesity and the cardiovascular risk factors from childhood into adulthood, it is now acknowledged that caregivers for children can play an important role in the prevention of type 2 diabetes and cardiovascular diseases later in life. However, there is a lack of clarity as to what IR means in childhood, and there are no data on treatment of isolated IR in children. Caregivers would benefit from a better understanding of how it is best assessed, in what clinical disorders it occurs, what are its consequences and whether it can be treated or prevented. To explore these issues, ESPE, LWPES, ISPAD, APPES, APEG, SLEP, and JSPE convened a panel of expert physicians for a consensus conference on IR in children.

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We are always in search of items of interest to the international community for inclusion in this newsletter and on the COPES website (www.COPESinternational.org). Contact the Coordinator or Vice Coordinator with your suggestions.

Upcoming Events

Dates and locations in **bold** are annual meetings of the affiliated societies.

2010

MARCH 4 - 6 Calgary, Canada	Canadian Pediatric Endocrine Group: 2010 Scientific Meeting www.interprofessional.ubc.ca/Canadian_Pediatric.htm
MARCH 26 - 30 Kyoto, Japan	The 14 th International Congress of Endocrinology (ICE2010) Contact: Prof. Kazuwa Nakao or Kenji Fujieda (Pediatric Filed) E-mail: nakao@kuhp.kyoto-u.ac.jp or ken-fuji@asahikawa-med.ac.jp http://www.congre.co.jp/ice2010/
MARCH 31 - APRIL 1 Tokyo, Japan	International Symposium on Pediatric Endocrinology (Official Satellite Symposium of the ICE2010) Contact: Prof. Kenji Fujieda or Dr. Tsutomu Ogata E-mail: ken-fuji@asahikawa-med.ac.jp or tomogata@nch.go.jp http://www.congre.co.jp/ispe2010/
MAY 31 - JUNE 2 Nairobi, Kenya	1st ASPAE SCIENTIFIC MEETING Contact: Dr Lucy Mungai Email: kiomungai@yahoo.com http://aspae.info/
AUGUST 2 - 4 Adelaide, South Australia	Australasian Paediatric Endocrine Group: 2010 Scientific Meeting Contact: Alexia Pena MD Email: apeg@willorganise.com.au www.apeg.org.au/ConferencesandEvents/AnnualScientificMeeting
SEPTEMBER 22 - 25 Prague, Czech Republic	49th ESPE Meeting Contact: Prof Jan Lebl E-mail: jan.lebl@lfmotol.cuni.cz www.espe2010.org
OCTOBER 7 - 9 Osaka, Japan	44th JSPE Meeting Contact: Dr. Keinosuke Fujita E-mail: fkeinosk@m5.gyao.ne.jp http://square.umin.ac.jp/jspe44
OCTOBER 27 - 30 Buenos Aires, Argentina	36th Annual Meeting of ISPAD Contact: Olga Ramos, MD E-mail: ramoso@interlink.com.ar 2010.ispad.org
OCTOBER 27 - 30 Costa do Sauipe (Bahia), Brazil	XXI Annual Meeting of SLEP Contact: Prof Gil Guerra-Junior gilguer@fcm.unicamp.br ; gileandrea@uol.com.br www.eventus.com.br/slep2010
NOVEMBER 3 - 5 Manchester, UK	38th Meeting of the British Society for Paediatric Endocrinology and Diabetes Email: conferences@bioscientifica.com
November 17 - 20 Xian, China	APPES Biennial Scientific Meeting Email: appes@willorganise.com.au

2011

SEPTEMBER 25 - 28 Glasgow, Scotland	50th ESPE Meeting
OCTOBER 19 - 22 Miami, USA	37th Annual Meeting of ISPAD Contact: Alan Delamater, PhD E-mail: adelamater@med.miami.edu

2012

SEPTEMBER 20 - 23 Leipzig, Germany	51st ESPE Meeting
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2013

SEPTEMBER 18-21
Rome, Italy

9th ESPE/LWPES Joint Meeting

For more international events, visit www.endo-society.org/apps/Events.

A short description/presentation of the **Canadian Pediatric Endocrine Group (CPEG)** and the **African Society for Paediatric and Adolescent Endocrinology (ASPAE)**, the younger COPES' affiliated Societies.

CPEG-GCEP (Canadian Pediatric Endocrine Group - Groupe canadien d'endocrinologie pédiatrique) is the official Canadian association for pediatric endocrinology. It started more than 20 years ago as a group of clinician-researchers participating in a pan-Canadian clinical study. It officially became an independent body in 2005. Membership mostly includes Canadian pediatric endocrinologists and pediatric endocrine nurses as well as fellows enrolled in pediatric endocrinology training programs. CPEG-GCEP meets once a year for a high level two-day scientific meeting that rotates through all pediatric endocrinology centres in Canada and covers all aspects of pediatric endocrinology and diabetes. Thanks to industry support, CPEG-GCEP offers research fellowships for Canadian trainees. Representatives of CPEG-GCEP sit on defined committees of the Lawson-Wilkins Pediatric Endocrine Society.

The **African Society for Paediatric and Adolescent Endocrinology (ASPAE)** is an international organisation with several members from African countries whose aim is to promote the highest levels of knowledge, research, education and clinical practice of paediatric endocrinology and metabolism throughout the Africa.

Founded in July 2009, when the first Fellows graduated at the pan African school for Paediatric Endocrinology in Nairobi under the Presidency Dr Lucy Mungai and mentorship of some members of European Society of Paediatric and Adolescent Endocrinology (ESPE), the Society aims to increase in both size and scope, becoming one of the largest and most leading international scientific communities of paediatric endocrinology.

The Society is dedicated to serve its members, the African children and the African scientific community. It also aims at being involved in promoting the interests of the general public and in advising on African health policy in the area of paediatric endocrinology. ASPAE is committed to welcoming and establishing close relationships with other Scientific Societies in the world.

A warm welcome (accueil chaleureux) to our Canadian and African Colleagues.

Welcome to my fellow Africans and Canadians is my best way to finish my two years as COPES' coordinator.

I thank you all for your support, especially the Presidents and Secretaries of affiliated Societies, with special thanks to Ragnar Hanas, Suttipong Wacharasindhu (next Coordinator), and Francesco Chiarelli for their constant and effective cooperation.

Luciano Cavallo

The pediatric endocrinology list serve is a lively international forum for discussing a wide range of interesting topics. To subscribe, send an email message to peds-endo-subscribe@yahoogroups.com or go to health.groups.yahoo.com/group/peds-endo for more information.

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The COPES newsletter publishes information on the meetings of the affiliated societies and other meetings of interest. Reports on activities of the Affiliated Societies and information on meetings, workshops, courses, fellowships, and exchange programs, as well as selected letters and brief summaries or reviews pertaining to newsworthy items are published in the Newsletter and on the website. All contributions are welcome, so please mail or fax your correspondence to the Coordinator or Vice-Coordinator.

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